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### **Ketamine Benefits 1 in 5 People with Treatment-Resistant Depression, Study Finds**

Shawn Radcliffe | July 13, 2023



- Ketamine is a federally approved anesthetic that can have psychedelic effects.
- Researchers report the substance was successful in a recent study in helping reduce symptoms in one in five people with treatment-resistant depression.
- Experts say the findings are promising, but they still recommend psychotherapy along with medication for treatment-resistant depression.

One in five people with treatment-resistant depression saw a dramatic improvement in their symptoms after a month of biweekly injections of a generic version of the substance ketamine.

That's according to a new study published in *The British Journal of Psychiatry*.

"We found that in this trial, ketamine was clearly better than the placebo — with 20 percent reporting they no longer had clinical depression compared with only 2 percent in the placebo group," Colleen Loo, a study author and a clinical psychiatrist at the University of New South Wales in Australia, said in a news release.



“This is a huge and very obvious difference and brings definitive evidence to the field which, in the past, only had smaller trials that compared ketamine with placebo,” she added.

However, researchers reported that once treatment was stopped, the benefits were not sustained for everyone, so ongoing treatment may be needed.

### **Limited options for treatment-resistant depression**

Ketamine is an anesthetic approved by the Food and Drug Administration that, at certain doses, has psychedelic effects.

However, it differs from psychedelics such as LSD and psilocybin in the way it acts on the brain.

In 2019, the Food and Drug Administration approved one form of this drug, known as S-ketamine (or esketamine), for treatment-resistant depression. This is given as a nasal spray.

When people talk about ketamine, they are generally referring to the generic form of ketamine used in the new study, which is also known as racemic ketamine.

In recent years, scientists and doctors have been exploring the use of ketamine and other psychedelics for treatment-resistant depression. This is a severe form of depression that hasn't responded to two or more types of antidepressant medications.

Some past research has found that about one-third of people with major depression don't see a complete improvement in their symptoms even after four stages of antidepressant treatment.

“Once people fall into that category of being treatment-resistant, their chances of recovery from depression with the tools that we currently have available — meaning psychotherapy, antidepressants and electroconvulsive therapy [ECT] — their chances of recovery long-term are extremely small,” Dr. Dave Rabin, a psychiatrist, neuroscientist and the founder of Apollo Neuroscience, told Healthline.

### **Ketamine as an alternative to electroconvulsive therapy**

Earlier randomized controlled trials have compared ketamine to an inactive placebo or a drug control for treatment-resistant depression. However, many of these studies had a small number of participants.

In addition, most of these studies used a saline solution as the placebo. This allowed participants to know whether or not they were receiving ketamine, which could potentially affect the results.

In the new study, researchers overcame this limitation by comparing ketamine to midazolam, a sedative that makes people feel relaxed or sleepy but doesn't improve symptoms of depression.

Researchers also enrolled people who had previously received ECT for their depression, a treatment that is sometimes recommended when antidepressant medications don't work.



“Most [ketamine] studies exclude people who have had ECT because it is very hard for a new treatment to work where ECT has not,” Loo said.

A recent study published in *The New England Journal of Medicine* reported that ketamine worked just as well as ECT for treatment-resistant depression.

“To have an alternative for people who are struggling with treatment-resistant depression that isn’t doing a hard electric reset to the brain [like ECT] is something that is really important for the community, and gives a lot of hope to people,” said Rabin.

Another difference with the new study is that ketamine was given subcutaneously (injected into the skin), rather than by intravenous (IV) infusion. This allowed researchers to test a method of delivery that is easier to do in the clinic.

“The nice thing about subcutaneous ketamine is it has a little bit more of a gradual onset of action and a gradual decline in action,” Dr. Steven Radowitz, the chief medical officer and co-founder of Nushama Psychedelic Wellness in New York City, told Healthline.

### **Details from the ketamine and depression study**

For the new study, researchers recruited 179 people with treatment-resistant depression from mood disorder clinics in Australia and New Zealand.

They randomly assigned people to receive either ketamine or the control drug, midazolam.

People received two injections a week in the clinic, where they were monitored for around two hours. The treatment lasted for a month. Participants assessed their mood at the end of the four weeks and one month later.

Serious adverse events among people taking ketamine in the trial were rare, with one major dissociative episode and one auditory hallucination.

Four participants taking ketamine dropped out of the study due to less serious side effects, including skin rash, increased anxiety, headache, and increased depression.

Expected short-term effects of ketamine treatment, such as increased blood pressure, went away within 2 hours after treatment, researchers reported.

### **Dose and setting can impact outcomes**

For one group of participants in the study, researchers started people out on a lower dose of ketamine and then increased it over time.

The researchers said they saw better results with this approach compared to keeping a steady dose throughout the trial.



Radowitz said in his clinic they also increase the dose for patients over time to “see how they’re responding and how comfortable they are with the experience.”

However, in general, they use a higher dose in his clinic than what was used in the study, which he said was “too low.”

He also pointed out that the study did not appear to take into account a person’s mindset and the setting — things such as music, lighting and the use of eyeshades, all of which are commonly used during psychedelic treatments in clinics.

“[Psychedelic] journeys are an unusual experience, so it’s important to feel safe when you’re doing these things,” Radowitz said. “Music is a vital part of psychedelic medicine. So is preparing people for the journey, and helping them integrate their experience afterward.”

While Radowitz said the new study had a “decent” outcome, he thinks they could have had better results if researchers had used a higher dose of ketamine and paid more attention to the treatment setting and patients’ mindset.

**Dr. David Mahjoubi**, an anesthesiologist and founder of Ketamine Healing Clinic of Los Angeles and Orange County, said while he always recommends that patients combine ketamine therapy with psychotherapy, some people may do well with just the drug treatment.

In addition, not all of the patients at his clinic have treatment-resistant depression.

“Somebody who has mild depression may want to try ketamine because they don’t want to go on a medication that they’d have to take orally every single day and that may have side effects,” he told Healthline.

As with the new study, Mahjoubi finds that longer-term benefits of ketamine therapy vary among people.

“I’ve had patients who did the initial IV infusion series who benefitted for over a year,” he said. “But some patients have needed to come back once a month to keep themselves optimized because they feel that the benefits wane after a month.”

Mahjoubi also prescribes an at-home nasal ketamine, which people can use on an “as needed basis to maintain the benefits.” This uses racemic ketamine, not the eskatmine version sold under the brand name SPRAVATO.

### **Psychotherapy boosts ketamine benefits**

Rabin agrees that preparing people for ketamine treatment — or any psychedelic treatment — and helping them integrate their experience afterward can improve outcomes.

This might include psychotherapy, cognitive behavioral therapy, or soothing touch therapy.



Apollo Neuroscience has developed a wearable device that uses low-frequency sound waves to provide soothing vibrations.

Rabin said the device is being used by clinicians in the United States and Canada alongside psychedelic therapy to improve treatment responses and patient comfort. It is also being tested in a clinical trial of MDMA psychedelic therapy, he said.

By adding in these types of approaches, “people are able to integrate what they experience during the treatment into their lives more effectively,” said Rabin.

In addition, “what we’re seeing is that when you add that therapy component onto the practice of psychedelic medicine — whether it’s MDMA, ketamine or any other psychedelic medicine — it seems that the effect is stronger and longer lasting,” he said.

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