ORIGINAL ARTICLE

D-cycloserine for treatment of numbing and avoidance in chronic post traumatic stress disorder: A randomized, double blind, clinical trial

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Background: Posttraumatic stress disorder (PTSD) tends to follow a chronic and treatment resistant course. Avoidance and numbing are symptoms associated with chronicity and impaired life quality. As D-cycloserine (DCS) can facilitate extinction of conditioned fear, we aimed to investigate the efficacy and tolerability of DCS for the treatment of numbing and avoidance in chronic PTSD. **Materials and Methods:** This was an 11-week, double-blind, cross-over trial conducted in 2012 and 2013, in out-patient University psychiatry clinics. The studied population was selected randomly among outpatients with chronic combat-related PTSD (based on DSM-IV-TR criteria for chronic PTSD), who were males over 18 and <65 years of age (n = 319). Seventy six eligible patients were randomly assigned to two groups. Patients entered a 1-week run-in period. The groups received either an add-on treatment of DCS (50 mg daily), or placebo (4-week). After a 2-week washout, the groups received cross-over treatments (4-week). Clinical, paraclinical assessments, and clinician administered PTSD scale (CAPS) were performed at baseline, and at the end of the 1st, 5th, and 11th week. Side-effects were also evaluated. The overall number of avoidance and numbing symptoms, symptom frequency, and symptom intensity were measured separately. **Results:** Neither frequency nor number of symptoms was significantly influenced. However, DCS treatment demonstrates a significant decrease in intensity of avoidance/numbing symptoms, and improvement in function (mean [standard error] = −4.2 [1.5], P = 0.008). Side-effects were not statistically remarkable. **Conclusion:** D-cycloserine can help as an adjunctive treatment to alleviate numbing and avoidance in combat-related chronic PTSD.

Key words: Avoidance, clinician administered posttraumatic stress disorder scale, N-methyl-D-aspartate receptor, numbing, posttraumatic stress disorder

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INTRODUCTION

Posttraumatic stress disorder (PTSD) can develop in individuals exposed to traumatic events. Regarding the violent nature of war, combat and its related experiences are an established cause of this disorder.[1] The lifetime prevalence of PTSD is approximately 7.8% in the general population, 10.4% in women, and 5% in men.[1,2] The prevalence among Iran Earth Force staff has been estimated 9.14%.[3] At least one-third of PTSD sufferers remain persistently symptomatic.[1,4] More than 50% of Iranian veterans in Iraq war suffer symptoms of chronic PTSD.[5] The symptoms may have a profound influence on patients, families, healthcare system and the society. The burden is felt not only by sufferers and their families but also by co-workers, employers, health care providers and wider society.[6] PTSD is resistant to many pharmacological therapies.[4] Among all symptom clusters, avoidance and numbing are symptoms associated with chronicity of the illness, and with decreased life quality;[7,8] notably, most therapies have little effect on this cluster of symptoms.[9,10]

D-cycloserine (DCS) is an antimicrobial agent, acting as an analogue of D-alanine and a partial agonist at N-methyl-D-aspartate (NMDA) receptor.[11,12] It appears to augment learning and facilitates extinction of conditioned fear, and has been tried for the treatment of various anxiety,[13-17] substance,[18] and cognitive disorders[19-21] as well as negative symptoms of schizophrenia.[22,23] However, studies focusing on DCS for treatment of PTSD have led to conflicting results.[4,5,11,24-28] The aim of the present study was to investigate the efficacy and tolerability of DCS in treatment of numbing and avoidance symptoms in chronic PTSD.

MATERIALS AND METHODS

Ethics and registration

The study was approved by the research and Medical Ethics Committee of the Isfahan University of Medical Sciences (IUMS) (Research Project Number: 391039). All steps of the study have been designed according to Helsinki declaration on Patient Safety.[29] Subjects

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were given written and oral information about the study process and drug profile; also, written informed consents were obtained. This trial has been registered with Iranian Registry of clinical Trials (Registration Number: IRCT2013121015741N1).

