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BRIEF REPORT

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

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Abstract

Enhancement of neurotransmission mediated at *N*-methyl-D-aspartate subtype of glutamate receptors (NMDAR) may be beneficial in post-traumatic stress disorder (PTSD). D-serine (DSR) is an endogenous full agonist at the NMDAR-associated glycine modulatory site. Twenty-two chronic PTSD outpatients were randomly assigned to participate in a 6-wk double-blind, placebo-controlled, crossover trial with 30 mg/kg.d DSR used as monotherapy or add-on pharmacotherapy. Outcome was assessed using the Clinician-Administered PTSD scale (CAPS), Hamilton Anxiety (HAMA) and Depression (HAMD) scales and the civilian version of the Mississippi Scale for Combat-Related PTSD (MISS). DSR treatment was well tolerated and resulted in significantly ($p=0.03$) increased DSR serum levels. Compared with placebo administration, DSR treatment resulted in significantly reduced HAMA ($p=0.007$) and MISS ($p=0.001$) scores and a trend ($p=0.07$) towards improved CAPS total scores. These preliminary findings indicate that NMDAR glycine site-based pharmacotherapy may be effective in PTSD and warrant larger-sized clinical trials with optimized DSR dosages.

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Key words: D-serine, NMDAR, PTSD, treatment efficacy.

Introduction

Accumulating evidence indicates that pharmacological manipulation of glutamatergic neurotransmission mediated at the *N*-methyl-D-aspartate subtype of glutamate receptors (NMDAR) may represent an innovative treatment approach for post-traumatic stress disorder (PTSD). Brain regions extensively implicated in the mediation of fear and anxiety (i.e. amygdala, hippocampus, prefrontal cortex) are characterized by high NMDAR levels (McDonald, 1996) and may show morphological changes as a result of stress-related disorders (Harvey *et al*. 2004; McEwen, 2001). NMDARs play a central role in stress response (McEwen, 1996), long-term potentiation and desensitization and are critically involved in learning and memory formation which are impaired in PTSD (Horner & Hamner, 2002). Moreover, both fear learning and extinction are blocked by NMDAR antagonists (Davis & Myers, 2002; Falls *et al*. 1992). These findings suggest a stage-dependent NMDAR-based interventional paradigm for PTSD. Theoretically, NMDAR antagonists ideally administered prior to the traumatic event may impair consolidation of traumatic memories. Conversely, in long-standing PTSD, in which learning deficits may impair normal extinction of aversive memories, NMDAR agonists may have therapeutic potential (Friedman, 2000; Garakani *et al*. 2006; Nutt, 2000).

In addition to their role in trauma-related fear learning, NMDAR mechanisms are also implicated in behavioural manifestations common to PTSD, including dissociation and perceptual alterations (Chambers

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et al. 1999). Glutamatergic control of both hippocampal-dependent associative learning and amygdala-dependent emotional processing during and after a stressful event might be significant factors in these information-processing distortions. Direct evidence for this hypothesis includes reports that NMDAR antagonism by ketamine can produce dissociative symptoms and perceptual alterations (i.e. depersonalization, de-realization, altered auditory and visual acuity) akin to those observed in PTSD (Newcomer & Krystal, 2001).

Consistent with these concepts, recent preclinical and clinical data suggest that enhancement of NMDAR function obtained by using partial [i.e. D-cycloserine (DCS)] or full [i.e. glycine, D-serine (DSR)] agonists at the NMDAR-associated glycine site may be beneficial in PTSD. DCS enhances fear extinction/exposure therapy in both animals and anxiety disorders (i.e. agoraphobia, social anxiety, obsessive–compulsive disorder) in humans (Norberg *et al*. 2008). Administration of both glycine (File *et al*. 1999) and DCS (Schwartz *et al*. 1996; Tsai *et al*. 1999) as continuous pharmacotherapy unrelated to cognitive-behavioural interventions was found to enhance memory in some human studies. Furthermore, in some clinical trials glycine and DSR, applied as adjuvant continuous treatment, reduce negative and cognitive symptoms severity in treatment-resistant schizophrenia patients (Heresco-Levy, 2005). These findings may be of relevance in the context of PTSD therapeutics, since PTSD impairments also include cognitive dysfunction and features such as affective numbing, anhedonia, and withdrawal from social/vocational activities.

