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# Safety of Ketamine in the Prehospital Setting

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## PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to conduct timely, rigorous, and independent systematic reviews to support VA clinicians, program leadership, and policymakers improve the health of Veterans. ESP reviews have been used to develop evidence-informed clinical policies, practice guidelines, and performance measures; to guide implementation of programs and services that improve Veterans' health and well-being; and to set the direction of research to close important evidence gaps. Four ESP Centers are located across the US. Centers are led by recognized experts in evidence synthesis, often with roles as practicing VA clinicians. The Coordinating Center, located in Portland, Oregon, manages program operations, ensures methodological consistency and quality of products, engages with stakeholders, and addresses urgent evidence synthesis needs.

Nominations of review topics are solicited several times each year and submitted via the [ESP website](#). Topics are selected based on the availability of relevant evidence and the likelihood that a review on the topic would be feasible and have broad utility across the VA system. If selected, topics are refined with input from Operational Partners (below), ESP staff, and additional subject matter experts. Draft ESP reviews undergo external peer review to ensure they are methodologically sound, unbiased, and include all important evidence on the topic. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. In seeking broad expertise and perspectives during review development, conflicting viewpoints are common and often result in productive scientific discourse that improves the relevance and rigor of the review. The ESP works to balance divergent views and to manage or mitigate potential conflicts of interest.

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### *Operational Partners*

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

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## DISCLOSURES

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# *Main Report*

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## ABBREVIATIONS TABLE

Abbreviation	Definition
AE	Adverse event
AIS	Abbreviated Injury Scale
APVU	Alert, Verbal, Pain, Unresponsive Scale
BAN	Breath actuated nebulizer
CI	Confidence interval
ED	Emergency department
EMS	Emergency medical services
EMT	Emergency medicine technician
FDA	Food and Drug Administration
ICU	Intensive care unit
IM	Intramuscular
IN	Intranasal
IO	Intraosseous
ISS	Injury severity score
IV	Intravenous
LOS	Length of stay
MME	Morphine equivalent dose
NEMO	National Emergency Medicine Office
NRS	Numerical rating scale
NSD	No significant difference
OR	Odds ratio
PTSD	Posttraumatic stress disorder
RC	Retrospective cohort
RCT	Randomized controlled trial
RSI	Rapid sequence intubation
SPID	Sum of pain intensity
TBI	Traumatic brain injury
VAS	Visual analog scale
VNRS	Verbal numerical rating scale

## BACKGROUND

Ketamine is a dissociative anesthetic that primarily acts as an N-methyl-D-aspartate (NMDA) receptor antagonist. It is FDA approved for procedural sedation and induction of general anesthesia and is used frequently in the hospital setting. Ketamine also has several pharmacologic properties that make it well suited for off-label use in the prehospital setting by emergency medical services (EMS) personnel, who are usually the first to treat patients with urgent or emergent medical needs. Prehospital care, defined as clinical care delivered by EMS prior to arrival at an emergency department (ED) or hospital, reduces patient morbidity and mortality and is an essential component of emergency medicine.<sup>3</sup> In addition to causing neuro-inhibition and anesthesia through antagonism of NMDA receptors, ketamine is active at opioid receptors and provides rapid onset analgesia at low doses. It also has effects at catecholamine receptors, which make it a favorable agent to use for rapid sequence intubation (RSI) among hemodynamically unstable patients as it leads to increases in heart rate, contractility, and mean arterial pressure.<sup>4,5</sup> Ketamine may be administered by intravenous (IV), intramuscular (IM), intraosseous (IO), or intranasal (IN) routes, adding to its usefulness in a range of clinical scenarios.

Guidelines and position statements from multiple professional societies support the use of ketamine for in-hospital analgesia and procedural sedation, prehospital pain management, RSI, and/or treatment of acute behavioral agitation.<sup>6–10</sup> Additionally, national EMS clinical guidelines include recommendations for the use of ketamine for pain management and treatment of behavioral agitation.<sup>11</sup> Ketamine has been broadly integrated into national and state EMS protocols and is now widely used as an agent for acute pain, sedation, and RSI in the prehospital setting. Within VHA, ketamine is an option for acute pain treatment and management of patients with acute behavioral agitation in the ED.<sup>12,13</sup>

Although ketamine is generally recognized as an effective treatment that is safe to use in the prehospital setting, its versatility as a pharmacologic agent has also led to concerns regarding its overuse or inappropriate use as a “catch-all” treatment, potentially placing some patients at unnecessary risk of harms. These concerns intensified following media reports of cardiac arrest and other adverse events occurring among people who received ketamine in the prehospital setting. After a man in Colorado died following ketamine administration by EMS personnel, the state passed a law in 2021 outlining criteria for ketamine use in the prehospital setting, including having the ability to weigh patients to determine appropriate dosing.<sup>14,15</sup> Potential adverse effects of ketamine include nausea and vomiting, hypotension, laryngospasm, and respiratory depression.<sup>16,17</sup> At higher doses, ketamine may also lead to “emergence phenomena,” which is characterized by euphoria, illusions, delirium, and/or hallucinations that can cause agitation and combativeness as ketamine is wearing off.<sup>18,19</sup> Estimates of the incidence of emergence phenomena vary, but studies have reported such reactions in up to 55% of patients treated with ketamine.<sup>18</sup> Lastly, some concern exists regarding the risk of elevated intracranial pressure with ketamine use among patients with head injury,<sup>5</sup> although large studies in this area have shown conflicting results,<sup>19</sup> and a Cochrane systematic review<sup>20</sup> reported no increase in intracranial pressure with ketamine among sedated and ventilated patients with severe traumatic brain injury (TBI).

Several existing systematic reviews<sup>21–25</sup> have examined the use of ketamine in the prehospital setting for acute pain, agitation, and RSI, and have generally found that ketamine is safe and effective when used appropriately. However, these reviews have largely included studies conducted in the ED and extrapolated findings to the prehospital setting. More evidence specific to the prehospital setting has become available as EMS providers seek to improve guidance for the field and ensure the safety of EMS treatment protocols. The VA Evidence Synthesis Program Coordinating Center (ESP CC) is responding to a request from the VA National Emergency Medicine Office (NEMO) for a review of

evidence on the safety of ketamine for acute pain management, sedation, and RSI in the prehospital setting. Findings will be used to inform national protocols for VHA paramedics and EMTs.

## METHODS

### REGISTRATION AND REVIEW

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews ([CRD420251029615](https://doi.org/10.1111/CRD4.20251029615)). A draft version of this report was reviewed by external peer reviewers; their comments and author responses are provided in the Supplementary Materials.

### KEY QUESTIONS AND ELIGIBILITY CRITERIA

The following key questions were the focus of this review:

- *Key Question 1 (KQ1)*: What are the harms of ketamine use for pain control, sedation, or rapid sequence intubation in the prehospital setting?
  - *Key Question 1a (KQ1a)*: What are the benefits of ketamine use for pain control, sedation, or rapid sequence intubation in the prehospital setting?

Study eligibility criteria are shown in the table below. Given our interest in identifying all potential safety concerns related to ketamine use among adults in the prehospital setting, we included all relevant studies for KQ1 regardless of study design and included studies with a mix of adult and older adolescent participants (rather than restricting inclusion criteria to studies of adults only).

Domain	Eligibility Criteria
Population	Adult patients receiving prehospital emergency care <sup>a</sup>
Intervention	Ketamine <sup>b</sup> (any administration method) for acute pain management, sedation, or RSI
Comparator	Any other intervention for acute pain management, sedation, or RSI or no comparator <sup>c</sup>
Outcomes	Harms (eg, mortality, nausea, vomiting, respiratory changes), benefits (eg, pain relief, sedation)
Study Design	Any, but may prioritize studies to fit timeline based on a best-evidence approach

Notes. <sup>a</sup> We also included studies of adults and older adolescents (aged 15 or older) if they otherwise met eligibility criteria; <sup>b</sup> We excluded studies of IV esketamine, the S(+) enantiomer of ketamine, due to its different pharmacologic properties compared to ketamine; <sup>c</sup> For KQ1a, we excluded studies without a comparison group.

### SEARCHING AND SCREENING

To identify articles relevant to the key questions, a research librarian searched Ovid Medline, CDSR and CENTRAL via Cochrane Library, CINAHL Ultimate, and Scopus from inception through April 8, 2025, using terms for ketamine and prehospital or emergency medical services (see [Appendix](#) for complete search strategies). Additional citations were identified from hand-searching reference lists and consultation with content experts. English-language titles, abstracts, and full-text articles were independently screened by 2 reviewers, and disagreements were resolved by consensus.