Study design and participants

This was an 11-week, double-blind, randomized, placebo-controlled, clinical trial, conducted in out-patient psychiatry clinics affiliated to the IUMS in Isfahan, Iran [Figure 1]. The studied population was selected randomly among outpatients with chronic combat-related PTSD (based on DSM-IV-TR criteria for chronic PTSD), who were males over 18 and <65 years of age, and whose records were registered in the university affiliated psychiatric outpatient clinics in Isfahan. Patient sampling, data collection and analysis, were conducted form late 2012 to mid-2013.

A total of 319 patients were screened for eligibility. Psychiatric and general medical records were reviewed; patients were excluded if, according to their records, they had criteria of another DSM-IV-TR diagnosis, or comorbid psychiatric condition including depression, suicidal or homicidal risk, or substance dependence, a serious medical problem, such as history of severe allergy or drug reaction, blood cell dyscrasia, cardiac infarction or arrhythmia, seizure, uncontrolled migraine, head trauma, and severe renal or hepatic insufficiency.[30-32] Patients were also required to be on a stable, adequate psychiatric treatment regimen for the past 3 months, otherwise they were excluded. Based on aforementioned exclusion criteria, among 319 screened patients, 209 were excluded in this step, and 18 refused to participate [Figure 2]. Screening and enrolment were accomplished by two psychiatrists, one senior resident of psychiatry and an expert psychologist. Sample volume was calculated to be 50 ($Z_\alpha = 1.96$, $Z_\beta = 0.84$). However, having predicted the sample loss, 76 subjects (~n + 15% n) were randomly selected among the eligible patients.

Procedure and assessment

The patients were interviewed based on structured, DSM-IV-TR criteria by a board certified attending psychiatrist to confirm the diagnosis of PTSD and to rule out other diagnoses or comorbidities.[4,31] Age, marital status, occupation, years of education, years of the disorder duration, psychiatric comorbidities, previous and current psychopharmacologic and psychotherapeutic treatments, concurrent medical illnesses and medications were registered, and clinician administered PTSD scale (CAPS) was filled as baseline. General and neurological physical examination, electrocardiogram, blood chemistry, hematology, thyroid, liver and renal function tests were performed, and patients who had abnormal results were excluded. Information about the study process and the drug profile was provided for patients, and written consents were

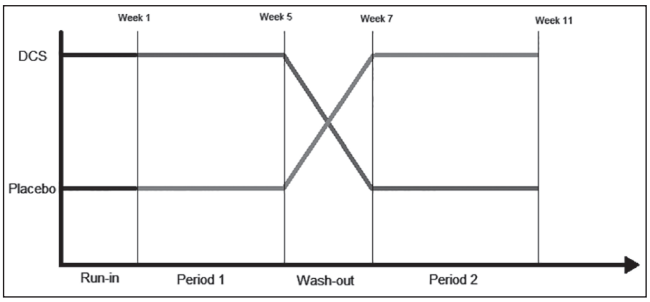

Figure 1: Line chart displaying the cross-over design. Note that both groups received placebo during run-in; while the groups received neither placebo nor DCS during wash-out. DCS = D-cycloserine