Previously we assessed in a pilot controlled 4-wk study the effects of DCS (50 mg/d) used as adjuvant to ongoing drug treatment in PTSD (Heresco-Levy *et al*. 2002). Although statistically significant differences *vs*. placebo were not registered, DCS treatment resulted in ~15% reductions in numbing, avoidance, and anxiety symptoms. In the present study we aimed to assess the therapeutic potential of DSR pharmacotherapy for chronic PTSD patients. In contrast to DCS, which is an anti-tuberculosis drug with partial agonist characteristics at NMDAR, DSR is a naturally occurring amino acid that modulates *in-vivo* NMDAR function, is more potent than glycine in activating NMDAR and is not known to affect any other neurotransmission system (Mustafa *et al*. 2004). DSR was found to selectively block NMDAR antagonist-induced effects and to improve schizophrenia symptoms when used as adjuvant treatment at a 30 mg/kg.d dose (Heresco-Levy *et al*. 2005; Tsai *et al*. 1998). We hypothesized that DSR treatment may lead to significant symptom reductions in chronic PTSD patients.

Methods

The study was performed at Herzog Memorial and Haemek hospitals in Israel and was approved by the Israel Ministry of Health. Written informed consent was obtained from patients after the study had been described to them orally and in writing. Subjects were men and non-pregnant or lactating women aged 18–60 yr who: (1) met DSM-IV criteria for a primary diagnosis of PTSD and had a score of at least 60 on the Clinician-Administered PTSD Scale (CAPS; Blake *et al*. 1995), (2) had PTSD symptoms for at least the previous 5 yr, and (3) were in generally good health as determined on the basis of medical history, physical examination and screening laboratory results. Subjects receiving psychotropic medications were required to have been treated with stable, clinically determined optimal medication doses for at least 2 months.

Subjects were excluded if they had current primary major depression or anxiety disorder, had a current mental disorder due to a general medical condition or history of bipolar disorder, schizophrenia, or other psychotic disorder. Patients who abused or were dependent on alcohol or other drugs within 12 months of randomization, used any investigational drug within 60 d of randomization, had electroconvulsive therapy within 6 months of randomization, had current involvement in criminal proceedings or compensation claims related to trauma, or had initiated or changed psychotherapy of any kind within 6 months of randomization, were excluded from the study.

A random-assignment, double-blind, placebo-controlled, crossover design was used. After a 2-wk (weeks −2 to 0) baseline assessment period, subjects were randomly allocated, without blocking, stratification, or other restrictions, to receive under double-blind conditions either DSR or placebo for 6 wk. DSR or placebo were given in addition to each patient's regular psychotropic medication, the dose of which remained fixed throughout the study, or as monotherapy in the case of unmedicated patients. After completion of the first treatment phase (weeks 0–6), patients underwent a 3-wk experimental treatment (i.e. DSR or placebo) washout period (weeks 6–9), after which they crossed over to the alternate experimental treatment for a final 6-wk treatment phase (weeks 9–15).

DSR and placebo were administered orally in identical capsules according to the same dose escalation schedule. Clinical and research staff, as well as

patients and their families, were unaware of and could not determine the study drug assignment by appearance or otherwise. Experimental treatment was initiated at a 10 mg/kg.d dose and was increased after weeks 1 and 2 of treatment to 20 mg/kg.d and the fixed 30 mg/kg.d dose, respectively. This DSR regimen was chosen on the basis of previous reports indicating its safety and effectiveness with chronic schizophrenia patients (Heresco-Levy *et al*. 2005; Tsai *et al*. 1998). The range of fixed absolute daily DSR doses was 1.6–3.0 g (mean ± S.D., 2.45 ± 0.3 g). Daily experimental treatment was administered in three divided doses.