### DATA ABSTRACTION AND RISK OF BIAS ASSESSMENT

Effect information, adverse event incidence, and population, intervention, and comparator characteristics were abstracted from all included studies. Data were first abstracted by 1 reviewer and

then checked by another. For randomized controlled trials (RCTs) and controlled observational studies that adjusted for baseline differences between groups (*ie*, controlled for potential confounding), 2 reviewers with systematic review methodology expertise independently evaluated internal validity (risk of bias) using the Cochrane Risk of Bias tools for randomized and nonrandomized studies.<sup>26,27</sup> Disagreements were resolved by consensus or discussion with a third reviewer with clinical and systematic review methodology expertise (see the Supplementary Materials for risk of bias ratings). We did not evaluate internal validity for non-comparative (single group) studies or comparative studies that did not adjust for baseline differences between groups, given that these study designs are inherently less rigorous with a higher risk of bias.

## SYNTHESIS

We synthesized findings from included studies by ketamine indication and outcome. We prioritized synthesizing findings from RCTs and controlled observational studies that adjusted for baseline differences between groups, as these studies used methodologies best suited to isolate the effects of ketamine administered in the prehospital setting relative to other interventions. Mortality outcomes (if available) are presented first, followed by serious adverse event outcomes and then non-serious adverse event outcomes. Because the focus of this review is on ketamine's safety, we present findings regarding effectiveness after discussing harms.

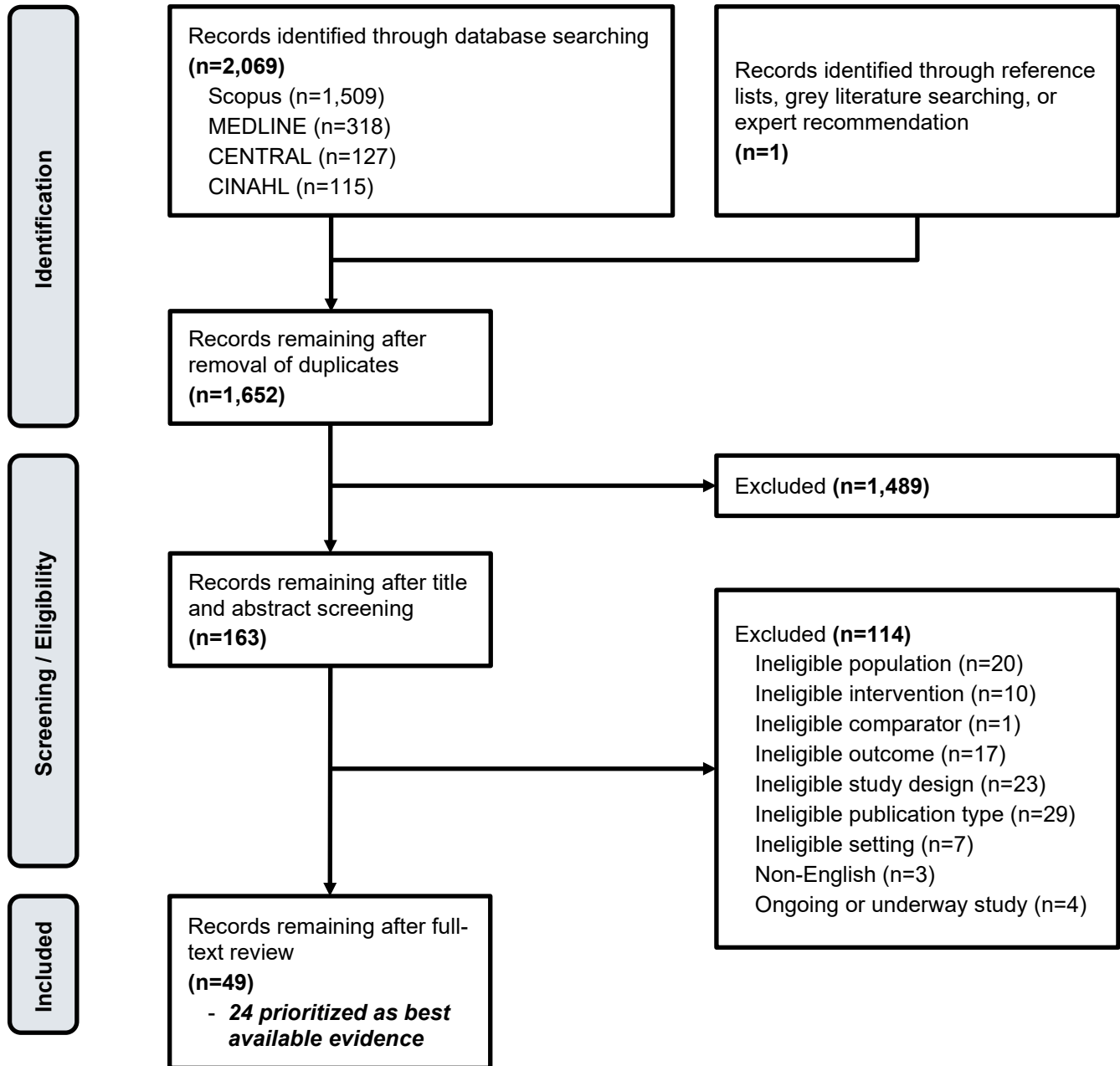
### ***Strength of Evidence***

For adverse event outcomes reported in at least 2 studies with the same comparator, we rated the strength of evidence using criteria that considers study methodological limitations, the consistency and certainty of findings, and the directness of outcomes (whether reported outcomes are relevant to patients and providers).<sup>28</sup> We used the following general algorithm: *high strength* evidence consisted of studies with consistent and precise findings at low risk of bias; *moderate strength* evidence consisted of studies with consistent and precise findings at low to moderate risk of bias; *low strength* evidence consisted of studies with moderate to high risk of bias and/or inconsistent or imprecise findings; and *insufficient* evidence consisted of studies with moderate or high risk of bias, indirect, inconsistent, and/or imprecise findings.

# RESULTS

## LITERATURE FLOW DIAGRAM

The literature flow diagram summarizes the results of the study selection process. A full list of excluded studies is provided in the Supplementary Materials.



## OVERVIEW OF INCLUDED STUDIES

Our search identified 1,652 potentially relevant articles after deduplication. Of these, 49 studies met eligibility criteria: 18 studies of ketamine for acute pain management,<sup>29–46</sup> 24 studies of ketamine as a sedative for patients with acute behavioral disturbance or agitation,<sup>1,2,14,47–67</sup> 4 studies of ketamine for RSI,<sup>68–71</sup> and 3 studies of ketamine that did not specify an indication.<sup>72–74</sup> We also identified 4 underway studies: 3 RCTs examining ketamine for pain and 1 RCT examining ketamine for sedation (see Supplementary Materials).

We prioritized synthesis of 24 studies<sup>1,2,14,34–49,68–72</sup> as the most rigorous and potentially informative evidence: 8 RCTs and 16 retrospective cohorts. Most of the prioritized cohort studies adjusted for baseline differences between groups but when this more reliable evidence was not available (as in the case of studies comparing different dosages of ketamine), we described findings from retrospective cohorts that did not adjust for baseline group differences. Characteristics of the prioritized studies are shown in Table 1. The studies that we did not prioritize either lacked a comparison group or did not employ methods to account for baseline differences between groups (*ie*, control for potential confounding), making it difficult to assess ketamine's effects.

In most of the 24 prioritized studies, ketamine was administered by EMS personnel from ambulance services. Exceptions were 2 studies<sup>43,45</sup> in which ketamine was administered for acute pain in US military combat settings and 4 studies<sup>68–71</sup> in which ketamine was given by air medical transport service personnel for RSI. Ketamine was usually given IV or IM and doses ranged from 0.2 to 2 mg/kg IV or 1 to 5 mg/kg IM, depending on the indication. In studies of ketamine for pain, the comparator was most often an opioid medication. In studies of ketamine for sedation, the comparator was most often a benzodiazepine, and in studies of ketamine for RSI, the comparator was usually etomidate. Four studies<sup>48,49,69,71</sup> compared different doses of ketamine. Notably, in studies of acute pain management or treatment of acute behavioral disturbance, patients often received more than 1 medication (*eg*, ketamine and an opioid). Studies used different methods to evaluate the effects of ketamine in these cases, often by assessing outcomes according to whether ketamine was the *first* medication administered.

