

No adverse cognitive effects of ketamine or esketamine for treatment-resistant depression

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Used for the treatment of depression that does not respond to standard antidepressant medications, the anesthesia drug ketamine—and the

related drug esketamine, recently approved for depression treatment—has no important adverse effects on memory, attention, or other cognitive processes, concludes a systematic review of medical research in the September/October issue of *Harvard Review of Psychiatry*.

"Current evidence suggests that [ketamine](#) and [esketamine](#) do not appear to exert significant deleterious neurocognitive effects in [treatment-resistant depression](#)," according to the new research, led by Breno Souza-Marques, BA, and Lucas C. Quarantini, MD, Ph.D., of Federal University of Bahia, Salvador, Brazil. In fact, some cognitive functions improved 7 to 13 days after repeated ketamine infusions.

Evidence supports cognitive safety of ketamine and esketamine for depression treatment

Ketamine is a widely used surgical anesthetic that produces a detached, dreamlike state. Multiple studies have shown that at low doses, ketamine can have rapid antidepressant effects—typically improving mood within 24 hours to 7 days. Similar benefits have been reported with esketamine, a version of the drug recently approved for use in patients with treatment-resistant [depression](#). Although ketamine is not yet approved for treatment of depression, some physicians prescribe it for that purpose on an "off-label" basis.

However, there are potential safety concerns with ketamine, which is "a highly sought-after recreational drug," according to the authors. Studies have reported [memory impairment](#) after long-term recreational use of ketamine, as well as in [medical studies](#) in which healthy volunteers received just one infusion. That's particularly worrisome because memory problems and other cognitive symptoms—such as difficulties with thinking and concentrating—are a key aspect of major depressive disorder. Cognitive symptoms may continue even after mood improves.

To investigate the cognitive safety of ketamine and esketamine, Mr. Souza-Marques, Dr. Quarantini, and colleagues searched the medical literature for studies in which one of these drugs was given to patients who had treatment-resistant depression. Definitions vary, but most experts consider depression "treatment-resistant" if it persists after the patient has tried at least two different antidepressants.

The team identified 14 studies that collectively involved 1,019 patients: One study of esketamine nasal spray for 44 weeks, seven studies of a single ketamine intravenous infusion, and six studies in which patients received six ketamine infusions over two or three weeks.

Neuropsychological performance assessment was variable for the ketamine studies (1 study at 40 minutes, 1 study at 24 hours, 1 study at 3 days, and 1 study at 7 days), while the esketamine study performed repeated assessments at 28 days, 20 weeks, 32 weeks, and 44 weeks.

The esketamine study showed no changes in cognitive performance. Five studies of ketamine actually reported improvements in memory, processing speed (the time it takes to complete a mental task), or cognitive flexibility (the ability to switch between mental tasks or thoughts).

Only one of the 14 studies reported cognitive impairment after ketamine treatment. Memory was worse 24 hours after six ketamine infusions, and processing speed was worse 24 hours after a single infusion, but these deficits were no longer present seven days after treatment. Moreover, the group that received multiple infusions showed improved processing speed, cognitive flexibility, and memory. Despite this encouraging evidence, further studies are needed to assess the longer-term neurocognitive effects of these drugs.

Some studies showed that individuals who had certain cognitive attributes before treatment—poorer attention, slower processing speed,

or better memory—were more likely to respond to ketamine. The researchers conclude, "Results suggest possible neuropsychological profiles predictive of antidepressant response to ketamine, such as lower attention, slower processing speed, or higher working [memory](#), that should be further assessed in future studies, as these results could provide time-saving evidence to clinicians and mental health practitioners."

More information: Breno Souza-Marques et al, Neurocognitive Effects of Ketamine and Esketamine for Treatment-Resistant Major Depressive Disorder, *Harvard Review of Psychiatry* (2021). [DOI: 10.1097/HRP.0000000000000312](#)

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