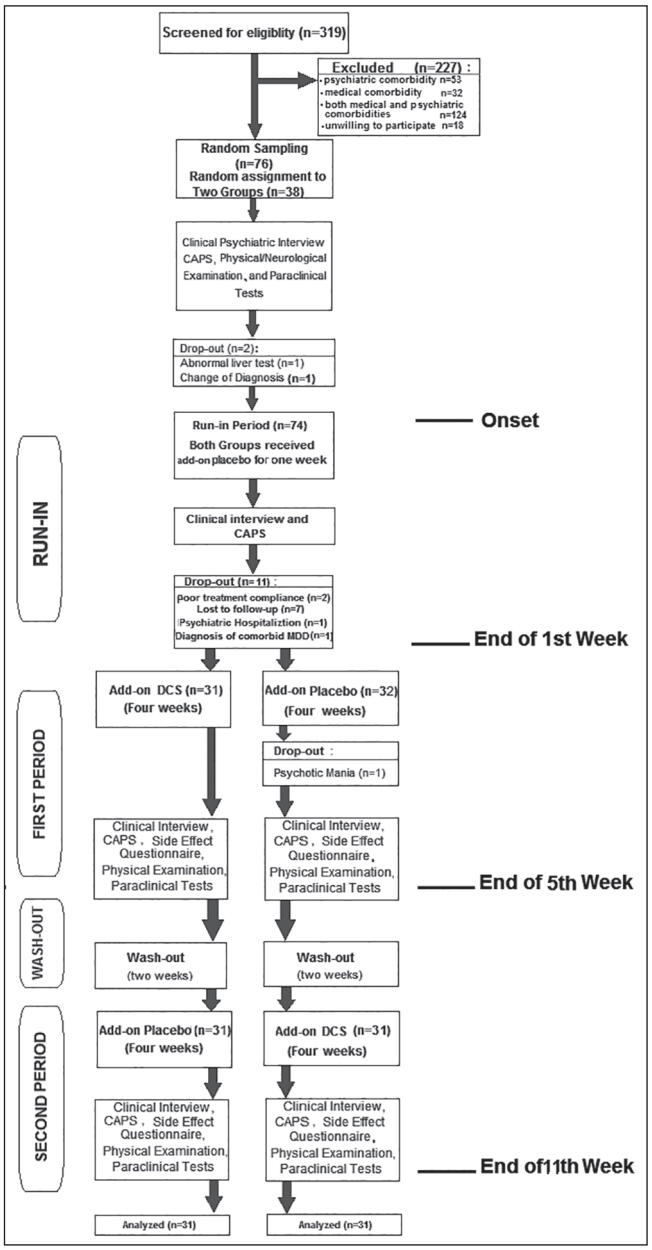

Figure 2: Flow diagram demonstrating the sequence of study steps and intervention periods. CAPS = Clinician administered PTSD scale; DCS = D-cycloserine

obtained. To provide a base line and to ensure patients' compliance and stability, all patients entered a 1-week run-in period, during which they received placebo. The previously stable therapeutic regimens were continued during the study course.[4,31] Patients were excluded if they had poor treatment adherence during the run-in period [Figures 1 and 2].

Primarily, 38 patients were randomly allocated to each group, using random-numbers table. However, the number decreased during the process due to drop-out [Figure 2]. The expert epidemiologist, who generated random allocation scheme, was not involved in other steps of the study. Furthermore, the two expert psychologists that implemented the random allocation and assignment did not participate in other parts of the trial. Allocation was concealed by means of sequentially coded sealed envelopes. During the next 4-week, one group received an add-on treatment of 25 mg of DCS (Eli-Lilly, Indianapolis, Indiana) twice daily,[4] while the other received placebo.[4,24] An attending professor of psychiatry administered the medication in the university clinic. As all patients were already on various psychopharmacologic treatments, either DCS or placebo was added to the stable previous regimen. At the end of this period (5th week), both groups were assessed through clinical interview, CAPS and drug side effect questionnaire by a senior resident of psychiatry. Physical exam, laboratory tests and electrocardiogram were performed. Both groups entered a 2-week washout period.[4] Following washout, the two groups received cross-over treatments for 4-week [Figures 1 and 2]. Psychiatric and general medical assessments were re-obtained at the end of the 11th week through clinical interview, CAPS, side effect questionnaire and paraclinical tests by the same senior resident. Patients, the psychiatrists who performed the interviews or administered medication, and a resident who filled the questionnaires and assessed clinical and paraclinical work-ups were blinded to the patients' group assignment [Figure 2].

