Lessons Learned From D-Cycloserine: The Promise and Limits of Drug Facilitation of Exposure Therapy

Thomas L. Rodebaugh, PhD, and Eric J. Lenze, MD

We, like many other psychiatrists, psychologists, and drug developers, look forward to a day when medication and psychotherapy are typically combined in a rational manner. At present, most such combinations in the field are at best accidental and represent incremental improvements, whereas at worst the 2 methods may clash. Set against this backdrop, recent and replicated findings that the medication D-cycloserine (DCS) can enhance psychotherapy are of particular interest, because DCS was applied to a psychotherapeutic intervention on the basis of basic research. DCS is thus a rare example of a medication brought from theory-based preclinical work to clinical trials.[1]

DCS Enhancement of Exposure Therapy

Anxiety disorders carry a high human and economic burden.[2] Exposure-based psychotherapeutic interventions (ie, those based on confrontation of feared situations or stimuli) are effective interventions that have been increasingly viewed as first-line treatments for anxiety disorders (eg, posttraumatic stress disorder [PTSD], according to the US Department of Veterans Affairs[3]). However, in practice, exposure therapy often requires numerous sessions to be effective and is hampered by low availability and high cost, as well as dropout and refusal. Speeding up response to exposure therapy is a promising way of improving the treatment of people with anxiety disorders, because a shorter course of therapy should limit dropout and refusal, as well as increase availability of treatment.

The neurobiological theory behind DCS enhancement of exposure therapy lies in the observation that exposure therapy represents new emotional learning, analogous to extinction of a fear response in animals.[4] Such new learning has been shown to be mediated through *N*-methyl-D-aspartate (NMDA) receptor activation.[4] DCS is an agonist of the NMDA receptor, increasing transmission of glutamate via the glycine binding site of this receptor.[4] Therefore, administration of DCS prior to exposure therapy ought to increase the fear extinction learning of these exposure sessions, speeding up or enhancing response.

Supporting that conclusion, a meta-analysis of human and animal studies found a medium-sized effect for combining DCS with exposure (in general) compared to exposure alone.[5] That meta-analysis also suggested that DCS might work at least in part due to its producing a *faster* response to exposure, not a greater overall response across standard treatment lengths. In other words, DCS might primarily advance treatment to its endpoint more rapidly, rendering shorter treatments as effective as a full course of treatment. For example, it has been estimated that 8 cognitive-behavioral therapy sessions would typically be needed in conjunction with DCS to treat obsessive-compulsive disorder effectively, whereas 16 or more would typically be needed without DCS.[6] The same authors estimate that the use of DCS would accordingly reduce treatment costs by at least $2,000 per patient.[6] A more recent meta-analysis[7] focusing on human studies has questioned whether effects of DCS are actually stronger early in treatment, somewhat contradicting the earlier meta-analysis[5] that combined human and animal data. However, early results from 1 of the 2 recent multisite National Institute of Mental Health studies of DCS enhancement of exposure therapy support the contention that DCS primarily speeds up response: in social anxiety disorder, DCS administration prior to exposure therapy sessions provided *faster* response, but not greater *overall* response.[8]

Preclinical findings may also help to predict when DCS will be helpful and when it will not. Preclinical evidence suggests that chronic administration of antidepressants may interfere with the effects of DCS.[9] Other preclinical evidence suggests that DCS may be particularly indicated when another condition that interferes with learning is present. For example, sleep-deprived rats recover a response to exposure when given DCS,[10] whereas typically such rats are slower to respond.

What We Don't Know Could Hurt Us

The list of questions about DCS is long. General questions include those of optimal dosage and timing of administration, discussed below. Two other important questions are (1) Can DCS also produce harmful effects? and (2) Do the effects of DCS remain consistent across anxiety disorders? Regarding the first question, some evidence indicates that DCS might enhance not only learning of safety (ie, with reduction of fear during the exposure session), but potentially also *learning of fear*.[11] If an exposure session does not produce some safety learning, DCS has the potential to produce a worse rather than better outcome. Allowing clinicians to choose which exposure sessions to reinforce at the end of those sessions might decrease the chances of harm. However, such an effect has yet to be clearly observed in humans.

