

### Maintaining Clinical Relevance: Considerations for the Future of Research into D-Cycloserine and Cue Exposure Therapy for Addiction

To the Editor:

Cue-drug memories are remarkably persistent, precipitating relapse after years of abstinence. Cue-exposure therapy (CET) attempts to suppress these memories but has had only modest success clinically (1). The cognitive enhancer D-cycloserine (DCS) might improve CET efficacy through improved contextual generalisation and prolonging of therapeutic effects.

The recent review by Myers and Carlezon (2) of this approach shows DCS-enhanced extinction (DCS/CET) is often efficacious in preclinical but not clinical studies. They highlight important limitations of extant clinical studies to account for this disparity and forward methods for maximizing the probability of finding a positive DCS/CET effect through constraining experimental variables to increase sensitivity to subtle drug effects.

Although we concur with some of their recommendations, we believe interventions for preventing relapse should address the following clinical utility criteria: 1) large, reproducible effects on reducing relapse rates, 2) long-lasting efficacy, 3) contextual invariance, 4) feasible clinical implementation (insensitivity to slight variations in procedure), 5) cost- and time-effectiveness. We believe that some of their recommendations are misaligned with these criteria and may therefore not expedite the development of efficacious antirelapse treatments.

The recommendation that researchers design studies to “to maximize the probability of detecting a DCS effect” suggests that previous research was insufficiently sensitive to observe subtle DCS effects. We feel that, given the number and sample sizes of extant clinical studies (an additional three have been published since their review showing null [3,4] or detrimental [5] DCS effects), such a type II error rate would suggest a small effect and therefore a very limited role in DCS/CET in addiction treatment. Notably, the opposite argument is not engaged (that some positive findings constitute type I errors).

Myers and Carlezon suggest minimizing type II error in DCS/CET studies with “sufficiently large sample size ... consistent data; CRs [conditioned responses] to drug cues in all participants ... obtained if necessary through exclusion of nonresponders... robust CR and slow extinction to avoid floor effects.” Ours (6,7) and recent (3–5) studies were well powered to detect medium/large DCS effects (criterion 1). Furthermore, aberrant mnemonic processes in addicts are inherently variable. By constraining variation in participant characteristics, we create a highly artificial experimental situation with very limited generalizability/validity for treatment applications (criterion 4).

If very large samples or minutely controlled experimental variables are required to observe DCS/CET effects, we doubt its promise in effecting meaningful improvements in addicts' prognoses. Clinical intervention tests should be designed to objectively appraise the impact on critical outcome variables (i.e., reduction in relapse rates or craving). The suggestion that “response measures in clinical studies should be chosen carefully so as not to overlook potentially subtle behavioral effects ... cue-elicited CRs such as autonomic reactivity, craving, and withdrawal might be most appropriate” abstracts away from the vital outcome measures for addiction treatments (the relationship between these variables and relapse is unclear). By selecting narrow, conceptually problematic response variables to observe subtle behavioural effects, we lose sight of the ultimate goal of this research.

Given the complex pharmacology of DCS, it is premature to assume a definitive dose-response relationship in humans. Studies have therefore largely used doses effective in anxiety disorders, administered so that peak plasma levels align with the acquisition and consolidation of CET (5,6). Recently null effects have been found across a wide range of doses (3–7) and the suggestion (2) that 125–250 mg doses are too high runs contrary to positive findings with equivalent (15/30 mg/kg) (8) doses in rats and metaregression of dose-response (9) in anxiety studies. Excluding participants because of comorbid antidepressant use is restrictive in clinical populations, as addiction and depression often co-occur. We agree that lack of participant supervision posttest (while DCS is active) is a major problem in clinical DCS/CET studies. However, extending inpatient treatment sessions by several hours to control this may constitute false economy (criterion 5), given the likely subtle beneficial DCS effects.

Clinical DCS/CET studies are influenced by preclinical addiction models and successful DCS/CET for anxiety. A disconnect exists between memory processes in anxiety and addiction; the latter is more complex (2), involving changes in *N*-methyl D-aspartate receptor subunit composition, particularly in alcoholism. The disparity between anxiety and addiction findings may be due to the basis in distinct neurochemical and motivational memory processes in humans. The incentive to maintain responding inculcated during CET is very different for the two disorders: successful treatment for anxiety results in the removal of an aversive outcome, whereas successful treatment for addiction results in the prevention of rewarding outcome, possibly explaining low transference of effects peri- to posttreatment in the latter. Drug memories may also be older and more habitual than those in anxiety disorders. A 40-a-day smoker will experience 14,600 reinforcer exposures per year, perhaps explaining why cue-drug memories are harder to ameliorate than cue-fear memories in anxiety. Similarly, preclinical addiction models use abbreviated learning compared with human addicts. Memory strength and age, rather than lack of test sensitivity, might best explain the disparate DCS/CET findings in rats, anxiety, and addiction. Many more CET sessions may therefore be needed to show DCS effects in humans; it is possible that inhibitory learning during CET must become as well learned and habitual as cue-drug memory to compete for expression. If so, DCS/CET would not meet criterion 5.

More fundamentally, DCS/CET may lack efficacy due to not targeting prepotent cue-drug memories. CET does not affect these memories but creates new inhibitory traces in a specific, novel, and often cue-impoverished context (the laboratory). Unless DCS/CET can be shown to have permanent and context-invariant (criteria 2 and 3) effects in potentiating CET-based extinction traces to consistently win out over prepotent traces, it will likely not reduce relapse rates. At the very least, researchers should consider conducting DCS/CET in realistic drug-taking environment to address problems with contextual modulation of cue-reactivity (10).

We feel more promising treatment approaches come from recent research into memory reconsolidation (11). Blocking reconsolidation of reactivated cue-drug memories could potentially degrade or abolish cue-drug memories, a more parsimonious and potentially permanent solution than temporary suppression with competing traces, however enhanced by drugs. Although we encourage further research into DCS/CET, we ask that it not lose sight of the ultimate goal of this endeavour in the pursuit of positive experimental effects.

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