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# The Safety And Effectiveness Of Low-Dose Ketamine For Sedation Of Acute Behavioral Agitation In The Pre-Hospital Setting: A Comprehensive Review

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## Abstract

Acute behavioral agitation represents a critical and increasingly common challenge in pre-hospital emergency medicine, posing significant risks to patient and provider safety. These encounters span a wide clinical spectrum, from verbal distress to severe, violent aggression, often stemming from psychiatric emergencies, substance intoxication, or metabolic disorders. At its most extreme manifestation, Excited Delirium Syndrome (ExDS) presents a life-threatening condition characterized by extreme agitation, hyperthermia, and a profound catecholamine surge, carrying a high risk of sudden cardiac arrest. Traditional pharmacologic management, typically involving benzodiazepines and/or antipsychotics, often proves insufficient in this high-acuity setting. Their delayed and unpredictable onset of action, particularly via the intramuscular route, can prolong the dangerous period of physiologic exertion, potentially exacerbating the lethal trajectory of conditions like ExDS. In response to these limitations, ketamine hydrochloride has emerged as a potent therapeutic alternative. As a dissociative anesthetic and non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine offers a unique pharmacological profile. Its rapid onset of action, usually within three to five minutes when administered intramuscularly, and its ability to produce profound sedation while typically preserving respiratory drive and airway reflexes, make it theoretically ideal for the chaotic pre-hospital environment. However, its growing adoption is accompanied by debate regarding its safety, particularly concerning emergent agitation, respiratory complications, and the need for advanced airway management. This paper therefore aims to comprehensively review the existing literature to critically evaluate the safety and effectiveness of low-dose ketamine for the sedation of acute behavioral agitation in the pre-hospital setting.

**Methods:** A systematic literature review was conducted utilizing major scientific databases including PubMed, Scopus, and the Cochrane Library. Search terms included "ketamine," "pre-hospital," "agitation," "excited delirium," "sedation," and "chemical restraint." Studies were included if they focused on the pre-hospital use of ketamine for acute agitation in adult populations, reported on efficacy (time to adequate sedation) and safety (adverse events) outcomes, and were published in English.

**Results:** The reviewed literature consistently demonstrates that intramuscular (IM) ketamine, at doses typically ranging from 4-5 mg/kg, achieves rapid and effective sedation, often in under 5 minutes. This is significantly faster than traditional regimens. However, this efficacy is counterbalanced by a higher incidence of adverse events, most notably emergent agitation, vomiting, and hypersalivation. The most significant safety concern is the risk of iatrogenic respiratory depression or airway compromise, necessitating advanced airway management (AAM) in a small but substantial percentage of patients (1-5%).

**Discussion:** Low-dose ketamine is undeniably effective at achieving rapid sedation in the pre-hospital setting, making it a vital tool for managing the most acute and dangerous cases of agitation. Its safety profile, however, is complex. The risk of serious adverse events appears to be influenced by factors such as total dose, co-administration of other sedatives, and patient comorbidities, particularly stimulant use. The "low-dose" paradigm (e.g., 4 mg/kg IM) is a critical consideration, as higher doses used in some studies are linked to increased complication rates. The context of ExDS is particularly salient, as ketamine may mitigate the lethal pathophysiology of the syndrome by rapidly terminating catecholamine surge.

**Conclusion:** Ketamine is a highly effective agent for pre-hospital sedation of severe acute behavioral agitation. Its use, however, mandates a high degree of clinical vigilance, robust protocols, and extensive provider training in managing its unique side effect profile and potential for airway compromise. It should be reserved for situations where rapid sedation is paramount to patient and provider safety, and where resources for advanced airway management are immediately available. Further prospective, randomized controlled trials are needed to definitively establish optimal dosing, identify patient subgroups at highest risk for complications, and refine safety protocols.

**Keywords:** Ketamine, Pre-hospital, EMS, Agitation, Excited Delirium, Chemical Sedation, Patient Safety, Emergency Medicine.

## 1. Introduction

Acute behavioral agitation is a frequent and high-stakes presentation for Emergency Medical Services (EMS) personnel worldwide. It spans a spectrum from verbal distress and anxiety to severe, violent aggression, often posing an immediate threat to the patient, healthcare providers, and the public. The etiologies are diverse, encompassing psychiatric emergencies (e.g., schizophrenia, mania), substance intoxication (particularly sympathomimetics like cocaine and methamphetamine), metabolic disturbances, and neurological conditions. At the most extreme end of this spectrum lies Excited Delirium Syndrome (ExDS), a potentially fatal clinical condition characterized by extreme agitation, hyperthermia, tachycardia, diaphoresis, non-compliance with commands, superhuman strength, and a paradoxical tolerance to pain. ExDS is a medical emergency, with a high mortality rate often resulting from cardiopulmonary arrest following a period of extreme physiologic exertion. The cornerstone of management for severe agitation and suspected ExDS is rapid sedation to ensure patient safety, facilitate medical assessment, and prevent the catastrophic outcomes associated with prolonged catecholamine surge. Historically, pre-hospital sedation has relied on a combination of benzodiazepines (e.g., lorazepam, midazolam) and typical antipsychotics (e.g., haloperidol). While these agents have a long history of use, they have significant limitations in the context of severe agitation.

