REVIEW ARTICLE

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Ketamine for Acute Pain in the ED: Mechanisms, Protocols, and Safety Considerations

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Abstract

Background: Acute pain is one of the most frequent presenting complaints in emergency departments (EDs). In the context of the global opioid crisis, there is increasing interest in effective non-opioid and opioid-sparing analgesic strategies. Ketamine, at subanesthetic doses, has emerged as a valuable option for acute pain management due to its unique pharmacologic profile.

Objectives: This narrative review aims to synthesize current evidence on the mechanisms of analgesia, clinical efficacy, dosing protocols, and safety considerations of ketamine for acute pain management in adult ED patients.

Methods: A comprehensive narrative review of the literature was conducted using recent randomized controlled trials, systematic reviews, meta-analyses, and international guidelines focusing on ketamine use for acute pain in emergency settings. Studies from diverse geographic regions and healthcare systems were included to provide a global perspective.

Results: Evidence consistently demonstrates that subdissociative-dose ketamine provides analgesia comparable to opioids for acute pain in the ED. Typical intravenous doses of 0.1–0.35 mg/kg, administered as a bolus or infusion, achieve rapid pain relief while preserving respiratory drive and airway reflexes. Ketamine is associated with higher rates of transient neuropsychiatric effects, such as dizziness and emergence reactions, but lower risks of respiratory depression compared with opioids. Alternative routes of administration, including intranasal and subcutaneous, offer additional flexibility in selected patients.

Conclusion: Ketamine is a safe and effective alternative or adjunct to opioids for acute pain management in the emergency department when used at appropriate subanesthetic doses. With proper patient selection, monitoring, and adherence to established protocols, ketamine can play a central role in multimodal ED analgesia strategies aimed at improving pain control while reducing opioid exposure.

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Introduction

Ketamine is increasingly used in emergency departments (EDs) worldwide as an analgesic, especially in the context of the opioid crisis and the push for multimodal pain management(1, 2). Its unique pharmacology – combining dissociative anesthesia with robust analgesia at subanesthetic doses – makes it attractive for acute pain. In practice, ketamine can spare opioids, mitigate tolerance/hyperalgesia, and preserve respiratory drive, while providing rapid pain relief(1, 3).

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However, its use requires familiarity with its mechanisms, optimal dosing protocols, and distinctive side-effect profile. This review summarizes ketamine's analgesic mechanisms, evidence of efficacy in ED acute pain, dosing strategies (bolus, infusion, adjunct use), comparison to opioids, and safety considerations (psychotomimetic and cardiovascular effects), drawing on the latest clinical trials, meta-analyses, and guidelines from diverse global settings.

Figure: Ketamine vials prepared for injection (e.g. 50 mg/mL concentration). Using such vials, an analgesic dose (e.g. 0.3 mg/kg for a 70-kg patient ≈21 mg) can be drawn and given as a weight-based bolus(2). Guidelines typically allow IV boluses up to ~0.35 mg/kg for analgesia, often followed by slow infusion (e.g. ~1 mg/kg/hr) for continued effect(3).

Pharmacological Mechanisms of Ketamine Analgesia

Ketamine's analgesic action is mediated by multiple receptor systems. Primarily, it is a non-competitive NMDA (N-methyl-D-aspartate) receptor antagonist in the central nervous system(2, 4). By blocking NMDA receptors on spinal and supraspinal neurons, ketamine interrupts "wind-up" and central sensitization to nociceptive input, reducing pain perception. Its blockade of NMDA also accounts for dissociative and psychotomimetic effects at higher doses(4, 5). Ketamine also inhibits hyperpolarization-activated cyclic nucleotide-gated (HCN1) channels and modulates other receptors: sodium and potassium channels, opioid receptors, GABA_A, dopamine, cholinergic, and serotonin (5-HT_2A) systems (2). This polypharmacology contributes to analgesia (through synergistic antinociceptive pathways) and to side effects. For example, ketamine can indirectly stimulate descending monoaminergic analgesic pathways by increasing norepinephrine and dopamine release and inhibiting their reuptake(4, 6).

Anti-inflammatory effects may also play a role in ketamine's pain relief. Experimental studies show ketamine attenuates microglial activation and pro-inflammatory cytokine release, which may blunt hyperalgesia and prolong pain relief beyond the drug's half-life (7). Clinically, even a single low dose (e.g. 0.15 mg/kg IV) can relieve pain in acute and chronic settings, suggesting secondary mechanisms (e.g. synaptic plasticity changes) may contribute. Importantly, racemic ketamine consists of S(+) and R(−) enantiomers, with S-ketamine being more potent at NMDA receptors (and more analgesic) and R-ketamine causing fewer psychotomimetic symptoms(6).