Symptoms and side-effects were assessed at weeks −2, 0 and bi-weekly throughout the two treatment phases using the CAPS (primary outcome measure) and Hamilton Rating Scale for Depression (HAMD), Hamilton Rating Scale for Anxiety (HAMA), and the self-rating Mississippi Scale for Combat-Related PTSD – civilian version (MISS) (secondary outcome measures). Systemic side-effects were recorded and reviewed using the Udvalg for Kliniske Undersgelser (UKU) Side Effects Rating Scale. Patients requiring psychotropic medications or dose changes during the study, as evidenced by side-effects or a CAPS total score increase $\geqslant 20\%$ were withdrawn from experimental treatment.

Blood samples for assessment of amino-acid serum levels were obtained at baseline and at the end of the first and second treatment phases. DSR and glycine serum levels were determined using HPLC analysis as previously described (Shleper *et al*. 2005); basal DSR levels $<10\,\mu$M were not detectable by this method. In addition, safety laboratory assessments (SMA 20, CBC, UA) were obtained bi-weekly throughout the study.

All statistical tests were two-tailed and were performed at the $\alpha = 0.05$ level of significance using SAS system version 9.1 (SAS Institute, USA). Data analysis for the primary and secondary outcome measures was performed using general linear mixed-model repeated-measures ANCOVAs. The change in rating-scale scores from baseline over time was assessed by modelling the difference from baseline as the dependent variable with baseline values as a covariate in the model. Additional variables included treatment phase (i.e. first, second), assessment time within treatment phase (i.e. weeks 0, 2, 4, 6), treatment (i.e. DSR, placebo), treatment order (DSR first–placebo second and vice versa) and the treatment × time interaction. The mixed-model approach permits analysis of cases with missing data at either follow-up point. The continuous secondary efficacy endpoints (HAMD, HAMA, and MISS scores) were analysed by the same method as the primary endpoints (CAPS scores). Comparisons of additional data including amino-acid serum-level difference from baseline under DSR and placebo treatment were performed using a paired *t* test or a non-parametric equivalent.

Table 1. Demographic and clinical characteristics of the sample[a]

Age (yr)	45.9 ± 11.0
Gender (M/F)	19/3
Ethnicity	
Sephardic Jewish/Ashkenazi Jewish/Arab	10/9/3
Years of schooling	12.4 ± 2.1
Duration of PTSD (yr)	13.6 ± 7.2
Type of trauma	
Military	8
Terrorist attack	8
Work/motor vehicle accident	4
Other	2
Pre-study rating-scale scores	
CAPS total	91.9 ± 15.9
HAMD	22.0 ± 6.4
HAMA	27.7 ± 6.4
Pharmacotherapy (no. of patients)	
Antidepressants	19
Anxiolytics	6
Hypnotics	4
Antipsychotics	2

PTSD, Post-traumatic stress disorder; CAPS, 17-item Clinician-Administered Post-traumatic Stress Disorder Scale; HAMD, 21-item Hamilton Rating Scale for Depression; HAMA, Hamilton Rating Scale for Anxiety.

[a] Values are mean ± S.D. for continuous variables and number of subjects for categorical values.

Results

Twenty-two patients fulfilled the inclusion criteria and were enrolled in the study (Table 1). Nineteen patients were receiving maintenance pharmacotherapy, three patients were unmedicated. All medicated patients were receiving therapeutic doses of antidepressant drugs (venlafaxine, citalopram, paroxetine, mirtazapine, or sertraline). Additional treatments included anxiolytics (oxazepam or lorazepam), hypnotics (brotizolam or cyclopyrolone) and antipsychotics (olanzapine, sulpride).

For all subjects symptoms were stable for at least 2 wk prior to experimental treatment initiation (see Supplementary Table S1, available online). Sixteen (73%) patients completed both treatment phases.