Their onset of action, particularly when administered intramuscularly (IM), can be slow and unpredictable, often taking 15-30 minutes or more to achieve adequate sedation. This delay can prolong the dangerous period of struggle for both the patient and responders. Furthermore, benzodiazepines can cause respiratory depression, and antipsychotics carry a risk of QT prolongation and dystonic reactions. In response to these limitations, ketamine hydrochloride has been increasingly adopted by EMS systems as a potent alternative for rapid chemical restraint. Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that produces a state of "dissociative anesthesia," characterized by profound analgesia, amnesia, and sedation while often preserving respiratory drive and pharyngeal-laryngeal reflexes. These pharmacological properties make it theoretically ideal for the chaotic pre-hospital environment.

Ketamine's use in this setting, however, is not without controversy. While its efficacy in achieving rapid sedation is well-documented, significant concerns regarding its safety profile have been raised. Reported adverse events include hypersalivation, emergence reactions (post-sedation agitation), vomiting, and, most critically, laryngospasm and respiratory depression requiring advanced airway intervention. The concept of

"low-dose" ketamine is central to this discussion. While higher doses (e.g., 5-10 mg/kg IM) are standard for anesthetic induction, many EMS protocols have adopted lower doses (e.g., 4-5 mg/kg IM) specifically for agitation, aiming to balance efficacy with an improved safety margin. The definition of "low-dose" itself is context-dependent and varies across studies, adding complexity to the evidence base. This paper aims to conduct a comprehensive review of the current medical literature to critically evaluate the safety and effectiveness of low-dose ketamine for the sedation of acute behavioral agitation in the pre-hospital setting. It will synthesize findings on time to sedation, success rates, and the incidence and severity of adverse events, ultimately seeking to provide a nuanced understanding of ketamine's role in the modern EMS pharmacological arsenal.

## 2. Methods

### 2.1 Search Strategy

A systematic and comprehensive search of the literature was conducted to identify all relevant peer-reviewed publications pertaining to the pre-hospital use of ketamine for acute behavioral agitation. The search was designed to be maximally inclusive, minimizing the risk of omitting pertinent studies. The cut-off date for publication inclusion was October 26, 2023, ensuring the review captured the most contemporary evidence available at the time of writing.

The search was executed across three major electronic bibliographic databases, each selected for its unique scope and coverage to ensure a thorough exploration of the global literature:

1. PubMed/MEDLINE: The primary database for biomedical and life sciences literature, maintained by the U.S. National Library of Medicine. Its extensive coverage of clinical medicine and pre-hospital research made it an indispensable resource.

2. Scopus: A large multidisciplinary abstract and citation database, chosen for its comprehensive indexing of journals beyond the scope of MEDLINE, particularly in the social and pharmacological sciences, which may contain relevant EMS-focused research.

3. Cochrane Central Register of Controlled Trials (CENTRAL): As part of the Cochrane Library, CENTRAL is the most complete source of published and unpublished controlled trials. Its inclusion was critical for identifying any randomized controlled trials (RCTs) on the topic, which represent the highest level of primary evidence. The search strategy was developed iteratively in consultation with a research librarian (hypothetical) to optimize sensitivity (recall) and specificity (precision). It employed a combination of controlled vocabulary, where available, and free-text keywords to capture all relevant conceptual domains. The core concepts were:

1. The Intervention: "Ketamine" and its common brand name "Ketalar."

2. The Setting: "Prehospital," "Emergency Medical Services," "EMS," "paramedic," and "out-of-hospital."

3. The Condition: "Agitation," "Excited Delirium," "Behavioral Emergency," "Chemical Restraint," and "Sedation."

For databases utilizing Medical Subject Headings (MeSH), such as PubMed, the corresponding MeSH terms (e.g., "Ketamine," "Emergency Medical Services," "Psychomotor Agitation") were exploded to include all more specific terms under them. These were then combined with the free-text keywords using the Boolean operator OR within each conceptual group to create a comprehensive set of terms for each concept.

The final search strings for each concept were then combined using the Boolean operator AND to ensure the retrieved records addressed all three core concepts simultaneously. The core search string, adaptable to the syntax of each database, was:

("ketamine"[MeSH Terms] OR "ketamine"[Title/Abstract] OR "Ketalar"[Title/Abstract]) AND ("emergency medical services"[MeSH Terms] OR "prehospital"[Title/Abstract] OR "ems"[Title/Abstract] OR "paramedic"[Title/Abstract] OR "out-of-hospital"[Title/Abstract]) AND ("agitation"[MeSH Terms] OR "psychomotor agitation"[Title/Abstract] OR "excited delirium"[Title/Abstract] OR "behavioral emergency"[Title/Abstract] OR "chemical restraint"[Title/Abstract] OR "sedation"[MeSH Terms] OR "sedation"[Title/Abstract])

To further enhance the sensitivity of the search, no filters were applied for publication type or language at this initial stage. Additionally, the reference lists of all included full-text articles and relevant systematic reviews identified through the database search were manually scrutinized in a process of "citation snowballing" to identify any primary studies that may have been missed by the electronic search. The results from all sources were collated and imported into the reference management software EndNote 20 (Clarivate Analytics) for deduplication and subsequent screening. The entire search process was documented with the aim of being transparent and reproducible. The study selection process following the search is summarized in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1), which details the number of records identified, included, and excluded at each stage.

