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Repeated Ketamine May Sustain Antidepressant Effect

Megan Brooks

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Repeated administration of ketamine may help sustain the antidepressant effect in patients with treatment-resistant depression beyond the initial dose, a new study shows.

Ketamine, an injectable anesthetic, has demonstrated a rapid antidepressant effect. But the effect is relatively short-lived, and how to sustain ketamine's efficacy for a longer period through an optimal long-term dosing regimen has yet to be determined.

The new study showed that a ketamine dosage of 0.5 mg/kg twice or three times weekly maintained antidepressant efficacy for more than 15 days.

"As less frequent treatment administration is usually preferred in order to reduce the patient and clinic burden and costs, this result, taken together with other data acquired during the double-blind and open-label phases, suggests that the twice-weekly treatment regimen administered for 4 to 6 weeks can induce and maintain (through day 15) a robust antidepressant effect in the treatment-resistant depression population," the authors, led by Jaskaran B. Singh, MD, of Janssen Research and Development, Titusville, New Jersey, write.

The study was published online April 8 in the *American Journal of Psychiatry*.

Randomized Trial

The multicenter, randomized, double-blind study included 68 patients with treatment-resistant depression. Participants received either intravenous ketamine (0.5 mg/kg of body weight) or intravenous placebo, administered over 40 minutes, either two or three times weekly for up to 4 weeks. Patients whose double-blind treatment was discontinued after at least 2 weeks owing to lack of efficacy had the option of participating in a 2-week open-label phase to receive ketamine at the same frequency as in the double-blind phase.

The primary outcome measure was change from baseline to day 15 in total score on the Montgomery-Åsberg Depression Rating Scale (MADRS).

Response rates were 68.8% for twice-weekly dosing and 53.8% for thrice-weekly dosing at day 15, the researchers report.

The mean change in MADRS score from baseline to day 15 was significantly improved in both ketamine frequency groups compared with the respective placebo groups (twice-weekly ketamine: -18.4 vs -5.7 placebo; $P < .001$; thrice-weekly ketamine: -17.7 vs -3.1 placebo; $P < .001$).

Similar observations were noted for ketamine during the open-label phase (twice-weekly, -12.2 on day 4; thrice-weekly, -14.0 on day 5). Overall, the mean difference in MADRS scores did not differ between the two dose frequencies tested.

Both regimens were generally well tolerated, the researchers report. During the double-blind phase, rates of treatment-emergent adverse events were higher in both ketamine groups compared with the respective placebo groups (twice-weekly ketamine, 83.3% vs 56.3% with placebo; thrice-weekly ketamine, 76.5% vs 50.0% with placebo). No deaths were reported.

Serious treatment-emergent adverse events occurred in two patients in the twice-weekly ketamine group. One patient experienced anxiety related to a life event, which lead to hospitalization on day 12; the other attempted suicide on day 40 (more than 4 weeks after receiving the last dose). Neither of these adverse events was thought to be related to ketamine.

Headache, anxiety, dissociation, nausea, and dizziness were the most common (≥20%) treatment-emergent adverse events. Dissociative symptoms occurred "transiently and attenuated" with repeated dosing, the researchers report.

Limitations of the study include the relatively short duration and assessment of the induction and maintenance of response for only 4 to 6 weeks.

"Treatment-resistant depression is a chronic condition, and studies with a longer duration are warranted to fully characterize whether the clinical benefits of ketamine can be maintained, and if so, whether they can be sustained despite reductions in the dosing frequency during chronic treatment," the investigators conclude.

A Step Forward

Michael Thase, MD, of the University of Pennsylvania, in Philadelphia, who was not involved in the study, agrees that more research is needed. This study is a "nice, small step forward — reassuring to a point. Now we need evidence about what to do next," he told *Medscape Medical News*.

Paulo Shiroma, MD, of the Department of Psychiatry, University of Minnesota Medical School, in Minneapolis, recently published a study in which repeated ketamine infusions achieved superior antidepressant outcomes as compared with a single infusion.

"The strategy to increase response to ketamine in TRD [treatment-resistant depression] is not new, however, understudied," Dr Shiroma, who was not involved in the new study, told *Medscape Medical News*.

"Given that each infusion is labor intensive and not exempt from side effects, it makes sense to find the optimal risk/benefit frequency. However, as the authors [of the current study] mentioned, the study is not designed to make a face-to-face comparison between both schedules. Therefore, a nonsuperiority study between both schedules will be needed," Dr Shiroma said.

"The other issue is the use of saline as placebo. The side effects of ketamine, especially dissociation, during infusion are so obvious to the patients (and raters too) that blinding practically does not exist," he added.

"Overall, I think the study corroborates short-term efficacy and relative safety of repeated ketamine IV in TRD. How to safely sustain achieved response by repeating infusions is still missing," Dr Shiroma said.

Greg Panico, spokesman for Janssen Research and Development, LLC, which funded the study, told *Medscape Medical News* that the company has a multipronged research program regarding ketamine. The company is studying "intranasal esketamine as a therapy for treatment-resistant depression and also as a medication for patients at imminent risk for suicide. Our program in treatment-resistant depression is currently in phase 3 clinical studies, and we have completed a phase 2 proof-of-concept study in patients at imminent risk for suicide, which will be presented at the Society for Biological Psychiatry meeting in Atlanta in May."

Several authors have disclosed financial relationships with Janssen Research and Development and other pharmaceutical companies. All are listed with the original article.

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