Ketamine: Dissociating Pain from the Patient

Jacob Powell, PharmD
PGY2 Emergency Medicine Pharmacy Resident
Atrium Health Cabarrus, Concord, NC
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Disclosures

The planner(s) and speaker(s) have indicated that there are no relevant financial relationships with any ineligible companies to disclose.

Learning Objectives

At the end of this session, learners should be able to:

- Review the fundamental concepts of multimodal analgesia and how multimodal analgesic regimens target pain pathophysiology
- Evaluate the emerging role of subanesthetic ketamine in the treatment of both acute and chronic pain across various treatment settings
- Appropriately identify patients that may benefit from subanesthetic ketamine for pain management
- Evaluate both the clinical benefits and safety of subanesthetic ketamine in pain management and describe strategies to mitigate any risks

Abbreviations

- ED: Emergency Department
- TCA: Tricyclic Antidepressant
- SNRI: Serotonin-Norepinephrine Reuptake Inhibitor
- COX: Cyclooxygenase
- NSAID: Nonsteroidal anti-inflammatory drug
- NMDA: n-methyl d-aspartate
- IV: Intravenous
- IN: Intranasal
- IM: Intramuscular
- BUD: Beyond use date
- APP: Advanced practice provider

The Burden of Pain

- 25% of Americans experience chronic pain
- 80% of ED visits are pain related
  - 15% are due to patient's chronic pain syndrome
- Approximately 10% of these visits lead to prescribing of an opioid
  - Misuse leads to increased risks of abuse and dependence

CDC. MMWR, 2022

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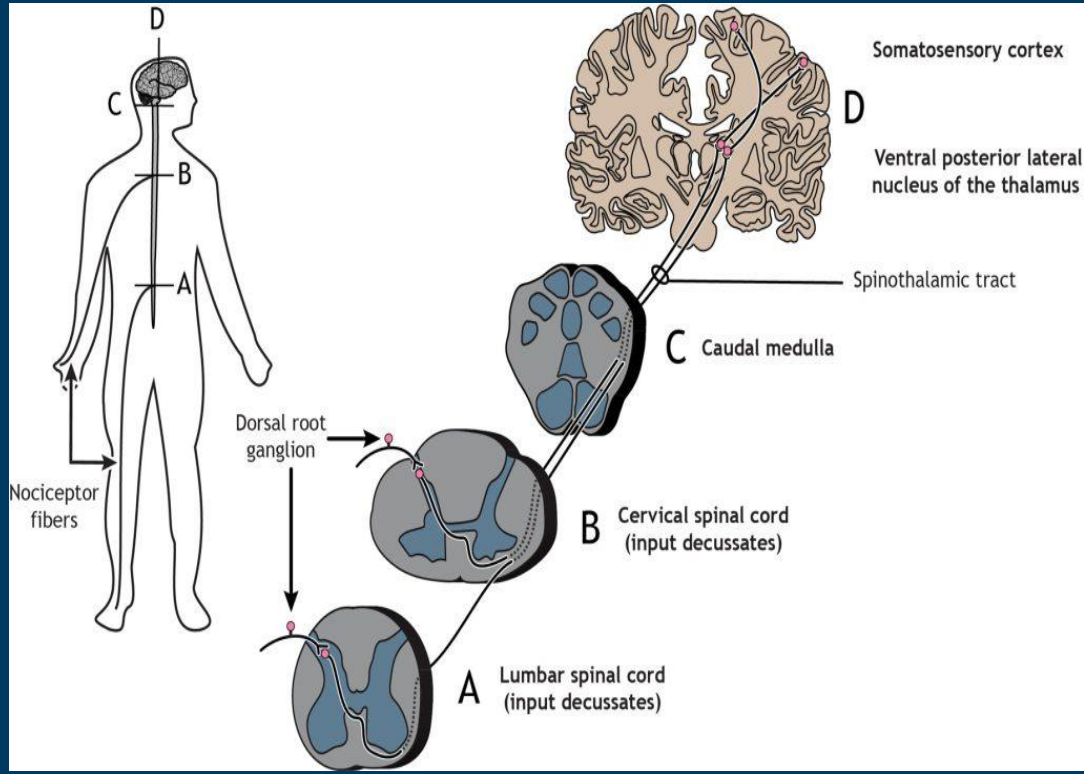
Pathophysiology

- Injury & inflammation
  - Tissue damage → inflammatory mediators → nociceptors
- Signal transmission
  - Nociceptive signals travel via peripheral nerves to the spinal cord
- Central perception
  - The thalamus and cortex process the signal → pain perception



McIntyre MK, et al. Introduction to Neuroscience. 2026
Pathophysiology of Pain. NCBI Bookshelf

