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Prescriptive variables for D-cycloserine augmentation of exposure therapy for posttraumatic stress disorder

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ABSTRACT

In recent years, several studies have demonstrated efficacy of D-cycloserine (DCS) enhanced exposure therapy across anxiety disorders. In this study we examined person-level variables that predicted response to DCS enhanced exposure therapy in a chronic, mixed trauma PTSD sample. The sample consisted of 67 treatment-seeking individuals, randomly allocated to receive exposure therapy augmented with DCS (50 mg) or identical looking placebo. We examined the following baseline predictors of treatment response: (1) demographic characteristics (age, gender, marital status, and education); (2) clinical characteristics (initial PTSD symptom severity, Axis I comorbidity, depression symptom severity, and antidepressants use); (3) personality characteristics (openness, conscientiousness, extraversion, agreeableness, and neuroticism). Outcome was measured with the PTSD Symptom Scale, Self-Report, which was assessed weekly during treatment. Two prescriptive variables were identified: conscientiousness and extraversion. For high conscientious participants, those who received DCS showed better outcome than those who received placebo. And for low extraversion, DCS showed superior outcome relative to placebo. Education was identified as a prognostic variable, it predicted response across both groups: higher education was related to worse outcome. Our results provide support for the influence of personality traits on DCS augmented exposure outcome and give more insight into possible working mechanisms of this novel treatment strategy. Ultimately, this may contribute to treatment matching strategies in order to improve treatment efficacy of exposure therapy for PTSD.

1. Introduction

Exposure therapy, a form of cognitive behavioral therapy (CBT), is an effective treatment for PTSD (cf. Powers et al., 2010). In exposure therapy, PTSD patients are repeatedly exposed to the traumatic memory (imaginal exposure) and to safe, but anxiety provoking, trauma-related stimuli (in vivo exposure). A proposed working mechanism of exposure therapy is fear extinction by effective emotional processing of the traumatic memory and incorporation of corrective information, namely the absence of anticipated harm (Foa and Kozak, 1986). Even though the efficacy and effectiveness of exposure therapy for PTSD are widely established, there is room for improvement, since loss of diagnosis rates tend to be around 40 to 65 percent (Bradley et al., 2005; Schnurr et al., 2007).

Attempting to improve treatment efficacy of exposure treatment for anxiety disorders, researchers have focused, among other strategies, on pharmacological enhancement of fear extinction. Augmentation of exposure therapy with the cognitive enhancer D-cycloserine (DCS), a partial agonist of the *N*-methyl-D-Aspartate (NMDA) glutamate receptor, has shown efficacy in the treatment of several anxiety disorders (see for meta-analyses: Bontempo et al., 2012; Norberg et al., 2008), although several studies have failed to demonstrate efficacy (Guastella et al., 2007; Litz et al., 2012; Tart et al., 2013). To date, two studies have examined the efficacy of DCS enhanced exposure treatment in PTSD patients and found mixed results. Our group (de Kleine et al., 2012) observed an effect of DCS on treatment response in a mixed-trauma population. More importantly, we found DCS to be beneficial in a subgroup of

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patients, namely those who needed all treatment sessions and had higher pretreatment PTSD symptoms. This finding suggests that DCS may be beneficial for a specific subsample of patients. Litz et al. (2012) examined DCS and exposure treatment in a male Veteran population and found that placebo outperformed DCS. Closer inspection of their data suggested that lack of within-session extinction resulted in the unfavorable outcome for DCS, considering the data suggesting that end-of-exposure fear is predictive of DCS enhanced exposure therapy outcomes (Smits et al., 2013b,c). Based on these studies it appears that DCS enhancement might have differential effects in PTSD patients.

Overall, hypotheses on why outcomes of DCS enhancement differ across studies are mainly of methodological nature – e.g. studies differed in treatment protocol length and DCS dosage (see for instance: Hofmann et al., 2011). In addition, it has been suggested that person-level variables, such as baseline symptom severity and antidepressant use, may influence DCS efficacy (de Kleine et al., 2012; Guastella et al., 2007; Rodebaugh et al., 2013; Siegmund et al., 2011). Most recently, Smits et al. (2013a) examined predictive factors of DCS enhanced exposure therapy in a large sample of social phobic patients. They found certain personality traits, namely agreeableness and conscientiousness, to be related to DCS augmentation effects. Specifically, DCS augmentation was evident only among individuals low in conscientiousness and among individuals high in agreeableness.

