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D-cycloserine for Treating Anxiety Disorders: Making Good Exposures Better and Bad Exposures Worse

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Introduction

In an attempt to improve the efficacy of psychotherapy for anxiety disorders, preclinical paradigms have recent been translated into novel treatment strategies.[1] Specifically, these studies have examined the role of glutamate, an excitatory neurotransmitter in the mammalian brain, in extinction learning. A receptor complex involved in this process is the N-methyl-D-aspartate (NMDA) receptor. Activation of the NMDA receptor requires binding of both glutamate and the co-agonist glycine. D-cycloserine (D-4-amino-3-isoxazolidone; DCS) is a partial agonist at the glycine recognition site of the glutamatergic NMDA receptor. Animal studies that employed fear-potentiated startle to a conditioned stimulus have demonstrated that this substance can augment extinction learning in rats.[1] The result of this translational work has shown for some studies that DCS can act as a cognitive enhancer to augment exposure strategies during cognitive-behavioral therapy of anxiety disorders.[2]

This line of research has gathered a significant amount of attention because it is a prime example of translational research, whereby basic neuroscience directly informs clinical science by identifying a compound and mechanism of treatment change. Following the initial excitement surrounding early DCS augmentation trials, a number of studies have been conducted that provide a more refined picture. These studies further have clarified some of the limitations and indications of DCS as an augmentation strategy.

A Brief Review of Clinical Studies

Most clinical trials examining DCS augmentation of exposure therapy for anxiety disorders were small scale pilot studies. Early studies have shown that DCS can augment a brief course of virtual reality exposure in patients with acrophobia, but not in subclinical spider-fearful individuals and individuals with snake phobia. [3,4] Inconsistent results have also been reported in studies examining DCS for obsessive-compulsive disorder, panic disorder,

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and posttraumatic stress disorder.[3,4] Interestingly, one of the posttraumatic stress disorder trials, which was conducted by our group, found that patients who received DCS reported even *more* symptoms at post-treatment than those who received placebo.[5]

Following some promising early findings showing that DCS can augment exposure therapy for social anxiety disorder, [6] we recently completed the largest DCS augmentation trial to date. This study showed that DCS was not associated with higher response or remission rates, as compared to placebo, but with a faster rate of improvement, suggesting that DCS is more likely to accelerate than to amplify exposure procedures.[7]

A cursory reading the literature might give the impression that the evidence of DCS is inconsistent and mixed. However, a more careful examination of these studies tells a remarkably consistent story, while pointing to important limitations of DCS augmentation strategies.

The Narrow Therapeutic Window of DCS

Dosing and dose timing of DCS are critically important. Most trials reporting positive results administer only a small dose (between 50 and 250 mg of DCS) 1–2 hours before 3–5 exposure sessions. Studies that report negative results often administered much higher doses of DCS (higher than 250 ms), chronically (i.e., before each of a 12 session treatment) and earlier than 1–2 hours prior to a session.[4]

Good NMDA occupancy and modulation of glutamate/glycine binding can be achieved with DCS at approximately $10e^{-6}$ to $10e^{-7}$ molar concentration. Accordingly, for a 75 kg person, a 50mg dose of DCS leads to a concentration of about $6.5 \times 10e^{-6}$ Molar. Trials that used doses of 50, 100, and 125 mg showed similar DCS augmentation effects. When administered at higher doses (500–1000 mg), DCS shows much weaker and sometimes even NMDA antagonistic effects, possibly because the agent is occupying different receptor subtypes.[3]

Timing is another important issue, because peak blood levels of DCS occur 4 to 6 hours after ingestion. Key extinction learning processes occur hours after the end of exposure sessions. Therefore, DCS is probably most effective when administered within 1–2 hours before the exposure sessions. This is supported by the results of animal and human DCS studies showing that studies administering DCS 1–2 hours before or after exposure achieved greater effects than studies administering DCS multiple hours before exposure.

