

Study identifies effective ketamine doses for treatment-resistant depression

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A study led by Massachusetts General Hospital (MGH) investigators identifies two subanesthetic dosage levels of the anesthetic drug ketamine that appear to provide significant symptom relief to patients with treatment-resistant depression. In the October 2018 issue of

Molecular Psychiatry they describe finding that single intravenous doses of 0.5 mg/kg and 1.0 mg/kg were more effective than an active placebo in reducing depression symptoms over a three-day period. Two lower dosage levels that were tested did not provide significant symptom relief, although some improvement was noted with the lowest 0.1 mg/kg dose.

"Treatment resistance in depression is a major issue, with more than half of patients not responding adequately to standard, appropriate antidepressant treatment," says Maurizio Fava, MD, executive director of the Clinical Trials Network & Institute in the MGH Department of Psychiatry and senior author of the *Molecular Psychiatry* paper. "There are only a few approved therapies that can help some patients with treatment-resistant depression, so we critically need more options to choose from."

Long used as a general anesthetic drug, [ketamine](#) has been found in several studies to rapidly relieve [depression symptoms](#) when given at low, subanesthetic doses. Most of those studies used a standard 0.5 mg/kg intravenous dose, leaving determination of the optimal dosage unclear. To investigate that question, the study tested four different ketamine dosages—0.1 mg/kg, 0.2 mg/kg, 0.5 mg/kg and 1.0 mg/kg—compared with an "active" placebo, a drug that induces side effects, the lack of which could lead participants to realize they are not receiving the medication being tested, potentially biasing their perception of symptom improvement.

The study enrolled 99 adults with treatment-resistant depression at six research centers—MGH, Baylor College of Medicine/DeBakey VA Medical Center, Icahn School of Medicine at Mt. Sinai, Stanford University School of Medicine, University of Texas/Southwestern Medical Center, and Yale University. Participants were randomized into five groups—the four dosage levels and the active control group, with neither they nor the research staff aware of group assignments—and

continued taking their previously prescribed antidepressants during the study period.

Participants were assessed with a standard depression rating scale the day they received the infusion and 2, 3, 5, 7, 14 and 30 days later. Additional instruments measured aspects of mood and suicidal thought. Dissociative symptoms such as memory loss and feelings of detachment from reality were assessed during and after ketamine infusion, and vital signs were measured after treatment and at all follow-up visits.

On the standard depression scale, participants receiving ketamine had significantly greater symptom improvement during the three days after infusion than did those in the active control group. Comparison of dosage levels, after adjusting for multiple comparisons, found statistically significant improvement compared to the control group only for participants receiving 0.5 mg/kg and 1.0 mg/kg doses. The low 0.1 mg/kg dose produced significant relief only prior to adjustment, and the 0.2 mg/kg dose did not show any significant benefits. It is possible that the lack of efficacy at the 0.2 mg/kg level could reflect the small size of treatment groups and the fact that participants in that group tended to be more treatment resistant to begin with, the authors note.

For most participants in the higher-dose groups, the benefits of ketamine treatment began to decrease on the third day after treatment and were no longer detectable after five days. There were no significant differences in the occurrence of adverse events among all study participants.

Co-author Cristina Cusin, MD, who directs the MGH Psychiatry ketamine clinic, says "These results support the clinical observation that one size—in this case the most studied dose of 0.5 mg/kg—does not fit all, as some patients may require a lower-than-average dose; and each patient needs a tailored treatment plan that may include ketamine, together with other medications and talk therapy. We still do not

understand which factors play a role in determining lack of response to treatments or which is the best possible strategy for patients suffering from severe depression."

Fava, the Slater Family Professor of Psychiatry at Harvard Medical School, adds, "Along with supporting the efficacy of intravenous ketamine for patients with treatment-resistant [depression](#), our study also suggests that even lower doses may be effective in some patients. Further investigation should examine the efficacy of repeat doses of ketamine, as well as whether higher doses may require less frequent administration."

More information: Maurizio Fava et al, Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD), *Molecular Psychiatry* (2018). [DOI: 10.1038/s41380-018-0256-5](https://doi.org/10.1038/s41380-018-0256-5)

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