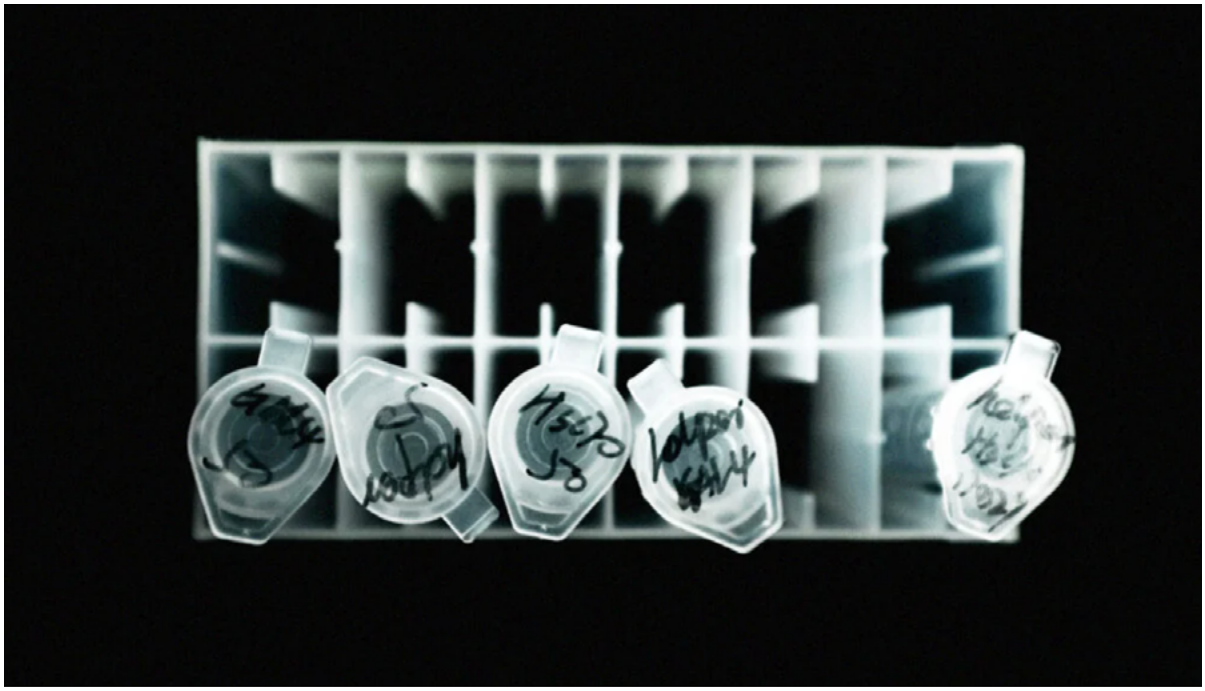
MEDICALNEWSTODAY

Ketamine injections effective for treatment-resistant depression, trial finds

Beth JoJack | July 20, 2023



Inexpensive ketamine injections are effective against treatment-resistant depression, study finds. Image credit: Pansfun Images/Stocksy.

A growing number of researchers are looking at psychedelics, a range of substances that can alter consciousness, as a possible treatment for depression.
Many are interested, specifically, in ketamine, a drug that has been used as an anesthetic for decades.

The *British Journal of Psychiatry* recently published a paper on a double-blind trial out of Australia that compared the ability of racemic ketamine to a placebo in reducing the symptoms of treatment-resistant depression.

Treatment-resistant depression is defined as depression that does not respond to two or more lines of treatment.

What are the different types of ketamine?

In 2019, the Food and Drug Administration (FDA) approved Spravato (esketamine), a commercially developed nasal spray, for treatment-resistant depression in adults and for depressive symptoms in adults with major depressive disorder with acute suicidal ideation.

Racemic ketamine is approved for use as anesthesia in the United States. Physicians also use it as a treatment for depression “off-label”, meaning they prescribe it for a different condition than

the specification approved by the FDA.

Racemic ketamine is also less expensive than Spravato.

For the current study, led by researchers at the University of New South Wales Sydney (UNSW) and the affiliated Black Dog Institute, participants received twice-weekly injections of racemic ketamine or a placebo.

Largest clinical trial yet

Dr. Colleen Loo, lead researcher on the trial and a clinical psychiatrist and professor of psychiatry at UNSW, told *Medical News Today* that she began looking at the effects of ketamine on depression in 2011. Previously, she had studied the use of ketamine within anesthesia for electroconvulsive therapy (ECT).

This clinical trial, she said, is the largest one to compare racemic ketamine with a placebo for treatment-resistant depression.

Dr. Loo pointed out another key aspect of the study: About one-quarter of the participants had already received and failed to respond to treatment with ECT.

"ECT is a highly effective treatment for severe and treatment-resistant depression, so it means these people had high-end treatment-resistant depression," she explained.

The fact that the study participants received injections of racemic ketamine rather than more expensive and time-consuming infusions is also noteworthy, according to Dr. Loo, as it means that this more affordable alternative is also effective.