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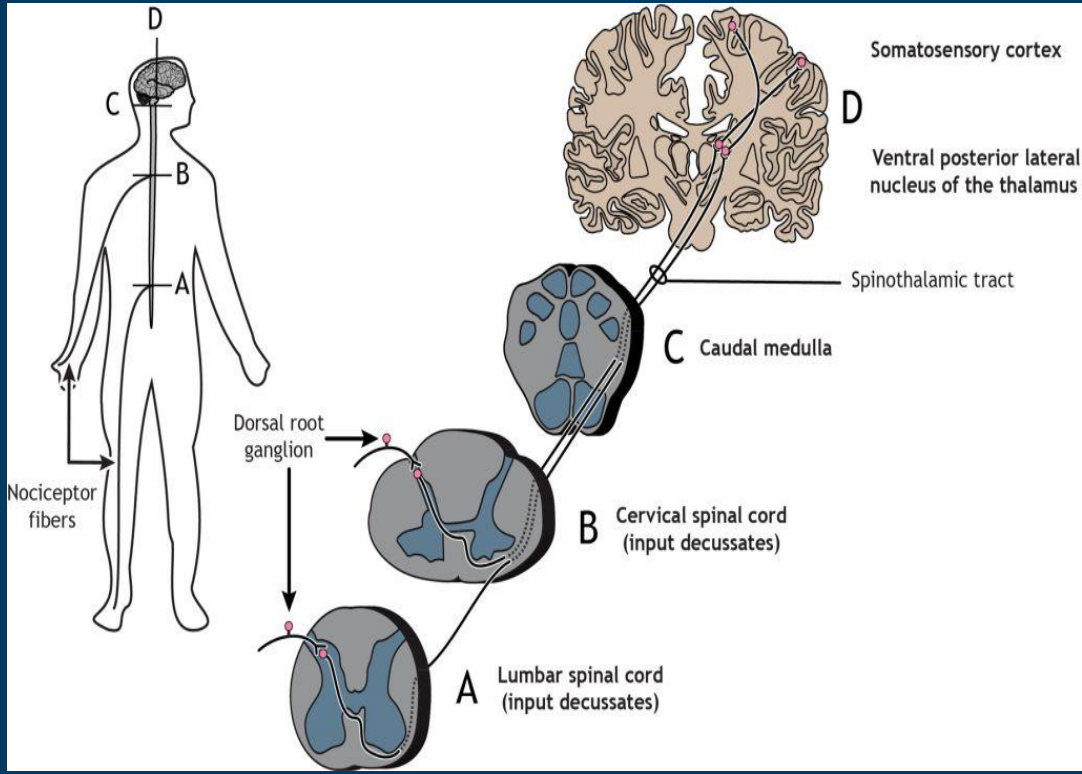
Pathophysiology cont.

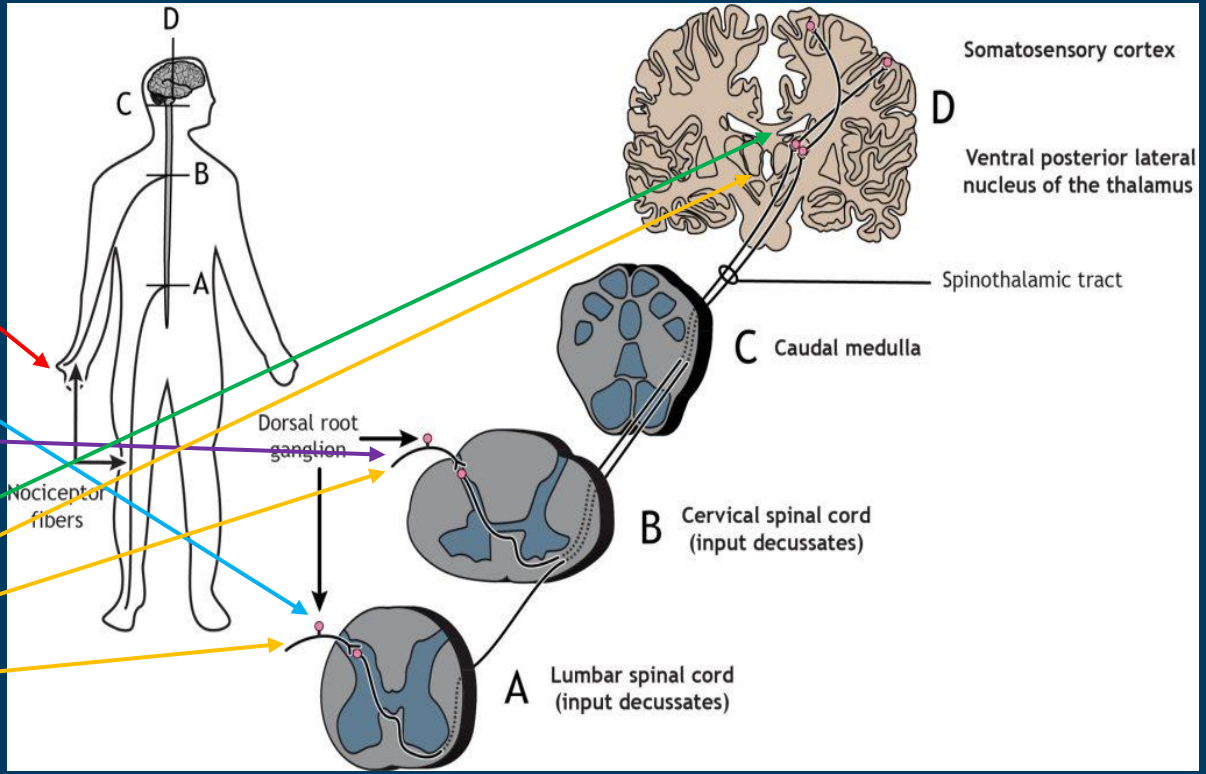
- Descending modulation
  - The brainstem sends inhibitory signals back down the spinal cord → dampening or amplify pain
- Net pain experience
  - Peripheral input vs. central inhibitory/facilitatory control



