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Augmentation Treatment of Psychotherapy for Anxiety Disorders with D-Cycloserine

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Abstract

Anxiety disorders are among the most common mental disorders. One of the most effective strategies to treat anxiety disorders is exposure therapy with or without cognitive intervention. Fear reduction in exposure therapy is similar to extinction learning. Preclinical studies suggest that extinction learning can be blocked by antagonists at the glutamatergic N-methyl-D-aspartate (NMDA) receptor, and facilitated with D-cycloserine (DCS), a partial agonist at the glycine recognition site of the NMDA receptor in the amygdala. DCS is an established antibiotic drug for the chronic treatment of tuberculosis in humans, but has only recently been investigated as an augmentation therapy for psychological treatment procedures. The review of the literature provides preliminary support for the use of acute dosing of DCS as an adjunctive intervention to exposure therapy for anxiety disorders, including specific phobia and social anxiety disorder. Negative results have recently been reported in the treatment of subclinical fears of animals. These studies suggest that DCS needs to be administered on an acute rather than a chronic dosing schedule, include sufficient time for memory consolidation, and be administered together with psychological treatment that leaves sufficient room for further improvement. It remains to be seen whether these highly promising findings represent reliable pharmacological strategies to enhance exposure therapy of anxiety disorders.

Keywords

Anxiety disorders; Augmentation therapy; D-cycloserine; Extinction learning; Memory enhancement; NMDA receptor agonists

INTRODUCTION

Anxiety disorders, such as social anxiety disorder, specific phobias, posttraumatic stress disorder, panic disorder, and agoraphobia are among the most common mental disorders in the population (26). The most effective strategies include exposure therapy with or without cognitive strategies, and pharmacotherapy, such as selective serotonin reuptake inhibitors (19).

Attempts to boost treatment response with combined psychotherapy and pharmacotherapy (i.e., antidepressants or benzodiazepines) have led to disappointing results (15,48). More recently, however, a novel strategy has emerged for the combination of pharmacotherapy and psychotherapy. This strategy is the result of studies that have mapped some of the core pathways and neurotransmitters involved in fear extinction. These studies suggest that D-

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cycloserine (DCS), a partial agonist at the glycine recognition site of the glutamatergic N-methyl-D-aspartate receptor (NMDA-R), can facilitate extinction of conditioned fear when given in individual doses prior to or soon after extinction trials in animals.

Exposure procedures are closely related to extinction learning paradigms. Animal research suggests that extinction is a form of acquired inhibition that suppresses a fear response. Hence, extinction is considered a form of learning in its own right, rather than an "unlearning" or "forgetting" of previous learning (5,42).

Important brain structures for Pavlovian fear and extinction learning include the hippocampus and the amygdala (58). Contextual fear conditioning is dependent on the structural integrity of the hippocampus and the amygdala, whereas cued fear conditioning depends on the amygdala but not the hippocampus (13,59). Although the specific role of the amygdala in memory formation is not completely understood (6), fear learning appears to involve movement of calcium ions into amygdala neurons, which is followed by a number of intracellular changes that leads to long-term changes in synaptic function and morphology (2,14). This mechanism can be facilitated by D-cycloserine (DCS).

PHARMACOLOGY

Glutamate is one of the most important excitatory neurotransmitters in the mammalian brain. This neurotransmitter performs an important role in brain circuitry underlying fear processing. Fear and extinction learning are both blocked by antagonists at the glutamatergic N-methyl-D-aspartate receptor (NMDA-R), which is critically involved in learning and memory. NMDA-Rs are heteromeric complexes (30) that generally consist of at least three subunits: NR1, NR2A, and NR2B (29). It has been shown that variations in the intracellular Ca^{2+} concentration regulate the induction of long-term synaptic plasticity at the glutamatergic synapses (3,41, 44). Liu and colleagues (38) demonstrated that long-term potentiation (LTP) is mediated by NMDA receptors containing NR2A subunits in pyramidal cells of the hippocampus in area CA1. Analysis of LTP in cells of this region (37) has shown that the process is governed by the "Hebb rule" (23) i.e., induction of LTP involves the NMDA class of glutamate-activated channels in the postsynaptic membrane (7) that only open if there is both presynaptic release of glutamate and also substantial depolarization of the postsynaptic membrane (45). This leads to an influx of Ca^{2+} ions (25,40) that then triggers an increase in synaptic weight (39). NMDA receptors in the amygdala are also considered essential for LTP, a process that underlies fear learning and extinction (2,14,33,35,66).