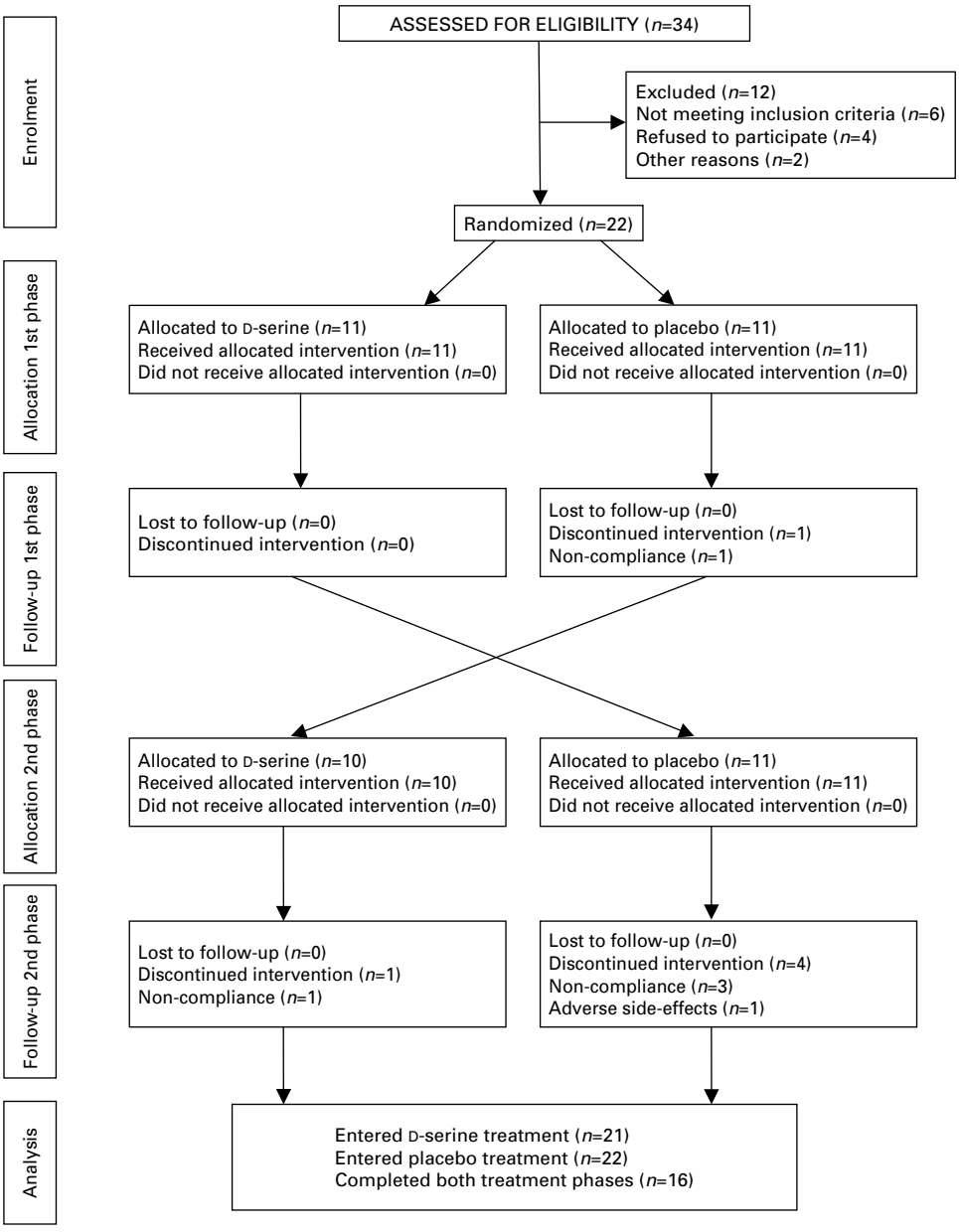

Fig. 1. Study flowchart.