The Persian version of CAPS (test-retest reliability = 0.86, Cronbach's α = 0.92) was used to evaluate patients' PTSD state and to assess intervention outcomes.[33] It is widely used for diagnostic purposes, and for tracking fine changes in symptom frequency or intensity over time or as a treatment outcome.[34,35] Since it is the most valid[34,35] and a highly reliable assessment tool for PTSD, it has become a standard criterion measure in this field.[33-35] CAPS is a structured interview corresponding to DSM-IV criteria, addressing all symptom clusters separately. B, C and D symptom clusters are rated for both frequency and intensity (including the impact of symptoms on patient's function). Frequency scores range from 0 to 4 (scale 0 = none of the time, 4 = most or all of the time), and the overall frequency score is calculated by summing frequency scores of all symptom. Likewise, intensity scores embrace 0-4 (scale 0 = none, 4 = extreme). Furthermore, intensity scores are summed to provide the overall intensity rating. Frequency and intensity scores are calculated for all symptom questions and/or for the three symptom clusters. Alternative scoring systems have also been suggested. Other questions assess criteria A, E and F. Besides, additional items inquire about guilt and dissociation. The whole interview consists of six clusters, including 60 questions. The overall score may range from 0 to 148. The present study focuses on criterion C (avoidance and numbing) which assesses seven symptoms through 21 questions; seven questions address the presence/absence of symptoms by means of yes/no answers, finally representing as the number of symptoms. Another seven questions assess the frequency of symptoms (scale 0 = none of the time, 4 = most or all of the time). And the other seven inquire how intensive the symptoms are and how they affect the patient's life and function.[33-35] Both frequency and intensity scores ranged from 0 to 28. CAPS was first filled for each participant as a base line, and then at the end of each intervention period.

The primary outcomes were the overall number of avoidance and numbing symptoms, symptom frequency, and symptom intensity, which were measured separately. Secondary outcomes were tolerability and safety of DCS assessed through the side effect questionnaire, clinical and paraclinical evaluation. Outcomes were measured at the end of each intervention period, that is, at the end of the 5th and 11th week of the trial.

Statistical analysis

The study was designed as cross-over; within-group analysis has been performed, and main effect has been measured. To qualify the design, period and carry-over effects were calculated. Missing data did not enter the analysis. *T*-test and paired *t*-test were used for between-group and within-group comparisons, respectively. Side-effects were analyzed through Chi-square in SPSS 16.0.2. (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0.2 Chicago, SPSS Inc.) An alpha level of 0.05 was used for all statistical tests.

RESULTS

A total of 319 patients were screened, and 76 patients entered the study; 38 patients were randomized to either group. Fourteen patients dropped out during the study process. Finally, 31 patients entered the analysis in each group [Figure 2].

Comparison of baseline profile of subjects in both groups, including age (mean [standard deviation (SD)] = 50.1 [6.2] vs. mean [SD] = 50.2 [5.9], P = 0.921), marital status (χ^2_1 = 0, P = 1), occupation ($\chi^2_{(2)}$ = 0.85, P = 0.959), years of education

(mean [SD] = 8.17 [3.92] vs. mean [SD] = 7.14 [4.08]; $Z = -1.25$, $P = 0.211$) and disorder duration (years) (mean [SD] = 28.78 [2.53] vs. mean [SD] = 28.58 [2.19]; $Z = -0.437$, $P = 0.662$), revealed no statistically significant differences.

Notably, all patients had already been on psychopharmacologic treatments, including various combinations of antidepressants, antipsychotics, mood stabilizers, sedative-hypnotics, and, etc. Among all participants, 7 patients followed marital therapy, two participated family therapy, and five received individual cognitive therapy.

Analysis of CAPS numbing and avoidance scores in the run-in period reveals that both groups had a similar profile except for the frequency of restricted range of affect ($t_{73} = 2.01$, $P = 0.047$) and intensity of decreased interest or participation in activities and related interference and impact on function ($t_{73} = 2.30$, $P = 0.024$).

The mean number of avoidance and numbing symptoms for DCS and placebo were 2.7 ± 2.3 and 5.2 ± 1.9 respectively at the end of the first-intervention period (5th week), and 3.7 ± 1.9 and 5.1 ± 1.7 respectively at the end of the second period (11th week). The mean difference of the total numbers of avoidance and numbing symptoms between DCS and placebo was found to be 1.13 ± 0.64, and, therefore, the main effect was nonsignificant ($t_{60} = 1.76$, $P = 0.083$). Carry-over and period effects were not significant either [Table 1].