Most studies only evaluated adverse events that occurred in the short-term (*ie*, within hours or days of receiving ketamine). Several studies examined composite outcomes of “any adverse event” or “any serious adverse event.” Otherwise, we categorized adverse events as gastrointestinal (nausea, vomiting, *etc*), cardiac (hypotension, cardiac arrest, arrhythmias, *etc*), respiratory (desaturation, pneumonia, aspiration, intubation, advanced airway management, *etc*), mental health/behavioral (emergence reaction, hallucinations, agitation, *etc*), and other (allergic reactions, dizziness, headache, visual disturbance, itching, *etc*). Effectiveness outcomes included measures of pain intensity, opioid requirements, need for additional sedation, intubation success, and ED or hospital length of stay. Relatively few studies evaluated mortality.

Several RCTs did not blind participants or providers to the intervention, a methodological limitation that may have biased self-reported outcomes. Several retrospective cohorts did not report information regarding co-interventions, which may have skewed outcome results, and some did not adjust for baseline differences between groups for all outcomes of interest. Detailed risk of bias assessments for prioritized studies are available in the Supplementary Materials.

**Table 1. Key Characteristics of RCTs and Controlled Observational Studies (Prioritized Studies)**

Study	Study Design Sample Size	Ketamine Indication	Population	Ketamine Details	Comparator	Outcomes Assessed
Andolfatto 2019 <sup>34</sup>	RCT N=120	Pain	Adult patients with pain requiring analgesia	0.5-1mg/kg IN to both nostrils + nitrous oxide	Placebo <sup>a</sup> + nitrous oxide	GI AEs, Any AEs, Mental/Behavioral AEs, Pain reduction
Bronsky 2019 <sup>35</sup>	RC N=200	Pain	Adult patients with severe pain	0.3 mg/kg IV every 20 min. (3 dose max)	Fentanyl	Cardiac AEs, Respiratory AEs, Any AEs, Pain reduction, Pain medication requirements
Cohen 2022 <sup>36</sup>	RC N=382	Pain	Trauma casualties (16+) with severe pain	Mean: 29 mg IV	Opioids alone	Pain reduction, Pain medication requirements
Galinski 2007 <sup>37</sup>	RCT N=73	Pain	Adult patients presenting with trauma and severe acute pain	0.2 mg/kg IV over 10 min. + morphine	Placebo <sup>a</sup> + morphine	GI AEs, Respiratory AEs, Other AEs, Mental/Behavioral AEs, Pain reduction, Morphine requirements
Jennings 2012 <sup>38</sup>	RCT N=135	Pain	Adult patients with moderate to severe traumatic pain	10-20 mg initial bolus IV + 10 mg every 3 min. + morphine	Morphine alone	GI AEs, Cardiac AEs, Other AEs, Any AEs, Mental/Behavioral AEs, Pain reduction
Johansson 2009 <sup>39</sup>	RCT N=27	Pain	Patients with bone fractures receiving morphine sulfate	0.2 mg/kg IV until NRS score below 4 + morphine	Morphine alone	GI AEs, Mental/Behavioral AEs, Pain reduction
Le Cornec 2024 <sup>40</sup>	RCT N=251	Pain	Adult patients with traumatic pain	20 mg IV over 2 min. + 10 mg every 10 min.	Morphine	GI AEs, Cardiac AEs, Other AEs, Any AEs, Mental/Behavioral AEs, Pain reduction, Morphine requirements
McArthur 2025 <sup>41</sup>	RC N=1480	Pain	Adult patients with pain	1 mg/kg via breath-actuated nebulizer	Fentanyl	Pain reduction
McMullan 2024 <sup>42</sup>	RCT N=199	Pain	Adult males with acute traumatic injuries requiring analgesia	50 mg IN + fentanyl	Placebo <sup>a</sup> + fentanyl	GI AEs, Respiratory AEs, Other AEs, Any AEs, Any serious AEs, Mental/Behavioral AEs, Pain reduction, Morphine requirements

Study	Study Design Sample Size	Ketamine Indication	Population	Ketamine Details	Comparator	Outcomes Assessed
Melcer 2023 <sup>43</sup>	RC N=202	Pain	US combat casualties with serious injury in Iraq or Afghanistan	Mean: 70.4 mg IV or IM during first 6 hours post-injury	Opioids	PTSD Diagnosis
Smyth 2025 <sup>44</sup>	RCT N=449	Pain	Patients (16+) with severe pain following traumatic injury	10 ml of 1mg/ml IV or IO over 5 min.; second dose given as needed (20 mg max)	Morphine	GI AEs, Cardiac AEs, Respiratory AEs, Other AEs, Any AEs, Any serious AEs, Mental/Behavioral AEs, ED LOS, Hospital/ICU admission
Torres 2020 <sup>45</sup>	RC N=4183	Pain	US combat casualties with head trauma	NR	No KET exposure	Survival to hospital discharge, Time to death
Wiel 2015 <sup>46</sup>	RCT N=66	Pain	Adult patients with orthopedic injuries secondary to trauma with severe acute pain	0.2 mg/kg initial bolus IV + continuous infusion IV at 0.2 mg/kg/hr + morphine	Placebo <sup>a</sup> + morphine	GI AEs, Mental/Behavioral AEs, Pain reduction, Morphine requirements
Brown 2022 <sup>14</sup>	RC N=7973	Sedation: behavioral disturbance	Patients (15+) presenting with a behavioral emergency	IM (dose NR)	Benzodiazepine, antipsychotic	Cardiac AEs, Respiratory AEs, Any serious AEs, Any AE, Need for additional sedation
Cunningham 2021 <sup>48</sup>	RC N=292	Sedation: agitation	Adult patients with acute agitation or agitated delirium	High dose (3 mg/kg IM + 1 mg/kg IM if needed)	Standard dose (4 mg/kg IM)	Respiratory AEs, Any AE, Staff injury, Additional restraint, Hospital admission, ED LOS
Muldowney 2024 <sup>2</sup>	RC N=376	Sedation: behavioral disturbance	Adult patients with acute behavioral disturbance	5 mg/kg IV or IM up to a max. of 500 mg	Benzodiazepine: Midazolam	Cardiac AEs, Respiratory AEs, Mortality, Need for additional sedatives, Hospital or ICU admission, Hospital LOS
Olives 2016 <sup>1</sup>	RC N=135	Sedation: agitation	Adult patients with agitation	5 mg/kg IM or 2 mg/kg IV	Benzodiazepines: Midazolam, Haloperidol	Intubation
Sergot 2024 <sup>49</sup>	RC N=2383	Sedation: behavioral disturbance	Adult patients with behavioral concerns	High dose (> 2 mg/kg IV or IO or 5 mg/kg IM)	Standard dose (≤ 2 mg/kg IV or IO or 5 mg/kg IM)	Cardiac AEs, Respiratory AEs, Improvement in agitation, Need for additional sedation

Study	Study Design Sample Size	Ketamine Indication	Population	Ketamine Details	Comparator	Outcomes Assessed
Tomasino 2023 <sup>47</sup>	RC N=319	Sedation: agitation	Adult patients with agitation and aggressive behavior	Mean: 94.6 mg IV; 101.1 mg IM	Benzodiazepine: Midazolam, Diazepam	Respiratory AEs, Hospital LOS
Asberry 2024 <sup>69</sup>	RC N=212	RSI	Adult patients undergoing prehospital RSI	Low dose (1 mg/kg IV or IO)	Full-dose KET (2 mg/kg IV)	Peri-intubation cardiac arrest
Krebs 2021 <sup>71</sup>	RC N=130	RSI	Adult patients intubated by EMS or air medical services	High dose (> 2 mg/kg IV)	Standard dose (≤ 2 mg/kg IV)	GI AEs, Cardiac AEs, Respiratory AEs, Mental/Behavioral AEs, Successful intubation
Kunkel 2022 <sup>68</sup>	RC N=306	RSI	Adult patients intubated by air medical transport	1 mg/kg or 2 mg/kg, (admin. method NR)	Etomidate	Respiratory AEs
Stanke 2021 <sup>70</sup>	RC N=113	RSI	Adult critically ill patients undergoing RSI	1.5-2 mg/kg IV	Etomidate	Cardiac AEs, First pass intubation success
Peters 2023 <sup>72</sup>	RC N=841	Any	Patients (15+) with moderate to severe TBI	NR	No KET exposure	Cardiac AEs, Respiratory AEs, Other AEs, Death within 6 months of injury

Notes. <sup>a</sup> Studies utilizing a placebo control group provided another pain medication to all patients (eg, ketamine + morphine vs placebo + morphine).