Twenty-one patients entered the DSR treatment phase and 22 patients entered the placebo phase (Fig. 1). Five of the six withdrawn patients completed at least one full treatment phase. One patient was withdrawn at study week 11, while receiving DSR treatment, due to non-compliance. Five patients were withdrawn at study weeks 4, 11 (two patients), and 13, respectively, while receiving placebo, due to non-compliance (three patients) and adverse side-effects (one patient).

Overall, throughout the study DSR treatment was well tolerated and no significant laboratory parameter alterations were registered. Baseline, post-DSR and post-placebo treatment assessments of DSR, L-serine, and glycine serum levels were obtained for part of the study subjects (see Supplementary Table S2, available online). DSR treatment led to a significant $\sim$10-fold increase in DSR levels across subjects (Wilcoxon test, $p=0.03$). Furthermore, the DSR levels achieved by patients ($n=7$) that received DSR during the second treatment phase ($146\pm126.26\,\mu$M) were $\sim$2-fold higher than the DSR levels of patients ($n=4$) that received DSR during the first treatment phase ($77.1\pm91.36\,\mu$M).

Table 2. Effects of treatment on CAPS, HAMD, HAMA and MISS scores[a]

	Treatment assignment	Week within treatment phase				
		0	2	4	6	F/p[b]
CAPS total	D-serine	83.11 ± 17.31	76.50 ± 17.65	69.33 ± 18.64	65.16 ± 19.63	$F_{1,89.8} = 3.26$
	Placebo	81.91 ± 21.97	82.79 ± 22.41	70.53 ± 23.84	66.33 ± 21.97	$p = 0.07$
CAPS B	D-serine	25.37 ± 6.91	22.50 ± 7.27	21.28 ± 5.41	20.63 ± 7.06	$F_{1,90} = 4.76$
	Placebo	26.27 ± 5.64	26.00 ± 6.57	22.95 ± 7.36	20.61 ± 7.01	$p = 0.03$
CAPS C	D-serine	30.63 ± 7.57	28.75 ± 6.90	24.56 ± 9.12	23.05 ± 8.75	$F_{1,97.5} = 3.41$
	Placebo	29.27 ± 11.10	31.32 ± 10.08	25.37 ± 10.38	23.22 ± 9.49	$p = 0.06$
CAPS D	D-serine	27.11 ± 4.76	24.75 ± 4.73	23.50 ± 6.31	21.47 ± 5.66	$F_{1,92.3} = 0.22$
	Placebo	26.82 ± 6.51	25.47 ± 7.01	22.21 ± 7.82	22.50 ± 7.96	$p = 0.64$
HAMD	D-serine	19.89 ± 4.47	18.50 ± 3.87	17.06 ± 4.61	15.05 ± 6.94	$F_{1,90.6} = 1.46$
	Placebo	20.59 ± 6.96	19.11 ± 5.84	16.26 ± 6.24	15.72 ± 5.57	$p = 0.23$
HAMA	D-serine	26.11 ± 7.68	24.26 ± 7.07	20.06 ± 8.43	17.67 ± 8.45	$F_{1,85.9} = 12.24$
	Placebo	26.57 ± 7.47	27.47 ± 7.88	23.29 ± 9.18	21.44 ± 9.95	$p = 0.007$
MISS	D-serine	116.80 ± 13.78	107.90 ± 18.01	110.20 ± 15.71	106.30 ± 21.10	$F_{1,77.6} = 10.68$
	Placebo	115.00 ± 19.68	112.20 ± 18.67	114.30 ± 20.07	112.0 ± 21.81	$p = 0.001$

CAPS, 17-item Clinician-Administered Post-traumatic Stress Disorder Scale; HAMD, 21-item Hamilton Rating Scale for Depression; HAMA, Hamilton Rating Scale for Anxiety; MISS, Mississippi Scale for Combat-Related Post-traumatic Stress Disorder – civilian version,

[a] Data represent mean ± S.D. D-serine data are $n = 21$, placebo data are $n = 22$.

