Slow-Release, Oral Ketamine Tablet May Reduce Severity of Treatment-Resistant Depression

The authors note that the oral, at-home treatment can a better alternative for patients by reducing inconveniences that come with the injectable and nasal administration methods.

According to the authors of phase 2 trial results published in a *Nature Medicine* study, a new tablet form of ketamine has demonstrated positive outcomes in the treatment of severe depression. This new slow-release tablet can be taken at home without the need for medical supervision, offering an alternative to existing clinic-based treatments—such as the injectable and nasal spray administration methods that require providers to monitor patients for about 2 hours for potential adverse effects (AEs)—which can be expensive and inconvenient for patients.[1]

For this randomized, open-label, multicenter phase 2 trial, a total of 231 adult patients with treatment-resistant depression were enrolled. Every patient had a Montgomery-Asberg Depression Rating Scale (MADRS) score of 20 or higher, with higher numerical scores signifying more severe depression.[1,2]

First, all patients received a 120 mg oral, open-label ketamine tablet (R-107) daily, 5 times per week. After an assessment on day 8, patients were randomly assigned to 1 of 5 groups, of which 4 received various strengths of R-107 and the other placebo, twice weekly for an additional 12 weeks. Doses were double-blind and ketamine doses included 30 mg, 60 mg, 120 mg, and 180 mg. If patients were unresponsive at the time of assessment on day 8, they were excluded from the double-blind, randomized segment of the trial. A total of 168 patients were included in this portion. The primary end point of the study was least square mean change in MADRS for each active treatment compared with placebo at the 13-week period, beginning with the 180 mg dose and using a fixed sequence step-down closed test procedure.[1,2]

According to the findings, the largest reduction in MADRS total score was 6.1 in the 180 mg treatment group (95% CI 1.00-11.16; P = .019), which was considered statistically significant. Additionally, the 30 mg, 60 mg, and 120 mg groups saw reductions of 1.9 (95% CI -3.08-6.92; P = .450), 0.7 (95% CI -4.32-5.70; P = .785), and 4.5 (95% CI -0.60-9.69; P = .083), respectively. The investigators also observed lower mean reductions in the 120 and 180 mg dose groups compared with the lower-dose groups. On day 92, women were also observed to have numerically greater reductions in MADRS scores (-10.1; -18.7 to -1.5), as well as patients aged 65 and older (-6.9; -12.3 to -1.6), those taking antidepressants (-6.5; -12.5 to -0.6), and those with a larger median body weight (-7.1; -14.0 to -0.1).[2]

“The kind of results we’re seeing look as good as other ways of giving ketamine, and are fascinating for 2 reasons. First of all, there's the practical clinical reason that this is a way of administering ketamine to treat depression that's much easier to give,” said Colleen Loo, MBBS, FRANZCP, MD, clinical pharmacist, researcher, and professor at the University of South Wales Black Dog Institute, in a news release. “Rather than having to come to the clinic and have an injection and have medical monitoring for 2 hours, once or twice a week, this is much more convenient and allows patients to have their treatment at home, making it as convenient as other antidepressant medications. It is also possible that some people may respond to one approach to treatment, such as the tablet, while others respond to another, such as the injection, so having more treatment approaches is very useful.”[1]

Further, during the open-label enrichment phase (days 1-8), there was a mean reduction in MADRS score of 18.5 (95% CI 17.37-19.69) at day 8. A total of 132 participants of 231 (57.1%) enrolled in the enrichment phase had achieved remission with a MADRS total score of 10 or less at day 8. Additionally, 168 participants (72.7%) of the total population achieved a response to treatment, which was defined as a 50% or greater reduction from baseline in MADRS score at day 8.[2]

At week 13, the investigators also observed numerically greater rates of remission and response in the ketamine groups compared with placebo; however, these were not considered statistically significant and were only significant for the 120 mg dose group. The 120 mg and 180 mg dose groups also had a higher probability of improvement in the severity of depression from the participant's perspective, compared with placebo (120 mg: 0.28; 0.06-1.25; 180 mg: 0.82; 0.19-3.51).[2]

"There's 1 school of thought that says what we call dissociative effects—where you're feeling a kind of altered reality and perception—are actually integral to the ability to improve the depression with ketamine. And that's very similar to the psychedelic-assisted therapy model that says changing your brain circuit functioning in that very profound way gives you new insights that help you to break out of your way of thinking, and that this acute kind of dissociative altered reality experience is necessary," said Loo in the news release. "But with this tablet form, you don't experience that because only a tiny amount is released into the bloodstream at a time, with ongoing slow release over days, and you don't experience the dissociation at all, and yet people are improving."[1]

During the enrichment phase, the most common AEs reported by patients were dizziness, headache, dissociation, fatigue, nausea, and feeling abnormal. Additionally, 26 patients (11.6%) reported experiencing dissociation. During the double-blind treatment phase, most of the AEs reported were similar to that of the enrichment phase and were mild (n = 131, 56.7%) or moderate (n = 42, 18.2%) in severity. Additionally, 10 severe AEs were reported in 8 participants and included headache (30 mg and 60 mg groups), severe depression (120 mg and 180 mg groups), 1 occurrence of suicide by day 42 (180 mg group), noncardiac chest pain (60 mg group), nausea (30 mg group), intervertebral disc protrusion (120 mg group), and nephrolithiasis and ureterolithiasis in 1 participant (placebo group). No serious AEs were considered to be related to treatment, and all—with the exception of 1 occurrence of complete suicide—were resolved.[2]

"If [R-107] does get through all those hoops and becomes an approved treatment, it certainly makes it much more convenient, not to mention cheaper, to use ketamine to treat severe depression," said Loo in the news release.[1]

References

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