These processes can be facilitated with D-cycloserine (DCS), an analog of D-alanine and a partial agonist at the glycine recognition site of the glutamatergic NMDA receptor. DCS works similarly to D-serine and binds to the same NMDA receptor. Studies have shown that DCS facilitates the process of extinction of conditioned fear when administered in individual doses prior to or soon after extinction trials in animals (9,13,31,32,50,57).

PHARMACOKINETICS

DCS is an established antibiotic medication for treating tuberculosis, but has only recently been investigated as an augmentation therapy for psychological treatment of anxiety disorders. For treating tuberculosis, DCS is generally chronically dosed at 500–1000 mg/day divided twice daily (51). Little is known about the optimal dose of DCS when used as augmentation of exposure therapy. Only two studies have examined the effects of acute treatment of DCS in enhancing exposure-based treatment for anxiety disorders (24,56). Ressler et al. (56) found no difference between the effects of 50 or 500 mg; the Hofmann study, which demonstrated positive therapeutic effects for DCS augmentation of cognitive behavioral treatment (CBT),

employed the drug at only a 50-mg dose. In both cases, DCS facilitated the effects of exposure therapy. Details of these results will be discussed further below.

DCS has excellent bioavailability (43); it is excreted primarily by the kidneys and its half-life is approximately 10 hours. It has been estimated that after a single oral 50 mg dose of DCS its peak cerebrospinal fluid levels reach 2.9 ± 0.96 mg/dL within 1 to 2 h after administration, although high-fat meals may delay its absorption (69). Therefore, administration of DCS at one hour prior to a session should result in peak cerebrospinal fluid (CSF) DCS levels during the actual exposure practices and consolidation phase. The administration of DCS at one hour before the session is also consistent with the two previous trials that showed positive results for DCS-induced augmentation of the efficacy of exposure based cognitive-behavioral therapy (24,56).

Competitive NMDA receptor agonists are usually associated with neurotoxicity due to unregulated calcium entry. However, other compounds that influence NMDA receptor function, such as DCS, have a more favorable profile. Infrequent side effects in patients on chronic dosing schedules (who were generally chronically ill with tuberculosis) include drowsiness, headache, confusion, tremor, vertigo, memory difficulties, paresthesias, and seizures. It should be noted, however, that no significant side effects with DCS were reported in three studies on healthy humans (11,65) who received single DCS pills (15 to 500 mg), with intervals of 3 to 7 days between administrations ($N = 62$). Furthermore, in chronic use of DCS in the treatment of negative symptoms of schizophrenia, there is evidence of acceptable tolerability albeit no consistent beneficial effects. For example, in four randomized, placebo-controlled, parallel trials of DCS at chronic dosing of 50 mg or placebo for 8 to 24 weeks for the treatment of the negative symptoms of schizophrenia (10,17,18,68), we found no significant difference in dropout rates ($N = 136$; 30.3% dropouts with DCS, 24.3% dropouts with placebo: Fisher's Exact p-value = 0.45) (49).

