Ketamine for Suicidality

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Q. What is ketamine?

A. Ketamine is a medication commonly used as an anesthetic. In recent years, single-intravenous infusion of ketamine has demonstrated rapid antidepressant effects in patients with treatment-resistant major depressive disorder (TRD; Murrough et al., 2013; Zarate et al., 2006). This rapid onset of action makes ketamine infusion a promising candidate for acute management of suicidal ideation in major depressive disorder (MDD). Ketamine is different from esketamine (a ketamine enantiomer), a drug that has been investigated in the form of a nasal spray as a potential therapy for TRD.

Q. What are the potential mechanisms of action underlying ketamine for suicidality?

A. The exact mechanism of action by which ketamine exerts its rapid antidepressant effect is not known, but is thought to be related to its role as a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist. The NMDA receptor is a presynaptic one that, when stimulated, prevents the release of glutamate into the synapse. Thus blocking the NMDA pre-synaptic receptor would increase the release of glutamate into the synapse and consequently lead to a transient increase in post-synaptic glutamate transmission. Alterations in the activity of glutamate, an excitatory neurotransmitter, may play a role in deficiencies in brain neuroplasticity linked to mood disorders (Maeng & Zarate, 2007). In addition to the NMDA receptor, other pathways have been identified as potentially related to ketamine's antidepressant action in preclinical studies, such as BDNF (brain-derived neurotrophic factor), glutamatergic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, eEF2 (eukaryotic elongation factor 2), GSK-3β (glycogen synthase kinase 3), and mTORC1 (mechanistic target of rapamycin complex 1; Strasburger et al., 2017).

Q. Is ketamine recommended as a treatment for suicidality in the Military Health System (MHS)?

A. Yes. The *2019 VA/DoD Clinical Practice Guideline for the Assessment and Management of Patients at Risk for Suicide* suggests offering ketamine infusion as an adjunctive treatment for short-term reduction in suicidal ideation in patients with the presence of suicidal ideation and major depressive disorder, with a "*Weak For*" strength of recommendation.

The MHS relies on the Department of Veterans Affairs (VA)/Department of Defense (DoD) clinical practice guidelines (CPGs) to inform best clinical practices. The CPGs are developed under the purview of clinical experts and are derived through a transparent and systematic approach that includes, but is not limited to, systematic reviews of the literature on a given topic and development of recommendations using a graded system that takes into account the overall quality of the evidence and the magnitude of the net benefit of the recommendation. A further description of this process and CPGs on specific topics can be found on the VA clinical practice guidelines website.

Q. Do other authoritative reviews recommend ketamine as a treatment for suicidality?

A. No. Other authoritative reviews have not substantiated the use of ketamine for suicidality.

Several other recognized organizations conduct systematic reviews and evidence syntheses on psychological health topics using similar grading systems as the VA/DoD CPGs. These include the Agency for Healthcare Research and Quality (AHRQ) and Cochrane.

- AHRQ: No reports on the use of ketamine as a treatment for suicidality were identified.
- Cochrane: A 2015 systematic review of ketamine and 10 other glutamate receptor modulators for depression in adults found that only ketamine was more effective than placebo at reducing depressive symptoms in the short term, with effects lasting no more than one week (Caddy et al., 2015). The authors of this review noted that very limited data on suicidality were available in the reviewed trials and that further randomized controlled trials (RCTs) with improved quality and longer follow-up periods are required (Caddy et al., 2015).

Q. Is there any recent research on ketamine for suicidality?

A. The systematic review conducted for the *2019 VA/DoD Clinical Practice Guideline for the Assessment and Management of Patients at Risk for Suicide* covered clinical studies and systematic reviews published from November 2011 to April 2018. A search conducted in September 2019 identified one recent RCT on the efficacy of ketamine for the treatment of suicidality that was not included in the CPG review. In this study, 26 participants with TRD and current, chronic suicidal ideation were randomized to receive either six ketamine infusions (0.5mg/kg over 45 minutes) or saline placebo over a three-week period (Ionescu et al., 2019). Participants were required to maintain their current antidepressant regimen prior to and during study treatment. Differences in suicidal ideation, measured using the Columbia Suicide Severity Rating Scale, between ketamine and placebo groups were not statistically significant at posttreatment. The sample size of this study was small, with only 14 participants completing the entire study. The authors concluded that, among outpatients with treatment-resistant depression and chronic suicidal ideation, the traditional dose of ketamine infusion may not be sufficient.

Q. What conclusions can be drawn about the use of ketamine as a treatment for suicidality in the MHS?

A. The *2019 VA/DoD Clinical Practice Guideline for the Assessment and Management of Patients at Risk for Suicide* offers a weak recommendation for use of ketamine infusion as an adjunctive treatment for short-term reduction in suicidal ideation in patients with MDD. The CPG recognizes several important considerations in regard to use of ketamine infusion, including limited access and barriers to treatment (e.g., often requiring administration in inpatient settings), absence of evidence to support continued administration for chronic suicidal ideation, and paucity of research on long-term and more severe outcomes (e.g., suicide attempts or deaths).

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