Ketamine: What You Need to Know

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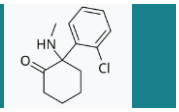
Brief History



- Anesthetic first synthesized 1962
- NMDA Antagonist
- Wide uses beyond anesthesia
- Schedule III controlled substance in the U.S.

Routes of Administration

- Intravenous (IV)
- Subcutaneous (SQ)
- Intramuscular (IM)
- Oral / Sublingual
- Intranasal
- Topical

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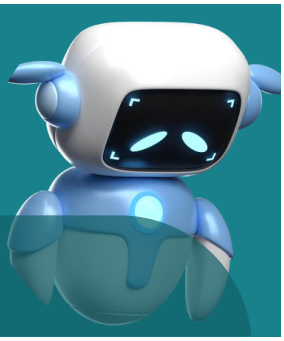
Treatment-Resistant Depression (TRD)



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Use of Ketamine in Treatment-Resistant Depression

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Clinical effectiveness and limitations

- Rapid effect
- Short duration of effect
- Repeated infusions
- Acute suicality
- Integration with psychotherapy

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Mechanism of Action

NMDA Receptor Antagonism

Non-competitive blockade of NMDA receptors reduces glutamate-mediated excitation, central sensitization, and wind-up pain. This is the primary analgesic mechanism.

Opioid Receptor Interaction

Interacts with mu and kappa opioid receptors. May reduce opioid tolerance and reverse opioid-induced hyperalgesia, allowing dose reduction.

Monoaminergic & Other Pathways

Modulates serotonin, norepinephrine, and dopamine reuptake. Enhances BDNF and synaptogenesis — underlying the rapid antidepressant effect.

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Why does it work for TRD?

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Alabama State Board of Medical Examiners Position Statement on the Off-Label Use of Ketamine for the Treatment of Treatment-Resistant Depression in Outpatient Settings

Only physicians can prescribe. Diagnosis of TRD must be confirmed by a psychiatrist
Must have diagnosis of major depressive disorder with or without suicidality
Contraindications: schizophrenia, schizoaffective disorder, uncontrolled HTN, pregnancy
Written informed consent, a complete history and physical, including a history of previous antidepressant use, obtain a urine toxicology screen
Means to monitor a patient's heart rate, blood pressure, respiratory rate and oxygen saturation level
Crash/code cart must be readily accessible. Prescribing physician ACLS certified and trained to establish an airway if necessary
No more often than twice a week. Can not be given at home. The patient must be driven home by a caregiver

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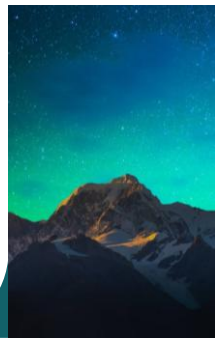
Esketamine

- **2019:** TRD when used in conjunction with another antidepressant
- **2020:** depression with acute suicidality when used in conjunction with another antidepressant
- **2025:** standalone medication in TRD



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Treatment course

- 56 mg, then 84 mg
- Twice weekly for 4 weeks
- Weekly for undefined period
- Twice weekly for undefined period
- After that?

Spravato® (esketamine) ©
nasal spray

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Use in Acute and Chronic Pain

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Clinical Indication: Refractory Pain

10–20%

of advanced cancer patients experience refractory pain

When to Consider Ketamine for Pain

- Opioid-refractory or opioid-resistant pain
- Dose-limiting opioid side effects (sedation, myoclonus, delirium)
- Neuropathic pain, central sensitization, or opioid-induced hyperalgesia
- Mucositis pain (topical ketamine mouthwash)

Typical Dosing (Adults)

- Oral: 10–25 mg TID–QID, titrate by 10–25 mg
- IV/SQ infusion: 50–100 mg/day, titrate 25–50 mg/day
- "Burst" approach: 2–5 day infusion course
- Max reported oral dose: 200 mg QID