There is some evidence that isolated dosing strategy, rather than chronic dosing, is crucial for the intended effect of DCS on the NMDA receptor. For example, Quartermain et al. (54) found that enhancement effects of DCS on extinction learning were disrupted by daily dosing for 15 days prior to testing, and Parnas et al. (50) reported that as little as 5 pre-exposures to DCS over 10 days eliminated the enhancement effect. This is consistent with the demonstration of desensitization of the NMDA receptor complex in cell culture with prolonged exposure to DCS and other glycinergic ligands (4). It is possible that isolated dosing avoids the compensatory changes in the NMDA receptor complex following chronic administration. Therefore, it has been suggested that DCS needs to be taken on an isolated rather than a chronic dosing schedule in order for it to have its intended effect on NMDA receptor activity (8,56). Accordingly, chronic dosing strategies may be one factor that explains the ultimate failure of DCS in the treatment of schizophrenia or Alzheimer's disease (12,49,55). In summary, the literature suggests that DCS is generally well tolerated and is most effective by isolated dosing. However, more research is needed to establish the dose-effect relationship of DCS.

PRECLINICAL STUDIES

The animal literature suggests that NMDA antagonists inhibit extinction. For example, a study by Falls et al. (13) showed that intra-amygdala infusions of an NMDA receptor antagonist shortly before extinction training dose-dependently blocked extinction. This impairment cannot be attributed to an effect on NMDA receptors outside the amygdala, an impairment of sensory transmission during extinction or state dependency (61).

Given that antagonists of the NMDA receptor in the amygdala reduce or block the effects of extinction, the question arises as to whether it might be possible to facilitate extinction by enhancing the functioning of the NMDA receptors. In a series of experiments Walker et al.

(67) administered DCS either systemically or directly into the amygdala of rats before extinction training. The retention of extinction was then tested the next day without drug administration. The results showed that DCS dose-dependently enhanced extinction in rats exposed to lights in the absence of shock but not in control rats that did not receive extinction training. Similarly, Ledgerwood and colleagues reported that DCS facilitates extinction of conditioned freezing when given either systemically or directly into the amygdala (31,32). Interestingly, DCS can still facilitate extinction when given up to about 3 h after extinction training, which is consistent with the idea that DCS acts to facilitate memory consolidation of extinction (57).

The research literature is most notable for the effects of DCS on extinction learning (57), although there are isolated reports of at least some facilitation of other learning tasks, including spatial learning in a Morris water maze (34), inhibitory avoidance learning (28), a visiospatial-guided delayed win-shift performance task (53), and a thirst-motivated linear maze learning task (54). These studies provide some support for the efficacy of DCS outside extinction learning, but leave open questions whether enhancement effects are more optimal around extinction-based or stress-based tasks.

CLINICAL STUDIES

DCS is an established drug for the chronic treatment of tuberculosis in humans. It has also been used to improve negative symptoms in schizophrenia (16,18,60), social behavior in autistic disorder (52), and cognitive functioning in Alzheimer's disease (62,63). Despite some early promise in the treatment of either schizophrenia or Alzheimer's disease, the weight of the evidence has been disappointing. For example, across 13 studies between 1995 and 2005, no significant effects were obtained in at least half of the trials (49). Likewise, a systematic review of 4 studies using DCS for Alzheimer's disease revealed that the drug was generally ineffective (27). The authors also noted that there was no significant difference between the DCS and placebo treated groups in dropouts due to side effects at any dose. Although the results were disappointing from the efficacy point of view, these studies were reassuring regarding tolerability of DCS, which was used in an elderly and generally medication-sensitive population. As noted, one potential reason for the lack of efficacy for DCS in these trials may be the reliance on chronic rather than isolated dosing strategies.

Exposure-based treatments in humans rely on extinction to treat the core fears underlying anxiety disorders, and the efficacy of DCS in animal models led to the recent application of DCS for humans with anxiety disorders. In an initial effort to demonstrate the utility of DCS as a method to enhance exposure therapy in humans, Ressler and colleagues (56) randomized 28 subjects with a Diagnostic and Statistical Manual-IV (DSM-IV) diagnosis (1) of specific phobia of heights (acrophobia) to 2 sessions of virtual reality exposure therapy preceded in double blind fashion by administration of single doses of placebo or DCS (50 or 500 mg) taken 2–4 h prior to each of the sessions. Exposure therapy combined with DCS resulted in significantly larger reductions of acrophobia symptoms at one week and 3 months following treatment with no difference in efficacy between the 2 doses and no reports of adverse effects from DCS administration. Subjects receiving DCS also showed significantly greater decreases in post-treatment skin conductance fluctuations during the virtual exposure and significantly greater improvement compared to placebo on general measures of real-world acrophobia symptoms that was evident early in treatment and was maintained at 3 months.