*Abbreviations.* AEs=adverse events; ED=emergency department; EMS=emergency medical services; HR=hour; ICU=intensive care unit; IM=intramuscular; IN=intranasal; IO=intraosseous; IV=intravenous; KET=ketamine; kg=kilogram; LOS=length of stay; mg=milligram; NR=not reported; RC=retrospective cohort; TBI=traumatic brain injury.

## ACUTE PAIN MANAGEMENT

### *Safety of Prehospital Ketamine for Acute Pain Management*

A single retrospective cohort<sup>45</sup> of 4,183 US combat casualties with head trauma from the Department of Defense Trauma Registry reported in-hospital mortality based on whether patients received ketamine (dosage not reported) for acute pain management in the prehospital setting and found no difference in survival to hospital discharge between groups (75.1% ketamine vs 83% no ketamine) after controlling for the presence of an airway intervention and mechanism of injury (OR = 1.09, 95% CI [0.76, 1.55]). Most patients (95%) did not receive ketamine, and it is unclear what other pain medications (if any) those patients received.

Two RCTs<sup>42,44</sup> comparing prehospital administration of ketamine to morphine or as an adjunct to fentanyl compared to placebo for acute pain management reported low rates (0–3%) of serious adverse events (a composite outcome commonly including cardiac arrest, invasive airway placement, or severe oxygen desaturation) with no differences based on receipt of ketamine. A single retrospective cohort<sup>35</sup> comparing ketamine to fentanyl for severe acute pain in the prehospital setting found that adverse events (hemodynamic instability or respiratory compromise) occurred among only 4 of 200 participants, all of whom received fentanyl. Ketamine doses ranged from 0.1–0.2 mg/kg IV and 0.5–1.0 mg/kg IN.

In 4 RCTs, patients who received ketamine had a higher incidence of visual disturbance,<sup>38,40</sup> emergence phenomena,<sup>38,40</sup> and sedation<sup>38–40,44</sup> (Table 2). Similarly, several RCTs comparing prehospital ketamine to placebo among patients already receiving another medication for acute pain (morphine, fentanyl, or nitrous oxide) found that patients who received ketamine had a higher incidence of dizziness<sup>34,42</sup> and overall neuropsychological effects.<sup>37,46</sup> No significant differences were reported in the occurrence of nausea and vomiting, hypertension, arrhythmia, respiratory problems, itching, fatigue, general discomfort, hearing changes, headache, hallucinations, or mood change in studies comparing rates of other adverse events between patients who received ketamine and those who received morphine or placebo. Findings for other adverse events including hypotension, feeling of unreality, and a composite outcome of any adverse event were inconsistent across studies.

One retrospective cohort<sup>43</sup> examined the rates of PTSD diagnosis at 1 and 2 years among US combat casualties in Iraq or Afghanistan who received ketamine (with or without opioids) or opioids alone for acute pain management in the prehospital setting. At 1 year after injury, rates of PTSD were lower among those who received ketamine compared opioids alone (3% ketamine vs 24% opioids alone, OR = 0.08, 95% CI [0.01, 0.71]), but only among those who had not sustained TBI. Among participants who had sustained TBI, the study did not find any differences in PTSD diagnoses between groups at 2 years post-injury.

Several other adverse events, including advanced airway management or need for oxygen, aspiration, and agitation or anxiety, were each only reported in a single study, limiting our ability to assess differences in these outcomes with ketamine compared to other medications used for acute pain (see Supplementary Materials for full details). Likewise, among noncomparative and unadjusted studies

(non-prioritized studies), adverse event reporting varied, and specific adverse events were often only reported in a single study (see Supplementary Materials for full study details).

**Table 2. Summary of Adverse Events of Prehospital Ketamine for Acute Pain Management**

Outcome	Comparator	Studies (Participants)	Summary of Findings	Consistency and Precision (Risk of Bias)	Strength of Evidence Summary
Any AE	Placebo	2 RCTs <sup>34,42</sup> (N range 120–199)	Increased occurrence of AEs with ketamine (62% KET vs 20% placebo, difference = 43%, 95% CI [24, 56]) in 1 study. No difference in occurrence of AEs in 1 study.	Inconsistent and imprecise findings across studies. (Moderate)	INSUFFICIENT It is unclear whether there is a difference in the occurrence of AEs overall with ketamine compared to placebo for acute pain management.
Any AE	Morphine	3 RCTs <sup>38,40,44</sup> (N range 135–449)	Increased occurrence of AEs with ketamine (40.8% KET vs 16.8% MOR, difference = 24%, 95% CI [12.8, 35.2] and 13.8% MOR vs 38.6% KET, difference -26%, 95% CI [-40.7, -10.6]) in 2 studies. No difference in AEs in 1 study.	Inconsistent and imprecise findings across studies. (Low–Moderate)	INSUFFICIENT It is unclear whether there is a difference in the occurrence of AEs overall with ketamine compared to placebo for acute pain management.
Cardiac: Arrhythmias	Morphine	2 RCTs <sup>38,44</sup> (N range 135–449)	No significant difference in tachycardia or arrhythmias between ketamine and morphine across studies.	Consistent but imprecise findings across studies. (Low–Moderate)	LOW There may be little to no difference in arrhythmias between ketamine and morphine for acute pain management.
Cardiac: Hypertension	Morphine	3 RCTs <sup>38,40,44</sup> (N range 135–449)	No significant difference in hypertension between ketamine and morphine across all studies.	Consistent and precise findings across studies (Low–Moderate)	MODERATE There is likely little to no difference in hypertension between ketamine and morphine for acute pain management.
Cardiac: Hypotension	Morphine	2 RCTs <sup>38,44</sup> (N range 135–449)	Less hypotension with ketamine (3% KET vs 10% MOR, OR = 0.2, 95% CI [0.1, 0.6]) in 1 study. No significant difference in hypotension in 1 study.	Precise but inconsistent findings across studies. (Low–Moderate)	LOW It is unclear if there is a difference in the incidence of hypotension with ketamine compared to morphine for acute pain management.

Outcome	Comparator	Studies (Participants)	Summary of Findings	Consistency and Precision (Risk of Bias)	Strength of Evidence Summary
GI: Nausea and/or Vomiting	Placebo	4 RCTs <sup>34,37,42,46</sup> (N range 66–199)	No significant difference in nausea/vomiting between ketamine and placebo in 3 studies. More nausea with ketamine (17% ketamine vs 5% placebo, difference = 12%, 95% CI [0.3, 24]) in 1 study.	Inconsistent and imprecise findings across studies. (Moderate)	LOW There may be little to no difference in nausea/vomiting between ketamine and placebo for acute pain management.
GI: Nausea and/or Vomiting	Morphine	4 RCTs <sup>38–40,44</sup> (N range 27–449)	No significant difference in nausea/vomiting between ketamine and morphine across all studies.	Consistent and precise findings across studies. (Low–High)	MODERATE There is likely little to no difference in nausea/vomiting between ketamine and morphine for acute pain management.
M/B: Emergence phenomena	Morphine	2 RCTs <sup>38,40</sup> (N range 135–251)	Increased occurrence of emergence phenomena with ketamine (20% KET vs. 0.9% MOR, difference = 19.1%, 95% CI [11.7, 26.5]) in 1 study. Nonsignificant increase in emergence phenomena in 1 study.	Consistent but imprecise findings across studies. (Low–Moderate)	LOW There may be increased occurrence of emergence phenomena with ketamine compared to morphine for acute pain management.
M/B: Feeling of unreality	Placebo	2 RCTs <sup>34,42</sup> (N range 120–199)	Increased feeling of unreality (27% KET vs 2% placebo, difference = 25%, 95% CI [13, 37]) in 1 study. No significant difference in feeling of unreality in 1 study.	Inconsistent and imprecise findings across studies. (Moderate)	LOW It is unclear whether there is a difference in feeling of unreality between ketamine and placebo for acute pain management.
M/B: Hallucinations, Mood change	Placebo	2 RCTs <sup>34,42</sup> (N range 120–199)	No significant difference in hallucinations or mood change between ketamine and placebo in 2 studies.	Consistent but imprecise findings across studies. (Moderate)	LOW There may be little to no difference in hallucinations or mood change between ketamine and placebo for acute pain management.
M/B: Neuropsychological effects	Placebo	2 RCTs <sup>37,46</sup> (N range 66–73)	Increased occurrence of neuropsychological effects with ketamine (36% KET vs 2% placebo, $p = 0.0002$ ) Nonsignificant increase in neuropsychological effects in 1 study.	Consistent but imprecise findings across studies. (Moderate)	LOW There may be an increased occurrence of neuropsychological effects between ketamine and placebo for acute pain management.