Regarding the second question, results of 2 recent studies[12,13] concerning PTSD suggest collectively that the effects of DCS may not be uniform across anxiety disorders. The exposures in these studies were imaginal (verbal recounting of the traumatic event), a standard technique in PTSD. In contrast, previous studies of DCS, in other disorders, focused on exposure that involved at least a visual simulation of currently feared events. It may be that DCS is less effective in enhancing the effects of imaginal exposure. For example, imaginal exposure may require more sessions before extinction learning begins, in which case administering DCS in early sessions could cause enhancement of fear memory.[13] However, the small sample size of these studies makes interpretation difficult.

At present, relatively few psychiatrists are likely to prescribe DCS, but this may change if findings continue to accrue. DCS is approved by the US Food and Drug Administration (for treatment of tuberculosis), which allows physicians to prescribe it for "off-label" uses, and the prospect of using such a medication in single doses to enhance psychotherapy is appealing. Unfortunately, in part because it has not undergone large phase 3 industry studies for this use, DCS has even less information available than would typically be the case for psychiatric medications. In addition to unanswered questions about efficacy, other questions remain regarding (1) the optimal therapeutic dose, (2) when the drug should be administered (ie, before vs after therapy sessions), and (3) whether coprescribed

medications or comorbid medical or psychiatric conditions interfere with its effects.

Regarding optimal dose, our read of the literature suggests that doses between 50 mg and 500 mg may be effective[7] and relatively free of side effects when given as single doses accompanying psychotherapy sessions. A dose of 250 mg appears well tolerated[5,14] and is more widely available than the 50-mg dose that has typically been used in studies. Regarding timing of administration, shortly (eg, 1–2 hours) before exposure appears most well supported at this time, although preclinical work and our understanding of the effects of DCS suggest that postexposure administration should also be effective.[5] However, this postexposure timing has not yet been clearly supported in humans, despite great interest in the possibility of being able to choose which exposure sessions to enhance with DCS. Finally, regarding possible interference of medications or conditions, findings in humans have provided no guidance thus far, although as noted above the preclinical literature suggests that there are likely to be contraindications, such as chronic use of antidepressants.[9]

Clinical Assay: A New Research Method for Testing DCS

We clearly have much to learn about DCS before it can be used clinically in an effective manner, yet it will be difficult for clinical trials to resolve these fundamental questions regarding dose, timing, and the best patient population for DCS. Although lengthy and expensive, standard clinical trials of psychiatric medications often fail to show any effects for medication, let alone moderator effects (ie, for whom the medication is most effective).[15] Clinical trials also rarely clarify the parameters of medication administration, such as optimal dose and timing. Yet, these questions also cannot be answered with preclinical models, given the dissimilarities between fear extinction in animals and exposure therapy in people with anxiety disorders.[16]

Faced with this dilemma, we developed a clinical assay approach that would provide answers regarding DCS relatively quickly. The model for our clinical assay is provided by the behavioral literature, in which brief 2-session tests of exposure augmentation have established several nonpharmacologic enhancements of exposure.[17–19] The profile of DCS includes an acute and early effect, making a brief test of exposure enhancement feasible. We use the term *assay* because we focused not on typical therapeutic encounters but, instead, on short and highly standardized procedures conducted over approximately 2 hours (1 hour in each visit for 2 visits) via a trained rater. Our clinical assay could therefore, with relatively minimal expense, randomize large numbers of participants, reaching the large sample sizes needed for adequately powered tests of the dose, timing, and patient characteristics that lead to the optimal response. However, we first focused on demonstrating that the assay could detect the effects of DCS. In a small randomized placebo-controlled study, we tested whether DCS 250 mg, administered once in an initial brief exposure session for social anxiety disorder, reduced fear in a second exposure session a week later.[20] Our assay was successful at demonstrating the effect of DCS: those randomly assigned to it were more likely to show a reduction of fear at the second session.

