

Antidepressant response within hours? Experts weigh evidence on ketamine as fast-acting treatment for depression

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Recent studies suggest that ketamine, a widely used anesthetic agent, could offer a wholly new approach to treating severe depression—producing an antidepressant response in hours rather than weeks. Two reviews of recent evidence on ketamine and related drugs for treating depression appear in the *Harvard Review of Psychiatry*.

Ketamine and related drugs may represent a "paradigm shift" in the treatment of [major depressive disorder](#) (MDD) and bipolar depression—especially in patients who do not respond to other treatments, according to a review by Carlos A. Zarate, Jr, MD and colleagues at the National Institute of Mental Health. A second article explores evidence on the mechanisms behind [ketamine](#)'s rapid antidepressant effects.

Growing Evidence, Clinical Caution about Ketamine for Severe Depression

Current treatments for MDD and bipolar depression have major limitations. Many patients with severe depressive symptoms don't respond to available antidepressant drugs. Even for those who do respond, it may take several weeks before symptoms improve.

Ketamine, an anesthetic, is one of several glutamatergic drugs affecting neurotransmitters in the central nervous system. Over the past decade, several studies have reported "rapid, robust, and relatively sustained antidepressant response" to ketamine, injected intravenously at low, subanesthetic doses.

Dr. Zarate and colleagues review the research on ketamine and other glutamatergic drugs for depression. Ketamine, by far the best-studied of these medications, is notable for its very rapid antidepressant effects. In patients with treatment-

resistant MDD, ketamine has produced initial reductions in depressive symptoms within two hours, with peak effects at 24 hours.

Ketamine may also rapidly reduce suicidal thoughts. Combined with other medications, ketamine has also produced rapid antidepressant effects in patients with treatment-resistant bipolar depression.

Prompted by these studies, some doctors are already using ketamine in patients with severe or treatment-resistant depression. However, since it is FDA-approved only as an anesthetic, use of ketamine in depressive disorders is "off-label," unregulated, and not standardized. Many questions remain about its short- and long-term side effects and potential for abuse.

"Efforts are underway to bring ketamine to market, standardize its use, and determine its real-world effectiveness," Dr. Zarate and coauthors write. They also present evidence on several other glutamatergic drugs. One [drug](#), esketamine, has been given "breakthrough therapy" status by the FDA for [patients](#) at imminent risk of suicide.

Cristina Cusin, MD of Massachusetts General Hospital and colleagues review neuroimaging studies evaluating ketamine's effects in the brain. The studies show ketamine-induced changes in several brain areas involved in the development of depression. Ketamine may exert its antidepressant effects by "acutely disabl[ing] the emotional resources required to perpetuate the symptoms of depression," as well as by increasing emotional blunting and increasing activity in reward processing.

Independent of how ketamine works or its ultimate role in clinical treatment, antidepressant response

to glutamatergic drugs points to an exciting conclusion: "that rapid antidepressant effects are indeed achievable in humans," Dr. Zarate and coauthors write. "This paradigm shift lends additional urgency to the development of novel treatments for MDD and bipolar [depression](#), particularly for patient subgroups that do not respond to currently available therapies."

More information: Dawn F. Ionescu et al. Ketamine-Associated Brain Changes, *Harvard Review of Psychiatry* (2018). [DOI: 10.1097/HRP.000000000000179](#)

Ioline D. Henter et al. Glutamatergic Modulators in Depression, *Harvard Review of Psychiatry* (2018). [DOI: 10.1097/HRP.000000000000183](#)

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