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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. Research has explored the cause of this delay and suggested that the antidepressant effect is not a result of the initial action (i.e., increasing intrasynaptic levels of monoamines) and instead is due to changes further downstream within the target brain cells with repeated use (Zarate et al., 2006). The glutamatergic system is now thought to play a role in the mechanism of antidepressant action. 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. Blocking the NMDA pre-synaptic receptor would therefore 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 MDD in the Military Health System (MHS)?

A: The 2022 *VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder* gives a "weak against" recommendation for ketamine or esketamine when choosing an initial pharmacotherapy and a "weak for" strength of recommendation for ketamine or esketamine as an option for augmentation in the treatment of MDD in patients who have not responded to several adequate pharmacological trials.

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. Recommendations for or against a treatment may be characterized as strong or weak based on a variety of factors (e.g., confidence in the quality of the evidence, weight of treatment benefits versus risks, feasibility). The CPGs also state if there is insufficient evidence to develop a 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: Yes. Other authoritative reviews support the use of esketamine for MDD.

Other recognized organizations conduct systematic reviews and evidence syntheses on psychological health topics using grading systems similar to the VA/DOD CPGs. Notable among these is Cochrane, an international network that conducts high-quality reviews of healthcare interventions.

- Cochrane: A 2021 systematic review of ketamine and other glutamate receptor modulators for depression in adults reported esketamine reduced depression rating scores over placebo at 24 hours, 72 hours, one week, two weeks, and four weeks. Ketamine was more effective than placebo in the proportion of patients who responded to treatment, increased remission rates, and reduced depression rating scores at 24 hours, 72 hours, and one week. However, there was less conclusive evidence on response to treatment and no differences in remission rates for ketamine compared to placebo at longer-term timepoints of two weeks, four weeks, and three months (Dean et al., 2021).

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

A: The 2022 *VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder* suggests against ketamine or esketamine when choosing an initial pharmacotherapy but suggests ketamine or esketamine as an option for augmentation in the treatment of MDD in patients who have not responded to several adequate pharmacological trials. As the research base continues to grow, clarity on the comparative effectiveness of esketamine and the optimal delivery and treatment combination will be needed. For additional guidance on selecting a treatment for MDD, please visit the PHCoE Clinician Resources section of the website and navigate to clinical support tools.

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