Outcome	Comparator	Studies (Participants)	Summary of Findings	Consistency and Precision (Risk of Bias)	Strength of Evidence Summary
M/B: Sedation	Morphine	4 RCTs <sup>38–40,44</sup> (N range 27–449)	Nonsignificant increase in sedation or decreased consciousness in 3 studies. No occurrence of sedation in 1 study.	Consistent but imprecise findings across studies. (Low–High)	LOW There may be a slightly higher occurrence of sedation or decreased consciousness with ketamine compared to morphine for acute pain management.
Other: Dizziness	Placebo	2 RCTs <sup>34,42</sup> (N range 120–199)	Increased dizziness with ketamine (8% KET vs 1% placebo, difference = 7%, [1, 13]) in 1 study. Nonsignificant increase in dizziness in 1 study.	Consistent but imprecise findings across studies. (Moderate)	LOW There may be an increased occurrence of dizziness with ketamine compared to placebo for acute pain management.
Other: Fatigue, General discomfort, Hearing changes, Headache	Placebo	2 RCTs <sup>34,42</sup> (N range 120–199)	No significant difference in fatigue, general discomfort, hearing changes, or headache between ketamine and placebo across studies.	Consistent but imprecise findings across studies. (Moderate)	LOW There may be little to no difference in fatigue, general discomfort, hearing changes, or headache between ketamine and placebo for acute pain management.
Other: Itching	Placebo	2 RCTs <sup>37,42</sup> (N range 73–199)	No difference in itching between ketamine and placebo across studies.	Consistent but imprecise findings across studies. (Moderate)	LOW There may be little to no difference in itching between ketamine and placebo for acute pain management.
Other: Visual disturbance	Morphine	2 RCTs <sup>38,40</sup> (N range 135–251)	Increased visual disturbance with ketamine (17.5% KET vs 4.4% MOR, Difference = 13.1, 95% CI [5.3, 20.9]) in 1 study. Nonsignificant increase in visual disturbance in 1 study.	Consistent but imprecise findings across studies. (Low–Moderate)	LOW There may be an increase in visual disturbance with ketamine compared to morphine for acute pain management.
Respiratory problems	Placebo	2 RCTs <sup>37,42</sup> (N range 73–199)	No significant difference in bradypnea or breathing problems between ketamine and placebo across studies.	Consistent but imprecise findings across studies. (Moderate)	LOW There may be little to no difference in respiratory problems between ketamine and placebo for acute pain management.

*Notes.* This table only includes outcomes with at least 2 studies examining the outcome with the same comparator.

*Abbreviations.* AE=adverse event; CI=confidence interval; GI=gastrointestinal; KET=ketamine; M/B=mental/behavioral; MOR=morphine; OR=odds ratio; RCT=randomized controlled trial.

### ***Benefits of Prehospital Ketamine for Acute Pain Management***

Ketamine appears to be at least as effective as an opioid medication for acute pain management in the prehospital setting based on consistent findings across 6 studies (Table 3). Several studies reported that ketamine was associated with greater reductions in pain severity compared to fentanyl<sup>35</sup> or another opioid,<sup>36,38,39</sup> while other studies reported no significant difference. Likewise, several studies<sup>35,40,42,46</sup> found that morphine requirements (an indirect measure of pain severity) were the same or lower among patients who received ketamine in the prehospital setting compared to other analgesics.

Among 4 studies comparing ketamine to placebo among patients also receiving another analgesic, ketamine was generally associated with improved pain outcomes, but findings were statistically significant in only 1 study.<sup>34</sup> A single RCT examined utilization outcomes between patients receiving ketamine or morphine for acute pain management in the prehospital setting and found no difference in ED length of stay, hospital admission, or critical care admission.<sup>44</sup>

**Table 3. Effectiveness Outcomes of Prehospital Ketamine for Acute Pain Management**

Author, Year	Study Design	Comparator	Direction of Effect	Findings [95% CI]
Bronsky, 2019 <sup>35</sup>	Retrospective Cohort	Fentanyl	Ketamine beneficial	50% pain reduction from baseline: 67% KET vs 19% FENT, <i>p</i> significant (value NR)
McArthur, 2025 <sup>41</sup>	Retrospective Cohort	Fentanyl	NSD	Effect size = -0.46 [-1.19, 0.28]
Cohen, 2022 <sup>36</sup>	Retrospective Cohort	Opioids alone	NSD	Mean pain change (VNRS): 4.3 KET vs 3.75 opioids, <i>p</i> = 0.095; effect size = 0.32 [-0.52, 1.16])
Jennings, 2024 <sup>38</sup>	RCT	Morphine alone	Ketamine beneficial	Mean pain change (VNRS): -5.6 KET vs -3.2 MOR; effect size = -2.4 [-3.2, -1.6]
Johansson, 2009 <sup>39</sup>	RCT	Morphine alone	Ketamine beneficial	Mean pain at hospital admission (NRS): 3.1 KET vs 5.4 MOR, <i>p</i> < 0.05
Le Cornec, 2024 <sup>40</sup>	RCT	Morphine	NSD	Mean pain change at 30 min. (VNRS): -3.6 KET vs -3.8 MOR; difference = 0.2 [0.5, 0.9]
Smyth, 2025 <sup>44</sup>		Morphine	NSD	SPID score: 3.5 KET vs 3.4 MOR; mean difference = 0.1 [-0.4, 0.6]
Andolfatto, 2019 <sup>34</sup>	RCT	Placebo + Nitrous oxide	Ketamine beneficial	≥ 2-point reduction at 30 min. (VNRS): 76% KET vs 41% placebo; difference = 35% [17, 51]
Galinski, 2007 <sup>37</sup>	RCT	Placebo + Morphine	NSD	Pain score (VAS) at 30 min.: 34.1 KET + MOR vs 39.5 placebo + MOR ( <i>p</i> = NS)
McMullan, 2024 <sup>42</sup>	RCT	Placebo + Fentanyl	NSD	≥ 2-point reduction at 30 min. (VNRS): 44.7% KET + FENT vs 36% placebo + FENT; difference = 8.7% [-5.1, 22.5]
Wiel, 2015 <sup>46</sup>	RCT	Placebo + Morphine	NSD	VAS final pain score: 3.1 KET + MOR vs 3.7 placebo + MOR ( <i>p</i> = NS)

**Abbreviations.** CI=confidence interval; FENT=fentanyl; KET=ketamine; min.=minutes; kg=kilogram; IM=intramuscular; IN=intranasal; IO=intraosseous; IV=intravenous; mg=milligram; MOR=morphine;

NRS=numeric rating scale; NS=nonsignificant; NSD=no significant difference; SPID=sum of pain intensity differences; VAS=visual analog scale; VNRS=verbal numeric rating scale.

## SEDATION

### *Safety of Prehospital Ketamine for Sedation*

A single retrospective cohort<sup>2</sup> by Muldowney et al reported mortality outcomes based on receipt of ketamine (5 mg/kg IM) or midazolam for sedation in the prehospital setting. In this study, which was conducted in the US among 376 patients experiencing acute behavioral disturbance in an urban EMS system, out-of-hospital, ED, and in-hospital mortality rates were low (0–2%) and did not differ between groups (ED deaths: 1% midazolam vs 0% ketamine, difference = 0.7%, 95% CI [-0.7, 2.1]; in-hospital deaths: 2% midazolam vs 1% ketamine, difference = 1.2%, 95% CI [-1.6, 4.0]; out-of-hospital deaths: 0% midazolam vs 0% ketamine).

