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

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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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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.

Relapse-prevention strategies focused on maintaining non-avoidant responses and continued use of self-exposure.

2.3. Measures

2.3.1. Clinician-rated diagnostic and symptom severity instruments

The *Structured Clinical Interview for DSM-IV* (SCID; First et al., 1995) was used to assess for anxiety and affective disorders, alcohol and substance abuse and dependence, and psychotic disorders at the pre-treatment visit.

The *Clinician-Administered PTSD Scale-IV* (CAPS; Blake et al., 1990) is semi-structured interview designed to assess DSM-IV symptoms of PTSD and associated features. The CAPS is the gold standard PTSD measure in the field and has excellent psychometric properties (see Weathers et al., 2001). A PTSD case was identified if subjects endorsed the requisite DSM-IV symptoms at least at a frequency of 1 and at an intensity of 2 (Weathers et al., 2001). The one-week version of the CAPS was used at the post-treatment interval (only). An independent CAPS rater (who was not part of the study team) rated the reliability of 30% of the taped interviews at each time interval. Overall, the intraclass correlation coefficients ranged from 0.91 to 0.99 across symptom clusters and was 0.97 for CAPS total score. The Kappa for CAPS diagnosis was 1.00.

2.3.2. Self-report questionnaires

The *PTSD Checklist* (PCL; Weathers et al., 1993) is a self-report inventory that assesses the severity of DSM-IV-defined PTSD symptoms. The PCL is widely used and has excellent reliability and validity (e.g., Weathers et al., 1993; Blanchard et al., 1996).

The *Revised Beck Depression Inventory* (BDI-II; Beck et al., 1996) is a 21-item self-report inventory measuring severity of depression in adults. The BDI-II is a widely used instrument with excellent internal consistency and convergent and discriminant validity (Beck et al., 1996).

The *Deployment Risk and Resilience Inventory- Combat Experiences Scale* (DRRI; King et al., 2006) is a 15-item measure of exposure to typical warfare experiences such as being fired upon and witnessing death. The DRRI-CES has demonstrated good internal consistency and is correlated with PTSD symptomatology in Iraq war veterans (Vasterling et al., 2010).

Subjective Units of Distress Scale (SUDS). SUDS scores ranging from 0 to 100 were used to assess the degree of participants' subjective distress during exposures (sessions 2–5). Therapists recorded SUDS before, during (peak), and after exposures.

Although additional measures were administered (see clinicaltrials.gov), we analyzed and reported the primary outcome for the trial (CAPS) and two secondary outcome measures (PCL, BDI-II). The PCL substantiates the primary outcome findings and the BDI-II was evaluated because of the high comorbidity of PTSD and depression among combat veterans. These measures are also used as the core primary and secondary outcomes in clinical trials with combat veterans with PTSD (Monson et al., 2006). No other outcomes were analyzed for this report.

2.4. Data analysis plan

At the beginning of the trial, we planned to recruit 68 veterans, allowing for an attrition rate of 30%, resulting in an intent-to-treat (ITT) sample size of 52, which allowed for sufficient power to detect a large effect ($d = 0.8$; 32). We stopped the trial because of sustained recruitment difficulties and because the grant ended. We determined if there was enough power to detect differences in the two arms with the ITT sample achieved. Given the N of 26, and a power = 0.80, effect sizes (d) would need to be >1.01 to yield statistically significant differences at alpha = 0.05. The effects sizes for the key time by arm interaction analyses exceeded this effect size threshold.

Multi-level regression analyses were conducted using the Hierarchical Linear and Nonlinear Modeling program (HLM 6; Raudenbush et al., 2005). Linear time was entered as a continuous variable on level 1 with condition on level 2 (the exposure therapy plus placebo condition was the reference group for these analyses). Full maximum likelihood estimation was employed. Because of the small sample size, Hedge's g was used to estimate effect sizes (Hedges and Olkin, 1985). Controlled Cohen's ds were calculated based on the between-groups t-test value (from the multi-level model using the relevant intercept or slope coefficient ratio) according to the formula $d = 2t/\sqrt{(df)}$ (Dunlop et al., 1996). Hedges g was calculated by multiplying d by the correction factor $J(df)$, which was computed using the following formula: $J(df) = 1 - 3/(4df - 1)$. Because multi-level regression does not produce a standardized regression coefficient, we report partial regression coefficients (pr) for comparison on a common metric.

