Low-Dose D-Cycloserine for Depression?

To the Editor: Ketamine's ability to bring about rapid and dramatic improvement in patients with refractory depression has biotech companies and clinicians scrambling for ketamine alternatives. D-cycloserine (DCS) showed efficacy in depression as early as 1959[1] but lay dormant until recently.

As published in the June 2015 issue of the *Journal*, Kantrowitz and colleagues used ketamine priming followed by a high dose of DCS (1,000 mg/d) with impressive results[2] (also refer to the study by Heresco-Levy et al[3]).

We[4] and a group led by Wilhelm in Boston[5] independently used a low-dose DCS (Table 1) strategy to facilitate cognitive-behavioral therapy–related memory consolidation. In a dose-finding study for negative symptoms in schizophrenia, Goff and coworkers[6] reported an optimal DCS dose of 50 mg/d. This glycine (associated with *N*-methyl-D-aspartate [NMDA] receptor) agonism concept of DCS, akin to rapastinel (formerly GLYX-13; under clinical trial), deserves a closer look.

Although the primary goal of these studies[4,5] was to enhance extinction learning in exposure treatment for OCD cases, both studies documented improvement in depressive symptoms (see Table 1). Although depressive symptoms were mild in both studies, lack of posttreatment group differences in OCD symptoms preclude a possibility that improved OCD symptoms contributed to the reduction in depression.

This report is not to claim an efficacy of DCS in depression but rather to suggest further studies on intermittent application of this old agent that works through NMDA mechanisms and would possibly help clinicians manage some of their depression cases.

References

1. Crane GE. Cyloserine as an antidepressant agent. *Am J Psychiatry*. 1959;115(11):1025–1026.
2. Kantrowitz JT, Halberstam B, Gangwisch J. Single-dose ketamine followed by daily D-cycloserine in treatment-resistant bipolar depression [letter]. *J Clin Psychiatry*. 2015;76(6):737–738.
3. Heresco-Levy U, Gelfin G, Bloch B, et al. A randomized add-on trial of high-dose D-cycloserine for treatment-resistant depression. *Int J Neuropsychopharmacol*. 2013;16(3):501–506.
4. Kushner MG, Kim SW, Donahue C, et al. D-cycloserine augmented exposure therapy for obsessive-compulsive disorder. *Biol Psychiatry*. 2007;62(8):835–838.
5. Wilhelm S, Buhlmann U, Tolin DF, et al. Augmentation of behavior therapy with D-cycloserine for obsessive-compulsive disorder. *Am J Psychiatry*. 2008;165(3):335–341, quiz 409.
6. Goff DC, Tsai G, Manoach DS, et al. Dose-finding trial of D-cycloserine added to neuroleptics for negative symptoms in schizophrenia. *Am J Psychiatry*. 1995;152(8):1213–1215.

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Table 1. Mean ± SD Beck Depression Inventory Scores at Baseline and Posttreatment in 2 Studies of Low-Dose D-Cycloserine Augmentation of Exposure Therapy

	Placebo		D-Cycloserine		
Study	Baseline	Posttreatment	Baseline	Posttreatment	Statistics
Minnesota data (placebo, n = 17; D-cycloserine 250 mg/wk, n = 15)[a]	10.6 (10.3)	9.5 (10.9)	13.4 (11.4)	3.3 (5.6)	Group × time: $F_{1,15} = 6.45$, $P = .023$
Boston data (placebo, n = 13; D-cycloserine 200 mg/wk, n = 10)[b]	10.9 (8.3)	8.7 (9.1)	15.5 (12.7)	1.9 (3.3)	Two-tailed *t* tests: $d = 0.99$ (Cohen *d* effect size), $P = .04$

[a]Data from Kushner et al.[4]
[b]Data from Wilhelm et al.[5]

Dr Kantrowitz and Colleagues Reply

To the Editor: In their letter, Kim et al accentuate our findings[1] that D-cycloserine (DCS) may have antidepressant properties. Kim et al suggest that intermittent treatment with lower-dose DCS (100–125 mg) may be helpful in a population with mild depression secondary to obsessive-compulsive disorder. As the authors state, the baseline levels of depression were mild, but the level of improvement was of a large effect size.

Kim et al suggest that the potential antidepressant properties of both DCS and rapastinel (formerly GLYX-13) are due to agonism at *N*-methyl-D-aspartate–type glutamate receptor glycine-site (NMDAR-GS).