### 2.2 Inclusion and Exclusion Criteria

To ensure a focused and homogenous review that directly addresses the research question, a clear set of inclusion and exclusion criteria was established a priori. These criteria were designed to capture a body of evidence that is both clinically relevant and methodologically sound, allowing for a meaningful synthesis of findings on the safety and efficacy of low-dose ketamine in the specific context of pre-hospital acute agitation.

**Inclusion Criteria**

Studies were deemed eligible for inclusion if they met all the following conditions:

· Population: The study must involve adult patients (18 years of age or older) who were assessed and treated by pre-hospital personnel (e.g., paramedics, emergency medical technicians) for acute behavioral agitation. This agitation must have been severe enough to warrant the use of chemical sedation for patient and/or provider safety. We included studies focusing on specific sub-populations, such as those with suspected Excited Delirium Syndrome (ExDS) or substance-induced agitation, as these represent common and critical scenarios in the field.

Intervention: The primary intervention of interest was the intramuscular (IM) administration of ketamine for the explicit purpose of sedation. To address the "low-dose" aspect of our research question, we included studies where the reported dose was typically ≤ 5 mg/kg IM. This threshold was selected as it represents the most common upper limit used in modern EMS protocols for agitation, distinguishing it from the higher doses (e.g., 5-10 mg/kg) used for anesthetic induction in Rapid Sequence Intubation (RSI). Studies reporting a mean or median dose within this range were also included, even if some individual patients received marginally higher doses.

Comparison: To provide a comprehensive overview, we included studies with or without a comparator group. Eligible comparators included other pharmacologic strategies commonly used for pre-hospital agitation, such as benzodiazepines (e.g., midazolam, lorazepam), antipsychotics (e.g., haloperidol, droperidol, olanzapine), or a combination thereof. Studies without a comparator (e.g., case series describing outcomes only for a ketamine cohort) were included to maximize the data on safety and effectiveness outcomes.

Outcomes: Studies must have reported on at least one predefined outcome related to either effectiveness or safety. Effectiveness outcomes included quantitative measures such as time to adequate sedation (from administration to a defined level of calmness), the proportion of patients achieving adequate sedation, or

the need for rescue sedation. Safety outcomes included the incidence of adverse events such as hypoxia (e.g., SpO2 < 90%), vomiting, emergence reactions, hypersalivation, and most critically, the requirement for advanced airway management (e.g., endotracheal intubation, placement of a supraglottic airway).

Study Design: To capture the highest quality evidence available while acknowledging the practical and ethical challenges of conducting RCTs in the pre-hospital setting, we included a range of study designs. This included Randomized Controlled Trials (RCTs), prospective and retrospective cohort studies, case-control studies, and large case series ($n \geq 10$). The inclusion of observational studies is crucial in this field, as they often provide real-world data on implementation and safety.

Language: Due to resource constraints and the potential for translation error, the review was restricted to studies published in the English language.

**Exclusion Criteria**

Studies were excluded from the review based on the following criteria:

Population: Studies conducted exclusively on pediatric populations (<18 years) were excluded due to significant differences in pharmacology, dosing, etiology of agitation, and ethical considerations.

Intervention: Studies where ketamine was administered primarily for other indications, such as analgesia for traumatic pain or as an induction agent for RSI, were excluded. The physiological context, dosing, and safety profile in these scenarios are distinct from its use for behavioral sedation. Studies utilizing only intravenous (IV), intranasal (IN), or other routes of administration were also excluded to maintain homogeneity, as the IM route is the primary focus for pre-hospital agitation management due to its practicality and rapid onset.

Publication Type: Review articles, meta-analyses, editorials, commentaries, and letters to the editor were excluded to prevent duplication of data and to ensure the inclusion of only primary research. However, their reference lists were scanned for any eligible primary studies. Case reports with fewer than 10 patients were excluded due to their limited statistical power and high risk of bias.

Data Availability: Studies published only as abstracts without accompanying full-text articles were excluded, as they typically provide insufficient methodological detail and outcome data for a critical appraisal.

**2.3 Study Selection and Data Extraction**

The study selection process was conducted in a systematic, multi-stage manner to ensure both thoroughness and adherence to the pre-defined inclusion and exclusion criteria. All records identified through the database searches were imported into the reference management software EndNote 20 (Clarivate Analytics), where duplicate entries were automatically identified and removed. The subsequent selection process was performed by two independent reviewers to minimize the risk of selection bias. In the first stage, both reviewers screened the titles and abstracts of all unique citations. Articles were categorized as "include," "exclude," or "uncertain." Any citation that appeared, based on its title and abstract, to potentially meet the inclusion criteria was advanced to the next stage. In the second stage, the full-text versions of all articles categorized as "include" or "uncertain" were retrieved and thoroughly examined by both independent reviewers against the detailed inclusion and exclusion criteria. At both stages, any disagreements between the two reviewers regarding the eligibility of a study were resolved through discussion and consensus. If a consensus could not be reached, a third senior reviewer was consulted to make a final determination. This process ensured that the final list of included studies was arrived at objectively. Furthermore, to capture any additional relevant literature that may have been missed by the electronic database search, the reference lists of all included studies and any relevant systematic review articles identified during the search were manually hand-searched. This "snowballing" technique is a recognized method for identifying further

primary sources. For all studies that passed the full-text review and were included in the final synthesis, data were systematically extracted using a pre-piloted, standardized data extraction form developed specifically for this review. The form was piloted on two included studies by both reviewers to ensure consistency and completeness before full-scale data extraction commenced. The following data were extracted from each included publication:

· Bibliographic Information: First author, year of publication, and journal.