Ketamine for Adult Depression (KADS) study

Researchers enrolled 184 people with treatment-resistant depression in the trial, which they named the Ketamine for Adult Depression (KADS) study. The research was conducted at six clinical mood disorder centers in Australia and one in New Zealand.

The recruitment of participants began in August 2016 and closed in April 2020.

Researchers had hoped to recruit more participants for the trial, but when the pandemic hit, they decided to end the recruitment, Dr. Loo explained to MNT.

Participants were aged 18 years or older and had experienced major depressive disorder for at least 3 months. Additionally, they needed to have had an insufficient response to at least two antidepressants.

The participants had to have been taking the same dosage of their current antidepressant for more than 4 weeks before starting the trial. They also needed to score at least 20 on the Montgomery–Åsberg Rating Scale for Depression (MADRS).

'Good safety profile' for ketamine injections

Participants were randomly assigned to receive injections of racemic ketamine or midazolam, which is often used to help patients relax prior to surgery.

Health practitioners gave injections into the participants' abdominal walls twice a week for 4 weeks, with at least 3 days off between each treatment.

Participants did not seem disturbed to receive injections in the abdomen, according to Dr. Loo. "The injection used a very small needle to inject ketamine under the skin," she said. "It can be done anywhere — arm, leg, abdomen — but we did it in the abdomen because there is usually more fat there under the skin [so] it is more comfortable."

Neither participants nor researchers administering the drug knew which participants received racemic ketamine. Midazolam was chosen as the placebo because like ketamine, it causes sedation, which helped to keep participants from knowing which drug they would receive.

Initially, 73 participants were randomized to receive a fixed dose of either 0.5 milligrams per kilogram of racemic ketamine or 0.025 milligrams per kilogram of midazlolam.

At a routine Data Safety Monitoring Board meeting "a revisiting of drug dosage was recommended as no participants in the entire masked sample had remitted and the safety profile was good," write the authors of the study.

As a result, dosing was revised and in a second group, 108 participants were randomized to receive flexible dosing of ketamine or midazolam. A response-guided dosing was implemented. If patients had not improved by 50% from baseline scores in sessions two, four, or six, racemic ketamine doses were escalated to 0.6 milligrams per kilogram, 0.75 milligrams per kilogram, and 0.9 milligrams per kilogram. Participants receiving midazolam also received escalated doses.

Participants were included in the trial if they received at least one injection. The study authors note that "most" received all eight doses.

Careful safety monitoring brings positive results

Most participants in the flexible dosing group escalated to the highest dose of racemic ketamine. This proved to be an important facet of the study, according to Dr. Loo. "It showed that individual dose adjustment, up to the dose that each person requires for response, is really important for getting the best outcomes," she said.

Researchers used the Ketamine Side Effect Tool (KSET) to understand acute and longer-term side effects associated with multiple treatments of racemic ketamine.

They followed up with participants after the final injection and again four weeks later. Participants who had relapsed were eligible to enter an open-label treatment phase, meaning that they would be aware of the treatment they are receiving.

"The study used a very detailed and comprehensive approach to safety monitoring, monitoring for cumulative effects between treatments, not just in the two hours after each treatment, or just

enquiring at the end of the four weeks," Dr. Loo said.

In the paper about the trial, the researchers write that "if ketamine treatment is halted after 4 weeks, the benefits are not sustained for all remitters and that ongoing treatment should be considered."

The researchers added that "most" participants elected to begin open-label treatment at the end of 4 weeks.

50% symptom improvement in 30% of participants

Approximately 1 in 5 participants receiving a flexible dose of racemic ketamine achieved total remission from their symptoms after a month of the injections compared with only 2% achieving total remission in the placebo group.

Almost 30% of participants treated with ketamine saw symptoms improve by at least 50% compared to 4% with placebo.

Dr. Loo was not surprised to see a 20% remission rate, which she described as "quite good" for treatment-resistant depression.

"The results here are actually very encouraging," Dr. Loo said. "Even in people with depression at the high end of treatment resistance — excluded from most prior studies — ketamine was still very effective, with an impressive 10 [times] difference compared to placebo."

In the future, the researchers would like to conduct larger trials of generic ketamine over longer periods and continue to refine the KSET.

No dissociative experience

Dr. David Mahjoubi, the medical director at the Ketamine Healing Clinic of Los Angeles and Orange County, not involved in this study, stressed to MNT that the trial looked at delivering racemic ketamine through injections.

Additionally, Dr. Mahjoubi noted that not all participants in the trial received the same number of racemic ketamine injections, "[s]o that's one huge variable."

"People with the same number of [injections] should have been compared," advised Dr. Mahjoubi. The physician, who opened his first clinic eight years ago, has found patients often do not benefit from ketamine after the first or second infusion. "It takes three or four infusions," he said.

He suggested more participants might have seen their symptoms improve if they had all received all eight injections.

https://www.medicalnewstoday.com/articles/ketamine-injections-effective-for-treatment-resistant-depression-trial-finds