

Q. What is esketamine?

A. Esketamine is the S (+) enantiomer of ketamine (one of two mirror image molecules that make up ketamine), a widely used anesthetic drug. In recent years, both ketamine and esketamine have been investigated as potential therapies for treatment-resistant depression (TRD). In 2019, the Food and Drug Administration (FDA) approved an esketamine nasal spray (Spravato), to be taken in conjunction with an oral antidepressant, for the treatment of TRD in adults (FDA, 2019). Esketamine nasal spray is available only at certified doctors' offices or clinics based on concerns over the side effects (such as sedation and dissociation) and the potential for abuse and misuse (FDA, 2019).

Q. What are the potential mechanisms of action underlying esketamine?

A. Traditional antidepressants, such as tricyclics (TCAs) and selective serotonin reuptake inhibitors (SSRIs), exert their effects by increasing intrasynaptic levels of monoamine neurotransmitters (like serotonin or norepinephrine), and may take several weeks to achieve full effects. In recent years, research has explored the idea that this delay may be due to the fact that the antidepressant effect is not a direct result of the initial action (i.e., increasing intrasynaptic levels of monoamines), but is due instead to changes further downstream within the target brain cells that occur with repeated use (Zarate et al., 2006). Another neurotransmitter that is now thought to play a role in the mechanism of antidepressant action is the glutamatergic system. 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). Ketamine is an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, and it is likely that NMDA-receptor antagonism is the primary mechanism of the antidepressant effects of ketamine (Sanacora & Schatzberg, 2015). 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 through the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which appears to enhance synaptic function and plasticity (Duman, Aghajanian, Sanacora, & Krystal, 2016; Sanacora & Schatzberg, 2015). Esketamine is one of two enantiomers of ketamine, and has a higher affinity for NMDA receptors than the R (-) ketamine enantiomer, arketamine.

Q. Is esketamine recommended as a treatment for major depressive disorder (MDD) in the Military Health System (MHS)?

A. **Not currently.** The 2016 *VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder* does not include esketamine, and gives a “*Strong Against*” strength of recommendation for ketamine outside of a research setting, given the limited information of safety and duration of effect. It is important to note that there is a difference between esketamine, and ketamine infusion. Ketamine, a racemic mixture, is the parent compound from which esketamine is derived, and ketamine infusion includes but is not limited to esketamine. It is the ketamine infusion and not esketamine which is recommended as an adjunctive treatment for short-term reduction in suicidal ideation in the 2019 *VA/DoD Clinical Practice Guideline for the Assessment and Management of Patients at Risk for Suicide* in patients with the presence of suicidal ideation and MDD, with a “*Weak For*” strength of recommendation.

The MHS relies on the VA/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 esketamine as a treatment for MDD?

A. No. Other authoritative reviews have not substantiated the use of esketamine for MDD.

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 comparative effectiveness reviews including studies on esketamine were identified.
- Cochrane: A 2015 systematic review of ketamine and other glutamate receptor modulators for depression in adults included only one trial on esketamine (Caddy et al., 2015).

Q. Is there any recent research on esketamine as a treatment for MDD?

A. An April 2020 literature search identified a recently published systematic review of adjunctive intranasal esketamine for MDD (Zheng et al., 2020). This review included four randomized controlled trials, with a total of 708 patients with MDD assigned to receive intranasal esketamine or placebo. Studies of adult patients with MDD and treatment refractory symptoms and/or suicidal ideation were included. Included studies were all double-blind, placebo-controlled trials, with follow-up periods ranging from eight days (Daly et al., 2018) to 28 days (Canuso et al., 2018; Fedgchin et al., 2019; Popova et al., 2019). All studies used the Montgomery-Asberg Depression Rating Scale (MADRS). Meta-analyses found that adjunctive intranasal esketamine was associated with significantly greater study-defined response (three RCTs) and remission (four RCTs) at the main endpoint. Significant differences in response and remission started at two hours, peaked at 24 hours, and lasted at least 28 days. Patients assigned to receive intranasal esketamine had a significantly higher rate of discontinuation due to intolerability, and adverse events were significantly more frequent. Using GRADE methodology, the review authors rated the certainty of evidence for the outcomes of interest as either “moderate” or “high.”

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

A. The 2016 *VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder* strongly recommends against ketamine for the treatment of MDD, and does not specifically address esketamine. These guidelines were published prior to FDA approval of esketamine nasal spray, and prior to the publication of the placebo-controlled research on esketamine. The next update of these guidelines will take this new evidence into account. As of April 2020, esketamine nasal spray is offered in the Department of Defense as a medical benefit that requires prior authorization through a physician from Tricare. Esketamine is a promising option for TRD. However, there are concerns about side effects and safety. The research base is emerging and much remains to be known on the effects of long-term use on the brain. Further research is needed to determine the potential for the adverse effects based on repeated and long-term use, the comparative effectiveness of esketamine, and the optimal delivery and treatment combination.

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