There were no significant differences between DCS and placebo regarding overall avoidance and numbing symptom frequency ($t_{60} = 1.14$, $P = 0.259$) [Table 2].

Significant reduction of overall symptom intensity and impact on function was observed in DCS treatment (mean difference [standard error] = −4.22 [1.53], $P = 0.008$). As significant carry-over effect was detected, implying inadequate washout period, the analysis has only been confined to the first-intervention period [Table 3].

No clinically significant adverse effect was observed with DCS; and none of the patients dropped out because of side effects. Clinical examination and paraclinical tests including electrocardiography, blood cell count and chemistry, thyroid, liver and renal function tests did not reveal considerable changes. Although nonsignificant, the reported side effects were mild head ($\chi^2_1 = 1.016$, $P = 0.313$) and mild nausea ($\chi^2_1 = 1.069$, $P = 0.301$). Patients reported no other adverse experiences. Therefore, DCS (50 mg/day) was found to be easily tolerated.

DISCUSSION

Since war is characterized by extreme violence, combat veterans are at high risk of developing PTSD.[1,4,36] The disorder tends to follow a chronic course in roughly one third of patients.[1,3-5] The burden of chronicity of PTSD is prominent in terms of individual health and function, family life, work-place behaviors, employment issues and health

Table 1: Cross-over effect on the number of symptoms

Questions	Run-in period		First period		Wash-out period	Second period	
	Intervention	Proportion (%)	Intervention	Proportion (%)		Intervention	Proportion (%)
Avoiding thoughts, feelings or conversation	Placebo	30/37 (81.1)	DCS	13/31 (41.9)		Placebo	27/31 (87.1)
	Placebo	28/37 (73.7)	Placebo	24/32 (77.4)		DCS	8/31 (25.8)
Avoiding activities, places or people	Placebo	28/37 (75.7)	DCS	19/31 (61.3)		Placebo	24/31 (77.4)
	Placebo	29/37 (78.4)	Placebo	24/32 (77.4)		DCS	14/31 (45.2)
Inability to recall important trauma aspects	Placebo	14/37 (37.8)	DCS	10/31 (32.3)		Placebo	23/31 (74.2)
	Placebo	9/37 (23.7)	Placebo	21/32 (67.7)		DCS	13/31 (34.2)
Diminished interest or participation in certain activities	Placebo	36/37 (97.3)	DCS	21/31 (67.7)		Placebo	25/31 (80.6)
	Placebo	37/37 (97.4)	Placebo	30/32 (96.8)		DCS	16/31 (51.6)
Feeling detached or estranged	Placebo	34/37 (91.9)	DCS	22/31 (71.0)		Placebo	26/31 (83.9)
	Placebo	34/37 (89.5)	Placebo	25/32 (80.6)		DCS	16/31 (51.6)
Restricted range of affect	Placebo	32/37 (86.5)	DCS	19/31 (61.3)		Placebo	20/31 (64.5)
	Placebo	26/37 (68.4)	Placebo	25/32 (80.6)		DCS	12/31 (38.7)
Sense of foreshortened future	Placebo	25/37 (67.6)	DCS	12/31 (38.7)		Placebo	12/31 (38.7)
	Placebo	21/37 (55.3)	Placebo	12/32 (38.7)		DCS	6/31 (19.4)
Mean (SD) of total number of avoidance/numbing symptoms			DCS	2.7 (2.3)		Placebo	5.1 (1.7)
			Placebo	5.2 (1.9)		DCS	3.7 (1.9)
Mean difference				1.13			
Main effect				$t_{(60)} = 1.76$; $P = 0.083$			
Period effect				$t_{(60)} = -5.88$; $P < 0.0001$			
Carry-over effect				$t_{(60)} = 1.12$; $P = 0.269$			