We conducted analyses of treatment effects (pre-to-post) on the ITT sample (i.e., all randomized participants, $n = 26$). We analyzed clinical significance and maintenance (post-treatment to 6-month follow-up) of treatment effects in a completer sample (exposure therapy plus DCS condition, $n = 9$; exposure therapy plus placebo condition, $n = 11$).

3. Results

3.1. Preliminary analyses

Participant characteristics are reported in Table 1. Preliminary analyses revealed no differences between the groups on ethnicity (white vs. non-white, χ^2 (2) = 0.87, $p > .10$), age ($t(24) = 0.31$, $p > .10$), combat exposure as measured by the DRRI-CES ($t(24) = 0.00$, $p > .10$), or medication use (i.e., meds vs. no meds, χ^2 (2) = 0.16, $p > .10$). Means and standard deviations of the primary outcome variable (CAPS) and two secondary (PCL, BDI-II) outcome variables at pre- and post- are reported in Table 2. No

Table 1
Participant characteristics of intention-to-treat sample at pre-treatment.

	All participants ($n = 26$)	DCS ($n = 13$)	Placebo ($n = 13$)	t or χ^2
Self-identified race/ethnicity				
White (vs. non-white)	20	11	9	0.87
Black	4	2	2	
Pacific Islander	1	0	1	
Haitian	1	0	1	
DRRI-CES	10.54 (2.77)	10.54 (2.54)	10.54 (3.10)	0.00
Age, mean (SD)	32.19 (9.31)	32.77(9.85)	31.62(9.10)	0.31
Most common additional SCID diagnoses (current)				
MDD	7	4	3	0.04
Alcohol use	5	2	3	0.16
Social anxiety	2	1	1	0.00
Stable psychotropics at diagnostic	11	5	6	0.16
Antidepressants	7	3	4	0.20
Anxiolytics	2	0	2	2.17
Anticonvulsants	3	1	2	0.38
Antipsychotics	4	2	2	0.00
Beta-blockers	0	0	0	0.00

Note. DRRI-CES = Deployment Risk and Resiliency Inventory, Combat Experiences Scale, SCID = Structured Clinical Interview for DSM-IV, MDD = Major Depressive Disorder.
*$p < .05$.

Table 2
Means (and standard deviations) of outcome variables as a function of condition and time of measurement: intent-to-treat sample ($n = 26$).

	DCS ($n = 13$)		Placebo ($n = 13$)		t
	Pre	Post	Pre	Post	
Primary outcome					
CAPS	69.85(23.24)	72.33(28.63)	73.38(16.35)	53.73(26.22)	0.45
Secondary outcomes					
PCL-M	37.85(8.76)	34.11(21.09)	39.00(8.77)	24.18(14.95)	0.23
BDI-II	24.85(15.31)	28.56(16.25)	21.48(9.24)	14.18(10.81)	0.68

Note. CAPS = Clinician-Administered PTSD Scale, PCL-M = Posttraumatic Stress Disorder Checklist, Military Version, BDI-II = Beck Depression Inventory-II.
*$p < .05$.

significant pre-treatment differences between conditions were evident for these outcome variables ($ts(24) < 0.68$, $ps > .10$).

3.2. Treatment condition effects

Results of multi-level regression analyses of the treatment condition effects are presented in Table 3. The controlled effect sizes for condition by time interactions for primary and secondary outcomes were medium to large with significant condition by time interactions for CAPS, PCL-M, and BDI-II, with exposure therapy plus placebo performing significantly better than exposure therapy plus DCS on all outcomes. Given the unexpected findings, after unblinding, the pharmacist conducted additional tests verifying that the drugs had been assigned correctly.