In summary, subanesthetic ketamine (usually defined as ≤0.5 mg/kg IV) produces analgesia primarily by NMDA antagonism, with supplementary contributions from other receptor effects(2, 4). Its dose-dependent NMDA blockade explains both analgesia and dissociation: lower doses relieve pain with minimal mental status change, whereas higher doses cause anesthesia and vivid hallucinations (5, 6). Importantly, ketamine preserves airway reflexes and respiratory drive even at anesthetic doses(6, 7), distinguishing it from opioids. Clinicians exploit these features by administering small, titratable IV boluses (often 0.1–0.3 mg/kg) or infusions for acute analgesia, balancing benefit against risk of emergence reactions.

Clinical Efficacy in ED Acute Pain

Ketamine has been studied extensively for ED analgesia. Numerous randomized trials and meta-analyses (across the US, Europe, Asia, and beyond) show that low-dose ketamine provides pain relief comparable to standard opioids. In the most direct comparison, Motov et al. (2015, USA) randomized 90 ED trauma patients with severe pain to ketamine 0.3 mg/kg IV versus morphine 0.1 mg/kg IV(8). Both groups had similar pain score reductions at 30 minutes (mean drop ~4 points on an 11-point scale), with no statistically significant difference. No serious adverse events occurred, though ketamine patients reported more transient dizziness. The authors concluded ketamine "provides analgesic effectiveness and apparent safety comparable to that of intravenous morphine" for short-term ED pain(8).

These findings are echoed in large meta-analyses. Zhang et al. (2025, China) pooled 20 RCTs (n≈2550) comparing IV low-dose ketamine to morphine for ED acute pain. Pain scores at 15–120 minutes were statistically indistinguishable between ketamine and morphine (standardized mean differences ~0)(9). Ketamine did not significantly change need for rescue analgesia. Similarly, Ying and Zuo (2023, China) reviewed 15 trials (n≈1600) of ketamine (≤0.5 mg/kg) vs opioids. They found "ketamine might have higher or

equivalent efficacy and safety" compared to opioids(10). These analyses affirm that ketamine, on average, matches opioid analgesia in the ED.

Other trials suggest ketamine can even surpass opioid analgesia in certain protocols. Moradi et al. (2022, Iran) compared 0.3 mg/kg IV ketamine with 2 mg IV haloperidol versus IV fentanyl (dose undisclosed). The ketamine+haloperidol group had significantly lower pain scores at 5, 10, 15, and 30 minutes post-dose. Fewer ketamine patients required rescue analgesia (9% vs 34% in the fentanyl group). The authors concluded that ketamine (with haloperidol to mitigate agitation) "worked better than fentanyl in controlling acute pain" (11). While combining a neuroleptic is not routine, this suggests that ketamine's analgesic potential can exceed that of opioids in some settings.

Table 1. Selected dosing protocols for ketamine analgesia in adult ED patients.

Route/Setting	Ketamine dose	Examples/notes	References
IV bolus (analgesia)	0.1–0.35 mg/kg (commonly ~0.3)	Single weight-based dose for acute pain. May repeat or follow with infusion (2).	[23†L142-L147], [41†L240-L244]
IV infusion	0.1–1.0 mg/kg/hr (often 0.1–0.5)	Often given after an initial bolus. E.g. 0.15 mg/kg bolus + 0.15 mg/kg over 30 min(1). Guidelines: ~1 mg/kg/hr max for acute pain(3).	[23†L155-L162], [41†L240-L244]
Adjunct (multimodal)	Ketamine added to opioid regimen	E.g. adding 0.1–0.3 mg/kg IV ketamine to reduce opioid needs(1). No single protocol – guided by patient response.	[23†L132-L139]
Intranasal (IN)	0.5–2 mg/kg (often ≈1 mg/kg or fixed 50 mg)	Rapid administration without IV. Pediatric trials used 1.5 mg/kg (12); adult EMS studies used ~50 mg (13).	[42†L269-L277], [44†L359-L367]
Subcutaneous (SC)	~20–50 mg (≈0.3–0.5 mg/kg)	Alternative route in resource-limited or difficult IV access settings. E.g. 20 mg used for ED trauma (14).	[45†L89-L97]