Pathophysiology of Pain. NCBI Bookshelf
McIntyre MK, et al. Introduction to Neuroscience. 2026

Pharmacology

- NSAIDS
  - Prostaglandin
- SNRIs/TCAs
  - Norepinephrine
- Ketamine
  - Glutamate
  - NMDA
- Acetaminophen
  - Ion Channels
- Opioids



McIntyre MK, et al. Introduction to Neuroscience. 2026 Pathophysiology of Pain. NCBI Bookshelf

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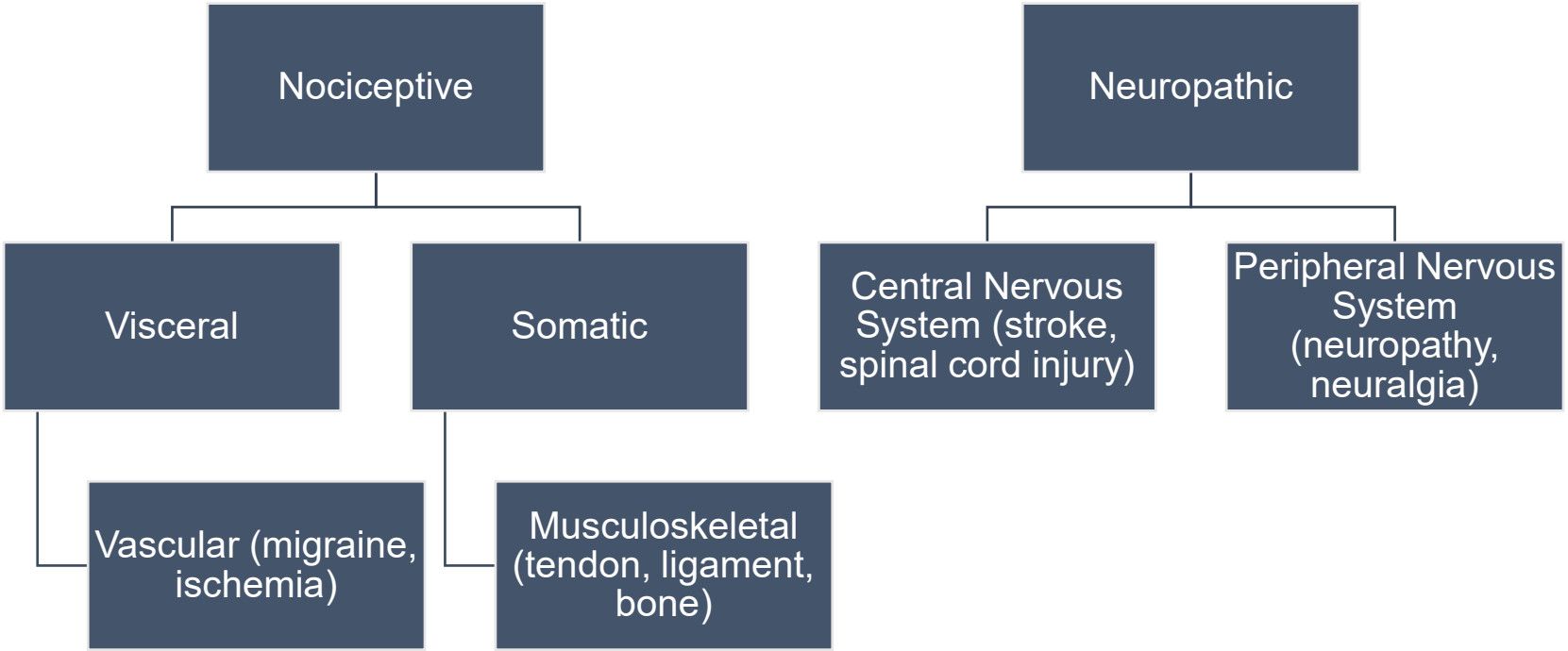
Common Types of Pain



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J Pain Symptom Manage. 2009;38(3):418-425.

Assessment of Pain

Provocative/Palliative

- What makes pain worse/better?

Quality

- What does it feel like?

Region

- Where is it located/spread?