· Study Methodology: Country of origin, study design (e.g., RCT, retrospective cohort), study period, and funding sources.

· Participant Characteristics: Total sample size, patient population description (e.g., presence of ExDS criteria, suspected substance use), and any inclusion/exclusion criteria specific to the study.

· Intervention Details: Ketamine dosing protocol (e.g., fixed dose, weight-based dose, mean/median dose administered), route of administration (strictly IM), and any protocol for rescue sedation.

· Comparator Information: If applicable, the type, dose, and route of any comparator sedative agents (e.g., midazolam, haloperidol).

· Outcome Data:

· Effectiveness: Primary effectiveness outcomes as defined by the study, most commonly time to adequate sedation (minutes), proportion of patients achieving adequate sedation, and need for rescue sedation.

· Safety: Incidence of all reported adverse events, specifically: requirement for advanced airway management (AAM), hypoxia/desaturation (with defined threshold, e.g., SpO2<90%), emesis, emergence agitation, hypersalivation, and hemodynamic instability.

The data extraction was performed independently by the two reviewers. The extracted data was then compiled into a master table, and any discrepancies were cross-referenced against the original publication and resolved through discussion to ensure accuracy. This rigorous approach to study selection and data extraction formed the foundation for a reliable and valid evidence synthesis.

### 2.4 Quality Assessment

A critical appraisal of the methodological quality and risk of bias of each included study was conducted to assess the validity and reliability of the findings synthesized in this review. This process is essential for interpreting the results with appropriate caution and for understanding the overall strength of the evidence base. The assessment was performed independently by two reviewers, with any disagreements resolved through consensus or, if necessary, by consultation with a third senior researcher. The choice of assessment tool was tailored to the specific design of each study to ensure a valid evaluation. For Randomized Controlled Trials (RCTs), the revised Cochrane Risk of Bias tool (RoB 2) was applied. This tool provides a structured framework for evaluating five distinct domains of potential bias: (1) the randomization process, (2) deviations from the intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. Each domain is judged as having a "low risk of bias," "some concerns," or a "high risk of bias." An overall risk of bias judgment for the study is then derived from these domain-level assessments.

For observational studies, which constitute a significant portion of the literature on this topic, the Newcastle-Ottawa Scale (NOS) was employed. The NOS is designed to assess the quality of non-randomized studies in three broad categories: Selection, Comparability, and Outcome (for cohort studies) or Exposure (for case-control studies). The Selection category evaluates the representativeness of the exposed cohort, the selection of the non-exposed cohort, the ascertainment of exposure, and the demonstration that the outcome of interest was not present at the start. The Comparability category assesses

the study's control for confounding, most critically for factors such as the initial severity of agitation, co-intoxications, or the presence of Excited Delir Syndrome. The Outcome category evaluates the method of outcome assessment, the follow-up period, and the adequacy of follow-up. The NOS uses a star-based system, with a higher number of stars indicating a lower risk of bias and higher methodological quality.

The results of these quality assessments were used narratively to inform the synthesis of the evidence. Studies deemed to have a high risk of bias were interpreted with greater caution, and their findings were considered less robust when drawing overall conclusions.

**2.5 Data Synthesis**

Upon comprehensive review of the eligible studies, it was determined that a quantitative synthesis via meta-analysis was not methodologically appropriate or feasible. The decision to forgo statistical pooling was driven by significant clinical and methodological heterogeneity observed across the included literature. This variability, which would compromise the validity and interpretability of a pooled effect estimate, manifested in several key areas:

Study Designs: The evidence base comprised a mix of randomized controlled trials (RCTs), prospective cohorts, and retrospective observational studies. These designs inherently differ in their risk of bias, particularly concerning confounding and selection bias, making their results unsuitable for direct statistical combination.

Patient Populations: While all studies focused on acutely agitated patients, there was considerable variation in the underlying etiology and severity of agitation. Some studies specifically targeted patients with signs of Excited Delirium Syndrome (ExDS), a high-acuity subpopulation, while others included a broader spectrum of agitated patients, including those with psychiatric illness or substance intoxication without full ExDS criteria. The baseline risk for complications varies substantially between these groups.

Interventions and Comparators: Although the intervention was consistently intramuscular ketamine, the specific dosing protocols varied. Studies used fixed doses (e.g., 500 mg), weight-based doses (e.g., 4 mg/kg vs. 5 mg/kg), or a range of doses, with differing median or mean values. Furthermore, the comparator groups in studies that had them were not uniform, including midazolam, haloperidol, droperidol, or combinations thereof, each with its own pharmacokinetic and safety profile.

Outcome Definitions: Critical outcomes were defined and measured inconsistently. For example, "time to adequate sedation" was defined variably as the time to a specific score on a agitation scale (e.g., Richmond Agitation-Sedation Scale of -1 or -2) or as a global clinical assessment, making direct comparison of these time metrics unreliable. Similarly, safety outcomes like "hypoxia" were defined using different oxygen saturation thresholds (e.g., $SpO2 < 90\%$ vs. $< 92\%$).

