Ketamine eases severe depression, but questions of dosage, duration remain

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Credit: Michael S. Helfenbein

Recent studies have confirmed observations made by Yale clinicians decades ago—the anesthetic ketamine provides rapid and robust relief to those suffering from the most severe forms of depression. However, there is also limited research to advise doctors on best doses and length of ketamine treatment, which patients will most benefit from treatment,

and whether ketamine can provide long-lasting relief for depression without dangerous side effects, according to a report published March 1 in the Journal *JAMA Psychiatry*.

The lack of research has put doctors in a difficult position, note the researchers, as more patients are asking for treatment with ketamine, which has not been approved for use for treatment of depression and has been abused as street drug called "Special K."

"In a nutshell, I feel confident telling patients who have had little help from previous treatments that ketamine provides meaningful relief from some of their worst symptoms for at least a few days or even weeks," said Dr. Gerard Sanacora, professor of psychiatry and director of the Yale Depression Research Program and primary author of the *JAMA* report. "But I can't tell them with any degree of certainty how long the benefit can be sustained or how safe it is to repeatedly administer the medication over periods of months or years."

The original link between ketamine and relief of depression was made in New Haven by John Krystal, chair of the Department of Psychiatry at Yale, and Dennis Charney, now dean of Mt. Sinai School of Medicine, who helped launch small-scale clinical trials of ketamine while at the National Institute of Mental Health.

Pharmaceutical companies are unlikely ever to pay for costly long-term studies because ketamine has been approved for use as an anesthetic for over 45 years and carries no patent protection. However, the American Psychiatric Association Council of Research Task Force on Novel Biomarkers and Treatments asked Sanacora and other medical experts to provide a consensus statement on the benefits and the risks of ketamine treatment because "off label" prescriptions for the depression have grown dramatically in recent years.

Multiple small-scale studies have all shown similar results—that infusion of ketamine can provide rapid and robust, if transient, relief for treatment-resistant depression. But the new report emphasizes many potential downsides and risks that need to be considered when considering the treatment option.

For instance, the safest and best treatment regimens have not been established, nor is it clear which patients might benefit the most from treatment. There are occasionally cardiovascular and behavioral reactions to treatment, but the standardized monitoring protocols have yet to be developed. It is also unclear whether long-term use of the treatment might lead to increased risk of substance abuse for some patients. For these reasons, doctors who administer the drug should undergo proper training, the experts said.

"While the treatment does offer tremendous promise, patients considering ketamine treatment for their mood disorder should be well informed of both the potential benefits and the risks associated with the drug, and should be aware of the limits of the field's existing knowledge related to the longer-term effectiveness and safety," Sanacora said.

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