DCS is not a full agonist at the NMDAR-GS; however, it is a partial agonist. The authors are correct that in lower doses (< 100 mg), DCS primarily potentiates NMDAR-GS function and has been shown to be partially effective in treatment of schizophrenia[2] and anxiety disorders.[3] Similar to other partial agonists at this receptor, DCS has a dose-dependent, biphasic effect, acting as an agonist at low doses but functioning as a net NMDAR antagonist[4,5] at higher doses (> 500 mg).[6–8]

Clinical data strongly support the concept that an antagonist-level dose is required for antidepressant action, as efficacy is consistently shown at ~1,000 mg,[1,9,10] but not at lower doses (250 mg).[11] Moreover, rapastinel, which the authors reference in support of the NMDAR-GS agonist theory, is also a partial agonist with a similar biphasic agonist/antagonist effect. Similar to the majority of clinical studies with DCS, antidepressant efficacy is shown only at antagonist doses.[12,13]

In support of Kim et al, D-serine, a full agonist[14] at the NMDAR-GS, may have antidepressant properties when used acutely.[15] We also note that the author's strategy of intermittent dosing may produce different pharmacodynamics than daily dosing.[16] We agree with the authors that further study of dosing strategies is needed.

References

1. Kantrowitz JT, Halberstam B, Gangwisch J. Single-dose ketamine followed by daily D-cycloserine in treatment-resistant bipolar depression. *J Clin Psychiatry*. 2015;76(6):737–738.
2. Goff DC, Cather C, Gottlieb JD, et al. Once-weekly D-cycloserine effects on negative symptoms and cognition in schizophrenia: an exploratory study. *Schizophr Res*. 2008;106(2–3):320–327.
3. Norberg MM, Krystal JH, Tolin DF. A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. *Biol Psychiatry*. 2008;63(12):1118–1126.
4. van Berckel BN, Lipsch C, Timp S, et al. Behavioral and neuroendocrine effects of the partial NMDA agonist D-cycloserine in healthy subjects. *Neuropsychopharmacology*. 1997;16(5):317–324.
5. van Berckel BN, Lipsch C, Gispen-de Wied C, et al. The partial NMDA agonist D-cycloserine stimulates LH secretion in healthy volunteers. *Psychopharmacology (Berl)*. 1998;138(2):190–197.
6. Emmett MR, Mick SJ, Cler JA, et al. Actions of D-cycloserine at the *N*-methyl-D-aspartate-associated glycine receptor site in vivo. *Neuropharmacology*. 1991;30(11):1167–1171.
7. Hood WF, Compton RP, Monahan JB. D-cycloserine: a ligand for the N-methyl-D-aspartate coupled glycine receptor has partial agonist characteristics. *Neurosci Lett*. 1989;98(1):91–95.
8. Watson GB, Bolanowski MA, Baganoff MP, et al. D-cycloserine acts as a partial agonist at the glycine modulatory site of the NMDA receptor expressed in Xenopus oocytes. *Brain Res*. 1990;510(1):158–160.
9. Crane GE. Cyloserine as an antidepressant agent. *Am J Psychiatry*. 1959;115(11):1025–1026.
10. Heresco-Levy U, Gelfin G, Bloch B, et al. A randomized add-on trial of high-dose D-cycloserine for treatment-resistant depression. *Int J Neuropsychopharmacol*. 2013;16(3):501–506.
11. Heresco-Levy U, Javitt DC, Gelfin Y, et al. Controlled trial of D-cycloserine adjuvant therapy for treatment-resistant major depressive disorder. *J Affect Disord*. 2006;93(1–3):239–243.
12. Burgdorf J, Zhang XL, Nicholson KL, et al. GLYX-13, a NMDA receptor glycine-site functional partial agonist, induces antidepressant-like effects without ketamine-like side effects. *Neuropsychopharmacology*. 2013;38(5):729–742.
13. Preskorn S, Macaluso M, Mehra DO, et al; GLYX-13 Clinical Study Group. Randomized proof of concept trial of GLYX-13, an N-methyl-D-aspartate receptor glycine site partial agonist, in major depressive disorder nonresponsive to a previous antidepressant agent. *J Psychiatr Pract*. 2015;21(2):140–149.
14. Kantrowitz J, Javitt DC. Glutamatergic transmission in schizophrenia: from basic research to clinical practice. *Curr Opin Psychiatry*. 2012;25(2):96–102.
15. Malkesman O, Austin DR, Tragon T, et al. Acute D-serine treatment produces antidepressant-like effects in rodents. *Int J Neuropsychopharmacol*. 2012;15(8):1135–1148.
16. Javitt DC. Harnessing N-methyl-D-aspartate receptors for new treatment development in psychiatry: positive lessons from negative studies. *Am J Psychiatry*. 2013;170(7):699–702.

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