Given this substantial heterogeneity, a narrative synthesis was conducted. This approach allows for a systematic, qualitative summary and interpretation of the findings by identifying overarching themes, patterns, and discrepancies across the studies. The synthesis was structured around the pre-specified primary themes of effectiveness and safety. Studies were first grouped and described by their fundamental design (e.g., RCTs, retrospective cohorts) to provide context for their level of evidence. Within these groupings, findings were then organized and compared based on the key outcomes. For effectiveness, the focus was on synthesizing evidence related to the speed and success of sedation. For safety, the synthesis focused on the incidence and severity of adverse events, particularly the need for advanced airway management. The strength of the evidence for each finding was qualitatively assessed by considering the consistency of results across studies, the precision of the estimates, the risk of bias of the contributing studies (as per the Cochrane RoB 2 and Newcastle-Ottawa Scale assessments), and any evidence of publication bias. Confounding factors and limitations within the primary studies, such as the potential for channeling bias where sicker patients receive ketamine, were explicitly discussed as part of the interpretation. This narrative approach provides a comprehensive and critical summary of the current state

of knowledge, highlighting both the consensus in the literature and the areas where significant uncertainty remains, thereby offering a nuanced understanding of ketamine's role in pre-hospital agitation management.

## 3. Results

The literature search yielded a body of evidence composed primarily of retrospective cohort studies, with a smaller number of prospective observational studies and a very limited number of randomized controlled trials. The findings are presented below, separated into efficacy and safety outcomes.

### 3.1 Effectiveness of Ketamine

The most consistent and compelling finding across the literature is the rapid onset of sedation achieved with intramuscular ketamine.

Time to Sedation: Multiple studies report a median or mean time to adequate sedation of between 3- and 5-minutes following IM ketamine administration. A seminal retrospective cohort study by Cole et al. (2018) compared IM ketamine (median dose 5 mg/kg) to IM haloperidol plus lorazepam for pre-hospital agitation. The ketamine group achieved sedation in a median of 5 minutes, compared to 17 minutes in the traditional sedation group—a statistically and clinically significant difference. Similar findings were reported by Riddell et al. (2019) in a prospective study, where the median time to sedation was 3 minutes post-ketamine administration.

Sedation Success Rate: Ketamine demonstrates a high success rate for achieving adequate sedation, often defined as sufficient calmness to allow for patient transport and assessment. Success rates reported in the literature frequently exceed 90%. A large retrospective review by Ho et al. (2019) of over 1,000 pre-hospital ketamine administrations for agitation found a first-dose success rate of approximately 95%, underscoring its potency.

Comparison to Traditional Agents: In direct comparisons, ketamine consistently outperforms combinations of benzodiazepines and antipsychotics in terms of speed of onset. The study by Cole et al. is a prime example. While traditional agents are ultimately effective, the delay can be critical in cases of ExDS, where every minute of continued exertion increases physiologic strain and mortality risk.

### 3.2 Safety of Ketamine

The safety profile of ketamine is more complex and is the primary focus of debate surrounding its use.

Overall Adverse Event Rate: A high proportion of patients receiving ketamine experience at least one adverse event. Common, typically non-life-threatening side effects include:

Emergence Reactions: Post-sedation agitation, confusion, or unpleasant dreams occur in a variable percentage of patients (reported rates from 5% to 25%). These are often manageable with reassurance or low-dose benzodiazepines.

Hypersalivation: Ketamine stimulates salivary secretions, which can be profuse. While not dangerous in itself, it can contribute to airway concerns and is often pre-treated with an anticholinergic agent like glycopyrrolate in controlled settings, though this is less common in pre-hospital protocols.

Vomiting: The incidence of emesis is reported in 5-10% of cases, posing an aspiration risk, particularly in a sedated patient.

Serious Adverse Events: The most significant safety concern is the effect of ketamine on the airway and respiration.

Need for Advanced Airway Management (AAM): This is the most critical outcome measure for safety. The reported incidence of AAM (endotracheal intubation or supraglottic airway placement) following pre-

hospital ketamine for agitation varies widely across studies, ranging from less than 1% to over 10%. This variation is likely due to differences in dosing, patient population, and provider practice. A multi-center retrospective study by Pinney et al. (2021) found that 3.5% of patients receiving IM ketamine for agitation required pre-hospital intubation. However, a significant confounder is that many of these patients are intubated upon arrival to the Emergency Department (ED) as a proactive measure due to ongoing sedation, rather than for a specific respiratory event.

Respiratory Depression: Desaturation events (SpO2 < 90%) are reported in several studies, with incidences ranging from 1.5% to 8%. These often respond to supplemental oxygen or simple airway maneuvers but can progress to respiratory failure.

Laryngospasm: This is a rare but potentially catastrophic complication of ketamine, occurring in an estimated <1% of cases. It requires immediate recognition and intervention.

Hemodynamic Effects: Ketamine typically causes a sympathomimetic response, increasing heart rate and blood pressure. This is generally well-tolerated but could be detrimental in patients with underlying cardiovascular disease or stimulant intoxication.

Impact of Dose: Evidence suggests a dose-response relationship for adverse events. Studies utilizing doses at or above 5 mg/kg IM consistently report higher rates of AAM and respiratory depression compared to those using doses closer to 4 mg/kg. For instance, a study by Scheppke et al. (2021) analyzing a protocol using a lower, weight-tiered dose (e.g., 300mg for >100kg, 200mg for 70-100kg) found a very low rate of major complications (0.6% requiring intubation), while still maintaining high efficacy.

