Single-Dose Ketamine Followed by Daily d-Cycloserine in Treatment-Resistant Bipolar Depression

To the Editor: Bipolar depression is a leading cause of disability in the United States. Recently, N-methyl-d-aspartate receptor (NMDAR) antagonists, such as ketamine, have been shown to induce remission in bipolar depression. Nevertheless, ketamine use is limited by transient effects and psychogenic potential during repeated administration. d-Cycloserine is a US Food and Drug Administration (FDA)-approved antituberculosis drug that acts as an NMDAR antagonist when used at high doses (>750 mg). d-Cycloserine targets the glycine co-receptor of the NMDAR and may have improved safety relative to ketamine (analogous to use of benzodiazepines vs barbiturates at γ-aminobutyric acid-A receptors). Antidepressant effects of d-cycloserine were first noted in the 1950s. However, double-blind, placebo-controlled studies at high doses were not conducted until recently. A large, between-group, large effect-size (d = 0.91, P = .005) difference was seen in unipolar depression, corresponding to a mean 48% reduction in symptoms. We report the first study of acute ketamine followed by daily d-cycloserine in bipolar depression (ClinicalTrials.gov identifier NCT01833897).

Method. Enrollment criteria included current bipolar disorder I or II (DSM-IV-TR), a Montgomery-Asberg Depression Rating Scale (MADRS) score > 20, and no current or chronic psychosis or substance dependence. Twelve subjects consented (Supplementary Figure 1), and 8 received ketamine and d-cycloserine (mean age = 37 ± 16 years, 5 women). Subjects were treatment-resistant to a clinically determined regimen for a mean 3.3 ± 4 months prior to enrollment. Patients remained on previously prescribed mood stabilizers or benzodiazepines, but antidepressants and antipsychotics not FDA-approved for bipolar depression were withdrawn.

After consent, subjects were prospectively treated with medications FDA-approved for bipolar depression (olanzapine/fluoxetine [n = 2], lurasidone [n = 4], or quetiapine [n = 2]), with treatment resistance further demonstrated by a nonsignificant, mean 0.2 ± 1 point change from screening MADRS of 29.0 ± 6 over a mean 4.2 ± 1 weeks. Subjects then received open-label ketamine hydrochloride (0.5 mg/kg administered intravenously over 60 minutes) followed by 8 weeks of d-cycloserine (titrated to 1,000 mg/d from a starting dose of 250 mg over 3 weeks) and pyridoxine, adjunctive to continued FDA-approved treatment and mood stabilizers. This slower rate of ketamine infusion was anticipated to increase tolerability. To minimize baseline MADRS inflation bias, primary outcomes were the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory. Statistical analysis was performed by linear, mixed-effects model regression, with follow-up paired t tests as required.

Results. Seven subjects completed the study, and 4 met remission criteria at 8 weeks (HDRS score < 7). On mixed-model analysis, a significant overall response over time was seen (F_{1,6,4} = 161.8, P < .001). Follow-up paired t test analysis suggested significant improvement from baseline at all rating points except at 2 weeks, with a large effect size seen at day 1 (Cohen d = 2.0 SD) and 8 weeks (Cohen d = 1.1 SD, Figure 1A and 1B). One subject was withdrawn after 1 week of d-cycloserine treatment for relapse after 1 day of ketamine treatment.

Acute response was predictive of response at 8 weeks (r = 0.82, Figure 1C). Study treatments were well tolerated, with mild sedation reported by 3 subjects, headaches by 2, and phosphenes by 1. One subject required a d-cycloserine dose reduction to 500 mg at 6 weeks for mild sedation, and 1 subject had hypompanic symptoms 2 weeks after stopping FDA-approved treatment for lack of efficacy. All other subjects remained on stable concomitant medications during the study. Five subjects requested to continue d-cycloserine after the study, with 3 successfully obtaining insurance coverage, further suggesting tolerability by the patients taking d-cycloserine.

Discussion. These findings provide proof-of-concept for further study of combined treatment with NMDAR antagonists and FDA-approved medications for bipolar depression. Although d-cycloserine is generally well tolerated by psychiatric populations,
majors risks include psychosis11 and seizures, a risk we minimized by concomitant treatment with antipsychotics and pyridoxine.

Recent publications12–14 of large cohorts of clinically treated patients with multidrug-resistant tuberculosis have been reassuring about the safety of d-cycloserine. Approximately 1,100 patients are included in these case series of patients treated with 500–1,000 mg of d-cycloserine daily for 6 to 24 months. Analysis of these cases is complicated by their uncontrolled nature and the fact that most patients were receiving multiple medications (about 5) and were often severely ill. Despite this, almost 95% of subjects completed treatment without incident across cohorts. Reported adverse effects of d-cycloserine included dizziness/vertigo (14.3%), headache (11.7%), sleep disturbances (11.5%), peripheral neuropathy (7.9%), depression (6.2%), tinnitus (5.1%), visual disturbances (4.4%), seizures (4%), and psychosis (3.4%).13 Only 2.1% of subjects stopped treatment because of adverse events.13 A recent meta-analysis14 was also reassuring on the relative safety of d-cycloserine. The pooled estimate for the frequencies of psychiatric adverse drug reactions was 5.7% (95% CI, 3.7–7.6) and 1.1% (95% CI, 0.2–2.1) for central nervous system–related adverse reactions. Overdose can result in coma; alcohol consumption may increase the risk of seizures.16 Limitations include the small sample and a non–placebo-controlled, open-label design. Consistent with prior ketamine-only studies,2 partial relapse was seen at 2 weeks. Further mood improvement after 2 weeks, however, is consistent with time-course of improvement seen in previous d-cycloserine–only studies.7 Since all subjects received both NMDAR antagonists, and had already shown highly significant improvement with ketamine, an assessment of d-cycloserine’s independent efficacy and safety in bipolar depression will require future study.

References

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List of Supplementary Material for the article

1. eFigure 1 Consort 2010 Flow Diagram

Disclaimer
This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.
Enrollment

Assessed for eligibility (n=12)

Excluded (n=4)
- Not meeting inclusion criteria (n=2)
- Declined to participate (n=2)

Received ketamine (n=8)

Received D-cycloserine (n=8)

Follow-Up

Completed D-cycloserine treatment (n=7)
Discontinued intervention (lack of efficacy) (n=1)

Analysis

- Included in mixed model analysis (n=8)