In another double-blind placebo-controlled study that was conducted at three U.S. sites, 27 patients with a principal DSM-IV diagnosis of social anxiety disorder (social phobia) were assigned to either receive exposure therapy plus DCS (50 mg) or exposure therapy plus pill placebo. The exposure practices of increasing difficulty consisted of giving speeches about

topics chosen by the therapists in front of the other group members or confederates and a video camera. At the conclusion of each exposure session, patients were encouraged to continue to apply home-practice strategies (such as giving speeches in front of a mirror). Although treatment primarily focused on public speaking, 51.9% of the subjects had a generalized subtype of social anxiety disorder, and 40.7% had at least one additional DSM-IV Axis I diagnosis. The level of social anxiety was assessed at baseline, post-treatment, and one month after the last session (1-month follow-up). The primary treatment outcome measure was the Social Phobia and Anxiety Inventory (SPAI; 64). Additional measures included the Liebowitz Social Anxiety Scale (36), and the Clinical Global Impression Scale, Severity (22). As shown in Fig. 1, the difference between the DCS and placebo group increased linearly with time, with the greatest treatment effects of DCS being evident at follow-up. Similar results were found for the other measures.

Together, the clinical outcome studies by Hofmann et al. (24) and Ressler et al. (56) provide support for the use of DCS as augmentation treatment of exposure therapy in patients with anxiety disorders. In contrast, research with nonclinical adults has yet to document an advantage for DCS augmentation of exposure. In particular, Gaustella and colleagues have conducted two sets of studies of DCS with nonclinical participants. In the first series of studies, the authors examined the effects of DCS vs. placebo in enhancing extinction in a *de novo* fear conditioning paradigm (20). No effect for DCS was found when fear acquisition and extinction were conducted on the same day. Likewise, in a revised design using fear-relevant stimuli (i.e., pictures of snakes for snake-anxious participants) and the separation of acquisition and extinction on separate days, no effect for DCS was evident.

Furthermore, Guastella and colleagues (20) used DCS in two studies of spider-fearful participants treated in a single session with information, cognitive-therapy, and up to two hours of exposure. All participants tended to respond well (e.g., in one study all participants were able to complete a post-treatment exposure test), and no difference between DCS and placebo augmentation was evident. These disappointing results may well be explained by the use of non-clinical participants and relatively strong (for the task) exposure interventions. In *de novo* fear conditioning, little extinction is commonly required to return healthy participants to pre-conditioning levels of arousal (46), and in the treatment of non-clinical as well as clinical fears of spiders, single session interventions lead to significant and long lasting changes (47). By way of contrast, studies showing a successful DCS enhancement effect (24,56) utilized clinical fears and one-third to one-half the standard number of exposure sessions. In reducing the strength of exposure interventions, these studies were fully in line with the animal research, where only half the standard number of extinction trials is used to allow sufficient levels of residual fear to detect the DCS enhancement effect (66).

Accordingly, in the studies by Guastella and colleagues (19–21) the combination of weak levels of fear (i.e., *de novo* and non-clinical fears), combined with relatively strong exposure interventions may have created extinction conditions where there was little room to show DCS enhancement due to ceiling effects. Nonetheless, the studies by Guastella and associates do provide a challenge to the field to better identify the setting conditions where strong DCS effects can be observed.

