



# A randomized add-on trial of high-dose D-cycloserine for treatment-resistant depression

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## Abstract

Antagonism of *N*-methyl-D-aspartate glutamatergic receptors (NMDAR) may represent an effective antidepressant mechanism. D-cycloserine (DCS) is a partial agonist at the NMDAR-associated glycine modulatory site that at high doses acts as a functional NMDAR antagonist. Twenty-six treatment-resistant major depressive disorder patients participated in a double blind, placebo-controlled, 6-wk parallel group trial with a gradually titrated high dose (1000 mg/d) of DCS added to their antidepressant medication. DCS treatment was well tolerated, had no psychotomimetic effects and led to improvement in depression symptoms as measured by Hamilton Depression Rating Scale (HAM-D;  $p=0.005$ ) and Beck Depression Inventory ( $p=0.046$ ). Of the 13 subjects treated with DCS, 54% had a  $\geq 50\%$  HAM-D score reduction vs. 15% of the 13 patients randomized to placebo ( $p=0.039$ ). A significant ( $p=0.043$ ) treatment  $\times$  pre-treatment glycine serum levels interaction was registered. These findings indicate that NMDAR glycine site antagonism may be a cost-effective target for development of mechanistically novel antidepressants. Larger-sized DCS trials are warranted.

Received 15 May 2012; Reviewed 10 July 2012; Revised 17 July 2012; Accepted 19 July 2012;

First published online 17 September 2012

**Key words:** D-cycloserine, depression, NMDAR, treatment.

## Introduction

The limited effectiveness and often delayed therapeutic benefit of presently available antidepressants, which mainly affect monoaminergic neurotransmission, raise the possibility that other neurotransmitter systems may contribute to the pathophysiology of depression and the mechanism of antidepressant action. Recent research is focusing on the role of glutamatergic systems in mood disorders and accumulating data indicate that antagonism of *N*-methyl-D-aspartate subtype of glutamatergic receptors (NMDAR) may represent an effective antidepressant mechanism (Sanacora *et al.* 2008; Zarate & Manji, 2008). NMDAR antagonists have antidepressant effects in many animal models predictive of antidepressant activity in humans (Skolnick *et al.* 2009). Repeated administration of different classes of antidepressants induces alterations in the expression of

NMDAR subunit messenger RNA and radioligand binding to this type of receptors in brain regions implicated in the pathophysiology of depression (Boyer *et al.* 1998). Sanacora *et al.* (2004) found elevated glutamate levels in the occipital cortex in patients with unipolar major depression. Recently, Ji *et al.* (2011) reported that high plasma levels of glycine, which acts as a compulsory co-agonist at the NMDAR-mediated glycine site, are associated with poor response to selective serotonin reuptake inhibitors (SSRIs) treatment in major depressive disorder (MDD).

During the last decade, a number of mechanistically diverse glutamatergic compounds have been assessed in MDD. Promising results were reported with acute i.v. administration of the NMDAR non-competitive antagonist ketamine, which results in robust and rapid symptom alleviation in patients with treatment-resistant depression, bipolar disorder and suicide ideation (Sanacora *et al.* 2008; Zarate & Manji, 2008). A recent clinical trial suggests that i.v. administration of the NMDAR-2B subunit-selective antagonist CP-101,606 may also induce relatively rapid antidepressant effects in treatment-resistant MDD patients (Preskorn *et al.* 2008). However, the clinical applicability of these treatments is limited by their administration route and propensity to

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Clinical Trial Registration: clinicaltrials.gov identifier: NCT00408031.

cause psychotomimetic effects. Furthermore, ketamine is a phencyclidine derivative with known dissociative and cognitive effects that possibly preclude its use as chronic treatment.