Adjunctive and alternative routes also show benefit. Intranasal (IN) ketamine has been studied primarily in pediatric trauma, where one large trial found IN ketamine 1.5 mg/kg noninferior to IN fentanyl 2 μg/kg (12). In adults, McMullan et al. (2024, US) tested adding 50 mg IN ketamine to IV fentanyl in prehospital trauma. They found no additional pain relief from ketamine beyond fentanyl alone (13) – suggesting that, in patients already receiving adequate opioids, low-dose IN ketamine may not further reduce pain. A recent Tunisian trial (Dhaoui et al. 2025) randomized 1,194 ED patients with musculoskeletal trauma to 20 mg ketamine SC vs 20 mg IN. Both routes gave similar pain reduction (~3.7–4.4 point NRS drop at 30 min), with no clinically important difference (14). These findings indicate that ketamine via IN or SC routes can be effective, providing flexibility where IV access is limited.

Table 2 summarizes key ED studies and meta-analyses. In general, evidence from around the world (US, China, Iran, Tunisia, etc.) indicates that subdissociative ketamine yields analgesia on par with opioids in acute pain, whether used as primary agent or adjunct(8-10). Some protocols report faster or more opioid-sparing relief with ketamine, but at the cost of more minor CNS effects. Overall, recent data support ketamine as a viable alternative to opioids for emergency analgesia, consistent with noninferiority seen in systematic reviews (10, 15).

Study (year, region)	Ketamine regimen	Comparator	Analgesia outcome	Adverse effects (ketamine vs comp)
Motov et al. (2015, US)(8)	0.3 mg/kg IV	0.1 mg/kg IV morphine	No difference in pain reduction at 30 min(8)	More dizziness (34% vs 11%) and emergence reactions with ketamine
Moradi et al. (2022, Iran) (11)	0.3 mg/kg IV + 2 mg IV haloperidol	IV fentanyl	Ketamine group had greater pain reduction (5–30 min) (11)	More agitation with ketamine (mitigated by haloperidol)
Zhang et al. (2025, China, meta)(9) (9)	IV ketamine ≤0.3 mg/kg	IV morphine	No sig. difference in pain (15–120 min)(9)	Dizziness ↑ (RR 1.48) and emergence ↑ (RR 19.1) with
Ying et al. (2023, China, meta)(10)	IV ketamine <0.5 mg/kg	IV opioids	Equivalent efficacy to opioids(10)	Psychological effects ↑ (RR 2.83, trend) with ketamine(10)
McMullan et al. (2024, US EMS) (13)	50 mg IN + IV fentanyl	IV fentanyl alone	No difference in pain relief at 30 min (13)	No significant difference in side effects (13)
Dhaoui et al. (2025, Tunisia)	20 mg SC vs	–	Both routes similarly reduced	Minor effects (nausea, sedation)

Table 2 highlights representative clinical trials and reviews comparing ketamine to opioids. Across settings, ketamine produced equivalent pain relief, though often with higher rates of certain side effects. For instance, Meta-analyses show no significant difference in pain scores up to 2 hours between ketamine and morphine, but consistently report more dizziness and psychomimetic phenomena with ketamine(9, 10).

Comparison to Opioid Therapy: Efficacy and Side Effects

When compared directly with opioids, ketamine's analgesia is comparable but its side-effect profile differs. Efficacy is similar: systematic reviews uniformly find ketamine is not inferior to morphine or fentanyl for acute pain in adults (10, 15). Many trials note equivalent reductions in NRS pain scores whether patients receive ketamine or an opioid. In some studies, ketamine may even provide faster relief (as in Moradi et al. above), or allow for opioid-sparing regimens. For example, ketamine can reduce the total opioid dose needed and block opioid tolerance and hyperalgesia(1). In practice, this means ketamine is a useful alternative or adjunct for patients with opioid contraindications (e.g. allergy, OUD history) or those who have not responded to opioids.

Side effects contrast sharply. Opioids (morphine, fentanyl) commonly cause nausea, vomiting, pruritus, respiratory depression, and hypotension, especially in bolus doses. In contrast, subdissociative ketamine typically increases blood pressure and heart rate (via sympathomimetic catecholamine surge) (16), and produces CNS effects such as dizziness, sedation, and dysphoria. It usually does not depress respiration at analgesic doses (6)(7). Meta-analyses quantify this: Zhang et al. found ketamine did not increase overall adverse events or nausea relative to morphine, but it did significantly raise the risk of dizziness (RR ~1.5) and "emergence phenomena" (hallucinations/delirium, RR ~19)(9). Ying et al. similarly noted a trend toward more psychological/neurologic events with ketamine (RR ~2.8 for psych, borderline significance) (10). In the Motov et al. RCT, one-third of ketamine patients became dizzy (vs 11% with morphine), and 11% had emergence reactions (none in the morphine group)(8). Conversely, fentanyl and morphine groups reported more sedation and nausea than ketamine groups in most trials.

