

Ketamine, clinically recognized for its anesthetic, analgesic and antidepressant effects, is a racemic mixture of arketamine and esketamine<sup>1</sup>. Although ketamine is traditionally classified as N-methyl-D-aspartate (NMDA) receptor antagonists and has affinity for multiple receptors<sup>2</sup>, its exact mechanism of action is not fully understood. Ketamine and its enantiomers have dissociative properties, can cause sedation and elevate blood pressure. See Table 1 for common adverse effects and contraindications.

Ketamine and esketamine are [Type 1 monitored drugs](#) under the [TPP Alberta program](#). Registration with TPP Alberta and the use of a TPP pad is required for prescribing these drugs. In 2019 and 2020, over 80 per cent of ketamine prescriptions were compounded preparations for use via various non-parenteral and parenteral routes of administration<sup>6</sup>. The remaining dispenses were for manufactured products.

Spravato®, an intranasal form of esketamine, was introduced to the Canadian market as an adjunctive therapy for treatment-resistant depression (TRD) in 2020. TRD is defined as failure of two or more antidepressant medications at adequate doses and duration<sup>7</sup>. The recommended dosing<sup>3</sup> for Spravato® is below anesthetic dose levels. Most adverse effects are transient and expected to improve or remain stable with repeated administration. The Health Canada approved product monograph requires patient monitoring at each treatment session for at least 2 hours<sup>3</sup> during and after Spravato® administration for any reactions. Given the risks of adverse effects with esketamine, the product is only available through physicians and pharmacists who are enrolled in the manufacturer's controlled distribution program<sup>3</sup>.

Prescription and intravenous administration of ketamine as an antidepressant treatment would be expected to be led by a psychiatrist with expertise in major depressive disorder (MDD) and TRD and with prior experience in using ketamine with patients. Medical support must be available to manage potential post-treatment reactions including any neurological/psychiatric and cardiorespiratory adverse events. Therefore, physicians who administer IV ketamine are expected to be adequately supported by a multi-disciplinary team capable of delivering resuscitation and airway support<sup>8</sup>, which includes an anesthesiologist, a physician qualified for advanced cardiac life support (ACLS) or an ACLS-qualified nurse.

**Table 1. Adverse effects and contraindications.**

**Potential adverse effects<sup>3-5</sup>:**

- High risk of dissociation and sedation post-administration requiring monitoring
- Increased blood pressure and pulse rate is most common, although hypotension, arrhythmia and bradycardia have also been reported
- Blurred vision, nystagmus and diplopia
- Dizziness, anxiety, headache
- Impaired coordination and concentration
- Irritative and inflammatory urinary tract and bladder symptoms, e.g. cystitis, are possible with chronic use
- Although less likely than opioids, respiratory depression is possible, especially in an overdose situation
- Carries risk of substance misuse or diversion

**Contraindicated for patients:**

- ✗ With known hypersensitivity
- ✗ At risk of serious consequences from an increase in blood or intracranial pressure, e.g. patients with significant hypertension, arteriovenous malformation, a history of intracerebral hemorrhage, a recent major cardiovascular event
- ✗ With a clinically significant unstable cardiovascular, cerebrovascular or respiratory condition

**Caution is advised against use in individuals with an active ketamine use disorder or those with a history of substance use disorder(s) who may be at high risk of developing a ketamine use disorder.**

For ketamine or esketamine prescribed for administration via the intramuscular, subcutaneous, intranasal, oral and sublingual routes in community settings, the treatment offered should be within the scope of practice for the prescriber and be provided with safeguards in place that ensure patient safety, such as post-treatment monitoring and follow-up appropriate to the clinical situation. This should be documented in the patient record. In the context of treating TRD, where a psychiatrist is not directly prescribing the therapy (e.g. in settings with limited availability of specialist care), a family physician with appropriate training and expertise may prescribe a ketamine or esketamine-based treatment for non-parenteral administration with ongoing consultation with a psychiatrist, as appropriate within the clinical context.

The literature supports that intravenous and intramuscular routes of administration have the highest predictable bioavailability and efficacy, whereas the subcutaneous,

intranasal or oral formulations vary profoundly in this respect<sup>9</sup>. Prescribers should not assume that non-parenteral routes are safer than the parenteral routes given the unpredictable bioavailability of these routes of administration and potential for significant inter-individual variability in response and blood-levels.