[b] p values are of the between treatment group comparisons of the reduction from baseline over time from the analysis of covariance model with treatment as the main effect and baseline values as a covariate.

No significant changes were registered in L-serine or glycine levels.

Experiment-wide, symptom reductions were registered in all assessment scales under DSR as well as placebo treatment (Table 2). No statistically significant treatment × assessment time interaction terms were found for any of the outcome measures. Nevertheless patients showed a statistically significant greater overall improvement under DSR than under placebo treatment on the change in HAMA ($p = 0.007$), MISS ($p = 0.001$) and CAPS cluster B re-experiencing ($p = 0.03$) scores. A trend in favour of DSR treatment was registered for CAPS total ($p = 0.07$) and CAPS cluster C avoidance/numbing ($p < 0.06$) scores.

DSR treatment led to a 20.9 ± 20.2% (95% CI 10.9–31) decline in CAPS total score *vs*. a placebo-induced decline of 14.6 ± 24.7% (95% CI 2.3–26.9). Cluster B and cluster C scores improved by 17.1 ± 28.5% (95% CI 2.9–31.3) and 23.5 ± 22.5% (95% CI 12.3–34.7), respectively, under DSR treatment and by 17.8 ± 26.1% (95% CI 4.8–30.8%) and 9.5 ± 43.6% (95% CI 12.2–31.2), respectively, under placebo. Along with the reduction in CAPS scores, improvements were registered in HAMD (22.7 ± 41.6%, 95% CI 2–43.3), HAMA (30.1 ± 33.5%, 95% CI 13.4–46.7), and MISS (7.1 ± 14.2%, 95% CI 0.01–14.1) scores under DSR treatment *vs*. 18.2 ± 25.4% (95% CI 5.6–30.8), 20.2 ± 36.9% (95% CI 0.5–39.8) and 3.2 ± 7.9% (95% CI 0.9–7.3), respectively, under placebo.

A significant treatment × phase interaction was registered in respect of the within-treatment phase change from baseline in rating-scale scores. Consequently, we also performed the outcome analysis for each treatment phase separately, in which the difference from baseline for each time-point was calculated in an ANCOVA model where baseline values were entered as a covariate. No significant differences were found between treatment groups in the mean change of rating-scale scores from baseline over time during the first phase of the study. In contrast, during the second study phase in which higher DSR serum levels were achieved, the average reductions from baseline in CAPS cluster B and total scores in the DSR arm were significantly ($p = 0.04$ and $p = 0.03$, respectively) larger than the reductions registered in the placebo arm (see Supplementary Table S3, available online).

Discussion

This study represents to our knowledge the first assessment of pharmacotherapy with an NMDAR-glycine site full agonist in PTSD. Six weeks' treatment with 30 mg/kg.d DSR, resulted in this preliminary investigation in reduced symptom severity on some of the assessment measures. Study-wide, the differences between DSR and placebo in changes from baseline to endpoint were significant for anxiety symptoms as measured by HAMA ($p = 0.007$) and for general self-reported PTSD symptomatology as measured by MISS ($p = 0.001$). The difference between DSR and placebo in CAPS total score reduction did not reach statistical significance ($p = 0.07$) at study-wide level. However, during the second phase of the study, possibly due to achievement of higher DSR serum levels, significantly greater DSR-induced than placebo-induced reductions were registered in CAPS total ($p = 0.04$) and CAPS B re-experiencing ($p = 0.03$) scores.