Muldowney et al<sup>2</sup> and another larger retrospective cohort by Brown et al<sup>14</sup> comparing sedation with ketamine compared to benzodiazepines or antipsychotics in the prehospital setting found no significant differences in rates of cardiac arrest between groups, which were overall low (0.1% to 2%) (Table 4). The larger of these 2 studies, Brown et al<sup>14</sup> ( $N = 7,973$ ), used propensity score matching to minimize baseline differences among groups and found that the risk of post-sedation cardiac arrest was small (0.1% to 0.2%) and similar among those who received ketamine (dosage NR), a benzodiazepine, or an antipsychotic as initial treatment. However, the incidence of invasive airway placement, which was the most frequent serious adverse event reported in this study, was higher with receipt of ketamine as initial treatment compared to benzodiazepines (2% ketamine vs 0.6% benzodiazepines, difference = 1.4%, 95% CI [0.7, 2.1]) and compared to antipsychotics (1.5% ketamine vs 0.3% antipsychotics, difference = 1.2%, 95% CI [0.4, 2.0]). This study also found a higher incidence of serious adverse events overall (specifically due to a higher incidence of post-sedation invasive airway placement and new-onset severe oxygen desaturation) with ketamine compared to benzodiazepines (4% ketamine vs 1.6% benzodiazepines, difference = 2.4%, 95% CI [1.3, 3.4]) and compared to antipsychotics (3.1% ketamine vs 1.1% antipsychotics, difference = 2.1%, 95% CI [0.8, 3.3]).

Muldowney et al<sup>2</sup> and another smaller retrospective cohort<sup>1</sup> did not find a significant difference in the need for invasive airway placement when ketamine (dose = 5 mg/kg IM) was used for sedation. In Muldowney et al, the odds of receiving advanced airway management were similar with midazolam and ketamine (adjusted OR = 1.02, 95% CI [0.44, 2.38]) and no differences were observed in emergency department intubation rates (14% midazolam vs 11% for ketamine). The second study<sup>1</sup> did not find a significant difference in the need for invasive airway placement when ketamine was conducted in the US among 135 patients treated by an EMS service that had implemented standing orders for ketamine in cases of “profound agitation,” defined as displays of active physical violence directed towards self or others when usual chemical or physical restraints may not be appropriate or safely used.<sup>44</sup> In this study, in which all patients were subsequently transported to an urban level 1 trauma center, receipt of ketamine at doses  $\leq 5$ mg/kg was not associated with need for intubation when adjusted for age, sex, ED arrival time (a surrogate measure for staffing and available resources), and co-administration of midazolam or haloperidol. In a retrospective cohort conducted in Italy that included 319 patients with psychomotor agitation, ketamine was significantly associated with a fraction of inspired oxygen (FiO<sub>2</sub>) requirement  $> 0.4$  through a Venturi face mask.<sup>47</sup> No patients in this study required intubation.

Two retrospective cohorts compared different dosages of ketamine in patients requiring sedation in the prehospital setting. One cohort<sup>49</sup> of 2,383 patients receiving ketamine for behavioral concerns compared a high dose (> 2 mg/kg IV/IO or > 5 mg/kg IM) to a standard dose ( $\leq$  2 mg/kg IV/IO or  $\leq$  5 mg/kg IM). A higher incidence of intubation was reported among patients receiving higher dose ketamine (6.4% high dose vs 3.3% standard dose, OR = 2.0, 95% CI [1.0, 3.9]). No significant differences were found for other respiratory outcomes including hypoxia or need for supplemental oxygen, or for cardiac outcomes including hypotension or cardiac arrest. A smaller retrospective cohort<sup>48</sup> of 292 agitated patients compared adverse events after a change in EMS protocol directed paramedics to give an initial lower dose of ketamine (3 mg/kg IM) followed by an additional dose (1 mg/kg IM) if adequate sedation was not achieved. This dosage was compared to the previously directed standard dose (4 mg/kg IM). No significant differences in intubation or a composite outcome of any adverse events were reported, but there were significantly more assaults or injuries to EMTs and ED staff after implementing the lower dose ketamine protocol (43.2% low dose vs 19.4% standard dose). However, most of the staff assaults occurred prior to ketamine administration and therefore the observed increase may not have been related to the change in ketamine dosing.

The most frequently reported adverse events in noncomparative and unadjusted studies included intubation, laryngospasm, and respiratory depression (see Supplementary Materials for full study details). In a single noncomparative study<sup>54</sup> of 68 patients treated with ketamine for severe agitation at a dance festival, 2 patients developed hypersalivation, 1 had transient apnea requiring approximately 2 minutes of assisted ventilation, and 1 was intubated due to persistent severe agitation.

**Table 4. Summary of Adverse Events of Prehospital Ketamine for Sedation**

Outcome	Comparator	Studies (Participants)	Summary of Findings	Consistency and Precision (Risk of Bias)	Strength of Evidence Summary
Cardiac arrest	Benzodiazepines	2 Retrospective cohorts <sup>2,14</sup> (N range 376–7973)	No significant difference in cardiac arrest between ketamine and benzodiazepines for sedation.	Consistent and precise findings across studies. (Moderate–Serious)	LOW There may be no difference in the occurrence of cardiac arrest between ketamine and benzodiazepines for sedation.
Respiratory: advanced airway placement or need for oxygen	Benzodiazepines	4 Retrospective cohorts <sup>1,2,14,47</sup> (N range 135–7973)	Increase in invasive airway placement (2% KET vs 0.6% BENZ, difference = 1.4, 95% CI [0.7, 2.1]) and oral/nasal airway placement (6.3% KET vs 1.9% BENZ, difference = 4.4, 95% CI [3.2, 5.7]) with ketamine in the largest study. Increase in need for oxygen with ketamine in 1 study. No significant difference in intubation or advanced airway management in 2 studies.	Inconsistent but precise results across studies. (Moderate–Serious)	LOW There may be an increase in advanced airway management or need for oxygen with ketamine compared to benzodiazepines for sedation.

*Notes.* This table only includes outcomes with at least 2 studies examining the outcome with the same comparator.

*Abbreviations.* BENZ=benzodiazepines; CI=confidence interval; KET=ketamine.

### ***Benefits of Prehospital Ketamine for Sedation***

Brown et al,<sup>14</sup> the large retrospective cohort described above, found less need for additional sedation when ketamine was used as initial treatment compared to benzodiazepines or antipsychotics (Table 5). However, Muldowney et al,<sup>2</sup> a smaller retrospective cohort also discussed above, found no difference in the need for additional sedation with ketamine compared to benzodiazepines. Two cohorts evaluating different doses of ketamine administered in the prehospital setting did not find a difference in the need for additional sedation or restraints based on dose.<sup>48,49</sup>

Muldowney et al<sup>2</sup> and another retrospective cohort<sup>48</sup> reported no significant differences in hospital admission or length of stay when ketamine was administered in the prehospital setting compared to benzodiazepines or when lower doses of ketamine were compared to standard doses. One retrospective cohort<sup>47</sup> reported shorter hospital length of stay for patients who received ketamine for acute agitation in the prehospital setting compared to benzodiazepines (2.48 days ketamine vs 2.66 days benzodiazepines,  $p = 0.03$ ), but this difference may not be clinically significant.

**Table 5. Effectiveness Outcomes of Prehospital Ketamine for Sedation**

Author, Year	Study Design	Comparator	Direction of Effect	Findings [95% CI]
Brown, 2022 <sup>14</sup>	Retrospective cohort	Benzodiazepines Antipsychotics	Ketamine beneficial	Need for additional sedation: 28% KET vs 39.7% BENZ, difference = -11.7%, [-14.7, -8.7] 25.7% KET vs 46.3% ANTIP, difference = -20.5%, [-24.6, -16.5]
Muldowney, 2024 <sup>2</sup>	Retrospective cohort	Benzodiazepines	NSD	No need for additional sedatives: 41% BENZ vs 41% KET, difference = 0.2%, [-10.4, 10.8]
Cunningham, 2021 <sup>48</sup>	Retrospective cohort	Low dose (3mg/kg) vs standard dose (4 mg/kg) IM KET	NSD	Need for additional restraint (any): 72.8% low dose vs 72% standard; OR = 1.04, [0.59, 1.85] Need for additional restraint (chemical): 56.8% low dose vs 57.3% standard; OR = 0.98, [0.58, 1.64]
Sergot, 2024 <sup>49</sup>	Retrospective cohort	High dose (> 2 mg/kg IV/IO or > 5 mg/kg IM) vs standard dose (≤ 2 mg/kg IV/IO or ≤ 5 mg/kg IM) KET	NSD	Need for antipsychotics: 0.4% low dose vs 1.9% high dose; OR = 4.6, [0.98, 21.3]

*Abbreviations.* ANTIP=antipsychotics; BENZ=benzodiazepines; CI=confidence interval; IM=intramuscular; IO=intraosseous; IV=intravenous; KET=ketamine; kg=kilogram; mg=milligram; OR=odds ratio.