Ketamine and its enantiomers are primarily metabolized in the liver, with involvement of hepatic CYP enzymes (major: CYP2B6, and 3A4; minor: CYP2C19 and CYP2C9)<sup>5, 6</sup>. Drug interactions with other medications are possible and require special consideration for appropriate management. Metabolized by-products primarily undergo renal elimination. The metabolism of ketamine produces several bioactive compounds that can have varied effects on the body depending on a patient's co-morbidities and hepatic or renal organ function.

For reasons already outlined, important considerations before prescribing ketamine include: prescriber experience; clinical evidence for the condition being treated; patient-specific factors, including medical and personal history, co-morbidities and organ function; treatment risk vs. benefit assessment; intended treatment plan; and goals of therapy.

Long-term safety and efficacy of esketamine<sup>10</sup>, or ketamine use<sup>11</sup> remain largely unknown, with evidence continuing to evolve. The most recent guidelines from the Canadian Network for Mood and Anxiety (CANMAT)<sup>8</sup>, acknowledge the expanding evidence base for the use of ketamine and esketamine for treatment-resistant depression (TRD) in limited clinical situations. Use of ketamine or its enantiomers for other psychiatric or pain conditions should be approached with caution. Table 2 provides an overview of current evidence. It is the responsibility of the individual prescriber to remain up-to-date on the evolving body of knowledge as part of continuing education relevant to their scope of practice.

In conclusion, irrespective of treatment indication, the systemic use of ketamine or esketamine-containing products in the community should only be offered in a manner that is appropriate to a patient's treatment plan, adequately ensures patient safety and complies with applicable CPSA Standards of Practice and CPSA Accreditation Standards. A level of assessment and care, similar to any TPP Alberta-prescribed product is necessary and formal monitoring - depending on the clinical circumstances, patient-specific factors and route of administration - is expected.

**Table 2. Ketamine: an overview of current evidence**

**Major depressive disorder (MDD):** Associated with significant reduction of depression severity and improvement in depressive symptoms starting within 2 hours after administration until day 14, particularly in treatment-resistant depression (TRD)<sup>12-19</sup>. Effects have been seen up to six weeks<sup>20</sup>. A meta-analysis of oral ketamine found preliminary evidence for a possible small effect in MDD with good tolerability<sup>21</sup>.

**Bipolar depression:** Possibly linked with significant improvement of depressive symptoms in individuals with treatment-resistant bipolar depression which continued for 3 days<sup>22</sup>.

**Suicidal ideation:** Evidence exists for reduced suicidal ideation in patients with major depressive disorder (MDD), bipolar depression, cancer and other conditions within 24 hours up to 14 days<sup>23, 24</sup>.

**PTSD:** Reported significant reduction in severity of PTSD, when assessed 24 hours post-infusion<sup>25</sup>.

**Complex regional pain syndrome (CRPS):** Moderate evidence to support pain parameter improvement for up to 12 weeks<sup>26, 27</sup>.

**Traumatic spinal cord injury pain:** There is weak evidence to support short-term reduction of traumatic spinal cord injury pain for up to 2-weeks<sup>26, 28</sup>.

**Chronic neuropathic pain:** May be a reasonable pain reduction treatment for refractory chronic neuropathic pain in ambulatory outpatients<sup>26</sup>.

**Other pain conditions (e.g., fibromyalgia, cancer pain, and headaches):** Weak or no evidence for immediate improvement of pain post intravenous administration<sup>26</sup>.

### Additional Resources:

1. [The Canadian Network for Mood and Anxiety Treatments \(CANMAT\) Task Force Recommendations for the Use of Racemic Ketamine in Adults with Major Depressive Disorder \(2020\).](#)
2. [Esketamine for Treatment-Resistant Depression. Ottawa: CADTH; 2019 April. \(CADTH issues in emerging health technologies; issue 176\).](#)

3. [Consensus Guideline on the use of Intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine and the American Society of Anesthesiologists. Regional Anesthesia and Pain Medicine 2018; 43\(5\)521-546.](#)
4. [A Consensus statement on the use of ketamine in the treatment of mood disorders. APA Research task force. JAMA Psychiatry 2017;74:399-405.](#)

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