The observed DSR-induced improvements are to be valued in the context of the study population characteristics and the placebo effects registered in the study. Study participants were chronic PTSD patients with >10 yr mean duration of illness and severe symptomatology, despite treatment, as reflected by a mean baseline CAPS total score of 91.9 ± 15.9. During the second study phase, under DSR treatment, mean CAPS total scores decreased from 81.0 ± 17.8 to 56.4 ± 17.3 which would correspond to a change from extreme to threshold – moderate PTSD symptoms (Tucker *et al*. 2007). Furthermore, study-wide, a robust ~30% reduction in anxiety HAMA-assessed symptoms was registered during DSR administration. Symptom reductions were also registered under placebo treatment, which is in line with relatively high rates of improvement on placebo reported in other chronic PTSD trials (e.g. Tucker *et al*. 2007). However, placebo effects were not statistically or clinically superior to DSR-induced symptom reductions by any of the assessment measures used in the study.

Hypothetically, a number of parameters, including patients' characteristics, DSR dose, treatment duration, and availability of concomitant psychotherapy may impact upon DSR efficacy. Less chronic and symptomatic patients than those in the present study may respond better to DSR treatment and in general, treatment duration longer than 6 wk may be optimal for chronic PTSD patients. More specifically, DSR doses larger than 30 mg/kg.d may be associated with increased efficacy. Recently, it was reported that adjuvant treatment of chronic schizophrenia patients with 60 mg/kg.d DSR resulted in improved neurocognitive performance (Kantrowitz *et al*. 2008) while similar effects were not registered in previous studies using 30 mg/kg.d DSR. Furthermore, promising results were reported using a combined interventional model in several anxiety disorders in which acute pharmacotherapy with the NMDAR glycine site partial agonist DCS was aimed at improving the learning that takes place during cognitive-behavioural therapy (Norberg *et al*. 2008). Assessment of this type of intervention is warranted also in PTSD and our findings suggest that DSR may also be efficacious in this context.

DSR regimens of 30–60 mg/kg.d were well tolerated by schizophrenia patients. The present study is the first to attempt DSR administration in non-schizophrenia patients and confirms that treatment, at least for 6 wk, with 30 mg/kg.d DSR is safe and devoid of significant side-effects. Additional studies are required to address the long-term safety issues related to the administration of DSR or other glycine site full agonists.

We hypothesize that DSR clinical effects were due to its action upon NMDAR-mediated glutamatergic neurotransmission. Clinical findings with different subject populations suggest that enhancement of NMDAR function obtained by treatment with amino acids (i.e. glycine, DSR) that act as endogenous allosteric modulators of the NMDAR glycine site may alleviate anxiety, negative and cognitive symptoms (File *et al*. 1999; Greenberg *et al*. 2007; Heresco-Levy, 2005). Furthermore, evidence for an anxiolytic potential of glycine reuptake inhibitors, was obtained using animal anxiety models (Depoortère *et al*. 2005). Of interest, some preclinical and clinical data also indicate anxiolytic effects of a number of NMDAR blocking agents, including PCP, MK-801 (Bergink *et al*. 2004) and memantine (Battista *et al*. 2007). However, the anxiolytic potential of these agents has not been established and there are clinical indications that NMDAR non-competitive antagonists such as PCP and MK-801 may actually exacerbate anxiety (Reimherr *et al*. 1986). Moreover, memantine preferentially blocks excessive NMDAR activity without affecting normal receptor function and has been shown to also affect serotonin, dopamine and nicotinic receptors (Lipton, 2007).

There are several limitations to the present study. First, this is a pilot preliminary investigation of the use of DSR in chronic PTSD requiring further replication and cross-validation. Additional limitations are the small sample size, the exclusive use of symptom rating scales as assessment measures, and the lack of neurocognitive testing for the assessment of DSR effects

upon cognitive parameters. Overall, the results of the present study suggest a promising line of investigation in PTSD pharmacotherapy and warrant further larger-sized studies to confidently determine DSR's effects profile in this disorder.

Note

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/pnp).

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[Clinical Trials Registration (http://www.clinicaltrials.gov/ct/show/NCT00215878).]

Statement of Interest

Dr Heresco-Levy has served as paid scientific consultant/lecturer to GlaxoSmithKline, Organon Pharmaceuticals and AstraZenca and is inventor in a pending patent related to the use of glutamatergic agents to treat movement disorders.

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