

Introduction¹⁻³

Ketamine is a general anesthetic drug that has gained traction in recent years for its potential to treat pain. Ketamine has an opioid-sparing effect and can improve pain that is refractory to standard therapy. The evidence base regarding the use of ketamine for pain is primarily anecdotal, consisting of case reports, case series, and small uncontrolled trials. In these reports, ketamine is most used as an adjunct to an existing opioid regimen.

Mechanism of Action^{4,5}

Inhibition of the NMDA receptor by ketamine results in decreased glutamate production in the central nervous system, which leads to analgesic effects. While NMDA receptor antagonism is thought to be primarily responsible for the analgesic effects of ketamine, recent evidence suggests that interaction with other receptors, such as GABA and opioid, may also contribute to analgesia.

Adverse Effects⁶⁻¹¹

The adverse effects of ketamine are primarily dose-related, predominantly occurring with doses above 1 mg/kg. They are more likely to occur with IV or SC ketamine than with oral forms.

- **Psychiatric**

The psychomimetic effects of ketamine are often the most bothersome and include vivid dreams, hallucinations or floating sensations, visual spatial disorders, blunted affect, emotional withdrawal, thought disorders, sedation, and delirium. To help prevent these effects, lorazepam or haloperidol may be administered concurrently.

- **Cardiovascular**

Effects on the cardiovascular system include elevated blood pressure and heart rate and an increase in stroke volume.

- **Other**

- Dizziness, drowsiness, light-headedness, anxiety, blurred vision, and headache have been reported with ketamine use.
- Effects on the gastrointestinal system include increased salivation and nausea and vomiting. Co-administration of an anticholinergic, such as glycopyrrolate or atropine as needed, may be helpful.

Dosing and Administration Considerations¹¹⁻²¹

- Ketamine is usually administered orally, subcutaneously, or intravenously for the management of pain. Other less common routes of administration include the rectal, intranasal, and topical.
- Although several routes of administration and dosing strategies have been studied for ketamine, no one route of administration or regimen has been shown to be superior to another.
- Limited evidence suggests that ketamine is effective and well tolerated when compounded into a gel alone or in combination with amitriptyline and applied topically for localized peripheral neuropathy.^{18,19}
- The use of low-dose ketamine for pain remains highly individualized to the patient and regimens are often based on the prescriber's experience or an established protocol:
 - Literature suggests an IV bolus of 0.15-0.3 mg/kg and IV infusion of 0.15-0.3 mg/kg/hr for pain²⁰
 - Literature suggests an oral dose of 0.5 mg/kg every 12 hours²⁰
- The effect of ketamine can persist for several days to weeks to months after analgesia is achieved, even with short-term use (i.e., a few days to a few weeks).^{7,21}

Dosage Forms

- Ketamine is available as a solution for injection, which can be administered orally or parenterally. It is commercially available in concentrations of 50mg/ml and 100mg/ml.
- When administered orally, ketamine solution for injection can be very bitter; therefore, diluting the dose just prior to administration with juice (preferably grape juice) or requesting a pharmacy to compound an oral solution (e.g., 20mg/ml) can facilitate administration.^{17,22}

Monitoring

The following monitoring parameters are recommended at baseline and observed regularly with the initiation, administration, and dose titration of ketamine:

- Vital signs (e.g., blood pressure, heart rate, respiratory rate, ECG)
- Presence of adverse effects such as psychomimetic effects (e.g., agitation, insomnia, fear, hallucinations), nausea/vomiting, excessive secretions, profound sedation or change in level of consciousness.
- Pain assessment

Summary

Ketamine is an NMDA-receptor antagonist that can be effective for the management of difficult-to-treat pain. However, due to the weak evidence base and its propensity to cause serious adverse effects, ketamine is best reserved as a third- or fourth-line choice for the management of neuropathic or chronic pain syndromes that have not responded well to opioids or other adjuvant therapies. To prescribe ketamine safely consider patient-specific factors along with related contraindications, pharmacokinetics, dosing, adverse effects, and monitoring parameters as well as federal, state, or local regulations or policies.