We have focused on NMDAR glycine modulatory site as an alternative molecular target in depression and hypothesized that a sustained antidepressant effect can be obtained with daily D-cycloserine (4-aminoisoxazolidine-3; DCS) treatment. DCS functions as a partial agonist at the NMDAR glycine site, with agonist effects predominating at low dose and antagonist effects predominating at high dose. DCS is used as a broad spectrum antibiotic for treatment of tuberculosis and has antidepressant properties in rodent models of depression (Zarate & Manji, 2008). In the 1950s, psychotropic effects of DCS were noted on symptoms such as anorexia, asthenia and insomnia in patients being treated for tuberculosis (Crane 1959, 1961). Following the discovery of DCS NMDAR-based activity and in view of theories linking NMDAR to schizophrenia, DCS has been assessed in treatment-resistant schizophrenia. At low doses, DCS produced beneficial effects in some studies; at higher doses (>250 mg/d) it was found to exacerbate psychosis (Tuominen *et al.* 2006). DCS has also been assessed in the treatment of anxiety disorders and for enhancement of learning and memory at doses of 50–500 mg/d with the primary goal of enhancing NMDAR function (Norberg *et al.* 2008).

We have previously reported an exploratory trial involving the addition of 250 mg/d DCS to the ongoing pharmacotherapy of treatment-resistant MDD patients. This DCS regimen resulted in symptoms reduction; however, it did not induce significant therapeutic effects *vs.* placebo (Heresco-Levy *et al.* 2006). We hypothesized that higher DCS dosages may be necessary in order to elicit antidepressant effects, although such dosages may carry the potential danger of unwanted psychotomimetic effects. Additional support for higher DCS dosages stems from the fact that DCS doses of  $\geq 500$  mg/d may be required to elicit a neuroendocrine response indicative of NMDAR antagonistic activity (i.e. increase in plasma levels of luteinizing hormone; van Berckel *et al.* 1997, 1998). Therefore, the objective of the present study was to determine whether adjuvant DCS treatment, administered using a slow titration-high dose regimen, results in significant symptom alleviation in treatment-refractory MDD. An additional goal was the assessment of correlations between glycine plasma levels and response to DCS treatment.

## Method

The study was performed at Herzog Memorial and Haemek hospitals in Israel and was approved by the institutional and Israel Ministry of Health review boards. Written informed consent was obtained from patients after the study had been described to them verbally and

in writing. Participants were out-patients aged 18–65 yr who fulfilled the following inclusion criteria: (1) DSM-IV diagnosis of recurrent MDD, established on the basis of semi-structured psychiatric interviews, review of all available medical records and confirmation by at least two board-certified psychiatrists; (2) insufficient therapeutic response during the current episode, defined as a  $\geq 20$  score on the 21-item Hamilton Depression Rating Scale (HAMD; Hamilton, 1960) despite two or more adequate antidepressant medication trials; (3) currently treated for at least 4 wk with a stable clinically determined dose of antidepressant medication; (4) no experimental treatment, electroconvulsive or transcranial magnetic therapy within  $\leq 6$  wk of screening; (5) judged clinically not to be at significant suicide risk; (6) good physical health as determined by medical history, physical examination and screening laboratory parameters (SMA 20, CBC, urinalysis). Patients with a DSM-IV diagnosis of bipolar disorder, a lifetime history of substance abuse/dependence or antidepressant or substance-induced hypomania or mania were excluded. Medical exclusion criteria were any unstable illness, hyper- or hypothyroidism and, for women, pregnancy or the initiation of female hormonal treatments  $\leq 3$  months of screening.

A random-assignment, double-blind, placebo controlled parallel group design was used. After a 2-wk baseline assessment period, subjects were randomly allocated using a block size of four to receive either DCS or placebo for 6 wk in addition to their regular psychotropic medication, the dose of which remained fixed throughout the study. DCS and placebo were administered orally in identical capsules according to the same dose escalation schedule. Clinical and research staff, patients and their families were unaware of and could not determine the study drug assignment by appearance or otherwise. A fixed, slow titration-high dose treatment schedule for pharmacotherapy with DCS was conceptualized and employed: 250 mg (one capsule)/d for 3 d  $\rightarrow$  500 mg (two capsules)/d for 18 d  $\rightarrow$  750 mg (three capsules)/d for 1 wk  $\rightarrow$  and 1000 mg (four capsules)/d for the last 2 wk. This dosing schedule was adopted in order to: (1) ensure the assessment of NMDAR-antagonist DCS doses; (2) minimize safety risk; (3) allow for patient withdrawal at relatively low doses in case of emergent side-effects. Starting from day 4, daily experimental medication was administered in two divided doses.

Symptoms and side-effects were assessed at weeks 2, 0 and bi-weekly throughout the study using HAMD, the Hamilton Rating Scale for Anxiety (HAMA; Hamilton, 1959) and the Clinical Global Impression–Severity of Illness Scale (Guy, 1976). In addition, the Beck Depression Inventory (BDI-II; Beck *et al.* 1996) ratings were obtained in a subset ( $N=20$ ) of patients. HAMD was the primary efficacy measure with BDI-II as co-primary for available subjects. Clinical response was defined as  $\geq 50\%$  decrease in HAMD scores from baseline and remission was

**Table 1.** Symptom levels by treatment and week

	Treatment	Treatment week					LOCF	F	d.f.	P	d
		Baseline	Week 2	Week 4	Week 6						
<b>HAMD</b>											
Total	D-cycloserine	25.1±5.6	17.8±8.1	15.4±10.9	11.6±10.0	13.1±9.4	8.49	180.7	0.005	0.91	
	Placebo	27.2±4.9	22.8±7.4	22.4±6.9	21.5±8.7	23.3±9.6					
Guilt	D-cycloserine	1.5±0.9	1.1±1.0	0.9±1.0	0.4±0.7	0.5±0.8	0.32	193.9	0.60	0.89	
	Placebo	1.4±0.9	1.2±0.9	1.0±0.9	0.9±0.9	1.1±1.0					
Depersonalization/ derealization	D-cycloserine	0.3±0.9	0.1±0.3	0.0±0.0	0.0±0.0	0.0±0.0	–	–	–	0.72	
	Placebo	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0					
Paranoia	D-cycloserine	0.1±0.3	0.2±0.4	0.2±0.4	0.1±0.3	0.2±0.4	2.54	185.3	0.12	0.31	
	Placebo	0.1±0.3	0.1±0.3	0.0±0.0	0.0±0.0	0.1±0.3					
<b>HAMA</b>											
	D-cycloserine	27.6±6.7	19.0±9.9	16.8±10.0	12.2±10.1	14.2±9.8	3.27	189.2	0.074	0.85	
	Placebo	26.7±5.8	22.7±7.2	21.1±4.9	19.5±5.8	21.0±7.9					
<b>CGI-S</b>											
	D-cycloserine	5.2±0.4	4.5±0.9	3.8±1.5	3.0±1.7	3.4±1.7	4.01	150.2	0.051	0.99	
	Placebo	5.3±0.6	4.9±0.8	4.9±1.1	5.0±0.8	4.8±1.2					
<b>BDI-II</b>											
	D-cycloserine	35.3±8.3	28.3±10.5	22.9±13.2	18.4±14.2	20.0±14.1	4.13	171.7	0.046	0.95	
	Placebo	35.3±7.5	29.6±6.7	30.3±6.1	27.9±7.3	31.1±9.9					

HAMD, 21 Item-Hamilton Depression Rating Scale; HAMA, Hamilton Rating Scale for Anxiety; CGI-S, Clinical Global Impression – Severity of Illness Scale; BDI-II, Beck Depression Inventory – Second Edition; LOCF, last observation carried forward. Statistical results ( $F/p$ ) are based upon results of mixed model regression using all available data. Effect sizes ( $d$ ) are based upon between-group (D-cycloserine *vs.* placebo) LOCF analyses. Data represent means  $\pm$  s.d.

defined as a HAMD score of  $\leq 7$  (Frank *et al.* 1991). HAMD items 2 (feelings of guilt), 19 (depersonalization/derealization) and 20 (paranoid symptoms) were used for monitoring the eventual emergence of dissociative and/or psychotic symptoms. Systemic side-effects were recorded and reviewed using the Udvalg for Kliniske Undersgelser (UKU) Side Effects Rating Scale (Lingjaerde *et al.* 1987). Patients requiring psychotropic medication or dose changes, as evidenced by emergence of side-effects or  $\geq 20\%$  HAMD total score increase, were withdrawn from experimental treatment.

Glycine serum levels were determined at baseline and end of study using HPLC analysis as previously described (Shleper *et al.* 2005). Pre-treatment glycine levels were compared to the levels of normal comparison subjects drawn from a previous study that assessed glycine levels in schizophrenia patients *vs.* controls, using a demographically similar population (Neeman *et al.* 2005). To increase comparability of the data, only subjects from this study with ages similar to those in the present investigation (age 37–69 yr) were included in the analysis ( $n = 23$ , 11 male/12 female).

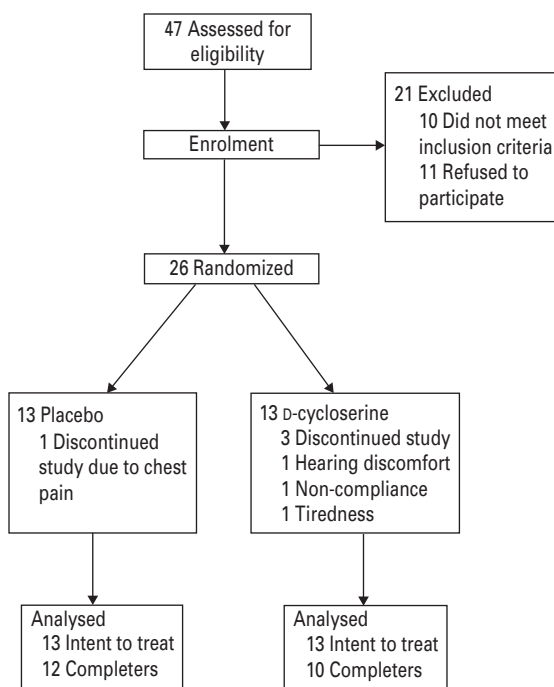
Primary data analysis was conducted by mixed-model regression (MMR) using all available data. Because exact effect sizes cannot be computed from MMR modelling, a secondary analysis assessed effect size of change scores from baseline to end of treatment based upon last observation carried forward (LOCF) measures for all subjects. Secondary analyses also compared the proportion of responders and remitters across groups and investigated

the relationship between response and pre-treatment serum glycine levels. All statistical tests were two-tailed and were performed at  $\alpha = 0.05$  level of significance using SPSS 18.0 (SPSS Inc., USA). Values are reported as mean  $\pm$  s.d.

## Results

Twenty-six patients (16 women, 10 men, mean age  $53.0 \pm 10.2$  yr) entered the study (Fig. 1). Subjects had a mean illness duration of  $15.4 \pm 14.4$  yr and a mean number of  $3.0 \pm 1.1$  previous depression episodes. The mean duration of the current episode was  $13.2 \pm 14.3$  months and all subjects were receiving ongoing treatment with one or more antidepressant drugs (Supplementary Table S1). Thirteen patients received DCS and 13 received placebo; 10 (77%) of the DCS-treated patients and 12 (92%) of the placebo-treated patients completed the study. The demographic and clinical characteristics of the patients randomized to receive DCS or placebo did not differ significantly. For both treatment groups, depression symptoms were stable for at least 2 wk prior to experimental treatment initiation (Supplementary Table S2).

DCS treatment led to significant improvement in depressive symptoms as measured by HAMD ( $p = 0.005$ ) and the BDI-II ( $p = 0.046$ ; Table 1). An analysis of variance conducted across HAMD and BDI-II scales showed a significant treatment  $\times$  time interaction ( $F_{1,15} = 5.58$ ,  $p = 0.032$ ), with no significant test  $\times$  time  $\times$  treatment



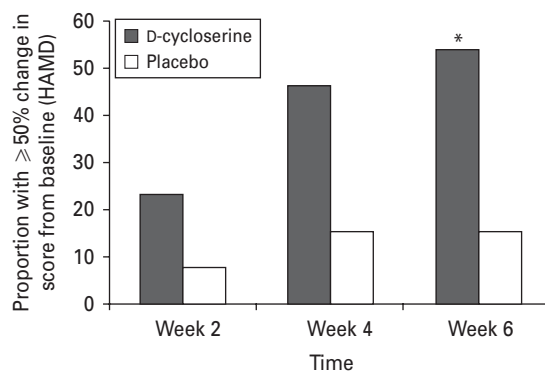
**Fig. 1.** Enrolment, randomization, withdrawals and completion of the study ( $n=26$ ). ('CONSORT' flow diagram.)

interaction ( $F_{1,15}=0.07$ ,  $p=0.8$ ), suggesting similar sensitivity of the two scales to treatment effects. Trends toward improvement were also observed for anxiety, as reflected in HAMA ( $p=0.074$ ) and overall severity of illness, as reflected in the CGI-S ( $p=0.051$ ). No significant change was observed in HAMD items potentially reflecting psychotomimetic phenomena, including depersonalization/derealization and paranoia, which remained negligible in both treatment groups throughout the study.

Overall, seven of 13 (54%) patients assigned to DCS qualified as responders (i.e.  $\geq 50\%$  HAMD total score reduction) *vs.* two of 13 (15%) assigned to placebo ( $\chi^2=4.24$ , d.f.=1,  $p=0.039$ ; Fig. 2). Five of 13 (38%) patients assigned to DCS were also considered remitters (i.e. HAMD total score  $\leq 7$ ) *vs.* two of 13 (15%) assigned to placebo, although this difference was not statistically significant ( $\chi^2=1.76$ , d.f.=1,  $p=0.19$ ).

Pre-treatment serum glycine levels for the patients entered in the study ( $371.9 \pm 160.9 \mu\text{M}$ ) were significantly greater than those previously observed in normal comparison subjects of similar age and demographic background ( $244.8 \pm 84.2 \mu\text{M}$ ,  $p=0.002$ ) and  $>90$ th percentile level (approx.  $300 \mu\text{M}$ ) previously reported by Sumiyoshi *et al.* (2004). A cut-off level of  $300 \mu\text{M}$  significantly distinguished depressed and control groups (Fisher's exact test  $p=0.033$ ), with only six of 23 control subjects having levels  $>300 \mu\text{M}$  *vs.* 12 of 20 depressed patients for whom levels were available.

When HAMD LOCF change scores were analysed as a function of pre-treatment glycine levels, including glycine  $<300 \mu\text{M}$  *vs.*  $\geq 300 \mu\text{M}$  as a factor, a significant



**Fig. 2.** Proportion of responders [ $\geq 50\%$  improvement on 21-item Hamilton Depression Rating Scale (HAMD)] during 6 wk adjuvant treatment with D-cycloserine ( $N=13$ ) and placebo ( $N=13$ ). \*  $p=0.039$ .

treatment  $\times$  glycine level interaction was registered ( $p=0.043$ ). Among patients with glycine levels  $\geq 300 \mu\text{M}$ , there was a  $13.6 \pm 7.4$  points reduction in HAMD score among patients receiving DCS ( $n=7$ ) *vs.*  $0.1 \pm 3.9$  points among those receiving placebo ( $n=7$ ), ( $d=2.36$ ,  $p<0.001$ ), suggesting robust antidepressant effects.

Four (15%) patients were withdrawn from the study (Fig. 1). One placebo-treated patient was withdrawn at week 2 due to the development of chest pain. Three DCS-treated patients were withdrawn at study weeks 3, 4 and 5 due to hearing discomfort, described as 'feeling the ears heavy', tiredness and non-compliance and non-compliance respectively. These complaints ceased following withdrawal from study. Overall DCS was well tolerated throughout the study. The UKU scale-registered side-effects did not differ significantly in the two treatment groups (Supplementary Table S3) and were all judged as mild, improbable to be due to the experimental treatment, not interfering with the patient's performance and not necessitating any type of intervention. No neurological side-effects (e.g. tremor, rigidity, seizures) were registered.

## Discussion

This clinical trial is the first, to the best of our knowledge, to provide proof of concept evidence that pharmacological antagonistic activity at the NMDAR-associated glycine site can induce antidepressant effects and reduce MDD severity in humans. In this study, the glycine site partial agonist DCS titrated up to 1000 mg/d produced a significant antidepressant effect, evident on both investigator-rated and self-report assessment scales, when used as add-on therapy in MDD patients refractory to treatment. After 6 wk treatment, there was a 7.8-point greater reduction in HAMD score in patients receiving DCS *vs.* those receiving placebo. In reviews of antidepressant trials in MDD, reported response rates at week 8 are 62% for bupropion hydrochloride, 63% for SSRIs and 65% for venlafaxine (Entsuah *et al.* 2001; Thase *et al.* 2005). In the

present 6 wk study focusing on treatment-resistant patients, 54% of DCS-treated subjects achieved treatment response, defined as  $\geq 50\%$  HAMD score reduction.

Our findings extend naturalistic observations indicating that DCS may influence mood-related symptoms when used for tuberculosis treatment and demonstrate for the first time beneficial DCS effects for rigorously diagnosed depression patients. Since DCS acts as a mixed agonist/antagonist at the NMDAR-associated glycine site and a previous trial assessing 250 mg/d DCS treatment (Heresco-Levy *et al.* 2006) did not show significant effects, the present results suggest that high (i.e.  $> 500$  mg/d) DCS dosages may be necessary for inducing NMDAR-antagonistic and antidepressant effects in MDD patients.

Short-lived dissociative disturbances and/or increased propensity for psychotic symptoms represent a concern with the use of NMDAR antagonists, as consistently reported following i.v. ketamine and CP-101,606 administration in MDD. In the present study, which investigated the effects of DCS daily oral treatment, no changes were registered in HAMD items, which may suggest the development of a dissociative or psychotic reaction. Possible reasons for lack of psychotomimetic effects include differences in the mechanisms of action of DCS, ketamine and CP-101,606, different route and time framework of administration, use of DCS in combination with antidepressants and the employment of a gradual-titration DCS dosage schedule.

Treatment refractory depression may be aetiologically distinct from other depression forms and may specifically involve disturbances in glycine metabolism (Ji *et al.* 2011). Consistent with this hypothesis, we found that glycine serum concentrations of our sample were greater than those of normal controls, 60% of the sample had pre-treatment serum glycine levels  $\geq 300 \mu\text{M}$  and DCS had robust antidepressant effects among patients with glycine levels  $\geq 300 \mu\text{M}$ . These findings support the hypothesis that treatment-resistant MDD may be associated with elevated glycine levels and indicate that treatments targeting the NMDAR-glycine site may be most appropriate for this type of patients.

Limitations of the present study include the small sample size and the limited number of assessment scales used. Furthermore, since DCS was used as adjuvant treatment, we cannot exclude pharmacological interactions between DCS and the ongoing antidepressant medications. Further larger-scale DCS studies are warranted. This line of investigation may contribute to the development of innovative antidepressant treatments and to the understanding of depression pathophysiology.

### Supplementary material

For supplementary material accompanying this paper, visit <http://dx.doi.org/10.1017/S1461145712000910>.

### Acknowledgements

This study was supported by a NARSAD Independent Investigator Award to Dr Heresco-Levy. The authors are entirely responsible for the scientific content of the paper. The authors thank Dr Herman Wolosker and Ms Elena Dikopolev for the assessment of glycine serum levels.

### Statement of Interest

Dr Heresco-Levy and Dr Javitt are inventors on filed patent applications concerning the use of D-cycloserine in major depressive disorder.

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