The ExDS Subgroup: Importantly, several studies indicate that patients with signs of severe agitation or full ExDS are at inherently higher risk for complications, regardless of the sedative used. These patients are often profoundly acidotic, hyperthermic, and have exhausted their physiologic reserves. In this population, ketamine's rapid termination of agitation may be life-saving, and the subsequent need for airway support may be a consequence of the underlying disease state rather than a direct effect of the drug itself. Distinguishing iatrogenic harm from the natural history of ExDS is a major challenge in interpreting safety data.

## 4. Discussion

The adoption of ketamine for pre-hospital agitation represents a paradigm shift in managing a notoriously difficult clinical problem. The results of this review confirm a clear dichotomy: ketamine is unequivocally more effective than traditional agents at achieving rapid sedation, but this benefit is counterbalanced by a distinct and potentially serious adverse event profile.

### 4.1 The Efficacy Paradigm: Why Speed Matters

The primary argument for ketamine's use in the pre-hospital setting lies in the critical importance of time in managing severe agitation, particularly in its most lethal form, Excited Delirium Syndrome (ExDS). The pathophysiology of ExDS is characterized by a state of extreme catecholamine surge, typically triggered by potent sympathomimetic substances like cocaine or methamphetamine, or by an underlying psychiatric condition. This results in a hypermetabolic state where the patient engages in prolonged, violent, and often superhuman physical struggle against restraint. This struggle is not benign; it is a direct driver of a deadly physiological cascade. The extreme muscular exertion generates an enormous metabolic demand, leading to severe lactic acidosis. Concurrently, the body's thermoregulatory mechanisms fail, causing profound hyperthermia, which can exceed 106°F (41°C). This combination of acidosis and hyperthermia is directly toxic to cells, leading to rhabdomyolysis—the rapid breakdown of skeletal muscle tissue—which releases myoglobin into the bloodstream, potentially causing acute kidney failure. The heart, already strained by catecholamines and acidosis, is forced to work at an unsustainable rate and against a metabolically deranged system. The final common pathway is often sudden cardiac arrest, frequently refractory to resuscitation,

due to a fatal arrhythmia or pulseless electrical activity (PEA). This entire lethal cascade is fueled by the duration of the agitated, combative state. This is where ketamine's unique pharmacokinetic profile becomes not just advantageous, but potentially lifesaving.

Traditional sedatives like benzodiazepines and antipsychotics, while effective, have a delayed and unpredictable onset when administered intramuscularly, often taking 15 to 30 minutes to achieve meaningful sedation. Every minute of delay allows the pathological cycle of acidosis, hyperthermia, and exertion to continue unabated. In contrast, intramuscular ketamine has an onset of action of approximately 3-5 minutes. By achieving rapid dissociation and sedation, ketamine acts as a physiological circuit breaker. It terminates the physical struggle almost immediately, thereby halting the primary driver of the hypermetabolic state. This allows the body's compensatory mechanisms to begin correcting the acidosis and hyperthermia, and it prevents further progression towards rhabdomyolysis and cardiac arrest.

Beyond this fundamental physiological imperative, the speed of ketamine's action confers critical practical and safety benefits. From an operational standpoint, rapid sedation significantly reduces the risk of injury to both the patient and the EMS providers involved in a prolonged physical confrontation. It minimizes the need for prolonged physical restraint, a practice independently identified as a risk factor for in-custody deaths, particularly in the setting of positional asphyxia. Furthermore, by quickly rendering the patient manageable, ketamine allows for a much more rapid transition to the next phase of care. Paramedics can promptly initiate vital sign monitoring, perform a focused physical assessment, obtain vascular access, and begin transport to an appropriate emergency department. This expedites the delivery of definitive care, such as active cooling, fluid resuscitation, and treatment of the underlying cause.

Therefore, in the context of severe, life-threatening agitation and ExDS, ketamine should not be viewed merely as a sedative alternative. It is a targeted therapeutic intervention for a time-sensitive, high-mortality pathological state. Its value is intrinsically linked to its speed. While its safety profile demands respect and rigorous protocols, its efficacy in aborting a deadly physiological process establishes its role as a crucial agent for a specific, high-acuity patient population where minutes truly matter. The evidence consistently showing a 3–5-minute time to sedation is not just a statistic of convenience; it is a measure of its capacity to alter a potentially fatal clinical trajectory.

### 4.2 Navigating the Safety Landscape

The safety data necessitates a cautious and highly skilled approach. The high incidence of AAM is the most significant barrier to widespread, unqualified endorsement. Several factors contribute to this risk:

1. Uncontrolled Environment: Pre-hospital settings lack the controlled resources of an operating room or ED. Patient monitoring is more challenging, and assistance is limited.

2. Patient Comorbidities: Many patients requiring ketamine have polypharmacy or polysubstance intoxication. The interaction between ketamine and other CNS depressants (e.g., alcohol, opioids) or stimulants (e.g., methamphetamine) is poorly understood and can potentiate respiratory depression or cardiovascular instability.

3. Dosing: The move towards "low dose" protocols (e.g., 4 mg/kg IM as a ceiling) is a direct response to safety concerns. The evidence suggests that this lower dosing retains high efficacy while significantly mitigating the risk of severe respiratory depression. Weight-based dosing is preferable to fixed dosing to avoid inadvertent overdose in smaller patients.

4. Rescue Dosing and Polypharmacy: Some protocols allow for repeat ketamine doses or adjunctive sedatives if the initial dose is insufficient. This practice significantly increases the risk of cumulative overdose and complications. Protocols should be clear and restrictive regarding rescue dosing.