Our test was a first step and does not answer some reasonable questions about the assay approach (eg, Is early response a good proxy for later response with DCS?). Our current conclusion regarding the clinical assay is that it has promise. We therefore encourage researchers to consider high-throughput designs, like our clinical assay, as a means of answering important clinical questions about DCS and related agents (eg, timing, dosage) with precision prior to conducting full-scale clinical trials to confirm such findings. For clinicians, our assay approach offers the promise of eventual answers to such pressing questions as dosage and timing for DCS.

Clinical Recommendations

The literature regarding DCS will surely continue to evolve, leading us to recommend that clinicians conduct a careful search of the literature before using DCS in their own practice. In the absence of future contradictory findings, there appears to be little reason not to consider the use of DCS, at least in regard to efficacy (at least reasonably good) and side effects (apparently minimal). It must be noted, however, that effective use of DCS requires clinicians to have either a thorough knowledge of exposure-based approaches or, alternatively, a close working relationship with a clinician who does. DCS thus stands to provide an added benefit to the field, by facilitating not only exposure sessions, but also the wider dissemination of exposure therapy itself, a vital technique in treating anxiety disorders.

Author affiliations: Department of Psychology, Washington University (Dr Rodebaugh), and the Department of Psychiatry, Washington University Medical School (Dr Lenze), St Louis, Missouri.
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Corresponding author: Thomas L. Rodebaugh, PhD, 1 Brookings Dr, Campus Box 1125, Psychology Bldg, St Louis, MO 63130 (rodebaugh@wustl.edu).

REFERENCES

1. Davis M, Ressler K, Rothbaum BO, et al. *Biol Psychiatry*. 2006;60(4):369–375.
2. Lepine J-P. *J Clin Psychiatry*. 2002;63(suppl 14):4–8.
3. Department of Veterans Affairs. PTSD Treatment Programs in the US Department of Veteran Affairs. http://www.ptsd.va.gov/public/pages/va-ptsd-treatment-programs. Updated July 2, 2012. Accessed August 27, 2012.
4. Davis M. *Dialogues Clin Neurosci*. 2011;13(4):463–474.
5. Norberg MM, Krystal JH, Tolin DF. *Biol Psychiatry*. 2008;63(12):1118–1126.
6. Chasson GS, Buhlmann U, Tolin DF, et al. *Behav Res Ther*. 2010;48(7):675–679.
7. Bontempo A, Panza KE, Bloch MH. *J Clin Psychiatry*. 2012;73(4):533–537.
8. Pollack MH. D-Cycloserine augmentation of CBT for social anxiety disorder: results from an RCT. Presented at: 52nd Annual NCDEU Meeting; May 29, 2012; Phoenix, AZ.
9. Werner-Seidler A, Richardson R. *Biol Psychiatry*. 2007;62(10):1195–1197.
10. Silvestri AJ, Root DH. *Physiol Behav*. 2008;93(1–2):274–281.
11. Kalisch R, Holt B, Petrovic P, et al. *Cereb Cortex*. 2009;19(1):187–196.
12. de Kleine RA, Hendriks G-J, Kusters WJC, et al. *Biol Psychiatry*. 2012;71(11):962–968.
13. Litz BT, Salters-Pedneault K, Steenkamp MM, et al. *J Psychiatr Res*. 2012;46(9):1184–1190.
14. Ressler KJ, Rothbaum BO, Tannenbaum L, et al. *Arch Gen Psychiatry*. 2004;61(11):1136–1144.
15. Kola I, Landis J. *Nat Rev Drug Discov*. 2004;3(8):711–715.
16. Graham BM, Langton JM, Richardson R. *Br J Pharmacol*. 2011;164(4):1230–1247.
17. Wells A, Clark DM, Salkovskis P, et al. *Behav Ther*. 1995;26(1):153–161.
18. Wells A, Papageorgiou C. *Behav Ther*. 1998;29(3):357–370.
19. Rodebaugh TL, Heimberg RG, Schultz LT, et al. *J Anxiety Disord*. 2010;24(7):663–671.
20. Rodebaugh TL, Levinson CA, Lenze EJ. A high-throughput clinical assay for testing drug facilitation of exposure therapy [published online ahead of print January 2, 2013]. *Depress Anxiety*.

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