Journal of Psychiatric Research 46 (2012) 1184–1190

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

A randomized placebo-controlled trial of D-cycloserine and exposure therapy for posttraumatic stress disorder

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ARTICLE INFO

Article history:
Received 6 February 2012
Received in revised form
4 May 2012
Accepted 10 May 2012

Keywords:
PTSD
DCS
Exposure therapy
Veterans
Imaginal

ABSTRACT

D-Cycloserine (DCS) is a partial NMDA receptor agonist that has been shown to enhance therapeutic response to exposure-based treatments for anxiety disorders, but has not been tested in the treatment of combat-related posttraumatic stress disorder (PTSD). The aim of this randomized, double-blind, placebo-controlled trial was to determine whether DCS augments exposure therapy for PTSD in veterans returning from Iraq and Afghanistan and to test whether a brief six-session course of exposure therapy could effectively reduce PTSD symptoms in returning veterans. In contrast to previous trials using DCS to enhance exposure therapy, results indicated that veterans in the exposure therapy plus DCS condition experienced significantly less symptom reduction than those in the exposure therapy plus placebo condition over the course of the treatment. Possible reasons for why DCS was associated with poorer outcome are discussed.

Clinicaltrials.gov Registry #: NCT00371176; A Placebo-Controlled Trail of D-Cycloserine and Exposure Therapy for Combat-PTSD; www.clinicaltrials.gov/ct2/results?term=NCT00371176.

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1. Introduction

Extinction involves enhanced neural plasticity in the basolateral nucleus of the amygdala, which is reliant on *N-methyl-d-aspartate* (NMDA) receptors (Royer and Pare, 2002), and NMDA agonists have been shown to enhance extinction learning. Specifically, D-cycloserine (DCS), a partial NMDA receptor agonist, enhances extinction of conditioned fear in infrahumans (e.g., Davis et al., 2006; Yamamoto et al., 2008). Because exposure-based treatments involve extinction learning (Milad et al., 2006), acute DCS administration may stimulate NMDA-glutamate synapses involved in emotional learning, thereby strengthening extinction learning and treatment effects (Ledgerwood et al., 2004; Rothbaum, 2008).

Small doses of DCS have been shown to enhance response to exposure-based therapy of specific phobia (Ressler et al., 2004), social anxiety disorder (Guastella et al., 2008; Hofmann et al., 2006), panic disorder (Otto et al., 2010), and obsessive-compulsive disorder (Kushner et al., 2007; Wilhelm et al., 2008), with medium to large effects (Norberg et al., 2008). Patients have required fewer sessions to achieve gains, had higher remission rates, and lower relapse rates (Hofmann, 2007; Kushner et al., 2007).

Because PTSD entails strong conditioning to a specific context (Milad et al., 2006), higher-order conditioning (Foa et al., 1989), and is associated with impaired extinction learning and retention (Blechert et al., 2007; Guthrie and Bryant, 2006; Milad et al., 2008, 2009), it is an ideal context to study the impact of DCS. Due to the very slight side-effect profile and low cost (see Hofmann, 2007), DCS may allow exposure therapy of PTSD to be delivered in fewer sessions to achieve more rapid and sustained change. If care can be delivered more efficiently, more resources will be available to meet the considerable demands for PTSD treatment, especially in the military and VA contexts. Only one study has been published testing DCS in PTSD patients (De Kleine et al., 2012). It found that DCS did not enhance overall treatment effects in a sample of civilian mixed trauma survivors, although DCS did increase the likelihood

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0022-3956/$ – see front matter Published by Elsevier Ltd.
doi:10.1016/j.jpsychires.2012.05.006

of treatment response in a subgroup of participants with severe symptoms who had completed all treatment sessions.

The primary aim of this randomized, double-blind, placebo-controlled trial funded by the VA as part of a joint VA/NIMH solicitation, was to determine whether DCS augments exposure therapy for PTSD in returning veterans. We hypothesized that DCS combined with brief exposure therapy would lead to more rapid and greater PTSD and depression symptom reduction relative to exposure plus placebo.

A secondary exploratory aim was to examine whether a brief exposure therapy could promote symptom relief among veterans with PTSD. New veterans are reluctant to engage in a lengthy therapy (e.g., Seal et al., 2010), and they have considerable stigma about mental health care and competing occupational demands and other logistical barriers to care (e.g., Hoge et al., 2004). As a result, we shortened the intervention for the veterans in this trial to six sessions.