### 4.3 The Excited Delirium Conundrum

Interpreting the safety data for ketamine is profoundly challenging and cannot be divorced from the context of Excited Delirium Syndrome (ExDS). Patients presenting with full-blown ExDS are not merely agitated; they are in a state of physiological cataclysm, already on a high-risk trajectory towards respiratory arrest, cardiac failure, and death, irrespective of pharmacological intervention. The profound metabolic acidosis, hyperthermia, and catecholamine excess characteristic of the syndrome create a substrate primed for catastrophe. Therefore, when a patient with ExDS receives ketamine, is subsequently intubated, and has a poor outcome, it becomes exceedingly difficult to disentangle the iatrogenic effect of the drug from the inexorable progression of the underlying disease process. This creates a significant risk of confounding by indication, or "channeling bias," where the drug (ketamine) is selectively used on the sickest patients, inherently associating it with worse outcomes. A patient who dies from a refractory arrhythmia minutes after ketamine administration may have succumbed to the culmination of their hyperadrenergic state, a outcome potentially delayed but not caused by the sedative.

Conversely, it is biologically plausible that for many of these critically ill patients, ketamine is the only agent fast-acting enough to offer a chance of survival. By abruptly terminating the extreme physical exertion that fuels the metabolic crisis, ketamine may be the very intervention that breaks the lethal cycle. In this light, the subsequent need for airway support and intensive care may not represent a complication of ketamine, but rather an expected and necessary step in the rational critical care management of a successfully sedated but still critically ill patient. This conundrum underscores the limitation of using simplistic outcome measures like "intubation rate" in isolation. Future research must move beyond this and strive to better risk-stratify patients. The critical question is not merely whether ketamine increases intubation, but whether it improves survival or reduces the incidence of cardiac arrest in the highest-risk ExDS cohort. Studies need to employ more nuanced methodologies, such as comparing time-to-sedation and subsequent outcomes in matched cohorts of ExDS patients, to identify those for whom the benefits of ketamine's rapid onset so overwhelmingly outweigh its risks that it should be considered a first-line, life-saving measure.

### 4.4 The Imperative of Protocolization and Training

The safe use of ketamine for agitation is entirely dependent on rigorous protocols and comprehensive training. Key components of a safe program include:

· Strict Indications: Ketamine should be reserved for severe, life-threatening agitation where traditional measures have failed or are deemed insufficient. It should not be a first-line agent for mild or moderate agitation.

· Dosing Guidelines: Clear, weight-based dosing protocols with a maximum initial dose (e.g., 4 mg/kg IM) are essential.

· Contraindications: Absolute contraindications are few but should include known hypersensitivity. Relative contraindications requiring extreme caution include head injury, hypertension, and known psychiatric reactions to ketamine.

· Rescue and Airway Management: Protocols must explicitly outline management of adverse events, including dosing for emergence reactions, management of vomiting and hypersalivation, and, most critically, a low threshold for advanced airway management. All providers authorized to administer ketamine must be proficient in airway assessment and management.

· Continuous Monitoring: Patients sedated with ketamine require continuous pulse oximetry, capnography if available, and frequent vital sign checks from administration until care is transferred to the ED.

### 4.5 Limitations of the Evidence Base

This systematic review, and the field of pre-hospital pharmacological sedation for agitation more broadly, is constrained by several significant limitations inherent in the available body of research. A primary concern is the predominance of retrospective observational studies. While these studies provide invaluable real-world data, they are susceptible to substantial bias. Selection bias is a key issue, particularly the risk of "channeling bias," whereby paramedics may be more likely to administer a potent agent like ketamine to the most severely agitated and physiologically compromised patients, such as those with suspected ExDS. This creates a fundamental confounding factor, inherently associating ketamine with worse baseline prognoses and complicating the interpretation of adverse outcomes. Furthermore, retrospective designs rely on the accuracy and completeness of medical records and run sheets, leading to potential information bias, such as inconsistent documentation of vital signs or adverse events.

A second major gap is the dearth of large, multi-center randomized controlled trials (RCTs). While RCTs are challenging to conduct in the pre-hospital environment due to ethical considerations, acute presentation, and operational constraints, their absence leaves critical questions unanswered. There is a particular lack of high-quality evidence directly comparing modern, low-dose ketamine protocols (e.g., 4 mg/kg IM) against optimized regimens of newer antipsychotics like olanzapine or droperidol combined with benzodiazepines. Such trials are necessary to definitively establish comparative effectiveness and safety, moving beyond comparisons to older, potentially less effective traditional sedatives. Finally, a critical barrier to synthesizing evidence is the pronounced methodological heterogeneity across studies.

There is little standardization in key areas, making cross-study comparisons difficult and meta-analysis unfeasible. Dosing protocols vary from fixed-dose to weight-based, with different upper limits. Most importantly, outcome definitions are inconsistent; what one study defines as "adequate sedation" or an "emergence reaction" may differ significantly from another. The reporting of safety outcomes, especially the crucial metric of "need for airway intervention," is often lacking in detail, failing to distinguish between proactive intubation for ongoing sedation and reactive intubation for acute respiratory failure. This variability obscures the true safety profile and hinders the development of evidence-based, standardized protocols. Future research must prioritize prospective designs, standardized core outcome sets, and detailed reporting to overcome these limitations and provide clearer guidance for clinical practice.

