Journal of Psychiatric Research 47 (2013) 168–174

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

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

Augmentation of exposure therapy with post-session administration of D-cycloserine

Candyce D. Tart [a,*], Pamela R. Handelsman [a], Lindsey B. DeBoer [a], David Rosenfield [a], Mark H. Pollack [c], Stefan G. Hofmann [b], Mark B. Powers [a], Michael W. Otto [b], Jasper A.J. Smits [a]

[a] Department of Psychology, Southern Methodist University, USA
[b] Department of Psychology, Boston University, USA
[c] Rush University Medical Center, USA

ARTICLE INFO

Article history:
Received 16 July 2012
Received in revised form
26 September 2012
Accepted 27 September 2012

Keywords:
Augmentation
CBT
Cognitive behavioral therapy
D-cycloserine
Exposure treatment
Randomized controlled trial
Acrophobia

ABSTRACT

Background: Pre-session administration of D-cycloserine (DCS) has been found to augment exposure therapy outcomes in a variety of anxiety disorders. To be able to enhance learning only for successful exposure sessions, it would be beneficial to have the option of administering DCS after rather than before the session, a strategy encouraged by pre-clinical work. We believe the present study is the first published report on the efficacy of post-session administration of DCS in humans.
Method: Adults ($N = 29$) with a DSM-IV diagnosis of acrophobia were randomized to receive two sessions of virtual reality exposure therapy (VRE) in combination with placebo or 50 mg of DCS. Instead of administering the pill prior to each of the sessions, as has been done in extant work, we administered the pill immediately following each session. Measures of acrophobia severity were collected at baseline, at each treatment session, 1-week post-treatment, and at 1-month follow-up.
Results: Mixed-effects repeated-measures ANOVAs and GLMMs revealed significant improvement in all outcome measures over time, but no between-group differences were observed. At post-treatment, 63.5% of patients in the placebo condition vs. 60.0% of those in the DCS condition were in remission. At 1-month follow up, 63.4% of those in the placebo condition vs. 66.6% of those in the DCS condition were in remission.
Conclusions: These findings do not support the application of post-session DCS administration for augmenting the efficacy of exposure-based treatments. Possible reasons for these findings are discussed. Trial Registry: The Trial is registered at ClinicalTrials.gov (NCT01102803).

1. Introduction

An exciting success of translational research is the use of D-cycloserine (DCS) as an augmentation strategy for exposure-based treatment (Anderson and Insel, 2006). Following pre-clinical research implicating the N-methyl D-aspartate (NMDA) receptor in fear conditioning and extinction learning (Baker and Azorlosa, 1996; Davis and Myers, 2002; Falls et al., 1992; Lee and Kim, 1998). Walker et al. (2002) demonstrated that rats administered DCS, a partial agonist at the NMDA receptor, prior to extinction training displayed enhanced dose-dependent extinction relative to rats administered saline. Replicated since (Myers and Davis, 2007), these findings encouraged the application of DCS for the augmentation of exposure treatment for anxiety disorders (Hofmann et al., 2011).

In the initial clinical trial, Ressler et al. (2004) enrolled 27 adults with DSM-III-R acrophobia into a 2-session virtual reality exposure (VRE) therapy protocol. The investigators selected this VRE protocol because VRE allows for carefully controlling exposure procedures and two 45-min sessions is considered a suboptimal dose, thus leaving sufficient room to detect augmentation effects. The efficacy of DCS augmentation was tested by randomly assigning patients to take either (a) pill placebo (PBO); (b) 50 mg of DCS; or (c) 500 mg of DCS 2–4 h prior to each of the 2 sessions. Relative to patients receiving PBO, those receiving DCS showed significantly greater reductions on in acrophobia severity during the 2-session intervention and the 3-month follow-up period with no differences between the two DCS doses.

The findings of the Ressler et al. (2004) study have since been replicated outside a VRE paradigm and extended across the anxiety

* Corresponding author. Tel.: +1 214 768 4125; fax: +1 214 768 3910.
E-mail addresses: candycetart@gmail.com (C.D. Tart), jsmits@smu.edu (J.A.J. Smits).

0022-3956/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jpsychires.2012.09.024

disorders (Hofmann et al., 2006; Kushner et al., 2007; Otto et al., 2010; Wilhelm et al., 2008). In a meta-analysis of 10 trials involving clinical samples, Norberg et al. (2008) reported a significant advantage of DCS over PBO augmentation for exposure-based treatment efficacy ($d = .60$).

