

Review Article

D-Cycloserine Augmentation of Exposure Therapy: Review and New Directions

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ABSTRACT

Although cognitive behavioral therapy (CBT) is an efficacious intervention for anxiety disorders, there is room for improvement. Pharmacological strategies have been investigated as a means to augment CBT efficacy. One such medication, d-cycloserine (DCS), has been shown to augment extinction learning which takes place within CBT. However, the literature on DCS as an augmentative strategy for CBT for anxiety disorder treatment is mixed.

Keywords: anxiety, d-cycloserine, CBT

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Cognitive behavioral therapy is the most effective psychotherapy for anxiety disorders.[2] Despite superior efficacy in comparison to other psychotherapeutic approaches, there is still considerable room for improvement. For example, a meta-analysis effect sizes (using Hedges's g) from randomized controlled trials of CBT for anxiety disorders ranged from 0.13 (small) to 2.08 (large), with an average effect size of 0.73.[2] Attempting to yield a synergistic effect, researchers have supplemented CBT with anxiety-reducing pharmacotherapies, but have seen little success. In fact, research suggests that augmenting exposure with anxiolytic drugs may actually negatively impact treatment outcomes, as individuals may attribute gains to medication rather than to their own self-efficacy.[3]

Accordingly, a more recent approach is to strengthen extinction learning within CBT using pharmacotherapy that affects the neurobiology implicated in fear extinction processes .[4] In other words, enhance the learning that occurs when an individual understands that previously feared situations or stimuli are safe. One structure, the N-methyl-D-aspartate (NMDA) receptor in the basolateral amygdala, plays an important role in controlling neural plasticity and memory, with recent research suggesting that NMDA activity mediates fear extinction.[5] Indeed, in rodents, a compound known as d-cycloserine (DCS) has been demonstrated to augment extinction learning by serving as a partial NMDA agonist.[6] This manuscript provides an abbreviated review of the history of clinical research involving DCS administration toward the treatment of anxiety disorders, describing how the knowledge gleaned from these trials can inform further study.

Brief Review of Clinical Research

Several studies translated these findings from the animal literature to the treatment of anxiety disorders in humans. The evidence base for DCS as an augmentation strategy for CBT treatment of anxiety disorders has been mixed, with some studies demonstrating promise, and others yielding null effects.[4] Importantly, DCS has predominantly been administered prior to exposure, which follows the animal literature on fear extinction (wherein rodents are administered DCS prior to extinction learning). A convergence of both basic and clinical research suggests that the traditional timing of DCS administration (i.e., dosing pre-extinction learning) may account for some of the discrepancies in the literature.

DCS Administration Considerations

The mixed efficacy of DCS trials may be partially explained by the fact that DCS not only augments fear extinction learning, but also fear memory reconsolidation, or the stabilization of a fear-related memory after initial fear acquisition.[7] When DCS has been administered, the length of extinction training (or memory reactivation) becomes a critical determinant as to whether or not facilitative effects will occur. Basic research indicates that during re-exposure to a feared stimulus, extinction processes tend to occur less in shorter sessions, while reconsolidation of the fear memory tends to dominate.[8] In longer sessions, extinction learning tends to dominate. Since DCS has the capacity to consolidate both extinction and reconsolidation processes, it may be vital to ensure that extinction learning is the predominant process occurring during DCS-augmented sessions. If extinction learning does not take place (i.e., fear does not decrease) during a DCS-augmented re-exposure, DCS administration may actually worsen symptoms by strengthening fear-related memories. Accordingly, administering DCS prior to exposure sessions may be problematic as not all exposures are effective (i.e., there is not always a reduction in fear). Administering DCS post-extinction learning and judiciously (only after sessions wherein extinction learning is evident) may prevent potentially deleterious effects of DCS.

Building on this line of research, Ledgerwood and colleagues (2003) tested the efficacy of post-extinction learning DCS administration in rodents and found that this strategy facilitated extinction learning with an effect comparable to that of pre-extinction learning administration.[9] Tart and colleagues (2013) were the first to administer DCS post-session in a clinical trial; however, this study did not find that DCS successfully augmented exposure therapy.[10] Keeping in mind that it may be important to consider whether extinction learning or fear memory reconsolidation is being augmented within the session, a re-analysis was performed to determine whether DCS administration might have been beneficial for those who evidenced successful exposure sessions (as indexed by those participants who experienced low levels of fear at the end of an exposure therapy session).[11] Indeed, there was a moderating effect of session success wherein DCS was only beneficial for those evidencing low end fear levels.[12] This finding has since been replicated, further indicating that not only is the timing of DCS administration important, but that it may also be imperative to consider the quality of the extinction learning taking place within the session.