For additional information about the use of ketamine for the treatment of pain, please visit:

[Safely Prescribing Ketamine for Pain.pdf \(enclarapharmacia.com\)](#) and [Ketamine for the Treatment of Refractory Pain - Enclara Pharmacia](#)

References

1. Marchetti, F et al. "Efficacy and safety of oral ketamine for the relief of intractable chronic pain: A retrospective 5-year study of 51 patients." *European journal of pain* (London, England) vol. 19,7 (2015): 984-93. doi:10.1002/ejp.624
2. Schwenk, Eric S et al. "Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management 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* vol. 43,5 (2018): 456-466. doi:10.1097/AAP.0000000000000806
3. Enclara Pharmacia. "Ketamine for the Treatment of Refractory Pain." *Palliative Pearls* (June 2023): 1-6. Enclara Pharmacia. Web. 5 Jan. 2024.
4. Carlton, S M, and R E Coggeshall. "Inflammation-induced changes in peripheral glutamate receptor populations." *Brain research* vol. 820,1-2 (1999): 63-70. doi:10.1016/s0006-8993(98)01328-6
5. Ma, Xiaofan et al. "Application of Ketamine in Pain Management and the Underlying Mechanism." *Pain research & management* vol. 2023 1928969. 16 Aug. 2023, doi:10.1155/2023/1928969
6. Fisher K, Hagen NA. Analgesic effect of oral ketamine in chronic neuropathic pain of spinal origin: A case report. *Journal of Pain and Symptom Management*. 1999;18(1):61-66.
7. Quibell, Rachel et al. "Ketamine." *Journal of pain and symptom management* vol. 50,2 (2015): 268-78. doi:10.1016/j.jpainsymman.2015.06.002

8. Visser, E, and S A Schug. "The role of ketamine in pain management." *Biomedicine & pharmacotherapy* = *Biomedecine & pharmacotherapie* vol. 60,7 (2006): 341-8. doi:10.1016/j.biopha.2006.06.021
9. Prommer, Eric E. "Ketamine for pain: an update of uses in palliative care." *Journal of palliative medicine* vol. 15,4 (2012): 474-83. doi:10.1089/jpm.2011.0244
10. Ketamine. Clinical Pharmacology powered by ClinicalKey. Philadelphia (PA): Elsevier. 2024- January 5, 2024.
11. Portenoy, RK, Ahmed E, Keilson YY. (2023). Cancer pain management: Role of adjuvant analgesics (coanalgesics). *UpToDate*. Retrieved January 5, 2024.
12. Okon, Tomasz. "Ketamine: an introduction for the pain and palliative medicine physician." *Pain physician* vol. 10,3 (2007): 493-500.
13. Kronenberg RH. Ketamine as an analgesic: Parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. *J Pain Pall Care Pharmacother*. 2002;16(3):27-35.
14. Campbell-Fleming J, Williams A. The use of ketamine as adjuvant therapy to control severe pain. *Clin J Oncol Nurs*. 2008;12(1):102-107.
15. Visser E, et al. The role of ketamine in pain management. *Biomed Pharmacother*. 2006;60(7):341-348.
16. Legge J, et al. The potential role of ketamine in hospice analgesia: A literature review. *Consult Pharm*. 2006;21(1):51-57.
17. Prommer EE. Ketamine for pain: An update of uses in palliative care. *J Palliat Med*. 2012;15(4):474-483.
18. Gammaitoni A, et al. Topical ketamine gel: Possible role in treating neuropathic pain. *Pain Med*. 2000;1(1):97-100.
19. Quan D, et al. Topical ketamine treatment of postherpetic neuralgia. *Neurol*. 2003;60(8):1391-1392.
20. Riccardi, Alessandro et al. "Narrative Review: Low-Dose Ketamine for Pain Management." *Journal of clinical medicine* vol. 12,9 3256. 2 May. 2023, doi:10.3390/jcm12093256
21. Hocking G, Cousins MJ. Ketamine in chronic pain management: An evidence-based review. *Anesth Analg*. 2003;97(6):1730-1739.
22. Craven R. Ketamine. *Anaesth*. 2007;62(Suppl 1):48-53.