To gain more insight into variables associated with outcome of DCS-enhanced exposure therapy for PTSD, we examined prescriptive variables of DCS efficacy outcome in our randomized clinical trial (de Kleine et al., 2012). Here, a *prescriptive* variable is an individual characteristic that predicts differences in outcome between DCS- and placebo- enhanced exposure therapy, and thus requires, statistically, demonstration of a significant interaction between the individual characteristic and treatment condition (DCS vs. placebo; Kraemer et al., 2002). Attempting to replicate and extend the findings reported by Smits et al. (2013a) we examined the potential prescriptive effects of personality traits, while also considering and controlling for demographic and clinical characteristics.

In addition to prescriptive variables we examined *prognostic* variables, or individual characteristics that are predictive of treatment outcome irrespective of experimental condition (i.e. DCS vs. Placebo; Fournier et al., 2009). Prognostic variables therefore require demonstration of a statistically significant main effect of the individual characteristics. Our selection of candidate prognostic variables was guided by previous findings of exposure therapy outcome prediction studies in PTSD patients. Clinicians often believe that exposure therapy is contraindicated for PTSD patients with comorbid disorders (Becker et al., 2004; Van Minnen et al., 2010), but empirical evidence is lacking (see Van Minnen et al., 2012 for overview). In fact, a recent meta-analysis showed a positive relationship between general comorbidity and treatment outcome (Olatunji et al., 2010), and some studies have documented better exposure treatment outcome for those with more depressive symptoms (Feeny et al., 2009; Rizvi et al., 2009). Of note, van Minnen et al. (2002) examined a range of possible predictors, including comorbidity and trauma characteristics, but found baseline PTSD symptom severity to be the only stable and reliable predictor of exposure therapy outcome. At the time of this writing, little research exists on the clinical predictors of DCS efficacy for enhancing exposure therapy outcomes. Given these observations, we examined the prescriptive and prognostic effects of initial PTSD symptom severity, while also considering the possible influence of depressive symptoms, and DSM-IV axis I comorbid disorders.

In sum, enhancing treatment efficacy of exposure therapy for PTSD with DCS appears a promising strategy. However, it is likely that, as in non-enhanced exposure therapy for PTSD, not all patients benefit from this treatment strategy. By identifying prescriptive variables, we hope to direct clinicians in the effective application of DCS and gain more insight into mechanisms of exposure therapy efficacy.

2. Material and methods

2.1. Participants

A full description of the sample characteristics and study procedures can be found elsewhere (de Kleine et al., 2012). Briefly, all 67 participants were regular referrals to two outpatient clinics, satisfying DSM-IV criteria for PTSD, confirmed by a structured diagnostic interview (Clinician Administered PTSD Scale (CAPS) (Blake et al., 1990)). Trauma-type was mixed and comprised sexual assault including childhood sexual abuse (52%), violent non-sexual assault (30%), a road traffic or other accident (4%), warzone experiences (3%), and miscellaneous (10%). Exclusion criteria were (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. The study protocol was approved by the medical ethics committee of the Radboud University Nijmegen Medical Centre and written informed consent was obtained from all volunteer participants.

2.2. Treatments

Participants were randomly assigned in double-blind fashion to receive exposure therapy and DCS ($N = 33$) or exposure therapy and placebo ($N = 34$). Both treatment groups received a standardized prolonged exposure therapy program (see Foa and Rothbaum, 1998), with a maximum of 10 sessions ($M = 7.22$ [2.58]). Twenty-two participants (33%) dropped out prematurely, leaving 45 protocol completers. There was no statistical significant difference in drop-out rate between groups (DCS: $N = 9$ (27%); placebo: $N = 13$ (38%); $\chi^2_1 = 0.913$, $p = .339$). Prior to the start of each exposure session, DCS (50 mg) or placebo (microcrystalline cellulose PH-102, identical in appearance) was administered.

2.3. Outcome measure

The primary outcome measure was the Dutch translation of the PTSD Symptom Scale, Self Report (PSS-SR; Foa et al., 1993; Mol et al., 2005), a 17-item questionnaire with which patients rate the frequency of PTSD symptoms. All participants completed the PSS-SR pre-treatment, before every treatment session, and post-treatment. Assessments were also conducted at 3-month follow-up, but data from the follow-up period were not used in this study.

2.4. Potential predictors

All potential predictors of treatment outcome were measured during the baseline assessment by trained independent assessors blind to treatment condition (Axis I comorbidity, antidepressants use), or self-report (demographic characteristics, PSS-SR, BDI, NEO). Each potential predictive variable was assigned to one of the following domains: