Pilot-controlled trial of D-cycloserine for the treatment of post-traumatic stress disorder

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Abstract

Dysfunction of glutamatergic neurotransmission may be relevant to the pathogenesis of post-traumatic stress disorder (PTSD). Preclinical and clinical evidence suggests that PTSD symptoms could be alleviated following enhancement of neurotransmission mediated at the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors. Eleven patients with chronic PTSD participated in a double-blind, placebo-controlled, cross-over trial with 50 mg/d D-cycloserine which acts as a partial agonist at the glycine regulatory site on the NMDA receptor. D-cycloserine treatment resulted in significant improvements in numbing, avoidance, and anxiety symptoms; however, similar effects were also observed during placebo treatment. In addition, D-cycloserine treatment resulted in a significant (p = 0.03), reduction in the perseverative error scores as measured by the Wisconsin Card Sorting Test. This pilot study is the first to assess the efficacy of a NMDA receptor modulator for PTSD treatment and its results warrant further, larger-scale investigation.

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Introduction

Post-traumatic stress disorder (PTSD) is a prevalent, serious condition often characterized by treatment resistance and a chronic course. Although several drug classes (e.g. antidepressant drugs, adrenergic agonists and antagonists, mood stabilizers and atypical neuroleptics) have been reported to be beneficial in treating PTSD (Davidson, 1997; Friedman, 1988; Marshall et al., 1998), presently there is no definitive pharmacotherapy for PTSD. Survival analyses demonstrate that over one third of people with lifetime PTSD fail to recover even after many years (Kessler et al., 1995). Moreover, clinical experience indicates that many PTSD patients are left with substantial degrees of distress and dysfunction, suggesting that pathophysiological substrates that are not affected by presently available pharmacological interventions may contribute to PTSD symptomatology.

Dysfunctions of several neurotransmitter systems have been proposed as contributing to PTSD (for review, see Charney et al., 1993). While historically most attention has been devoted to alterations in noradrenergic and serotonergic functions, during the last decade an accumulating body of evidence suggests that pharmacological manipulation of glutamatergic neurotransmission may represent an additional treatment approach for PTSD (Charney et al., 1993; Friedman, 2000; Nutt, 2000). Glutamate is the primary excitatory transmitter in the brain and it is intimately involved in consciousness, learning and memory (Collingridge and Bliss, 1995). Stressors may be registered and remembered when they lead to enough glutamate release to activate the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors which then leads to production of long-term memories (Glue et al., 1993). Since drug treatments in PTSD are usually initiated well after the traumatic event, which may be too late to prevent the laying down of brain traces for the memories, behaviours and affect that trauma causes, the main clinical challenge in the treatment of long-standing PTSD is the deletion of psychic trauma sequelae. It has been proposed that the continued ability of conditioned
stimuli to elicit traumatic memories and flashbacks in PTSD may result from a deficit in the neural mechanisms involved in response reduction or memory extinction (Charney et al., 1993). Extinction may not erase the original aversive memories, but instead could involve the learning of new memories that mask or inhibit the original ones (e.g. Bouton and Bulles, 1985; McAllister and McAllister, 1998). Thus, post-trauma learning and memory deficits in PTSD patients may be instrumental in the maintenance of the indelible character of the original traumatic memories. Since learning and memory processes are dependent on NMDA receptor activity, enhancers of NMDA receptor-mediated neurotransmission may have therapeutic effects in PTSD. This hypothesis is supported by preclinical and clinical data. In rodents, NMDA antagonists infused into the amygdala prevent the extinction of fear-potentiated startle (Falls et al., 1990), while D-cycloserine (DCS), that acts as a partial agonist at the NMDA receptor-associated glycine site, has positive effects on memory consolidation and retrieval processes in several animal models (Handelman et al., 1988; Monahan et al., 1989; Thompson et al., 1992). Moreover, positive DCS effects have been reported on indirect memory deficits in elderly volunteers (Jones et al., 1991) and Alzheimer’s disease patients (Schwartz et al., 1996). Thus, the ability of glycine site modulators to improve cognitive parameters by stimulating NMDA receptor function raises the intriguing question whether this class of compounds may also attenuate memory-related dysfunctions associated with PTSD.

Additional support in favour of assessing the therapeutic potential of glycine site agonists in PTSD derives from the clinical trials performed during the last decade with these compounds in schizophrenia (for review, see Heresco-Levy, 2000). Administration of glycine site agonists (i.e. glycine, D-serine and DCS) resulted in improved cognitive parameters in treatment-resistant schizophrenia (Goff et al., 1995; Heresco-Levy et al., 1999; Tsai et al., 1998). Furthermore, glycine, D-serine and DCS were all found to significantly reduce the severity of negative symptoms in treatment-resistant patients, without causing exacerbations of psychotic features. These findings may be of relevance in the context of PTSD treatment, since the symptomatology of this disorder is also characterized by features such as affective numbing, anhedonia and withdrawal from social/vocational activities and interactions. Moreover, since brain glutamate and dopamine systems are interrelated but functionally opposed (Carlsson and Carlsson, 1990), administration of NMDA receptor agonists in PTSD may also be beneficial via an indirect reduction of dopaminergic neurotransmission. Stress-induced hyperactivity of central dopamine systems may be linked to specific PTSD symptoms, including anxiety, panic attacks, hypervigilance and exaggerated startle (Charney et al., 1993).

The purpose of this pilot study was to investigate possible benefits of DCS treatment in chronic PTSD. DCS has been in use for over 30 yr as a broad spectrum antibiotic for the treatment of tuberculosis and urinary tract infections. It readily penetrates the blood–brain barrier and acts as a relatively selective partial agonist at the NMDA receptor glycine site over a narrow range of concentrations (Thompson et al., 1992; Watson et al., 1990). Recent clinical trials have indicated that in schizophrenia DCS efficacy against negative symptoms and cognitive deficits may be maximal at a 50 mg/d regimen (Goff et al., 1995, 1999). We hypothesized that DCS pharmacotherapy may also be beneficial for PTSD patients and may suggest an additional therapeutic approach for the disorder. The present study represents, to our knowledge, the first investigation of a glycine site agonist for the treatment of PTSD.

**Method**

Subjects were outpatients meeting DSM-IV diagnostic criteria for PTSD, chronic type, established on the basis of semi-structured psychiatric interviews, review of all available medical records and confirmation by at least two board-certified psychiatrists. PTSD status was determined according to DSM-IV criteria as measured by the Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1990). Subjects receiving psychotropic medications were required to have been treated with stable, clinically determined optimal medication doses for at least 3 months. Medication doses remained fixed throughout the study. Subjects were excluded if they met the criteria for additional DSM-IV diagnoses or had a concurrent medical or neurological illness. Complete medical and neurological examinations, clinical laboratory tests and EKG, were performed before trial inclusion. The research protocol was approved by the appropriate review boards and written informed consent was obtained from subjects following complete description of the study orally and in writing. A total of 11 patients entered the study (Table 1).

The study had a total length of 12 wk using a double-blind, placebo-controlled, cross-over design. An initial 2-wk assessment period was followed by 4 wk of adjunct treatment with either 25 mg DCS twice daily, or matched placebo. Patients then underwent a 2-wk experimental treatment washout, followed by 4 wk of cross-over treatment. Clinical assessments were...
obtained bi-weekly throughout the study using the CAPS, the Mississippi Scale for Combat-Related PTSD, civilian version (MISS) (Vreven et al., 1995), the 21-item Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960), the Hamilton Rating Scale for Anxiety (HAMA) (Hamilton, 1959), and the UKU Side Effect Rating Scale (Lingjaerde et al., 1987), administered by a single trained research psychiatrist. The rater, the treatment teams, the patients and their families were unaware of, and unable to determine, the study drug assignment by appearance or otherwise.

A battery of neurocognitive tests, including the Wisconsin Card Sorting Test (WCTS) (Heaton, 1981), the Hebrew version of the Auditory Verbal Learning Test (Vakil and Blachstein, 1993), and the Benton Visual Retention Test (Benton et al., 1974), was administered to each subject at baseline and at the end of the two treatment arms. Complete blood count, serum protein and electrolytes, hepatic enzymes and kidney function parameters were assessed bi-weekly throughout the study.

Statistical analyses were performed using the SPSS for Windows (SPSS Inc., Chicago IL, USA) computer program. All cited \( p \) values are two-tailed, with a significance level of 0.05. Prior to statistical analysis all variables were tested for normality using the one-sample Kolmogorov–Smirnov test (SPSS). No significant deviations from normality were observed (all \( p > 0.35 \)).

**Results**

Six patients were randomized to receive DCS during the first treatment phase; 5 received placebo. Seven patients completed the entire trial. Four patients (subject nos. 2, 4, 5 and 8, see Table 1) were withdrawn at study week 6 (3 patients) and week 10, respectively, due to medical problems not related to the experimental medication or study procedures. All withdrawn patients completed at least one treatment phase; 3 patients were withdrawn after receiving 4 wk of treatment with DCS, and 1 after 4 wk placebo treatment. Thus DCS–response data were available for 10 subjects and placebo–response data for 8.

Comparison of symptom scales scores during DCS treatment revealed that DCS induced significant reductions in CAPS numbing and avoidance (CAPSC) cluster \( (p < 0.001) \) and total \( (p = 0.03) \) scores, as well as in MISS \( (p < 0.01) \) and HAMA \( (p < 0.01) \) scores (Table 2). However, similar improvements in these symptom domains were also registered during the placebo-treatment phase and ANOVAs performed with within-subject factors of treatment phase (DCS/placebo) and study week within-treatment phase (0, 4 wk) did not reveal any treatment or treatment-by-time effects (Table 2). In order to evaluate the degree to which order effects may have influenced statistical results, separate analyses were conducted for patients who received...
DCS during the first vs. second treatment phase. Analyses focused on those measures, CAPSC, MISS, and HAMA, where there appeared to be greater statistical response during treatment with DCS than placebo. For CAPSC, statistically significant improvement was observed during DCS treatment whether patients received DCS during the first ($t = 4.40$, d.f. $= 5$, $p = 0.007$) or second ($t = 3.67$, d.f. $= 3$, $p = 0.035$) treatment phase. In contrast, no significant improvement was observed among patients who received placebo during either phase individually ($p > 0.1$). Similarly, significant improvement in MISS was observed during DCS treatment both for patients who received DCS first ($t = 2.65$, d.f. $= 5$, $p = 0.045$) as well as for those who received it second ($t = 4.70$, d.f. $= 3$, $p = 0.018$). In contrast to those measures, HAMA scores responded significantly to placebo only among patients who received DCS first ($t = 6.43$, d.f. $= 2$, $p = 0.02$), and significantly to DCS only among patients who received placebo first ($t = 4.38$, d.f. $= 3$, $p = 0.02$), suggesting an order effect. When non-parametric tests were used instead of parametric tests to evaluate improvement, the improvements in CAPSC ($z = 2.69$, $p = 0.007$) and MISS ($z = 2.81$, $p = 0.005$) remained significant.

Among the neurocognitive parameters assessed, DCS treatment induced a significant ($p = 0.03$) improvement in WCST perseverative error scores (Table 3). In contrast, placebo treatment did not improve significantly the performance of any of the neurocognitive tests employed in the study. In order to evaluate whether the change in WCST performance during DCS treatment was due to repeated exposure, $t$ tests compared retest vs. baseline performance collapsed across treatment order. Performance at the end of the first ($t = 2.12$, d.f. $= 9$, $p = 0.07$) and second ($t = 1.12$, d.f. $= 8$, $p = 0.3$) treatment phases was not significantly different from baseline, suggesting that observed changes during medication were not attributable solely to repetition effects. Statistically significant between-treatment groups differences in the performance of neurocognitive tests were not registered.

DCS treatment was well tolerated and no adverse effects on blood chemistry, haematology, liver and kidney function parameters were registered.

**Discussion**

Chronic PTSD is a difficult to treat condition and overall, few controlled trials of pharmacological agents in PTSD have been conducted (Davidson, 2000). This pilot study is the first to examine the effects of a modulator of NMDA receptor-mediated neurotransmission in the treatment of PTSD. Due to the small sample examined and the relatively short period of
treatment, the findings of this trial should be considered preliminary.

The most significant effect registered with the 50 mg/d DCS dose used in the present study was a reduction in the numbing and avoidance PTSD symptoms cluster. This effect may suggest an improved capacity to deal with traumatic memories and daily events which remind of the trauma and includes a reduction in negative symptom-like parameters such as emotional numbing and lack of participation in meaningful activities. Significant symptom improvements were registered, however, also during the placebo-treatment phase, leaving open the question of whether DCS may actually serve as an effective treatment in chronic PTSD. The relatively large placebo effect could have been due to factors such as reassurance, increased motivation and compliance and secondary gain. PTSD patients, in general, have high rates of service use. Epidemiological studies in the USA estimate that 38% of people with PTSD are in treatment in a given year (Kessler, 2000). This rate of treatment is comparable with that found among people with major depression and is higher than that seen among people with any other anxiety disorder or substance abuse. Moreover, it suggests that with some PTSD patients, non-specific factors associated with the treatment situation may have therapeutic effects.

A significant reduction in perseverative errors as measured by the WCST was also registered with DCS treatment, while AVLT and BVRT performance were not affected. This may suggest, rather than a specific memory improvement, an increased executive functions plasticity which may be related to the observed improvement in the ability to face traumatic stimuli. No neurocognitive parameters improved during placebo treatment. However, these findings should be interpreted with caution, due to potential practice effects and the inclusion of multiple measures.

Since negative symptoms also respond preferentially to treatment with glycine agonists of the NMDA receptor in schizophrenia (Heresco-Levy, 2000), the improvement of negative symptom-like parameters of PTSD patients observed in this study raises the possibility that this symptom domain may be related, across diagnostic frameworks, to an underlying dysfunction of glutamatergic neurotransmission. This hypothesis remains, at this stage, highly speculative. As seen with schizophrenia patients (Goff et al., 1995, 1999; Heresco-Levy et al., 2002), the DCS regimen used in this study was well tolerated, and no significant side-effects or alterations in clinical laboratory parameters were registered.

Although statistically significant differences were not registered vs. placebo in the present trial, the

<table>
<thead>
<tr>
<th>Measure</th>
<th>Treatment phase</th>
<th>Two-tailed t test (d.f. = 9)*</th>
<th>ANOVA treatment phase (d.f. = 2,6)</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>DCS</td>
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<td>WCST</td>
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<tr>
<td>Categories</td>
<td>4.4 (2.0)</td>
<td>4.1 (2.2)</td>
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<td>22.4 (9.6)</td>
<td>17.3 (5.3)</td>
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<td>AVLT</td>
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<tr>
<td>Total recall</td>
<td>33.5 (8.8)</td>
<td>34.1 (12.7)</td>
<td>32.9 (9.0)</td>
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<td>Delayed recall</td>
<td>6.2 (2.8)</td>
<td>5.1 (2.8)</td>
<td>5.2 (2.1)</td>
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<tr>
<td>Recognition</td>
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<tr>
<td>BVRT</td>
<td>6.4 (1.7)</td>
<td>6.9 (1.7)</td>
<td>7.3 (1.8)</td>
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* Placebo group (d.f. = 7).

Abbreviations: WCST, Wisconsin Card Sorting Test; AVLT, Auditory Verbal Learning Test; BVRT, Benton Visual Retention Test. Values are mean (S.D).
DCS-induced effects registered warrant further, larger scale investigation, since they may lead to an innovative approach to PTSD drug treatment. Future studies should include increased DCS dosages and longer treatment periods and may also assess the efficacy of additional glycine site agonists of the NMDA receptor.

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References