Severity

- Pain intensity on scale of 1-0

Timing

- Duration, frequency, pattern

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Lapum J et al. The PQRSTU Assessment. 2019

Multimodal Analgesia

Targeting of various receptors at once to mitigate expression of pain

Goal is to minimize use of opioids → minimizing adverse effects such as respiratory depression, opioid dependence

Has been shown to reduce opioid consumption by 30-50% in post-operative patients

Pathophysiology of Pain. NCBI Bookshelf
Mayo Clin Proc Innov Qual Outcomes. 2021

Multimodal Analgesia

Mechanism	Medications
NMDA receptor antagonist	Ketamine
Serotonin-norepinephrine reuptake inhibitors (SNRI)	Duloxetine, Milnacipran, Venlafaxine
Tricyclic Antidepressants	Amitriptyline, Nortriptyline, Desipramine
Anticonvulsant (α2δ voltage-gated Ca^{2+} channel binder)	Gabapentin, Pregabalin
Sodium channel blockade	Local anesthetics (e.g., lidocaine)
Central analgesic (prostaglandin inhibition)	Acetaminophen
COX inhibitors (anti-inflammatory)	NSAIDs (e.g., ibuprofen, diclofenac, ketorolac, celecoxib)
Alpha 2-adrenergic agonists	Clonidine, Dexmedetomidine

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ASRA. Multimodal Analgesia: Role of Non-Opioid Analgesics. 2019.
Cochrane Database Syst Rev. 2023

Why Ketamine?

- Provides effective analgesia and sedation through various routes of administration
- Preserves hemodynamics and respiratory status
- Reduces reliance on narcotics/opioids for pain management
- NMDA antagonism is useful in opioid-induced hyperalgesia

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Rosenbaum A, et al. Ketamine. 2024.

Assessment Question #1

Which of the following is a benefit of multimodal analgesia?

a) Allows for higher doses of opioids

b) Increases number of medications taken by the patient

c) Decreases opioid utilization and risk of opioid induced adverse effects

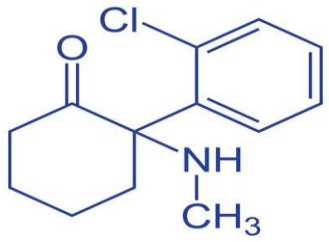
d) Relies on only one mechanism of analgesia

Analgesic Mechanism of Action

Mechanisms

- Primary: N-methyl-D-aspartate (NMDA) receptor antagonist
- Decreases pain signal processing and produces dissociative state by interrupting cortical-limbic pathways
- Weakly interacts with opioid, dopamine, and monoaminergic systems at high/prolonged doses
- Blocks NMDA-mediated central sensitization, restoring opioid receptor responsiveness in opioid-induced hyperalgesia

Ketamine



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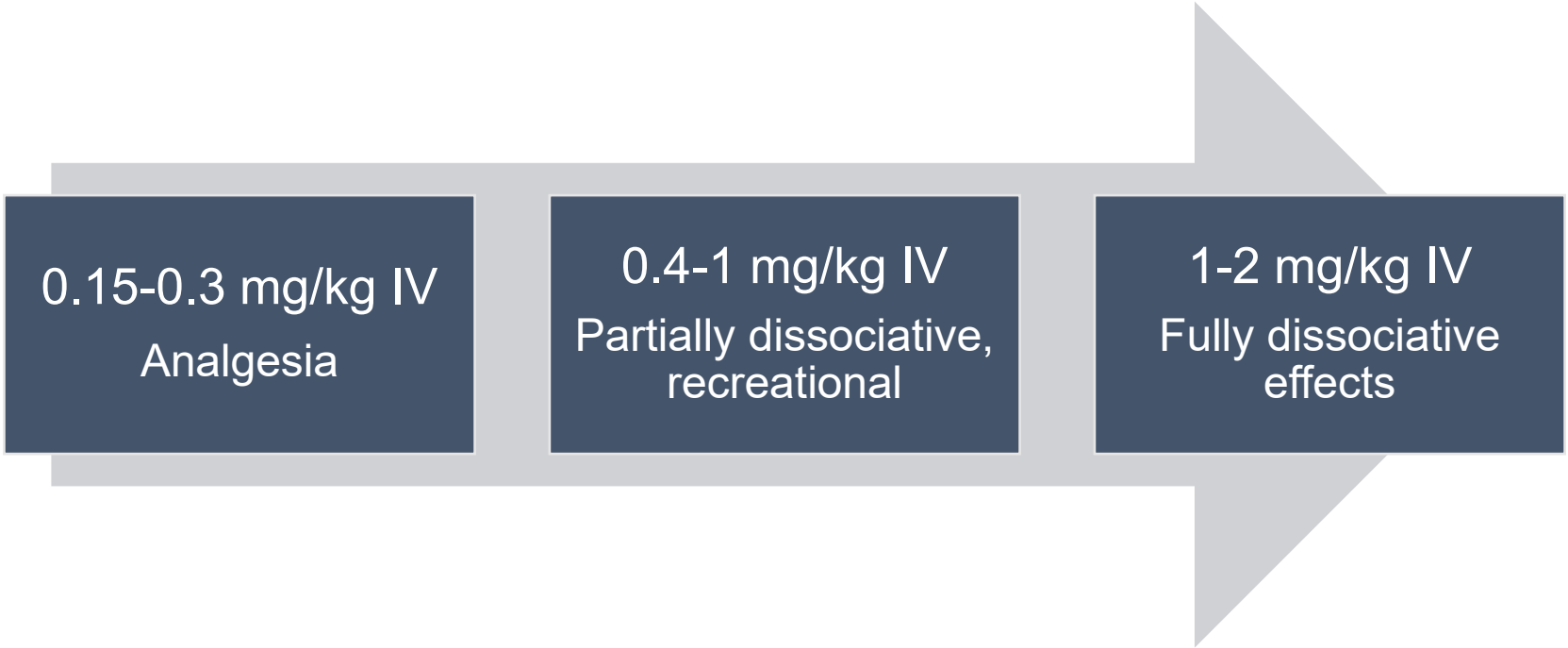
Rosenbaum A, et al. Ketamine. 2024.
FDA Ketalar® Label. 2017.