Practical Approach

- Used as adjunct to opioids, not replacement
- Consider empiric 25–50% opioid dose reduction if hyperalgesia suspected
- Short-term "burst" may reduce opioid tolerance for several weeks
- Always maintain PRN opioid availability

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Acute Pain

- Emergency Department settings
- Perioperative pain management
- Blunts central sensitization
- Trauma
- Sickle-cell crisis
- Renal colic
- Postoperative settings

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Chronic pain

- Neuropathic pain
- Complex regional pain syndrome
- Other refractory pain conditions

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Side Effects & Safety Considerations

Common Side Effects

- Psychotomimetic effects (vivid dreams, hallucinations, dissociation, dysphoria)
- Cardiovascular: transient ↑ HR and BP (10–50% above baseline)
- Nausea and vomiting
- Dizziness, lightheadedness
- Increased secretions
- Drowsiness or cognitive changes

Cautions & Contraindications

- Poorly controlled hypertension or tachyarrhythmias
- Severe angina or myocardial ischemia
- Increased intracranial pressure
- History of psychosis (relative)
- Glaucoma
- Hepatic impairment (oral route — significant first-pass metabolism)
- Concurrent use of MAOIs

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Monitoring & Practical Considerations

Monitoring Parameters

- Vital signs (HR, BP) at baseline and after doses
- Pain scores (before and after administration)
- Psychotomimetic effects — assess at each dose
- Level of consciousness / sedation scale
- Adjust monitoring based on patient goals of care

Team Coordination

- Specialist oversight recommended (pain, palliative care)
- Pharmacy consultation for compounding/dosing
- Nursing education on administration and monitoring
- Clear communication with patient and family about expectations

Setting Considerations

- Inpatient preferred for IV initiation and titration
- Home use possible with robust hospice support
- SQ and oral routes more practical for home settings
- Access may be unit- or discipline-restricted at some facilities

Goals-of-Care Alignment

- Clarify whether goal is pain relief, mood, or both
- Discuss realistic expectations with patients/families
- Balance monitoring burden vs. comfort-focused care
- Vital signs assessment may be modified per palliative goals

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Risks of ketamine use disorder

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Recreational ketamine use

- Club drug
- Urologic Toxicity
- Hepatobiliary Effects
- Tolerance

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Special Populations & Considerations

Pharmacokinetic Notes

- Oral bioavailability is only ~17–20% due to extensive first-pass hepatic metabolism
- Active metabolites (norketamine, hydroxynorketamine) accumulate with chronic or oral use — PK not fully characterized
- Variable hepatic metabolism creates wide inter-patient variability
- No established dose adjustment guidelines for renal or hepatic impairment in palliative care
- Drug interactions: caution with CNS depressants, MAOIs, memantine

Pediatric Patients

Very limited data on ketamine analgesia in children with cancer. Intranasal ketamine has some evidence for acute pain in pediatric settings. Individualized assessment essential.

Elderly / Frail Patients

Start at lower doses. Higher sensitivity to psychotomimetic and cardiovascular effects. Delirium risk may be elevated. Close monitoring and gradual titration recommended.

Patients with Delirium

Ketamine may worsen or trigger delirium. Generally considered a relative contraindication. Weigh carefully against potential pain or mood benefits.

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Key Takeaways

- Ketamine is a versatile agent with analgesic, antidepressant, and anxiolytic properties — uniquely suited to the complex needs of palliative patients.
- Evidence for analgesia in cancer pain is mixed; the largest RCT did not show benefit over placebo. Short-term "burst" infusions may still be considered empirically.
- Antidepressant evidence is more consistently positive: rapid-acting effects offer advantages when standard treatments are too slow.
- Side effect profile is manageable but requires appropriate monitoring. Psychotomimetic and cardiovascular effects are the primary concerns.
- Ketamine use in palliative care requires multidisciplinary collaboration, shared decision-making, and alignment with patient goals of care.

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Thank you

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