CONCLUSIONS

Exposure-based interventions offer some of the best outcomes of available psychological treatments for anxiety disorders. Nevertheless, too many patients do not have a significant response to initial intervention and many do not achieve remission after acute treatment. Similarly, the response rates for pharmacologic interventions clearly show room for further improvement. The hope that response rates would be boosted significantly by combined

pharmacologic (e.g., serotonin reuptake inhibitors) and psychological treatments has thus far been disappointing. The addition of DCS to exposure therapy represents a new paradigm in which a pharmacologic intervention is used to directly enhance the efficacy of a psychosocial intervention.

Recent advances in animal research have mapped some of the core pathways and neurotransmitters involved in fear. As noted above, animal experiments suggest that fear learning and extinction are both blocked by antagonists at the glutamatergic NMDA receptor, which is critically involved in learning and memory. Moreover, DCS, a partial NMDA agonist appears to augment learning in animals and in some human trials. The process of extinction of conditioned fear is facilitated by DCS when given in individual doses prior to extinction (exposure) trials in animals. These findings from the animal laboratory have recently been replicated in patients with height phobia (56) and social anxiety disorder (24). However, other trials with subclinical student samples did not find DCS to facilitate exposure procedures and extinction learning. Additional research is clearly needed to examine the conditions that have to be met for DCS to show its therapeutic effects. Despite these cautionary notes, the role of DCS in enhancing extinction learning is one of the potential successes of translational research: basic science studies of the neurobiological circuits of fear and extinction that lead to the study of NMDA partial agonists in animal learning paradigms, and ultimately, to the demonstration of similar effects in the clinical study of humans.

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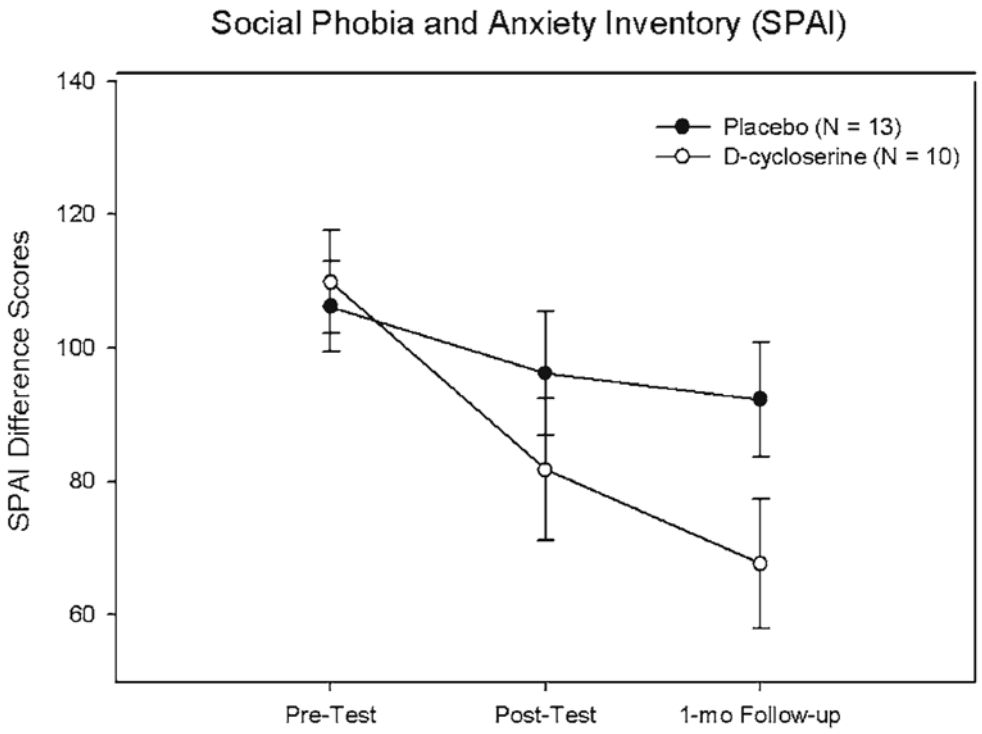

Fig. 1.
Means and standard errors of self-reported social anxiety among treatment completers. Figure reprinted from ref. 24 with permission from American Medical Association.