New Directions

This brief literature review justifies one important next step in research on DCS augmentation of exposure therapy, namely developing an algorithm for the effective application of this augmentation strategy. As outlined in Hofmann et al., 2015), our group is currently conducting a randomized control trial (ClinicalTrials.gov identifier: NCT02066792) examining the optimal timing for administration (pre- or post-exposure) and whether administration should be delivered judiciously (i.e., only to those who evidence successful fear extinction via low levels of end fear).[8] To this end, the study randomizes 156 adults diagnosed with social anxiety disorder (SAD) to 5 sessions of CBT augmented with placebo, pre-session DCS administration, untailored post-session DCS administration, and tailored post-session DCS administration (wherein individuals only receive DCS after successful sessions; i.e., when end fear levels are low). Additionally, a subset of participants will also be enrolled in a DCS (or placebo)-augmented fear extinction laboratory experiment. This experiment, in addition to the outcomes of the larger clinical trial, will aid in determining whether the mechanism of action for DCS is via increased fear extinction retention.

The outcomes of this study will not only have important clinical implications if DCS is to be disseminated as an anxiety treatment augmentation strategy, but also point toward a useful research paradigm (i.e., translating findings from animal research toward both the development and refinement of treatment strategies for psychopathology). Previous studies examining moderators of DCS efficacy have been unavoidably limited in their post-hoc scope; an advantage of this trial is that the aims were developed based on replicated proof-of-principle research. It is our hope that, rather than simply combining treatment strategies aiming for a synergistic effect, future research will continue to translate basic neuroscience not only toward the development of novel clinical applications, but also to elucidate under what circumstances these applications may or may not be successful. For example, future research on DCS might focus on illuminating specific predictors of session success to guide judicious administration.

REFERENCES

1. Hofmann SG. D-cycloserine for treating anxiety disorders: Making good exposures better and bad exposures worse. Depression and Anxiety 2014; 31: 175-177.
2. Hofmann SG, Smits JA. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. The Journal of Clinical Psychiatry 2008; 69: 621.
3. Powers MB, Smits JA, Whitley D, Bystritsky A, Telch MJ. The effect of attributional processes concerning medication taking on return of fear. Journal of Consulting and Clinical Psychology 2008; 76: 478.
4. Otto MW, Kredlow MA, Smits JA, Hofmann SG, et al. Enhancement of psychosocial treatment with d-cycloserine: Models, moderators, and future directions. Biological Psychiatry.
5. Davis M, Myers KM. The role of glutamate and gamma-aminobutyric acid in fear extinction: clinical implications for exposure therapy. Biological Psychiatry 2002; 52: 998-1007.
6. Walker DL, Ressler KJ, Lu KT, Davis M. Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. The Journal of Neuroscience 2002; 22: 2343-2351.
7. Lee JL, Milton AL, Everitt BJ. Reconsolidation and extinction of conditioned fear: Inhibition and potentiation. The Journal of Neuroscience 2006; 26: 10051-10056.

8. Hofmann SG, Carpenter JK, Otto MW, Rosenfield D, Smits JA, Pollack MH. Dose timing of d-cycloserine to augment cognitive behavioral therapy for social anxiety: Study design and rationale. Contemporary Clinical Trials 2015; 43: 223-230.

9. Ledgerwood L, Richardson R, Cranney J. Effects of D-cycloserine on extinction of conditioned freezing. Behavioral Neuroscience 2003; 117: 341.

10. Tart CD, Handelsman PR, DeBoer LB, Rosenfield D, Pollack MH, Hofmann SG, Smits JA. Augmentation of exposure therapy with post-session administration of D-cycloserine. Journal of Psychiatric Research 2013; 47: 168-174.

11. Smits JA, Rosenfield D, Otto MW, Powers MB, et al. D-Cycloserine enhancement of fear extinction is specific to successful exposure sessions: evidence from the treatment of height phobia. Biological Psychiatry 2013b; 73: 1054-1058.

12. Smits JA, Rosenfield D, Otto MW, Marques L, Davis ML. D-cycloserine enhancement of exposure therapy for social anxiety disorder depends on the success of exposure sessions. Journal of Psychiatric Research 2013a; 47:1455-1461.

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