Proportion = Proportion of patients who reported experiencing the symptom; % = Percentage of patients who reported experiencing the symptom; DCS = D-cycloserine; SD = Standard deviation

Table 2: Cross-over effect on end-point mean scores of symptom frequency

Questions	First period		Wash-out period	Second period		Main effect				Carry-over effect	Period effect
	Intervention	Mean (SD)		Intervention	Mean (SD)	Mean difference	*P*	*t*	df	*P*	*P*
Avoiding thoughts, feelings or conversation	DCS	1.0 (1.3)		Placebo	1.9 (0.94)	0.19	0.421	0.810	60	0.084	0.386
	Placebo	1.7 (1.1)		DCS	0.52 (0.96)						
Avoiding activities, places or people	DCS	1.2 (1.2)		Placebo	1.5 (1.0)	0.19	0.289	1.070	61	0.456	0.254
	Placebo	1.5 (1.0)		DCS	0.81 (0.98)						
Inability to recall important trauma aspects	DCS	0.61 (1.1)		Placebo	1.5 (1.0)	−0.11	0.597	−0.532	61	0.803	0.559
	Placebo	1.4 (1.2)		DCS	0.77 (1.0)						
Diminished interest or participation in certain activities	DCS	1.1 (1.1)		Placebo	1.6 (1.1)	0.14	0.456	0.750	61	0.367	0.417
	Placebo	1.5 (.85)		DCS	0.77 (0.95)						
Feeling detached or estranged	DCS	1.2 (1.1)		Placebo	1.5 (0.93)	0.21	0.252	1.157	61	0.214	0.221
	Placebo	1.5 (1.1)		DCS	0.77 (0.92)						
Restricted range of affect	DCS	1.1 (1.0)		Placebo	1.1 (0.99)	0.39	0.033	2.185	61	0.730	0.024
	Placebo	1.6 (1.0)		DCS	0.71 (0.90)						
Sense of foreshortened future	DCS	0.71 (1.1)		Placebo	0.77 (1.1)	0.11	0.482	0.708	61	0.385	0.481
	Placebo	0.71 (.97)		DCS	0.42 (0.88)						
Total avoidance/numbing symptom frequency score	DCS	6.8 (6.1)		Placebo	10.1 (3.9)	1.14	0.259	1.140	60	0.276	0.214
	Placebo	10.0 (5.2)		DCS	4.8 (5.1)						

DCS = D-cycloserine; SD = Standard deviation

Table 3: Cross-over effect on end-point mean scores of symptom intensity and interference with function

Question	First period		Wash-out period	Second period		Main effect				Carry-over effect	Period effect
	Intervention	Mean (SD)		Intervention	Mean (SD)	Mean difference	*P*	*t*	df	*P*	*P*
Avoiding thoughts, feelings or conversation	DCS	1.1 (1.4)		Placebo	1.9 (1.0)	0.24	0.346	0.950	61	0.283	0.260
	Placebo	1.9 (1.3)		DCS	0.58 (1.1)						
Avoiding activities, places or people	DCS	1.1 (1.2)		Placebo	1.5 (1.1)	0.19	0.304	1.637	61	0.368	0.261
	Placebo	1.5 (1.0)		DCS	0.74 (0.99)						
Inability to recall important trauma aspects	DCS	0.68 (1.2)		Placebo	1.6 (1.2)	−0.06	0.801	−0.253	61	0.757	0.779
	Placebo	1.6 (1.3)		DCS	0.81 (1.1)						
Diminished interest or participation in certain activities	DCS	1.7 (1.5)		Placebo	2.0 (1.3)	0.69	0.009	2.717	60	0.760	0.002
	Placebo	2.6 (0.96)		DCS	0.94 (1.2)						
Feeling detached or estranged	DCS	1.4 (1.1)		Placebo	1.7 (0.95)	0.24	0.182	1.351	60	0.275	0.138
	Placebo	1.7 (1.2)		DCS	0.84 (0.97)						
Restricted range of affect	DCS	1.3 (1.3)		Placebo	1.3 (1.1)	0.54	0.009	2.735	60	0.856	0.005
	Placebo	1.8 (1.2)		DCS	0.68 (0.91)						
Sense of foreshortened future	DCS	0.55 (0.96)		Placebo	0.77 (1.2)	0.03	0.856	0.183	61	0.389	0.854
	Placebo	0.65 (0.98)		DCS	0.35 (0.84)						
Total avoidance/numbing symptom intensity and function impairment score	DCS	7.8 (6.5)		Placebo	10.8 (4.5)	–		–		<0.001	0.034
	Placebo	12.1 (5.5)		DCS	4.9 (5.5)						
	P	0.008		–	–						