2. Materials and methods

2.1. Participants

Twenty-six veterans of the Iraq and Afghanistan wars who had a primary diagnosis of PTSD (designated by the patient as the most important source of distress) participated in the trial; patient flow is depicted in the CONSORT diagram (see Supplemental materials). Data were collected at the VA Boston Healthcare System Jamaica Plain campus. Exclusion criteria included: a lifetime history of bipolar disorder, schizophrenia, psychosis, delusional disorders or obsessive-compulsive disorder; organic brain syndrome; past history of reported seizures; use of Isoniazid; cognitive dysfunction that could interfere with capacity to engage in therapy; significant medical conditions, including renal insufficiency, that would increase risks of drug toxicity; and a history of substance or alcohol dependence (other than nicotine) in the last 6 months (or otherwise unable to commit to refraining from alcohol use during the acute period of study participation). Patients with suicidal ideation or suicidal behaviors within 6 months prior to intake were also excluded. Patients were required to be stabilized on psychotropic medications for at least two months; changes in psychotropic medications were assessed via self-report at each time point.[1] Additionally, patients were excluded if they were participating in ongoing exposure-based psychotherapy for PTSD. Concurrent supportive therapy was acceptable; participating in non-exposure-based PTSD therapy was acceptable if initiated more than three months prior to study participation. The study was carried out in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of the VA Boston Healthcare System, and informed consent of participants was obtained after the nature of the procedures had been fully explained. No participants reported serious side effects during the trial.

2.2. Procedures

After completing a telephone screen, eligible patients were scheduled for an in-person assessment and medical evaluation. Patients meeting eligibility criteria were randomly assigned to exposure therapy plus DCS ($n = 13$) or exposure therapy plus placebo ($n = 13$). Randomization was blocked and stratified based on PTSD scores (CAPS scores < 75 or ≥ 75). Initially blocks were of 8 participants, but due to slower recruitment than anticipated, blocks were reduced to 3 participants. Participants were enrolled by a research assistant. The randomization allocation sequence was implemented by a pharmacist (not part of the research team), who assigned participants to conditions according to a computer generated randomization list. All research team members, therapists, assessors, and participants were blind to condition. Data were collected between March 2007 and April 2011; the trial was stopped at the end of the funding period.

Baseline diagnostic assessments were completed by study therapists. This allowed the therapist to both learn about the primary trauma to be targeted in therapy and to build rapport. Subsequent assessments were conducted by doctoral-level independent assessors blind to patient condition. Interview assessments of PTSD symptoms occurred at baseline, post-treatment, and at 3, and 6-month follow-up. Self-reported PTSD and depression symptom data were gathered at the beginning of each treatment session.

Treatment began one week after the initial assessment. Participants attended a total of 6 sessions of 60–90 min. DCS administration was yoked to the therapy sessions that entailed imagine exposure (sessions 2–5). The DCS-augmented group received 50 mg of DCS 30 min prior to sessions 2–5, whereas the placebo-augmented group received a placebo pill at these four occasions. For sessions in which imaginal exposures were conducted (sessions 2–5), participants were asked to arrive at least 30 min prior to the start of session for a repeat medical evaluation including alcohol breath analysis and to take the DCS or placebo. They completed questionnaires while waiting. Imaginal exposures began approximately 20 min after the start of session (i.e., 50 min after the drug was administered).

2.2.1. Description of treatment

The treatment was a brief, manualized exposure therapy adapted from a protocol developed and successfully employed in numerous trials by Bryant and colleagues (e.g., Bryant et al., 2005). Dr. Bryant trained the study clinical supervisor (the second author, a doctoral-level clinical psychologist with extensive experience in exposure therapy for PTSD), who implemented training with study therapists. Therapists were doctoral-level clinicians with previous experience and training in CBT for anxiety disorders.

Because an exploratory aim was to examine the efficacy of a briefer therapy, the therapy consisted of six sessions (four exposure sessions). The exposure therapy consisted of only imaginal exposures and no *in vivo* exposures (which is not atypical for combat-related PTSD), and there was no formalized homework (e.g., listening to recordings of imaginal exposures). Homework was not used because patients in both arms would have received exposures without DCS (or placebo), which would defeat the primary aim of the study.

Session 1 (60 min) focused on building rapport, psychoeducation about PTSD, providing a detailed explanation of the extinction model of trauma-memory processing, and explaining imaginal exposure procedures.

Sessions 2–5 (90 min) consisted of check-in and review, followed by a 50-min imaginal exposure and then 10 min of discussing the meaning and implication of the event. Exposures focused on the patient's most distressing war-trauma memory.

Session 6 (60 min) entailed a review of treatment gains, discussion of relapse-prevention strategies, and termination.

[1] While participants were asked to maintain stable psychotropic medication regimens, clinical need was given priority. Over the course of the trial six participants in total had medication changes (4 placebo, 2 DCS). Of those participants in the placebo condition, 3 increased or added medications, and 1 decreased medication usage. In the DCS condition, 1 increased medication usage, and 1 decreased medication usage. There were no statistically significant differences between conditions on medication changes.