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POSITION STATEMENT

Ketamine use for treatment resistant depression or posttraumatic stress disorder

Ketamine is a medication mainly used for starting and maintaining anesthesia. It induces a trance-like state while providing pain relief, sedation, and memory loss.[1]

Ketamine has been tested as a rapid-acting antidepressant [2] for treatment-resistant depression (TRD) in bipolar depression, and major depressive disorder. [3] Ketamine's antidepressant effect has a short duration of action. [4] Meta-analyses have shown overwhelming clinical evidence to support the acute efficacy of ketamine in severely unwell populations, but a lack of data on optimal dosing and the effect of long-term treatment. [4, 5] Currently, ketamine is not approved for the treatment of depression, and so this is an off-label use. As of June 2017, esketamine, the *S*(+) enantiomer of ketamine, is in phase III clinical trials for intranasal treatment of depression.[6]

Ketamine hydrochloride is given by a single intravenous infusion at subdissociative doses (less than those used in anesthesia), and preliminary data indicate it produces a rapid (within 2 hours) and relatively sustained (about 1–2 weeks long) reduction in symptoms in some people. [7] Initial studies have resulted in interest due to its rapid onset, [8] and because it appears to work by blocking NMDA receptors for glutamate, a different mechanism from most modern antidepressants. [9]

Ketamine acts as a selective agonist of the NMDA receptor (NMDAR), an ionotropic glutamate receptor. [10] It binds specifically to the dizocilpine (MK-801) site of the NMDA receptor, near the channel pore, and is an uncompetitive antagonist. [11] Ketamine may also interact with and inhibit the NMDAR via another allosteric site on the receptor. [12] Its full mechanism of action is not well-understood as of 2017. [10]

A study conducted in mice suggests that ketamine's antidepressant activity is not caused by ketamine inhibiting the NMDA receptor, but rather by sustained indirect/downstream activation of another type of ionotropic glutamate receptor, the AMPA receptor, by a metabolite, (2*R*,6*R*)-hydroxynorketamine; Arketamine is also an indirect/downstream AMPA receptor activator. [13]

Ketamine is also used as a recreational drug. [14]

A Hayes report regarding the use of ketamine as primary therapy in treatment resistant unipolar depression (TRD) or posttraumatic stress disorder (PTSD) evaluated the available evidence based literature as of September 2017 and arrived at the following conclusions: score of C for TRD and score of D2 for PTSD. The literature search identified 13 randomized controlled, randomized comparative or randomized crossover trials that met inclusion criteria and evaluated ketamine for TRD (12) or PTSD (1). The sample sizes were between 16 and 72 patients. They utilized parenteral infusion (11), subcutaneous (1) and inhalation (1). Comparisons were drawn against ECT, midazolam, placebo or saline. None of the studies provided efficacy follow-up beyond 4 weeks. The 13 reviewed studies found that ketamine reduced depression or PTSD symptoms and suicidal ideation 24 hours posttreatment; however, the results of these studies are mixed at longer-term follow-up. While studies comparing ketamine with saline (7) found that ketamine consistently improved

outcomes compared with saline 1 to 4 weeks posttreatment, studies comparing ketamine with midazolam (4) found that differences between groups dissipated by the 1-week follow-up. One comparative study looked at a randomized trial of 3 ketamine infusions or ECT and found no statistically significant differences between these therapies in reduction of mean depression scores after the final treatment, 24-hours follow-up, or 7-day follow-up. One study evaluated a single ketamine versus placebo treatment given in randomized order to 41 patients with PTSD and found that ketamine treatment was associated with a statistically significant improvement in mean PTSD score (as measured by the Impact of Event Scale) 1 day after treatment, but the statistical significance after this point was not reported even though patients were followed for 1 week.

In conclusion, a moderate-size body of low-quality evidence has consistently found that ketamine reduces symptoms of severe treatment-resistant unipolar depression, symptoms of PTSD, or suicidal ideation at short-term follow-up of 1 to 3 days posttreatment; however, the findings at longer-term follow-up of 1 to 4 weeks are mixed. The majority of the studies administered only a single dose of ketamine; the safety and effectiveness of repeated administration of ketamine for treatment of depression or PTSD is unknown. Additional large, well-designed studies with adequate follow-up are needed to evaluate the long-term effects of prolonged ketamine treatment, to assess simplified ketamine administration via intranasal or subcutaneous routes, to determine the efficacy and safety of ketamine for PTSD treatment, and to evaluate the efficacy and safety of ketamine relative to ECT for unipolar depression. As the beneficial effects of ketamine may be limited to 24 hours posttreatment, it is important to establish the safety and effectiveness of repeated administration of ketamine. There is currently a paucity of studies investigating repeated administration of ketamine for unipolar depression or PTSD.

Centers for Medicare & Medicaid Services have not put out any NCD addressing the use of ketamine for TRD or PTSD. Several representative payer organizations do not have coverage policies for ketamine monotherapy for unipolar depression or PTSD.

Given the limited evidence based support at this time, MHN considers ketamine therapy for mood disorders or PTSD as experimental and investigational.

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