Serial Ketamine Infusions More Effective for Depression?

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Serial infusions of the N-methyl-D-aspartate (NMDA) antagonist ketamine at a lower dosage than commonly used may be more effective than a single infusion in reducing symptoms of depression, new research suggests.

A small study of 10 patients with major depressive disorder (MDD) showed that half achieved remission after receiving up to 4 intravenous (IV) infusions of ketamine 0.5 mg/kg twice weekly. Of those who experienced remission, 2 had sustained improvement 4 weeks later.

In addition, overall scores on 2 different suicidal ideation measures were significantly decreased post infusion. And there were no significant increases in adverse events reported between baseline and post treatment.

"It's surprising both that [this treatment] works and how rapidly it has effects," said coinvestigator Timothy Lineberry, MD, from the Department of Psychiatry and Psychology at Mayo Clinic in Rochester, Minnesota, in a release.

"It sometimes can work in hours to reduce depressive symptoms and suicidal ideation. Our goal is to begin to determine how the drug can be administered safely in routine treatment," said Dr. Lineberry.

The investigators add that future ketamine-for-depression research should also focus on determining the optimal frequency of infusions, test relapse prevention strategies, and optimal dosing parameters.

The study was published in the May issue of the Journal of Psychopharmacology.

Single vs Multiple Infusions

The researchers note that although previous research has shown improvement in depressive symptoms with a single infusion of ketamine, side effects during treatment are common.

In addition, "it is not known whether serial infusions or lower infusion rates result in greater efficacy."

Last year, as reported by Medscape Medical News, results from a small study were presented at the New Clinical Drug Evaluation Unit Annual Meeting showing that patients with treatment-resistant depression had significant symptom improvement after receiving 6 low-dose infusions of ketamine.

For the current study, 10 adult patients (mean age, 47.2 years) who had experienced a severe depressive episode as part of their MDD or bipolar II disorder were enrolled. All had failed to respond to at least 2 previous antidepressants.

They received twice-a-week infusions of ketamine 0.5 mg/kg over 100 minutes until remission was achieved or until 4 infusions had been administered.

Depressive symptoms were measured the morning of each scheduled treatment session, 2 hours post infusion, and the following morning using the Montgomery-Åsberg Depression Rating Scale (MADRS). Remission was defined as a score of 9 or less on the MADRS.

The Young Mania Rating Scale (YMRS), the Brief Psychiatric Rating Scale (BPRS), the Scale for Suicide Ideations (SSI), and the Suicide Status Form (SSF) were also administered to monitor for possible treatment-related adverse events.

All participants were asked about altered sensory experiences during the infusions and were kept in a recovery room 30 minutes post infusion. Although they were hospitalized for the first infusion, all were treated as outpatients for subsequent infusions.

Weekly follow-up was conducted in person or by phone up to 4 weeks after infusion completion.
More Is More?

Results showed significant improvement in total mean MADRS scores from baseline to endpoint (33.3 vs 16.7, respectively; P = .0009), and 8 patients were classified as responders with at least 50% improvement in symptom scores.

Interestingly, 3 of these participants "responded after only one infusion, while the other five responders needed two infusions," report the investigators.

Five of the participants achieved remission, as measured on the MADRS, with only 1 of these receiving a single infusion.

"Thus, a preliminary conclusion is that limiting ketamine trials to only one infusion may result in remission rates less than what might be achieved with serial infusions," write the researchers.

Two of the patients who achieved remission remained depression-free 4 weeks after treatment.

The total mean score on the SSI for all 10 patients also improved significantly from baseline to endpoint (P = .007), as did the mean SSF score (P = .026).

Scores on the YMRS and BPRS did not change significantly. When asked about specific side effects, one patient reported having brief and limited hallucinations during treatment, and some reported experiencing drowsiness or dizziness. None experienced a significant increase in blood pressure or a heart arrhythmia during infusion.

The investigators note that future studies will need to determine which patients will respond best to this type of treatment and "to test relapse prevention strategies."

"While patients and clinicians are excited about ketamine's potential, we know that more and more research lies ahead before we know which depressive conditions can be addressed with ketamine safely...in routine clinical practice," said Dr. Lineberry.