In summary, ketamine and opioids achieve similar analgesia, but ketamine causes more neuropsychiatric side effects while opioids cause more opioid-typical side effects. Clinicians must weigh these differences. For patients at risk of respiratory compromise, ketamine's respiratory safety is an advantage; for patients prone to anxiety or disorientation, opioids may be more tolerable. Some providers mitigate ketamine's emergence effects by premedicating with benzodiazepines (e.g. midazolam) or by using slow infusions instead of boluses(1, 5). Multimodal protocols often use ketamine to reduce opioid dose, capitalizing on synergistic analgesia.

Safety Considerations

Cardiovascular effects. At subanesthetic doses, ketamine typically raises heart rate and blood pressure due to stimulated catecholamine release(16). This can improve hemodynamics (especially in shock or hypovolemia) but is hazardous in severe hypertension or unstable coronary disease. Ketamine has a direct negative inotropic effect that is normally masked by sympathetic stimulation(16); in catecholamine-depleted states (e.g. prolonged shock), the negative inotropy may predominate, causing hypotension(17). As a result, guidelines caution use in "decompensated" cardiac patients. For stable acute pain, mild blood pressure elevations are usually tolerated or even beneficial(16). Clinicians should monitor vitals continuously. If severe hypertension or tachycardia occur, slowing the infusion or giving a small benzodiazepine can help.

Respiratory effects. Unlike opioids or propofol, ketamine preserves respiratory drive and airway reflexes at analgesic doses (7). It can cause bronchodilation and is often used safely in asthma exacerbations. Rarely, high doses may increase secretions or provoke laryngospasm, but these are infrequent in subdissociative use. Nevertheless, all protocols recommend readiness to manage airway issues (pulse oximetry, suction available).

Neurologic/psychiatric effects. The hallmark risks are emergence reactions (disorientation, visual/auditory hallucinations, vivid dreams, delirium) and dysphoria. These are dose-dependent and more common in naïve or anxious patients. Stereotypically, 10–30% of patients may experience mild emergence at 0.3 mg/kg(8). Older consensus suggests preemptive benzodiazepines or calming environments to reduce this. Ketamine increases intracranial pressure (ICP) only at high, anesthetic doses; at analgesic doses on ventilated patients, it appears safe(17). In awake, spontaneously breathing patients, transient ICP or intraocular pressure rises have been reported, but their clinical significance is minimal for short ED doses(18). Thus, while tradition advised against ketamine in head-injured or glaucoma patients, recent evidence suggests subanesthetic use is relatively safe in these situations(17, 18). Nevertheless, clinicians should use caution and consult neurology if severe CNS pathology is present.

Other effects. Nausea/vomiting occurs with ketamine but generally less often than with opioids. Skin vasodilation is minimal. Ketamine can increase

salivation (muscarinic agonism), so an antisialagogue (e.g. glycopyrrolate) may be given if excessive. Miosis (pupil constriction) or diplopia can occur transiently. Rarely, opioid-type itching can also happen. Renal and hepatic toxicity are negligible at single low doses, though repeated high-dose infusions have caused urinary symptoms and elevated LFTs in chronic use.

Contraindications and precautions. Most acute pain protocols treat ketamine as if it were moderate sedation. Contraindications include active psychosis (schizophrenia, acute manic episodes), severe uncontrolled hypertension, ischemic heart disease, decompensated shock, and high-risk pregnancy(18). While active substance abuse is listed as a contraindication in some anesthesia sources(19), acute pain guidelines note that many ED patients have OUD, and do not exclude them from ketamine use(2). Pregnancy is a relative contraindication – animal data raise concerns, and uterine blood flow changes are possible – so ketamine is generally avoided unless benefit clearly outweighs risk. Elevated intraocular pressure is less of a concern at low doses(18). Age is not an absolute barrier in adults, but in the elderly one should use conservative doses (e.g. 0.15 mg/kg) due to increased sensitivity.

Monitoring and resource requirements. Because ketamine retains sedation potential, patients receiving IV analgesic ketamine should have continuous cardiac and respiratory monitoring (pulse ox, ECG, BP cuffs). Many institutions require that providers administering ketamine are ACLS-certified and experienced in moderate sedation, with resuscitative equipment on hand(19). Infusions over 1 mg/kg/hr or boluses >0.35 mg/kg, per consensus guidelines, should be done in a monitored setting (similar to PSA settings)(3). However, boluses ≤0.3 mg/kg for analgesia are often given on the floor or in ED with standard monitors. Discharge criteria include return to baseline mental status, stable vitals, and ability to eat/drink, typically within 30–60 minutes after the last dose(19).