In all trials of DCS augmentation to date, the administration of DCS has been *before* instead of *after* the exposure session. However, post-session administration of DCS would offer the clinician and patient the advantage of select use of this augmentation strategy (i.e., only after sessions deemed successful). Indeed, the judicious use of DCS – administration following only the most successful exposure sessions – is supported by observations that repeated dosing appears to rapidly cause tolerance to DCS (Lopes et al., 1997; Parnas et al., 2005; Quartermain et al., 1994). Importantly, DCS dosing only after successful exposure sessions addresses the clinical concern that DCS may be applied to exposure sessions that accidentally sensitized the patient to fear cues. Recent research in fear reconsolidation validates this clinical concern. Specifically, when memories are retrieved, they become temporarily destabilized and vulnerable to intervention that may attenuate, modify, or stabilize the original memory (Lee, 2008; Monfils et al., 2009; Schiller et al., 2010). As such, during this time-limited state, memories are amenable to updating with new information, and hence sensitizing events or inadequate learning during exposure procedures may lead to reconsolidation. Research further suggests that, when the period of the initial conditioning sessions is brief, reconsolidation processes are dominant, whereas extinction processes dominate in longer sessions (Eisenberg et al., 2003; Lee et al., 2006). Therefore, DCS has the potential to augment extinction learning when the conditioned stimulus (CS) is re-exposed sufficient times for extinction to occur. In contrast, if stimulus re-exposure during memory reactivation is relatively brief compared to the strength of conditioning, little extinction is induced and DCS may augment reconsolidation (i.e., if the memory is in the labile state) (Lee et al., 2006). Although the bounds around reconsolidation effects in humans have yet to be investigated, research suggests that this period of lability, in which reconsolidation can occur, persists for approximately 6 h in animals (Nader et al., 2000). Hence, the application of post-session DCS administration only when exposure is judged to be adequate has the potential for avoiding unwittingly strengthening fear associations (Litz et al., 2012).

Pre-clinical data offers evidence in support of the potential efficacy of post-session DCS augmentation. For example, Ledgerwood et al. (2003) found that post-extinction subcutaneous administration of DCS in rats facilitated extinction and these effects were comparable to that observed with pre-extinction administration. Timing, similar to dosage, followed a linear trend such that peak extinction facilitation was observed when DCS was administered either immediately afterward or 30 min post-training, and diminished results were found at 120 min post-training administration. No benefits of DCS were observed at 240 min post-training administration (Ledgerwood et al., 2003). Parnas et al. (2005) have since replicated these findings.

The present study investigates whether post-session oral administration of DCS facilitates exposure-based CBT outcomes for anxiety disorders. Replicating the procedures of the first study examining the efficacy of pre-session DCS in humans (Ressler et al., 2004), we randomized 29 adults with height phobia to receive two sessions of VRE in combination with either PBO or 50 mg of DCS. Instead of administering the pill two to 4 h before each of the two VRE sessions, as was done in the Ressler et al. (2004) study, we administered the pill immediately *after* each of the two VRE sessions. Measures of acrophobia severity were collected at baseline, at each treatment session, 1-week post-treatment, and at 1-month follow-up. We hypothesized that, relative to participants receiving placebo-augmented VRE, those receiving DCS-augmented VRE would show decreased acrophobia symptoms at post-treatment and follow-up.

2. Materials and method

2.1. Participants

Participants ($N = 29$; $M_{age} = 33.38$) with acrophobia were recruited from Southern Methodist University and the greater Dallas area. Inclusion criteria were: (a) age 18–65; and (b) meeting DSM-IV-TR criteria for acrophobia. Exclusion criteria were: (a) a subjective distress score (SUDS) of <50 on the BAT; (b) a lifetime history of bipolar disorder, schizophrenia, psychosis, delusional disorders, or obsessive-compulsive disorder; current or recent diagnosis of substance or alcohol abuse or dependence; (c) current or recent suicidality or suicidal behavior; (d) current or recent diagnosis of PTSD, panic disorder, or eating disorder; (e) any physical or psychiatric condition that could interfere with the capacity to engage in therapy; (f) history of head trauma causing loss of consciousness, seizure, or ongoing cognitive impairment; (g) pregnancy; (h) concurrent psychotropic medication or psychotherapy or prior non-response to exposure therapy for acrophobia.

2.2. Experimental design

Eligible participants were assigned to one of two blinded arms – VRE therapy plus pill placebo ($N = 14$) or 50 mg of DCS ($N = 15$). Randomization was done by research staff not involved in the trial using minimization procedures (Scott et al., 2002) and stratifying on gender, therapist, and time of day of treatment sessions (before or after 4 pm). Assessments occurred at baseline, prior to each treatment session, at one-week post-treatment, and at 1-month follow-up. Consistent with the original study (Ressler et al., 2004), the primary outcome measures were the BAT, AAVQ, AAQ (Cohen, 1977), ATHQ (Abelson and Curtis, 1989), and the CGI (Guy, 1970).

2.3. Procedures

2.3.1. Screening

Respondents to study advertisements were briefly screened by a research assistant before being invited to the clinic for formal eligibility screening. After signing informed consent, participants were administered the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2001) and clinician-rated instruments. The study physician reviewed the medical history information and prescribed all study medications. The senior author (JAJS) verified assessment of entry criteria and diagnoses.

2.3.2. Treatment

The two-session VRE protocol was identical to the protocol used by Ressler et al. (2004). Treatment started one week following baseline assessment. Assessment of clinical status and safety occurred prior to each session. In the first session (60 min), therapists reviewed the rationale for exposure and the cognitive-behavioral model of acrophobia. Therapists then led participants through their first graded VRE exposures. The virtual reality environment simulated a hotel with a glass elevator, and a series of catwalks, balconies, and rooftop in which participants could stand and look around while wearing a virtual reality helmet and goggles. Participants reported their subjective fear levels (i.e., subjective units of distress [SUDS]) (Wolpe, 1958) on a 0–100 scale (0 indicates no fear, 100 indicates extreme fear or panic) every 5 min