At post-treatment, 36.4% of the completers in the placebo condition compared with 33.3% of those in the DCS condition no longer met criteria for PTSD on the CAPS ($p > .10$, Fisher's exact test). However, because even minor symptom improvement can result in loss of PTSD diagnosis on the CAPS, we also examined responder status, defined as a reduction of 10 or more points on the CAPS (Schnurr et al., 2007). At post-treatment, 50% ($n = 10$) of the completer sample met criteria for responder status; 70% of participants in the exposure therapy plus placebo condition and 30% of participants in the exposure therapy plus DCS condition met criteria for responder status ($p > .10$, Fisher's exact test). Three participants reported clinically significant worsening of symptoms from pre- to post-treatment (increase of 10 or more points on the CAPS; Schnurr et al., 2007); all three of these participants were in the exposure therapy plus DCS condition.

These results were robust despite missing data at post-treatment. We explored a shift in post-treatment scores in our primary outcome (CAPS) by a constant, Δ, until statistical significance was lost at $\Delta = 20$. This roughly follows the sensitivity analysis approach under a pattern mixture missingness model (Daniels and Hogan, 2008). This revealed that missing scores would have had to be twenty CAPS scale score points lower than their simply imputed values to undermine the significant result. This lends credibility to our unexpected findings.

Table 3
Multi-level regression effects of time and condition by time[a] for primary and secondary outcomes from pre- to post-treatment: intent-to-treat sample.

	B	t	pr	p	g
Primary outcome					
CAPS					
Time	−41.49	−3.05	1.01	<.01	0.94
Condition × time	20.88	2.35	0.99	<.05	0.73
Secondary outcomes					
PCL-M					
Time	−3.80	−5.82	0.28	<.001	0.88
Condition × time	1.28	3.02	0.24	<.01	0.46
BDI-II					
Time	−2.49	−3.57	0.40	<.01	0.58
Condition × time	1.12	2.473	0.28	<.05	0.40

Note. CAPS = Clinician-Administered PTSD Scale, PCL-M = Posttraumatic Stress Disorder Checklist, Military Version, BDI-II = Beck Depression Inventory-II.
[a] Reference group is placebo.

3.3. Maintenance of treatment condition response

Means and standard errors of outcome variables at 3-month and 6-month follow-up are presented in Table 4. Multi-level regression analyses of change (reported in Table 5) revealed no significant effects of time or significant time by condition interactions for growth curves from post-treatment to 6-month follow-up.

3.4. Post-hoc analyses of SUDS ratings

To explore differences between the conditions in terms of response to the exposures, we conducted post-hoc analyses examining mean SUDS scores pre- and post-exposure, as well as mean peak SUDS scores during the exposures in the ITT sample (Figs. 1–3). There were no significant effects of initial status for these three variables (i.e., the conditions were equivalent in terms of SUDS ratings at pre-, peak, and post-exposure in the first exposure session; $Bs < 9.61$, $ts < 0.98$, $prs < 1.00$, $ps > .10$, $gs < 0.39$). However, for pre-exposure SUDS there was a significant effect of time ($B = -9.58$, $t = -2.26$, $pr = 1.07$, $p < .05$, $g = 0.51$) qualified by a significant time by condition interaction ($B = 6.80$, $t = 2.44$, $pr = 0.87$, $p < .05$, $g = 0.54$) with DCS participants reporting higher pre-exposure distress only after the first exposure session. For post-exposure SUDS there was a trend for time ($B = -7.30$, $t = -1.87$, $pr = 1.07$, $p < .10$, $g = 0.42$) but no significant time by condition interaction ($B = 4.05$, $t = 1.57$, $pr = 0.90$, $p > .10$, $g = 0.36$). For peak SUDS, there was no significant effect of time, or time by condition interaction ($Bs < 2.84$, $ts < 0.97$, $prs < 1.10$, $ps > .10$, $gs < 0.22$).

We also compared the two conditions on within-session decrements in distress (i.e., reductions from peak exposure SUDS to post-exposure SUDS). There were no significant group differences between the exposure therapy plus placebo ($M = 24.50$, $SD = 20.05$) and exposure therapy plus DCS ($M = 28.10$, $SD = 25.33$) conditions in within-session decrements during the first exposure session ($t(20) = -0.37$, $p = .71$, $d = -0.16$). However, although there was no statistically significant group difference between the exposure therapy plus placebo ($M = 35.00$, $SD = 22.02$) and exposure therapy plus DCS ($M = 22.87$, $SD = 19.75$) conditions during the second exposure ($t(17) = 1.23$,

Table 4
Means (and standard deviations) of outcome variables at 3-month and 6-month follow-up: completer sample ($n = 20$).