## **RAPID SEQUENCE INTUBATION**

### ***Safety of Prehospital Ketamine for Rapid Sequence Intubation***

We did not identify any studies that evaluated mortality when ketamine was used in the prehospital setting for RSI compared to other medications.

Two cohorts<sup>68,70</sup> comparing ketamine (1–2 mg/kg IV) to etomidate for patients undergoing RSI in the prehospital setting reported mixed results on the incidence of hypotension (Table 6). A retrospective cohort<sup>68</sup> of 306 patients intubated by air medical services reported a lower incidence of hypotension (defined as systolic blood pressure [SBP] < 90 mmHG or a  $\geq 5$  mmHG decrease in SBP for those already hypotensive) with ketamine compared to etomidate as the induction agent (4.2% ketamine vs 9.6% etomidate,  $p = 0.028$ ). However, another retrospective cohort<sup>70</sup> of 116 patients intubated by EMS or air medical services reported no significant difference in hypotension (defined as a 20% or greater decrease in SBP from baseline) with ketamine compared to etomidate (18% ketamine vs 16% etomidate,  $p = 0.79$ ). Most patients received etomidate (70%–84%) in these studies and rocuronium and succinylcholine were co-administered along with ketamine or etomidate. Inconsistent findings may be due to differences in the definition of hypotension and/or lack of full adjustment for baseline differences between groups in 1 of the studies.<sup>70</sup>

Two cohorts<sup>69,71</sup> compared different doses of ketamine in patients undergoing RSI. In 1 of these studies, a retrospective cohort<sup>71</sup> of 130 patients undergoing RSI that compared standard dose ( $\leq 2$  mg/kg IV) to high dose ( $> 2$  mg/kg IV) ketamine, patients receiving high dose ketamine had higher rates of hypotension, bradycardia, oxygen desaturation, laryngospasm, and agitation. No significant differences were reported between groups in the incidence of vomiting, hypertension, cardiac arrest, or tachycardia. Another retrospective cohort<sup>69</sup> of 212 patients undergoing RSI compared half dose ketamine (1 mg/kg IV/IO) to standard dose ketamine (2 mg/kg IV/IO) and reported no differences in peri-intubation cardiac arrest based on dose. However, this study did not report baseline patient characteristics by intervention group or control for baseline group differences. These critical methodological limitations lower the usefulness of these findings.

**Table 6. Summary of Adverse Events of Prehospital Ketamine for RSI**

Outcome	Comparator	Studies (Participants)	Summary of Findings	Consistency and Precision (Risk of Bias)	Strength of Evidence Summary
Hypotension	Etomidate	2 Retrospective cohorts <sup>68,70</sup> (N range 113–306)	Less hypotension with ketamine (4.2% KET vs 9.6% ETO, $p = 0.028$ ) in 1 study. No significant difference in hypotension between ketamine and etomidate in 1 study.	Inconsistent and imprecise findings across studies. (Moderate–Serious)	INSUFFICIENT It is unclear if there is any difference in hypotension between ketamine and etomidate for RSI.

*Notes.* This table only includes outcomes with at least 2 studies examining the outcome with the same comparator.

*Abbreviations.* ETO=etomidate; KET=ketamine; RSI=rapid sequence intubation.

### ***Benefits of Prehospital Ketamine for RSI***

Among studies utilizing ketamine for prehospital RSI, only 2 studies<sup>70,71</sup> reported on intubation success (Table 7). Compared to high dose ketamine ( $> 2$  mg/kg IV), standard dose ketamine ( $\leq 2$  mg/kg IV) resulted in fewer instances of multiple intubation attempts and unsuccessful intubation. No significant differences were reported in first pass intubation success between ketamine and etomidate, with high rates of success in both groups (96%–97%).<sup>70</sup>

**Table 7. Effectiveness and Utilization Outcomes of Prehospital Ketamine for RSI**

Author, Year	Study Design	Comparator	Direction of Effect	Findings [95% CI]
Krebs, 2021 <sup>71</sup>	Retrospective cohort	Standard dose ( $\leq 2$ mg/kg) vs high dose ( $> 2$ mg/kg) IV ketamine	Standard dose beneficial	Multiple intubation attempts: 23.8% standard dose vs 50% high dose; OR = 3.2 [1.5, 6.8] Unsuccessful intubation: 5% standard dose vs 16% high dose; OR = 3.6 [1.0, 12.7]
Stanke, 2021 <sup>70</sup>	Retrospective cohort	Etomidate	NSD	First pass intubation success: 97% KET vs 96% ETO ( $p = 0.85$ )

*Abbreviations.* CI=confidence interval; ETO=etomidate; IV=intravenous; KET=ketamine; kg=kilogram; mg=milligram; NSD=no significant difference; OR=odds ratio.

## ANY INDICATION

Several studies did not specify the indication for prehospital ketamine use. A retrospective cohort<sup>72</sup> using data from a previously conducted RCT examining the use of tranexamic acid for patients with moderate to severe TBI reported no differences in death within 6 months of injury, cardiac events, arrhythmia, hypotension, hypertension, or hypoxia between those with and without ketamine exposure in the prehospital setting. However, patients with exposure to ketamine had a significantly higher incidence of seizure activity (3.1% ketamine vs 1% no ketamine,  $p = 0.01$ ), but significantly lower incidence of intracranial pressure elevation (56.3% ketamine vs 82.3% no ketamine,  $p = 0.048$ ). Most participants in the study (84%) did not receive ketamine in the prehospital setting.

Additionally, a retrospective cohort<sup>73</sup> of combat casualties from the Department of Defense Trauma Registry examined interventions associated with survival after prehospital intubation for any indication and reported that more patients who survived at least 7 days after injury received prehospital ketamine compared to those who did not survive at least 7 days after injury (29% survivors vs 17% non-survivors), but this difference was not significant in adjusted models of survivorship (OR =1 .43, 95% CI [0.96, 2.11]) and this study was not specifically designed to compare ketamine to other interventions. A noncomparative cohort<sup>74</sup> of trauma patients receiving air medical services in the UK reported no deaths on the scene after administration of ketamine for any indication.

## DISCUSSION

The aim of this systematic review was to synthesize evidence on the safety of ketamine administration for acute pain, sedation, and RSI in the prehospital setting to inform national protocols for VHA paramedics and EMTs.

Evidence regarding mortality following ketamine administration in the prehospital setting is limited to 3 retrospective cohorts (1 in which ketamine was used for acute pain, 1 in which ketamine was used for sedation, and 1 study in which the indication for ketamine was not reported).<sup>2,45,72</sup> None of these 3 studies found a significant difference in mortality between patients receiving ketamine compared to other medications given for the same indication. However, the small number of studies, small sample sizes with limited power to detect differences in mortality, and variability across studies in patient populations, indications for ketamine, co-interventions and comparator medications, and mortality outcomes (eg, survival to hospital discharge vs mortality within 6-months of injury) prevents conclusions from being drawn regarding mortality risk with prehospital administration of ketamine. This evidence should be considered preliminary.

While we did not formally include studies of esketamine, an enantiomer of ketamine with distinct pharmacologic properties that is used widely by EMS personnel in Europe, it is worth noting that a retrospective cohort<sup>75</sup> from the Netherlands of 1,451 patients with suspected severe TBI undergoing RSI from air medical services did not find a significant difference in 30-day mortality with etomidate compared to esketamine for RSI (32.9% etomidate vs 33.8% esketamine; adjusted OR = 1.08, 95% CI [0.67, 1.73]). Overall mortality rates were high in this study (32%–34%), likely owing to the severe nature of patients' injuries requiring air medical transport and RSI.

Among studies of prehospital ketamine administration for acute pain or sedation, the incidence of serious adverse events was generally low and did not significantly differ between ketamine and comparator medications. Two RCTs<sup>42,44</sup> comparing ketamine to morphine or as an adjunct to fentanyl compared to placebo for acute pain management in the prehospital setting reported low rates (0–3%) of serious adverse events overall (a composite outcome commonly including cardiac arrest, invasive airway placement, or severe oxygen desaturation) with no differences based on receipt of ketamine. Similarly, 2 retrospective cohorts,<sup>2,14</sup> including 1 large cohort ( $N = 7,973$ ), of patients with acute behavioral disturbance comparing ketamine to benzodiazepines or antipsychotics for sedation found that rates of cardiac arrest were low overall (0.1% to 2%) and did not significantly differ between groups.