The study was funded by Mayo Clinic. The study authors have reported no relevant financial relationships.


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Ketamine Metabolite Has Promise in Depression

Megan Brooks
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Hydroxynorketamine (HNK), a by-product of the psychoactive drug ketamine, may treat symptoms of depression just well as ketamine without the unwanted side effects, new research suggests.

HNK also has therapeutic potential for treating neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD), the researchers say.

Several studies have shown that ketamine has rapid antidepressant effects in people with treatment-refractory major depression. It has also shown promise in posttraumatic stress disorder.

But the clinical use of ketamine is "limited because the drug is administered intravenously and may produce adverse effects, such as hallucinations and sedation to the point of anesthesia," Irving Wainer, PhD, senior investigator with the Intramural Research Program at the National Institute on Aging, in Baltimore, Maryland, notes in a statement.

"We found that the HNK compound significantly contributes to the antidepressive effects of ketamine in animals but doesn't produce the sedation or anesthesia, which makes HNK an attractive alternative as an antidepressant in humans," he said.

The study is published in the July issue of Anesthesiology. Dr. Wainer is listed as a co-inventor on a patent application for the use of ketamine metabolites in the treatment of bipolar disorder and major depression.

"Attractive" Ketamine Alternative

There are a number of key differences between ketamine and HNK, the researchers note.

Dr. Irving Wainer

"HNK targets a specific subtype of the nicotinic acetylcholine receptors, the alpha-7 nicotinic receptor, that are located at the nerve junctions, while ketamine targets the N-methyl-D- aspartate (NMDA) receptor, which is located throughout the body," Dr. Wainer explained. "The effect of ketamine on the NMDA receptor is the source of the drug's anesthetic activity as well as its unwanted side effects."

He and his colleagues used a rat model to see whether HNK could produce the same beneficial effects attributed to ketamine without ketamine's unwanted side effects. They gave rats intravenous doses of ketamine, HNK, and another ketamine by-product called norketamine.

HNK, like ketamine, not only produced potent and rapid antidepressant effects but also stimulated neuroregenerative pathways and initiated the regrowth of neurons in rats' brains, the researchers report.

HNK also reduced production of the endogenous compound D-serine, overproduction of which is associated with neurodegenerative disorders such as AD and PD.
"The body makes D-serine from L-serine, and HNK stops this process," Dr. Wainer explained. "D-serine is a key coagonist and a necessary trigger for the NMDA receptors located at the nerve junctions. By reducing D-serine, you reduce the activity of the NMDA receptor and the neuroinflammation associated with a number of CNS [central nervous system] diseases."

Increased D-serine blood and brain levels have been detected in patients with AD and PD, he added, "and we think that HNK is a novel and potentially effective way of reducing D-serine in these patients."

He noted that inhibition of NMDA receptor activity is "an accepted therapeutic approach to the treatment of AD, as demonstrated by the use of memantine [Namenda, Forest Laboratories, Inc]. We feel that HNK, which can be given as a pill, will be at least as effective as memantine, with less side effects. The next step in the process is to test this hypothesis in animal models of these diseases," he said.

Growing Understanding

"This study contributes to a growing understanding of the antidepressant mechanisms of action of ketamine at the cellular level," James W. Murrough, MD, assistant professor, Departments of Psychiatry and Neuroscience, and associate director, Mood and Anxiety Disorders Program, Icahn School of Medicine at Mount Sinai in New York City, who was not involved in the study, told Medscape Medical News.

"The authors replicated a previous finding that ketamine administered to animals increased the activity of the mTOR pathway, thereby promoting protein synthesis," he explained. "Prior research has shown that this stimulation of the TOR pathway is important for synaptogenesis — essentially, the creation or strengthening of synapses in the brain.

"This synaptogenesis effect of ketamine is opposed to the effects of stress and is believed to underlie ketamine's antidepressant action, at least in part. The authors extended this work in the current article by showing that certain metabolites of ketamine, in addition to ketamine itself, had stimulatory effects on mTOR," Dr. Murrough said.

Dr. Wainer and several of the study's authors are listed as coinventors on a patent application for the use of ketamine metabolites in the treatment of bipolar disorder and major depression. Dr. Murrough has disclosed no relevant financial relationships.

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