	DCS ($n = 9$)		Placebo ($n = 11$)	
	3-Month	6-Month	3-Month	6-Month
Primary outcome				
CAPS	62.57 (26.65)	62.20 (32.17)	58.20 (26.17)	55.50 (27.02)
Secondary outcomes				
PCL-M	33.29 (14.68)	29.20 (13.16)	26.91 (16.40)	27.25 (15.83)
BDI	24.57 (14.43	22.25 (17.73)	13.90 (10.59)	15.38 (11.43)

Note. CAPS = Clinician-Administered PTSD Scale, PCL-M = Posttraumatic Stress Disorder Checklist, Military Version, BDI-II = Beck Depression Inventory-II.

Table 5
Multi-level regression effects of time and condition by time[a] for primary and secondary outcomes from post-treatment to six-month follow-up: completer sample ($n = 20$).

	B	*t*	pr	*p*	*g*
Primary outcome					
CAPS					
Time	5.82	1.15	0.98	>.10	0.34
Condition × time	−5.06	−1.52	1.07	>.10	0.45
Secondary outcomes					
PCL-M					
Time	2.42	1.19	0.88	>.10	0.34
Condition × time	−0.99	−0.72	1.26	>.10	0.21
BDI-II					
Time	3.15	1.21	0.92	>.10	0.35
Condition × time	−2.18	−1.20	1.26	>.10	0.34

Note. CAPS = Clinician-Administered PTSD Scale, PCL-M = Posttraumatic Stress Disorder Checklist, Military Version, BDI-II = Beck Depression Inventory-II.
[a] Reference group is placebo.

$p = .23$), the effect size was moderately large ($d = 0.59$). Moreover, there was less decrement in SUDS in the exposure therapy plus DCS condition ($M = 30.50$, SD = 15.35) relative to the exposure therapy plus placebo group ($M = 14.66$, SD = 14.82) at the third ($t(17) = 2.28$, $p = .36$, $d = 1.10$) exposure session. Patients in the exposure therapy plus DCS condition also had significantly less distress reductions within the fourth exposure session ($M = 39.20$, SD = 16.92 vs. $M = 19.33$, SD = 19.14, respectively) ($t(14) = 2.16$, $p = .04$, $d = 1.15$).

3.5. Overall response to exposure therapy

To examine whether the brief therapy produced significant symptom reduction, we calculated the growth curves from pre-treatment to 3- and 6-month follow-ups, collapsed across condition using the ITT sample. At 3-months, CAPS scores decreased ($B = -14.07$, $t = -3.51$, pr = 1.13 $p < .01$), as did the PCL ($B = -10.02$, $t = -4.66$, pr = 10.95 $p < .01$) and the BDI-II ($B = -5.77$, $t = -2.88$, pr = 1.87 $p < .01$) and, at 6 months, CAPS scores showed a trend toward decreasing ($B = -3.83$, $t = -1.93$, pr = 1.40, $p = .061$), PCL scores significantly decreased ($B = -4.99$, $t = -4.15$, pr = 0.73, $p < .001$), and BDI-II scores did not significantly decrease ($B = -2.12$, $t = -1.39$, pr = 1.57, $p = .17$).

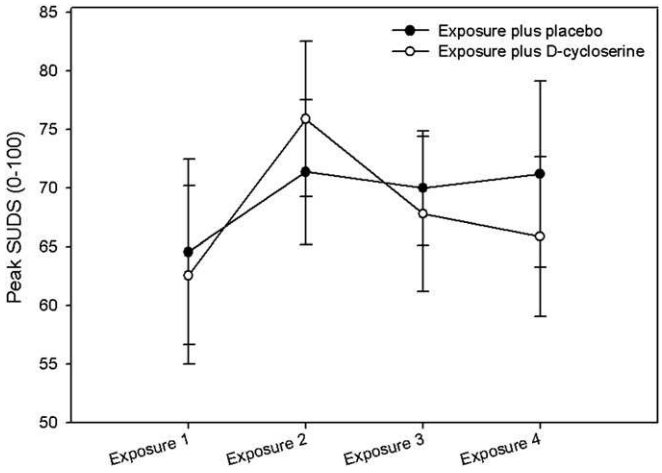

Fig. 2. Mean peak exposure SUDS scores by condition.

