Repeated ketamine infusions reduce PTSD symptom severity

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Repeated intravenous (IV) ketamine infusions significantly reduce symptom severity in individuals with chronic post-traumatic stress disorder (PTSD) and the improvement is rapid and maintained for

several weeks afterwards, according to a study conducted by researchers from the Icahn School of Medicine at Mount Sinai. The study, published September XX in the *American Journal of Psychiatry,* is the first randomized, controlled trial of repeated ketamine administration for chronic PTSD and suggests this may be a promising treatment for PTSD patients.

"Our findings provide insight into the treatment efficacy of repeated ketamine administration for PTSD, an important next step in our quest to develop novel pharmacologic interventions for this chronic and disabling disorder, as a large number of individuals are not sufficiently helped by currently available treatments," says Adriana Feder, MD, Associate Professor of Psychiatry at the Icahn School of Medicine at Mount Sinai and lead author of the study. "The data suggests repeated IV ketamine is a promising treatment for people who suffer from PTSD and provides evidentiary support to warrant future studies to determine how we can maintain this rapid and robust response over time."

Previous to the current study, Mount Sinai researchers conducted the first proof-of-concept, randomized, controlled trial of a single dose of intravenous ketamine for PTSD, which showed significant and rapid PTSD symptom reduction 24-hours post-infusion. First approved by the U.S. Food and Drug Administration as an anesthetic agent in 1970, ketamine acts as an antagonist of the N-methyl-d-aspartate (NDMA) receptor, an ionotropic glutamate receptor in the brain. In contrast, widely used antidepressants target different neurotransmitters—serotonin, norepinephrine, and dopamine—and can take weeks to even months to work. These drugs are considered ineffective in at least one third of cases, and only partially effective in an additional third.

"The data presented in our current study not only replicates, but also builds on our initial findings about ketamine for PTSD, indicating that in

addition to being rapid, ketamine's effect can be maintained over several weeks. PTSD is an extremely debilitating condition and we are pleased that our discovery may lead to a treatment option for so many who are in need of relief from their suffering," said Dennis S. Charney, MD, Anne and Joel Ehrenkranz Dean of the Icahn School of Medicine at Mount Sinai and President of Academic Affairs for the Mount Sinai Health System and senior author of the paper.

For the current study, participants were randomly assigned to receive six infusions of ketamine, administered three times per week over two consecutive weeks, compared to six infusions of the psychoactive placebo control midazolam (chosen because its pharmacokinetic parameters and nonspecific behavioral effects are similar to those of ketamine) administered and evaluated over the same schedule. Individuals in this study had severe and chronic PTSD from civilian or military trauma, with median duration of 14 years and nearly half of the sample taking concomitant psychotropic medications. The primary traumas reported by participants included sexual assault of molestation, physical assault or abuse, witnessing violent assault or death, having survived or responded to the 9/11 attacks, and combat exposure. All study participants were assessed at baseline, at week 1 and week 2, as well as on each infusion day by teams of trained study raters who administered the Clinician Administered PTSD Scale for DSM-5 and the Montgomery-Asberg Depression Rating Scale (MADRS), standard rating scales for the assessment of PTSD and depression.

Significantly more participants in the ketamine group (67 percent) attained at least 30 percent or more reduction in symptoms from baseline at week two than those in the midazolam group (20 percent). Furthermore, ketamine infusions were associated with marked improvements across three of the four PTSD symptom clusters—intrusions, avoidance, and negative alterations in cognitions and mood. In the subsample of ketamine responders, improvement in

PTSD symptoms was rapid, observed 24 hours after the first infusion, and was maintained for a median of 27.5 days following the primary outcome assessment day. In addition to PTSD symptom improvement, the ketamine group exhibited markedly greater reduction in comorbid depressive symptoms than the midazolam group, which is notable given the high comorbidity of depression in individuals with PTSD. Study findings further suggested that repeated ketamine infusions are safe and generally well-tolerated in individuals with chronic PTSD.

"Future studies may include administering additional doses over time and examining repeated ketamine infusions combined with trauma-focused psychotherapy, to help us determine how we can maintain this robust response over the long term," added Dr. Feder. "We want people suffering with PTSD to know that hope is on the horizon and we are working diligently to collect the information that will help bring them the relief they so desperately need."

More information: Adriana Feder et al, A Randomized Controlled Trial of Repeated Ketamine Administration for Chronic Posttraumatic Stress Disorder, *American Journal of Psychiatry* (2021). DOI: 10.1176/appi.ajp.2020.20050596

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