It is further important to note that in animal studies, DCS only revealed positive effects on learning when administered in isolated (i.e., acute) dosing. When administered chronically (i.e., repeatedly over an extended period of time), the NMDA receptor complex can become desensitized, leading DCS to effectively work as an NMDA antagonist. Similarly, long-term exposure to all major classes of antidepressants (such as selective serotonin reuptake inhibitors, tricyclics, and monoamine reuptake inhibitors) are associated with neurochemical changes at the glycine binding site of the NMDA receptor complex, altering the action of DCS.[1] Other evidence points to subject characteristics that moderate DCS response. For example, a re-analysis of our large DCS trial for social anxiety disorder [7] suggests that

DCS augmentation appears particularly useful for patients low in conscientiousness and high in agreeableness.[8]

These results point to the very narrow therapeutic window of DCS: it needs to be administered without any concomitant medication, acutely, and in small doses approximately 1–2 hours before exposures. In addition to these limitations, there is also a "darker side" of DCS, because there is now ample evidence to suggest that DCS not only enhances extinction leaning, but it can also enhance fear memory reconsolidation.

The Darker Side of DCS

Animal studies have shown that NMDA antagonists impair the reconsolidation of fear memories, whereas DCS enhances reconsolidation of fear memory when administered into the basolateral amygdala.[13] A crucial factor that determines whether DCS augments extinction learning or reconsolidation is the length of memory reactivation and extinction training sessions: When the extinction session is brief, reconsolidation processes are dominant, whereas extinction processes dominate in longer sessions.[13] Similarly, if stimulus re-exposure during memory reactivating is relatively brief compared to the strength of conditioning, little extinction is induced and DCS can augment reconsolidation of fear memory. DCS can worsen symptoms by enhancing reconsolidation of fear memory in humans in case a sufficiently therapeutic degree of extinction learning does not occur (i.e., if extinction is too short, or if there is insufficient within-session decrease in fear). Therefore, if fear does not sufficiently decrease during exposure therapy, fear memory reconsolidation may occur and DCS can facilitate this counter-therapeutic process. In other words, DCS can make "good" exposures better and "bad" exposures worse.

Consistent with this notion is a re-analysis of our recent trial.[7] In this study, we observed that, despite the lack of overall DCS effects, post-session DCS administration did augment exposure sessions if the exposure sessions were successful.[10] More specifically, we found that relative to patients receiving placebo, patients receiving DCS evidenced significantly greater clinical improvement when they reported low fear at the end of their previous exposure session. In contrast, when exposure end fear was high, patients receiving DCS exhibited less clinical improvement at the following session than patients receiving placebo. Similarly, patients receiving DCS only evidenced lower clinical severity at post-treatment than patients receiving placebo when the average end fear at each session was in the mild to moderate range. These moderating effects of exposure success as indexed by post-treatment fear were not better accounted for by within-session extinction, suggesting that post-treatment fear (as opposed to a change in fear) is a good index for predicting DCS augmentation effects.

In another study,[11] we tested whether these moderating effects of session end fear on DCS efficacy would be evident when DCS is administered post-session (instead of pre-session). The main outcome analysis for the parent trial for this re-analysis had revealed no evidence of post-session DCS augmentation of virtual reality therapy in height phobics on average.[12] However, consistent with predictions, the effects of post-session DCS administration on clinical improvement was again moderated by the level of fear experienced just prior to

concluding exposure sessions. Patients receiving DCS exhibited significantly greater improvement in symptoms relative to patients who received placebo when subjective fear was low at the end of the exposure. In contrast, when end fear was still elevated, patients receiving DCS improved less compared to those receiving placebo. Thus, these data indicate that if fear does not decrease during exposure, fear memory reconsolidation may occur and DCS may facilitate this counter-therapeutic process.

Conclusion

A number of preclinical and clinical studies suggest that DCS may act as a cognitive enhancer during extinction learning and exposure therapy. However, other studies report negative findings. The studies to date suggest that DCS is a potentially effective cognitive enhancer, but with a narrow therapeutic window (i.e., it needs to be administered without any concomitant medication, acutely, and in small doses approximately 1–2 hours before exposures). In addition, DCS appears to make “good” exposures better and “bad” exposures worse, because it not only enhances cognitive processes during extinction learning, but also during fear memory reconsolidation. Therefore, it could be argued that the decision to administer DCS should be made post-session, contingent on the level of fear reduced (i.e., extinction learning achieved) by the end of the session.

Support for such tailored post-session administration of DCS comes from some animal studies that have documented success with post-session DCS administration up to 2 hours following training. Some pilot work from our own group shows that post-session administration of DCS is efficacious when linked to successful exposure sessions. Another possibility is to include a clinical assay to detect patients who are likely to benefit from DCS-augmented treatment. This is in line with a general move toward personalized medicine with this uniquely translational approach of treating a common mental health problem.

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