4. Discussion

This is the first clinical trial to examine DCS-enhanced imaginal exposure therapy for combat-related PTSD. Although veterans in the two conditions started the trial with similarly high symptom levels, those in the exposure therapy plus DCS arm had higher symptoms over the course of the treatment (while DCS was administered), relative to patients in the placebo arm. DCS not only did not facilitate change, it was associated with poorer outcome from pre- to post-treatment than placebo administration. This result held for both the primary (i.e., interviewer assessed PTSD symptoms) and secondary (i.e., self-reported PTSD and depression symptoms) outcomes. Of note, the two arms had equivalent SUDS ratings prior to the initial exposure session (when DCS was first administered), but patients in the DCS arm reported an increase in pre-exposure SUDS ratings after the first exposure (before their second exposure session), whereas participants in the placebo arm reported a decrease in pre-exposure SUDS after the first exposure. Our findings are broadly consistent with De Kleine et al. (2012) who also failed to show an overall augmentation effect for DCS. It is of note that de Kleine et al. found a narrow subgroup who appeared to benefit from DCS (patients with high initial scores and who completed all treatment sessions). The results of our study and de Kleine et al. suggest that, unlike other disorders, PTSD requires

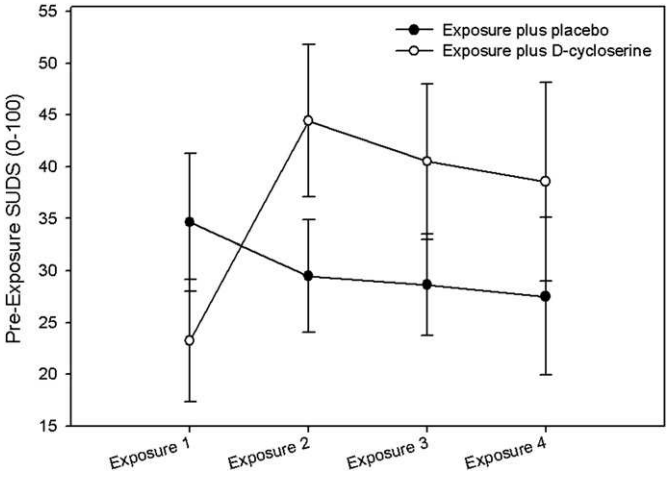

Fig. 1. Mean pre-exposure SUDS scores by condition.

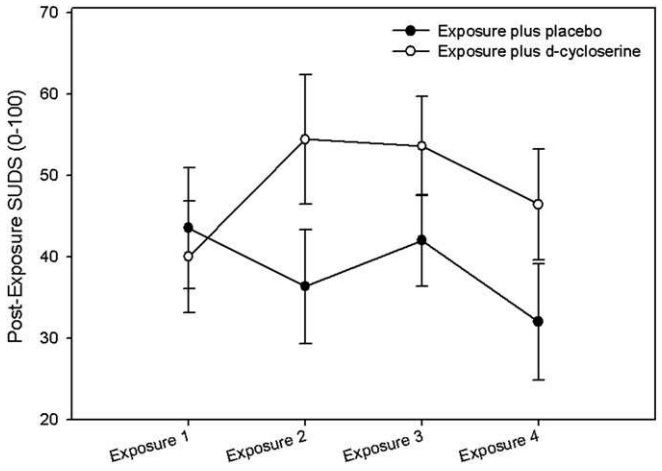

Fig. 3. Mean post-exposure SUDS scores by condition.

careful attention to clinical moderators and mediators and that a one-size-fits-all to cognitive enhancers may be counter-indicated.

Although speculative, one explanation of these findings is the possibility that DCS inadvertently enhanced reconsolidation of the trauma memory. Recent research has demonstrated that when memories are retrieved and brought into consciousness (reactivated), they become temporarily destabilized and alterable (Nader and Hardt, 2009; Tronson and Taylor, 2007). During this labile state, memories are amenable to updating with new information, before being consolidated again (i.e., reconsolidated). For extinction and reconsolidation to work together optimally, extinction learning would need to occur, and while the reactivated memory is in its labile state, reconsolidation would then be of a therapeutically updated memory (i.e., associated with a decrement in fear; see Schiller et al., 2010; Quirk et al., 2010). However, in our trial, we had evidence of less successful within-session extinction learning in the participants who received DCS, meaning that, in the absence of sufficient extinction, these patients may have reconsolidated their trauma memory in a particularly intense form.