Dose Dependent Effects



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Rosenbaum A, et al. Ketamine. 2024.

Routes of Administration for Pain Management

- Oral
- Nebulization
- Intravenous
- Intranasal
- Intramuscular

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Rosenbaum A, et al. Ketamine. 2024.

General Principles

Can be used in both inpatient and outpatient settings

Efficacious in all types of severe pain (i.e. chronic, traumatic, abdominal/flank pain, etc.)

Sub-dissociative dosing is used alone or in conjunction with other analgesics

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Rosenbaum A, et al. Ketamine. 2024.

Pharmacokinetics

Highly lipophilic

- Initial redistribution half-life: ~7-15 min

Extensively metabolized via CYP2B6 and CYP3A4

Elimination half-life: ~2.5-3 hours

Excretion: mainly urine (~91% over 1-2 days)

- Metabolites: norketamine, hydroxynorketamine , dehydronorketamine, and hydroxyketamine

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Rosenbaum A, et al. Ketamine. 2024.

Adverse Effects

Behavioral

- Confusion, hallucinations, agitation, emergence delirium

Respiratory

- Laryngospasm

Cardiovascular

- Tachycardia, hypertension

Motor

- Spastic jerking, nystagmus

GI

- Vomiting, increased salivation/secretions
- Hepatotoxicity

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Ketamine (Rosenbaum, 2024), et al.

Warnings/Precautions

Avoid

- Pregnancy
- High risk coronary artery disease
- Age < 3 months
- Severe hepatic failure
- Active psychosis
- Cocaine intoxication

Use Caution In

- History of schizophrenia
- Breastfeeding
- Hypertension, presence of aneurism
- Heart failure, pulmonary hypertension

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CHOC. Low-Dose Ketamine Infusion for Analgesia. 2021.
ASHP et al. Ketamine Use in Prehospital & Hospital Treatment. 2020

Subanesthetic Intravenous Bolus Ketamine

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IV Bolus Ketamine

Common Indications

- Procedural Pain
- Acute Trauma
- When opioid-related adverse effects are a concern (e.g., hypotension/respiratory depression risk)
- Opioid tolerant patients

Settings

- Emergency Department
- Pre-hospital/EMS

Dosing schemes

- 0.1-0.3 mg/kg IV
- May give slow IV push over 1 minute or IV piggyback over 10-15 minutes
- Can be repeated as needed for additional analgesia

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Rosenbaum A, et al. Ketamine. 2024.
Orhurhu V J, et al. StatPearls. 2025.

IV Bolus Ketamine

Onset of action

- 10-30 seconds

Monitoring

- Baseline heart rate, respiratory rate, blood pressure
- Continuous SpO2
- Every 15 min, then until procedure complete/supplemental O2 discontinued

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Rosenbaum A, et al. Ketamine. 2024.

IV Bolus Dosing Strategies

Lovett et al. 2021

Objectives

- Compare 0.15 mg/kg vs 0.30 mg/kg IV sub-dissociative ketamine for analgesia in ED patients with acute moderate-severe pain
- Test noninferiority of lower dose vs higher dose for pain reduction at 30 minutes

Methods

- Randomized, double-blind, noninferiority trial
- Adults 18-59 yrs with acute pain in ED
- Ketamine infused over 15 min

Primary endpoint: Numeric Rating Scale (NRS) pain score at 30 min

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Lovett S, et al. *Acad Emerg Med*. 2021.

IV Bolus Dosing Strategies

Results

- Mean NRS at 30 min:
  - 0.15 mg/kg: 4.7 (95% CI 3.8-5.5)
  - 0.30 mg/kg: 5.0 (95% CI 4.2-5.8)
  - Mean difference: 0.4 (95% CI; 0.8 to 1.5)

Adverse effects: Similar at 30 min between groups

Conclusion

- 0.15 mg/kg IV subdissociative ketamine is noninferior to 0.30 mg/kg for ED acute pain at 30 min
- Suggests lower dose (0.15 mg/kg) may be appropriate dosing strategy

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Lovett S, et al. *Acad Emerg Med*. 2021.

Subanesthetic Intranasal Ketamine

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IN Ketamine

Common indications

- Adult/Pediatric acute pain in the ED or prehospital setting
- When IV access delayed/difficult
- Burn care: dressing changes – reduces secondary hyperalgesia vs opioids

Avoid IN route if nasal obstruction/trauma/bleeding present

Common dosing

- 1 mg/kg IN
- Fixed 50 mg IN in adult traumatic pain

Preparation

- **Not the manufactured esketamine nasal spray for depression**
- Concentration: 10 mg/ml or 50 mg/ml vial
- Target volume ~0.3–0.5 mL per nostril (max 1 mL per nostril)
- Attach a mucosal atomization device to the end of the syringe

Administration

- Spray rapidly into the patient's nostril
- Split total dose between both nostrils to improve absorption

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Seak YS, et al. J Clin Med. 2021.