The large cohort<sup>14</sup> ( $N = 7,973$ ) of patients requiring sedation for acute behavioral disturbance found that receipt of ketamine was associated with an increased incidence of invasive airway placement, which was the most frequent serious adverse event reported in this study. However, 2 smaller cohorts<sup>1,2</sup> of patients requiring sedation for acute behavioral disturbance or agitation did not find that receipt of ketamine was associated with higher intubation incidence. Several study authors discussed the subjective nature of decisions to intubate, which may be informed by multiple factors including a provider's personal practice, comfort treating patients in a dissociated state, and resources available to monitor a potentially unstable patient.<sup>1,50</sup> When considered in this context, intubation rates may not directly reflect ketamine safety. Nonetheless, given that existing evidence is inconsistent, further research is needed to clarify the potential increased risk of intubation when ketamine is used for sedation in the prehospital setting.

Studies of ketamine for acute pain management in the prehospital setting, which accounted for nearly half of prioritized studies overall, provide the most informative evidence regarding the incidence of non-serious adverse events. Overall, these studies found that compared to opioids or placebo, ketamine may be associated with a higher incidence of neuropsychological effects, sedation, dizziness, visual disturbance, and emergence phenomenon. Nausea and vomiting, dizziness, disorientation, and hallucinations were among the most common non-serious adverse events reported overall.

Only 2 retrospective cohorts<sup>68,70</sup> evaluated the risk of hypotension with ketamine for RSI compared to etomidate in the prehospital setting and had inconsistent results. Relative to studies of prehospital ketamine for acute pain and sedation, the safety of ketamine for RSI in the prehospital setting has been less frequently studied and represents an important area for future research.

Across studies, doses of ketamine ranged from 0.1–0.2 mg/kg IV and 0.5–1 mg/kg IN for pain control, 1–5 mg/kg IM for sedation, and 1–2 mg/kg IV for RSI. Two retrospective cohorts compared adverse event incidence with different dosages of ketamine in patients requiring sedation for acute behavioral disturbance in the prehospital setting. One of these cohorts<sup>49</sup> found that higher dose ketamine was associated with a higher incidence of intubation, but the same finding was not observed in the second cohort.<sup>48</sup> Neither study found that higher ketamine doses were associated with a higher incidence of other adverse events. In 2 cohorts comparing different ketamine doses among patients who required RSI, 1 cohort<sup>71</sup> found that high dose (> 2 mg/kg IV) ketamine was associated with a higher incidence of hypotension, bradycardia, oxygen desaturation, laryngospasm, and agitation but not vomiting, hypertension, cardiac arrest, or tachycardia. The other cohort<sup>69</sup> compared a lower dose of ketamine (1 mg/kg IV/IO) to standard dose ketamine (2 mg/kg IV/IO) for RSI and reported no differences in peri-intubation cardiac arrest incidence. The applicability of these findings is unclear given that protocols for prehospital ketamine may specify standard weight-based ketamine dosing for sedation or RSI that are lower than the “high dose” ketamine used in some of these studies. However, the trend towards potentially higher rates of some adverse events with higher ketamine doses warrants consideration by EMS personnel, who must often estimate patient weight and could be at risk of administering a higher dose than intended.

Ketamine appears to be at least as effective as other medications commonly used for acute pain management, sedation for acute behavioral disturbance, and RSI in the prehospital setting. Ketamine resulted in similar or higher levels of pain relief compared to opioids or fentanyl in patients requiring prehospital acute pain management. Likewise, prehospital ketamine was more or similarly effective for sedation and RSI, although fewer studies reported effectiveness outcomes for these indications. While studies have evaluated the potential risks associated with higher ketamine doses, as discussed above, less is known about the lowest effective ketamine doses for certain indications, such as sedation. Establishing the lower threshold of effective ketamine doses for acute pain, sedation, and RSI in the prehospital setting represents another area for future research.

## LIMITATIONS

Although we identified a large body of evidence evaluating prehospital ketamine administration, studies varied widely in terms of the indication for ketamine, comparators and co-interventions, and outcomes assessed, making it difficult to draw strong conclusions regarding ketamine’s safety for a specific indication. Additionally, half of the included studies lacked a comparison group or did not adequately control for baseline differences between intervention groups, limiting our ability to understand whether benefits and harms differed based on receiving ketamine or could be explained by

other factors. Conducting research in the prehospital setting is inherently challenging due to patient acuity, limited resources, and unpredictable care environments, as well as the challenge of systematically integrating data from different points along the patient's course from prehospital care, the ED, and the hospital. However, there is a growing interest in conducting research in this field, which is reflected in the observation that more than half of studies included in this review were published within the last 5 years. Recent innovations in mobile health technologies, providing tools for linking and transmitting patient data to hospitals, may improve the feasibility of research in this field.<sup>3</sup>

Most systematic reviews focus on the benefits of interventions, and systematically synthesizing the harms of an intervention presents some unique challenges. Published clinical trials and observational studies of interventions often lack systematic and/or detailed reporting of harms, limiting the information available to systematic reviewers.<sup>76</sup> Systematic reviewers must also attempt to discern selective reporting of harms or “spin” in the way studies present harms data.<sup>77</sup> In this review, we focused on a thorough synthesis of harms, including consideration of heterogeneity in reporting of harms data across studies and overall study risk of bias. However, our synthesis was still limited by our reliance on the information available in published studies.

## **FUTURE RESEARCH**

Although there is a large volume of literature on this topic, existing evidence still has some important gaps. Across all studies of ketamine used for different indications in the prehospital setting, mortality data are scant. Future research powered to detect differences in mortality and cardiac arrest rates would help to further establish ketamine as a safe option for prehospital use. Because patient deaths and cardiac arrests are rare events, large-scale database studies, such as those conducted within VHA, may be best suited to evaluate these outcomes. Additionally, future research could help to clarify the risk of adverse events when ketamine is used for sedation in cases of acute behavioral disturbance, specifically whether ketamine used for this indication is associated with an increased incidence of intubation or severe oxygen desaturation. The most informative studies to address this question would be RCTs or cohort studies that adjust for baseline differences between groups. Similarly, further comparative evidence examining ketamine for acute pain management in the prehospital setting would help to confirm the incidence of visual disturbance and emergence phenomena.

Compared to studies of ketamine for acute pain and sedation, fewer studies have evaluated ketamine used for RSI in the prehospital setting. Future research for this indication would help to determine whether there is any difference in risk of hypotension and other adverse effects with ketamine compared to etomidate. Given the higher potential for adverse events with higher doses of ketamine, future research could also help determine the lower thresholds of effective ketamine dosing for acute pain, sedation, and RSI in the prehospital setting. Other future research considerations include identifying best practices to accurately assess patient weight in the prehospital setting and evaluation of implementation efforts to ensure that existing protocols regarding ketamine dosing are followed.

Finally, recreational use of ketamine is increasing based on survey data and poisonings reported to US Poison Centers,<sup>78–80</sup> and it is unclear how a higher prevalence of ketamine use in the population may impact management decision or outcomes when ketamine is used in the prehospital setting, particularly in cases of undifferentiated acute behavioral disturbance or agitation.

## CONCLUSIONS

Ketamine has been broadly incorporated into national and state EMS protocols for the management of patients with urgent and emergent conditions and has a long history of use as a medication for procedural sedation and anesthesia in the hospital setting. Overall, based on existing evidence, ketamine does not appear to increase the risk of serious adverse effects compared to other medications used for acute pain management, sedation, and RSI in the prehospital setting, with the exception of a potentially higher rate of intubation or severe oxygen desaturation when ketamine is used for acute behavioral disturbance compared to benzodiazepines or antipsychotics. However, the evidence is limited by study methodological weaknesses, variability in co-interventions and comparators, and differences in how harms were reported across studies. Evidence on mortality was limited to 3 retrospective cohorts with varying patient populations, comparators, and outcome definitions and should be considered preliminary. Future research could help to address current evidence gaps. Large database studies could help to confirm that prehospital administration of ketamine is associated with a relatively low risk of mortality or cardiac arrest (rare events overall) compared to alternative medications. RCTs or well-designed cohort studies would provide further insight into the potential risks of ketamine for sedation in cases of acute behavioral disturbance.

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