equately powered, randomized, controlled trials are necessary to fully evaluate the efficacy of extended-release methylphenidate in TRD.

► These authors studied 60 treatment-resistant patients in a 4-week comparison of augmentation with placebo versus extended-release methylphenidate. They were unable to demonstrate a statistically significant difference between the groups although there were numeric trends favoring methylphenidate. Perhaps a more adequately powered trial could clearly demonstrate benefit for the extended-release formulation of methylphenidate (Concerta) in treatment-resistant depression. That certainly would be my prediction. As I mentioned in the discussion of the Birkenhäger et al[1] article, I frequently end up using atypical antipsychotics in this group. However, probably my first choice in those patients is to use the extended-release methylphenidate. There are data suggesting that beginning treatment of depressed patients concurrently with stimulants and an antidepressant can lead to a faster and better response. There are also data that document response with the use of the stimulants as an augmentation strategy. I am currently using Concerta in both of these situations with good results, at least in my clinical experience.

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Reference

1. Birkenhäger TK, van den Broek WW, Moleman P, Bruijn JA. Outcome of a 4-step treatment algorithm for depressed inpatients. *J Clin Psychiatry*. 2006;67:1266-1271.

A Randomized Trial of an *N*-methyl-D-aspartate Antagonist in Treatment-Resistant Major Depression

Zarate CA, Singh JB, Carlson PJ, et al (NIH, Bethesda, Md)

Arch Gen Psychiatry 63:856-864, 2006

Context.—Existing therapies for major depression have a lag of onset of action of several weeks, resulting in considerable morbidity. Exploring pharmacological strategies that have rapid onset of antidepressant effects within a few days and that are sustained would have an enormous impact on patient care. Converging lines of evidence suggest the role of the glutamatergic system in the pathophysiology and treatment of mood disorders.

Objective.—To determine whether a rapid antidepressant effect can be achieved with an antagonist at the *N*-methyl-D-aspartate receptor in subjects with major depression.

Design.—A randomized, placebo-controlled, double-blind crossover study from November 2004 to September 2005.

Setting.—Mood Disorders Research Unit at the National Institute of Mental Health.

Patients.—Eighteen subjects with *DSM-IV* major depression (treatment resistant).

Interventions.—After a 2-week drug-free period, subjects were given an intravenous infusion of either ketamine hydrochloride (0.5 mg/kg) or placebo on 2 test days, a week apart. Subjects were rated at baseline and at 40, 80, 110, and 230 minutes and 1, 2, 3, and 7 days postinfusion.

Main Outcome Measure.—Changes in scores on the primary efficacy measure, the 21-item Hamilton Depression Rating Scale.

Results.—Subjects receiving ketamine showed significant improvement in depression compared with subjects receiving placebo within 110 minutes after injection, which remained significant throughout the following week. The effect size for the drug difference was very large (d = 1.46 [95% confidence interval, 0.91-2.01]) after 24 hours and moderate to large (d = 0.68 [95% confidence interval, 0.13-1.23]) after 1 week. Of the 17 subjects treated with ketamine, 71% met response and 29% met remission criteria the day following ketamine infusion. Thirty-five percent of subjects maintained response for at least 1 week.

Conclusions.—Robust and rapid antidepressant effects resulted from a single intravenous dose of an *N*-methyl-D-aspartate antagonist; onset occurred within 2 hours postinfusion and continued to remain significant for 1 week.

► This group at the NIMH tested the hypothesis that antagonizing the *N*-methyl-D-aspartate receptor would have an antidepressant effect. Subjects were given an IV infusion of ketamine or placebo. The ketamine response was significantly greater in terms of reducing depression at 110 minutes after injection. These improvements lasted throughout the following week. In fact, the effect size was surprisingly large, with 71% meeting response criteria and 29% remission criteria the day after ketamine infusion. Thirty-five percent maintained this response for at least a week. As I mentioned for the muscarinic receptors strategy, this too is a potential strategy for inpatients (ie, giving IV medications with the hope of a rapid antidepressant response). In some ways, this could well be a paradigm shift in our field to bring rapidly effective somatic treatments in the inpatient treatment of depression.

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Controlled trial of D-cycloserine adjuvant therapy for treatment-resistant major depressive disorder

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J Affect Disord 93:239-243, 2006

Background.—Compounds that reduce *N*-methyl-D-aspartate receptor (NMDAR) function, including NMDAR antagonists and partial agonists at the NMDAR-associated glycine (GLY) site, may act as antidepressants. The antibiotic drug D-cycloserine (DCS) acts as a partial agonist at the NMDAR-GLY site. Preclinical and clinical data suggest that at dosages ≥100 mg/day