IN Ketamine

Bioavailability ~25–50%

Onset within ~10 minutes and may last up to ~60 minutes

Monitoring

- Allow for 10 min onset to occur prior to assessing pain, vitals, mental status

Seak YS, et al. *J Clin Med*. 2021.

Assessment Question #2

Which of the following is important to remember when administering intranasal ketamine for pain?

a) The manufactured esketamine nasal spray is a suitable option for these patients

b) Onset of action may be delayed compared to IV bolus administration

c) The larger the volume, the better it will be absorbed

d) Intranasal administration is not recommended in pediatric patients

Subanesthetic Intramuscular Ketamine

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IM Ketamine

Settings

- Adult/Pediatric acute pain in the ED or prehospital setting
- When IV access delayed/difficult
- Outpatient clinic for chronic pain, migraines
  - Used when IV access is unattainable or infusion duration is undesirable

Dosing

- 0.35-1 mg/kg IM
- Concentration: 10 mg/ml or 50 mg/ml vial
- Max quantity: 1-2 ml for adults, 1 ml for pediatrics
- Can be repeated 1-2x per week for 2-6 weeks, then every 2-6 weeks thereafter

Riccardi A, et al. J Clin Med. 2023
Orhurhu VJ, et al. StatPearls. 2025
Gutierrez JJ, et al. StatPearls. 2023

IM Ketamine

Bioavailability 93%

Onset ~15 minutes, duration ~60 min

Monitoring

- Injection site discomfort
- Duration of monitoring

Riccardi A, et al. J Clin Med. 2023.
Orhurhu VJ, et al. StatPearls. 2025

Comparing Administration Routes

Fuller et al. (2024)

Objective

- Evaluate efficacy & safety of low-dose ketamine (<0.5 mg/kg) for acute pain

Settings

- Prehospital (civilian + military) and ED

Methods

- Scoping narrative review of prospective & retrospective studies (pre-Jan 30, 2024)
- Total studies included: n = 64
- Prehospital: n = 21 (4 RCTs)
- Emergency Department: n = 43 (28 RCTs)

Outcomes

- Pain score reduction (NPS/VAS)
- Opioid consumption (opioid-sparing effect)
- Adverse events
- Rescue analgesia use

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Fuller et al. *Am J Emerg Med* 2024

Results

IV Ketamine

- 8 RCTs, n = 1,191
- Noninferior to morphine for pain reduction within first 60 min
- Adjunct use reduced opioid requirements by 15–50%
- Doses <0.5 mg/kg not associated with significant serious adverse events

IN Ketamine

- Prehospital RCT, n = 120
- ≥2-point pain reduction: 76% ketamine vs 41% IN fentanyl
- Absolute difference 35% (95% CI 17–51%), p = 0.002
- Higher rate of minor AEs (dizziness, dissociation); no serious cardiopulmonary events

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Fuller et al. *Am J Emerg Med* 2024

Results

IM Ketamine

- Dosing was typically 0.5-1 mg/kg
- Dissociative symptoms reported around 0.43-0.65 mg/kg
- Prehospital retrospective cohort, n = 158
- 98% effective; mean pain reduction 9/10 → 3/10
- Respiratory depression rare (5%) and transient (<30 sec)

Conclusions

- Noninferior to opioids
- Demonstrates meaningful opioid-sparing (15-50% across studies)
- Associated primarily with minor, transient adverse effects
- Effective via IV, IN, and IM routes in ED and prehospital settings

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Fuller et al. *Am J Emerg Med* 2024

Subanesthetic Ketamine Continuous Infusion

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Ketamine Continuous Infusion

Common Indications

- Neuropathic pain
- Complex Regional Pain Syndrome
- Phantom limb pain
- Spinal cord injury pain
- Refractory headache disorders
- Post-operative pain
- Sickel cell pain crisis

Settings

- Does not require ICU admission
- Can be administered in ICU, non-ICU floor, outpatient clinic
- Preserves a normal level of wakefulness

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Cohen et al., Reg Anesth Pain Med. 2018

General Dosing Strategy

Parameters

- 0.05-1 mg/kg/hr

Inpatient

- Duration can span from 2 hours to multiple days

Outpatient

- Duration typically 1-4 hours
- Frequency is often patient specific
  - Every 3 weeks to 3 months

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Cohen et al., Reg Anesth Pain Med. 2018

anesthesiology, critical care, pain mgmt, and palliative/hospice

Inpatient Setting

Wake Market Protocol	Mountain West Order set
• 0.05 - 0.5mg/kg/hr, max of 1 mg/kg/hr • Maximum of 0.5 mg/kg/hr in pediatric patients • Restricted to Regional Anesthesia and Acute Pain Management Service, pain APPs, physicians, and fellows	• 0.06-0.25 mg/kg/hr • Restricted to PACU, ICU, pain management, or palliative/hospice

Cohen et al. Reg Anesth Pain Med 2018
Advocate Health. Ketamine sub-anesthetic infusion protocol (inpatient). 2025.