Animal studies have demonstrated that NMDA antagonists impair the reconsolidation of fear memories (Przybyslawski and Sara, 1997; Suzuki et al., 2004; Torras-Garcia et al., 2005), whereas DCS enhances reconsolidation of fear memory when administered into the basolateral amygdala (Lee et al., 2006). It appears that if there is a sufficient decrement of fear during exposure, DCS may augment this process because it facilitates extinction learning. If fear does not decrease during exposure, fear memory reconsolidation may occur and DCS may also facilitate this counter-therapeutic process. In other words, it appears that DCS might make a good exposure better and a bad exposure worse.

An additional aim of this study was to determine whether a brief six-session course of early exposure therapy could effectively reduce PTSD symptoms in returning veterans. At the 6-month follow-up, among participants in the placebo condition, 50% no longer met criteria for PTSD and 66% met criteria for responder status (defined as a reduction of 10 or more points on the CAPS). Overall, 58% and 54% of the sample met criteria for responder status at 3- and 6-month follow-up, respectively. Although this positive result requires replication in a randomized controlled trial, the finding suggests that a short course of imaginal exposure therapy promotes symptom improvement for returning veterans. Given that many returning veterans with PTSD may not attend a full course of CBT due to logistical and psychological barriers to care (e.g., Seal et al., 2010), symptom relief in a brief treatment context may create positive expectancies for future treatment and foster further symptom improvement by shifting maladaptive coping strategies. If replicated, this finding has public health implications for military and veteran agencies who manage large numbers of PTSD cases.

This trial had a small sample size, which needs to be taken into account when interpreting the results; although despite this limitation, we had sufficient power to detect differences between the conditions on our outcome measures. However, it is possible that we were not able to detect group differences at pre-treatment that may have affected outcome or unique but unmeasured characteristics of the participants that may have affected external validity. Due to the small sample size, we were also unable to examine the influence of medication changes over the course of treatment, as well as possible interactions between DCS and other psychotropic medications, and thus cannot rule out the possibility that unidentified medication changes during treatment may have disadvantaged the DCS group; this question should be examined in future research. One reason for our small sample size was the reluctance on the part of many of our potential participants to take part in a PTSD treatment that included an experimental medication. Thus, our sample included an inadvertently select group of participants who were amenable to trying an experimental drug treatment. Finally, we note that our study employed only male veterans. One study showed that male non-veteran PTSD patients are less likely to maintain treatment than females following exposure (Felmingham and Bryant, 2012). It is possible that a different pattern may have been observed in a sample with more balanced gender representation.

In summary, this study raises timely questions for the field regarding the mechanisms of DCS in augmenting exposure therapy for anxiety disorders, and suggests that it may function differently across disorders. The results failed to find clear value for augmenting imaginal exposure therapy for PTSD with DCS. Future studies should examine whether DCS facilitates reconsolidation in human conditioning trials and whether the impact of DCS is moderated by within-session extinction.

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Contributors

Drs. Litz, Salters-Pedneault, Bryant, Hofmann, and Otto designed the study and wrote the protocol. Dr. Hermos was the study physician and Dr. Steenkamp conducted therapy. Dr. Salters-Pedneault undertook the statistical analysis, and Drs. Litz, Salters-Pedneault, and Steenkamp wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of interest

Drs. Litz, Salters-Pedneault, Steenkamp, Hermos, and Bryant reported no biomedical financial interests or potential conflicts of interest. In the last 2 years, Dr. Otto has received research support from Merck (Organon). Dr. Otto is also a recipient of an NIMH grant to study the effects of D-cycloserine in combination with exposure-based therapy for panic disorder. Dr. Hofmann is a paid consultant by Schering-Plough for research unrelated to this study, and he is supported by NIMH grant MH078308.

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Appendix A. Supplementary data

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jpsychires.2012.05.006.

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