DCS = D-cycloserine; SD = Standard deviation

care services.[6-8] Despite many available pharmacologic therapies, the disorder is treatment resistant.[4,36] Notably, among many symptoms of PTSD, numbing and avoidance are closely associated with chronicity and decreased life quality; besides, they show little response to current treatments.[7,8]

This cross-over trial is among the few studies focusing on clinical efficacy of add-on DCS in the treatment of avoidance and numbing in chronic PTSD.[4,24,25] Our finding suggests that adjunctive DCS (50 mg/day) can help ameliorate the intensity of emotional numbing and avoidance, and improve patients' function by modifying the impact of symptoms on their lives. Yet it failed to diminish the frequency and the number of symptoms. It is noteworthy that the aforementioned dosage of DCS turned out to be safe and well-tolerated.

From a neurochemical point of view, an aspect of PTSD is disability in extinction of traumatic injury.[11]

Stressors are registered and remembered when they activate NMDA receptor which consequently produces a long-term memory.[4] On the other hand, symptoms like diminished interest, restricted affect, detachment, and social withdrawal, very much like negative symptoms of schizophrenia, have been suggested to be associated with dysfunction or dysregulation of NMDA receptor.[4,23] As DCS plays a partial agonist role at glycine regulatory site on NMDA synaptic receptor complex, it has positive effects on new learning, memory consolidation and retrieval processes in rodent studies.[4,24] Previous studies on the efficacy of DCS in treatment of PTSD have demonstrated disconsonant results. In a controlled trial by de Kleine *et al*., augmentation of exposure therapy with DCS did not enhance the overall treatment outcome; but it yielded higher symptom reduction in more severe PTSD cases.[26] Moreover, controlled trial by Litz *et al*. indicated that imaginal exposure plus DCS in combat-related PTSD leads to increased PTSD symptoms.[27] On the other hand, a recent pilot-controlled trial by Difede *et al*. showed greater remission rate of PTSD symptoms.[25] Furthermore, Heresco-Levy *et al*. used DCS for treatment of PTSD in a pilot-controlled study; DCS treatment was not only associated with a significant decrease in total PTSD scores but also with a noticeable reduction in numbing, avoidance and anxiety; yet similar improvements were also found during placebo treatment.[4] The inconsistency of results of different studies can be viewed in terms of methodology; as in some studies, subjects were solely males, while in others patients were majorly females. Furthermore, trials have addressed different trauma types; as some have focused on sexual assaults while others have studied combat-related PTSD.[24] Our present study suggests that DCS can function as an adjunctive therapy to reduce the intensity of numbing and avoidance in chronic PTSD, and can help improve patients' function in this regard.

The fact that subjects of our sample were exclusively males, exposed to combat trauma, may interfere with generalizablity. Moreover, regarding the significant carry-over effect in the assessment of intensity and function impairment, a 2-week washout appears to be insufficient. Besides, a decreasing, but nonsignificant trend in the number of symptoms during DCS treatment suggests that a larger sample volume may lead to more obvious results. Patients were either receiving disability payment or litigating to receive support pension; therefore, treatment results might have been influenced.

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AUTHORS' CONTRIBUTIONS

All authors have contributed in designing and conducting the study. AA and FR collected the data. MRM analyzed data. All authors have assisted in preparation of the first draft of the manuscript or revising it critically for important intellectual content. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

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