Recent Guidelines and Consensus Statements

Professional societies have issued guidance on ketamine use. In 2018 the American Society of Regional Anesthesia (ASRA), American Academy of Pain Medicine and ASA published joint guidelines covering ketamine for pain (acute and chronic)(3). For acute pain, they recommend initial IV boluses ≤0.35 mg/kg and infusions up to 1 mg/kg/hour for patients without contraindications(3). These guidelines note that evidence for acute pain is moderate (versus chronic pain where evidence is weaker) and support ketamine as an alternative or adjunct when opioids are inadequate or inappropriate. They also emphasize screening for contraindications (see above)(2, 18)and advanced preparation to manage side effects(19).

Regional emergency medicine societies likewise endorse subdissociative ketamine. For example, Emergency Care BC's analgesia guide recommends IV ketamine 0.1–0.3 mg/kg for severe pain, repeating or infusing as needed (Table 1)(3). The Indian Health Service (US) formulary notes ketamine's use in acute pain, highlighting that it can improve blood pressure and is useful in low-resource settings. No major international emergency medicine organization has banned ketamine analgesia; on the contrary, there is a growing global recognition (e.g. in Africa and Asia) of ketamine's utility where opioids are scarce or risky.

Recent meta-analyses provide a global perspective. A WestJEM review (mostly US trials) found similar conclusions to the Asian analyses: no difference in pain outcomes, and a modest increase in ketamine's minor side effects (10). A Scandinavian Journal of Trauma review (Zhang et al. 2025) re-affirmed equivalence with morphine using data up to mid-2025(9). These pooled results reflect diverse healthcare settings (China, US, Middle East, etc.), supporting broad applicability.

Clinical Relevance and Recommendations

For clinicians, the take-home messages are: Ketamine at subdissociative doses is a safe and effective tool for adult acute pain in the ED, with efficacy comparable to opioids. It is particularly useful for opioid-tolerant patients, trauma patients, or situations requiring hemodynamic stability. Protocols should use doses up to ~0.3 mg/kg IV or equivalent, and consider infusion or multi-modal regimens as needed (Table 1). When using ketamine, be vigilant for emergence reactions and be prepared with reassurance or anxiolytics. Educate patients that feeling "dreamy" or dizzy can occur but usually resolves quickly. Always monitor continuously and ensure discharge criteria are met.

Although ketamine may seem daunting, evidence and guidelines underscore that when used judiciously, its benefits in acute analgesia outweigh its manageable risks (3, 9). Global research supports its role: high-quality trials from North America, Europe, Asia, and Africa consistently find ketamine to be an effective opioid alternative. Institutions can safely implement ketamine protocols by adhering to published dosing ranges (see Table 1) and safety recommendations. With appropriate use, ketamine can become a mainstay of ED pain management, improving patient comfort while mitigating reliance on opioids.

Conclusion

Ketamine has evolved from a dissociative anesthetic into a well-established analgesic option for acute pain management in the emergency department.

Accumulating evidence from randomized trials, meta-analyses, and international guidelines demonstrates that subdissociative ketamine provides analgesic efficacy comparable to opioids while offering important advantages, including preservation of respiratory drive, hemodynamic stability in many settings, and opioid-sparing effects. Although ketamine is associated with a higher incidence of transient neuropsychiatric side effects, these reactions are generally mild, dose-dependent, and manageable with appropriate protocols and monitoring. When used judiciously, ketamine represents a valuable component of multimodal pain management in the ED, particularly for patients with opioid intolerance, opioid use disorder, or high risk of respiratory compromise. Future research should focus on refining dosing strategies, identifying optimal patient populations, and further clarifying long-term safety outcomes in emergency care settings.

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Conflicts of Interest

The authors declare that they have no conflicts of interest relevant to this manuscript.

Authors' Contributions

Hossein Meskar and Keihan Shabankhani conceived the study concept and design. Hossein Meskar, Ramin Razavi, and Ali Zarei conducted the literature review and data synthesis. Goli Aezzi Pashakollaei and Mostafa Jamali Jehizdani contributed to manuscript drafting and critical revision with an emphasis on emergency medicine perspectives. Keihan Shabankhani supervised the project, critically reviewed the manuscript for important intellectual content, and finalized the submission. All authors read and approved the final manuscript.

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