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Further Considerations

- Must be infused with locked smart infusion pump
- Requires nursing double-check at initiation and dose change
- Monitoring hemodynamics every 30 min x2, then every 4h thereafter

Cohen et al. Reg Anesth Pain Med 2018
Advocate Health. Ketamine sub-anesthetic infusion protocol (inpatient). 2025.

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Ketamine Infusion on Non-ICU Units

Sheehy et al. (2017)

Study Design

- Longitudinal cohort from 2006-2014
- 30 patients
- Continuous IV ketamine ≤1 mg/kg/hr
- Administered on regular inpatient floor (non-ICU) with monitoring

Pain Outcomes

- Mean pain score decreased from 6.65 (95% CI 6.39–6.91) to 4.38 (95% CI 4.06–4.69) $p < 0.001$
- Greater reduction with longer infusion duration ($p = 0.004$)

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Sheehy KA, et al. J Pain Res. 2017

Ketamine Infusion on Non-ICU Units

Opioid-Sparing Effect

- Oral morphine equivalents decreased from 2.74 mg/kg/day (95% CI 2.47–3.00) to 2.06 mg/kg/day (95% CI 1.81–2.31) $p<0.001$
- 52% achieved ≥20% reduction in opioid use
- Greater reduction with longer infusions ($p = 0.022$)

Safety

- No hallucinations or psychotic effects requiring intervention
- No hemodynamic instability requiring vasoactive agents

Conclusion

- Continuous subanesthetic ketamine infusions on regular hospital floors were associated with significant pain reduction and opioid sparing effect, demonstrating feasibility and safety outside of the ICU

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Sheehy KA, et al. J Pain Res. 2017

Wake Market Outpatient Protocol

Administered in pain clinic

Overseen by pain provider

Dosing

- 0.05 mg/kg/hr and increase the infusion rate approximately every 30 minutes
- Same range as inpatient protocol (commonly 0.3 - 0.5mg/kg/hr, max of 1 mg/kg/hr)
- Ideal Body Weight is used
  - Max. dosing weight of 70 kg

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Advocate Health. Ambulatory sub-anesthetic ketamine infusion guideline. 2024

Ketamine in Chronic Pain

Odutla et al. 2023 – Meta Analysis

Objective

- Evaluate the efficacy and safety of intravenous ketamine infusion vs control for chronic pain across multiple trials and conditions

Participants

- 16 studies included involving 1,080 chronic pain patients, including neuropathic pain, fibromyalgia, CRPS, phantom limb pain
- 5 studies in outpatient setting, 11 inpatient

Outcomes

- Primary: Pain score reduction
- Secondary: Quality of sleep, side effects (nausea, hallucinations, sedation)

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Odutola & Gupta, et al. Med Adv 2023

Ketamine in Chronic Pain

Results

- Pain reduction: Significant mean reduction in pain with ketamine vs control (−1.05 (95% CI −1.72 to −0.39; p = 0.002)
- Median infusion dose: 0.3 mg/kg/hr
- Median infusion duration: 61 hours
- Quality of sleep: No significant difference (95% CI −0.12 to 0.12; p = 1.00)
- Adverse effects: No significant difference between ketamine vs placebo

Conclusions

- IV ketamine infusion is efficacious and overall safe for chronic pain, showing significant pain reduction compared to control with no increased adverse effects

Odutola & Gupta, et al. Med Adv 2023

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Subanesthetic Oral Ketamine

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Oral Ketamine

Common Indications

- Refractory cancer pain
- Neuropathic pain syndromes
- Considered after inadequate response to opioids or adjuvants

Settings

- Inpatient: transition from IV ketamine infusion after positive response
- May be continued outpatient
- Alternative to continuous infusion

Common Dosing

- 0.5-1.5 mg/kg/day divided 3-4 times daily
- Titrate by 10-25 mg every 48-72hr (max 800 mg/day)

No standardized IV:PO conversion ratio

- 3:1 conversion is commonly used clinically

Riccardi A, et al. J Clin Med. 2023
UIC Drug Information Group. 2022
VA PBM, VHA Hospice/Palliative Care Ketamine Guidance. 2024

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Oral Ketamine

Preparation Inpatient

IV ketamine solution administered orally

- 20 mL of 50 mg/mL ketamine + 80 mL NS
- Final concentration: 10 mg/mL
- Often flavored to mask bitterness

Preparation Outpatient

Must be compounded at a compounding pharmacy

- Common compounded strength: 40 mg/5 mL oral solution
- Refrigerated; typical beyond-use date: ~14 days
- **No FDA-approved oral product for pain**

Pharmacokinetics

Oral bioavailability ~16-29% (extensive first-pass metabolism)

- Peak plasma concentration ~20-30 minutes

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Riccardi A, et al. J Clin Med. 2023
UIC Drug Information Group. 2022

Oral Ketamine In Chronic Pain

Marchetti, et al. (2015)

Objective

- Assess efficacy and safety of oral ketamine for relief of intractable chronic pain in patients treated at home over 5 years

Methods

- Retrospective 5-year cohort (51 patients, 60% neuropathic pain)
- Ketamine initially trialed IV (1.5-3.0 mg/kg/day) then converted to oral OR started directly oral
- Oral doses delivered in 3-4x daily intakes, titrated up from 0.5 mg/kg in 15-20 mg increments

Outcomes

- Primary: Pain reduction
- Secondary: Opioid-sparing effect and safety/adverse events

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Marchetti F, et al. Eur J Pain. 2015.