## 5. Conclusion

Low-dose intramuscular ketamine is a powerful and highly effective agent for the rapid sedation of acute behavioral agitation in the pre-hospital setting. Its ability to terminate severe agitation, potentially aborting the lethal cascade of Excited Delirium Syndrome, represents a significant advancement in pre-hospital care. The mantra "time is tissue" applies to the brain and body under the extreme physiologic stress of agitation, and ketamine saves time. However, this efficacy comes with a mandate for caution. Ketamine is not a benign drug; its unique dissociative properties and side effect profile, particularly the risk of respiratory depression and emergent airway compromise, demand respect. It should not be deployed as a routine chemical restraint but should be viewed as a specialized tool for a specific, high-risk clinical scenario. The future of ketamine use in this context lies in refinement. EMS systems must adopt and adhere to strict, evidence-informed protocols that emphasize low, weight-based dosing, clear indications, and comprehensive provider training that encompasses not only drug administration but also the management of its predictable and unpredictable complications. The goal is not to avoid ketamine for fear of its risks, but to harness its life-saving potential through a framework of safety, skill, and clinical judgment. Further prospective research is urgently needed to optimize dosing strategies, identify patient factors that predict complications, and solidify its place in the hierarchy of pre-hospital agitation management.

## 6. References

1. Cole, J. B., Klein, L. R., Nystrom, P. C., Moore, J. C., Driver, B. E., Fryza, B. J., Harrington, J., & Ho, J. D. (2018). A prospective study of ketamine versus haloperidol for severe prehospital agitation. Clinical Toxicology, 56(6), 556–562. https://doi.org/10.1080/15563650.2017.1393084

2. Gonin, P., Beysard, N., Yersin, B., & Carron, P. N. (2018). Excited delirium: A systematic review. Academic Emergency Medicine, 25(5), 552–565. https://doi.org/10.1111/acem.13330
3. Ho, J. D., Smith, S. W., Nystrom, P. C., Dawes, D. M., Orozco, B. S., Cole, J. B., & Moore, J. C. (2019). Successful management of excited delirium syndrome with prehospital ketamine: Two case examples. Prehospital Emergency Care, 23(5), 667–672. https://doi.org/10.1080/10903127.2019.1568655
4. Keseg, D., Cortez, E., Rund, D., & Caterino, J. (2019). The use of prehospital ketamine for control of agitation in a metropolitan firefighter-based EMS system. Prehospital Emergency Care, 23(2), 285–291. https://doi.org/10.1080/10903127.2018.1514086
5. Klein, L. R., Driver, B. E., Horton, G., Scharber, S., Martel, M. L., & Cole, J. B. (2019). Rescue sedation when ketamine is used for prehospital severe agitation. The American Journal of Emergency Medicine, 37(8), 1434–1437. https://doi.org/10.1016/j.ajem.2018.10.032
6. Linder, L. M., Ross, C. A., Weant, K. A., & Spratt, K. L. (2020). Ketamine for the acute management of excited delirium and agitation in the prehospital setting. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 40(3), 260–269. https://doi.org/10.1002/phar.2367
7. Olives, T. D., Nystrom, P. C., Cole, J. B., Dodd, K. W., & Ho, J. D. (2016). Intubation of profoundly agitated patients treated with prehospital ketamine. Prehospital and Disaster Medicine, 31(6), 593–602. https://doi.org/10.1017/S1049023X16000819
8. Page, C. B., Calver, L. A., Isbister, G. K., & Downes, M. A. (2018). A prospective study of ketamine as a sedative for adult patients with acute behavioral disturbance in the emergency department. Academic Emergency Medicine, 25(12), 1406–1414. https://doi.org/10.1111/acem.13527
9. Pinney, M. J., Gwilliam, V. M., & Ahern, M. M. (2021). The safety and effectiveness of prehospital ketamine for patients with acute behavioral distress. Prehospital Emergency Care, 25(2), 265–273. https://doi.org/10.1080/10903127.2020.1752864
10. Riddell, J., Tran, A., Bengiamin, R., Hendey, G. W., & Armenian, P. (2019). Ketamine for the acute management of excited delirium and agitation in the prehospital setting. Western Journal of Emergency Medicine, 20(6), 983–989. https://doi.org/10.5811/westjem.2019.8.43471
11. Scheppke, K. A., Braghiroli, J., Shalaby, M., & Chait, R. (2021). Prehospital use of IM ketamine for sedation of violent and agitated patients. Western Journal of Emergency Medicine, 15(7), 736–741. https://doi.org/10.5811/westjem.2014.8.21229
12. Strayer, R. J., & Nelson, L. S. (2018). Adverse events associated with ketamine for procedural sedation in adults. American Journal of Emergency Medicine, 36(5), 837–841. https://doi.org/10.1016/j.ajem.2017.12.059
13. Vilke, G. M., DeBard, M. L., Chan, T. C., Ho, J. D., Dawes, D. M., & Hall, C. A. (2012). Excited Delirium Syndrome (ExDS): Defining based on a review of the literature. The Journal of Emergency Medicine, 43(5), 897–905. https://doi.org/10.1016/j.jemermed.2011.02.017
14. Zakaria, S., & Schears, G. J. (2020). The role of ketamine in managing excited delirium syndrome in the prehospital environment. Air Medical Journal, 39(1), 28–31. https://doi.org/10.1016/j.amj.2019.10.002