Oral Ketamine In Chronic Pain

Results

- Mean effective oral dose: 2 mg/kg/day
- Pain Reduction: Seen in 44% of patients; mean pain reduction 67 ± 17%
- Partially effective: 20% of patients; mean pain reduction 30 ± 11%
- Opioid-sparing (with or without pain reduction): mean reduction of opioid use 63 ± 32%
- Treatment failure: 22%

Patients on baseline opioid therapy

- Lower failure rate (7% vs 36%; $p < 0.02$)
- Fewer adverse effects (33% vs 68%; $p < 0.01$)

Safety

- ~50% experienced adverse effects; only 8 stopped therapy
- Reported AEs included headache, hallucinations, malaise, dizziness, sedation

Conclusion

- Oral ketamine reduced or abolished pain in ~66% of chronic, refractory pain patients
- Demonstrated substantial opioid-sparing effect

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Marchetti F, et al. Eur J Pain. 2015.

Assessment Question #3

Based on available literature, which of the following is true regarding ketamine's role in analgesia?

a) Ketamine has been consistently proven superior to other opioids

b) Ketamine has been consistently proven inferior to other opioids

c) Ketamine has been shown to be noninferior to most opioids with an opioid sparing effect

d) Ketamine should not be used for analgesia

Subanesthetic Nebulized Ketamine

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Nebulized Ketamine

Common Settings

- Adult/Pediatric ED for acute pain
- Useful when IV access delayed/unavailable
- Benefit: Non-invasive, alternative to opioids

Dosing

- 0.75 mg/kg, 1 mg/kg, or 1.5 mg/kg via nebulizer
- Lowest studied effective dose: 0.75 mg/kg
- May repeat dose based on response
- Estimated nebulized bioavailability: ~20-40% of IV dose

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Drapkin J, et al. Clin Pract Cases Emerg Med. 2020

Nebulized Ketamine

Preparation

- IV ketamine solution injected into nebulizer cup
- Administer via breath-actuated nebulizer
- Can dilute with 0.9% Sodium Chloride per device volume needs

Onset

- 15 minutes

Duration

- 60-120 minutes
- Tmax ~15-22 minutes

Adverse Effects / Monitoring

- Mild dizziness, fatigue, mood changes reported
- No significant hemodynamic instability in case reports
- Monitor pain score, mental status, BP, HR, RR, SpO_2

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Drapkin J, et al. Clin Pract Cases Emerg Med. 2020

Patient Selection for Ketamine

- Patients with opioid-refractory pain or escalating opioid requirements, including opioid-induced hyperalgesia
- Opioid-tolerant or opioid-dependent patients where further opioid escalation may worsen central sensitization
- Pain driven by neuropathic mechanisms or central sensitization
- Patients at high risk of opioid-related adverse effects (respiratory depression, hypotension)

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Riccardi A, et al. J Clin Med. 2023

Mitigating Adverse Effects

Dissociative reaction (e.g. agitation, hallucinations, confusion or delirium)

- Adults: Lorazepam 1-2 mg IV x1 (repeat if needed)
- Pediatric: Lorazepam 0.05-0.1 mg/kg (max 2mg) IV
- Reduce dose if reaction is tolerable; discontinue if unsafe to patient or care team

Hypersalivation

- Atropine 0.01 mg/kg (max 0.5 mg) IV

Laryngospasm

- Administer slowly if giving IV push
- Jaw thrust → intubation in severe cases

Advocate Health. Ketamine sub-anesthetic infusion protocol (inpatient). 2025.
Riccardi A, et al. J Clin Med. 2023

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Assessment Question #4

Which of the following is an appropriate strategy to mitigate an emergence reaction secondary to ketamine?

a) Increase the infusion rate

b) Add on additional opioid therapy

c) Ensure patient does not receive ketamine again

d) Administer IV dose of a benzodiazepine

Summary/Conclusion

- Ketamine is a versatile medication that has been proven to adequately provide analgesia and reduce need for opioid use
- It is useful as adjunctive therapy in patients that are opioid tolerant or are at risk for respiratory depression
- It can be administered in a variety of ways, inpatient and outpatient, for adult and pediatric patients alike
- While its safety profile is favorable, patient's vitals, oxygen status, and mental status must be monitored during and after administration

Questions?

Jacob Powell
Jacob.powell@advocatehealth.org

Ketamine: Dissociating Pain from the Patient

Jacob Powell, PharmD
PGY2 Emergency Medicine Pharmacy Resident
Atrium Health Cabarrus, Concord, NC
March 31, 2026