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SUMMARY WITH CRITICAL APPRAISAL

Ketamine for Pharmacological Management of Aggression and Agitation in Pre-Hospital Settings: A Review of Comparative Clinical Effectiveness, Safety and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AMSS	Altered Mental Status Scale
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
CI	Confidence interval
ED	Emergency department
HTA	Health technology assessment
IM	Intramuscular
IV	Intravenous
JBI	Joanna Briggs Institute
MA	Meta-analysis
NA	Not applicable
NR	Not reported
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
SD	Standard deviation
SR	Systematic review

Context and Policy Issues

Rapid stabilization of patients with acute aggression and agitation using either pharmacological or physical restraint is frequently needed to prevent injury of patients, bystanders and providers.[1] Pharmacological restraint need to have quick onset of action, be easily administered, and be safe for patients.[1] Benzodiazepines and antipsychotics such as haloperidol are probably the most often used medication to control acutely agitated patients.[1] However, these drugs have slow onsets of action (in 15 to 30 min) when given intramuscularly, and have significant adverse events including respiratory failure, cardiac dysrhythmias, and prolongation of the QTc interval that may result in cardiac death.[1]

Ketamine, an *N*-methyl-D-aspartate receptor antagonist, has been used in the emergency department for many indications including local anesthesia, procedural sedation, pain management, asthma and depression.[2-4] Ketamine can be administered via intramuscular (IM), intravenous (IV), subcutaneous, or intranasal route.[2] It has been suggested that ketamine may be useful for the control of agitated patients due to its short onset of action (less than 5 minutes), duration of 30 min, and having few hemodynamic changes.[1] In 2017, the American College of Emergency Physicians endorsed the use of ketamine for sedation of agitated patients in the emergency department (ED), despite limited evidence.[5] The literature is also relatively sparse regarding the effectiveness and safety of ketamine for sedation of agitated patients in the prehospital settings, in which a physician is absent.[6]

The aim of this report is to review the comparative clinical effectiveness and safety of ketamine for pharmacological management of aggression and agitation in pre-hospital settings or any setting. The report also reviews evidence-based guidelines regarding the pharmacological management of aggression and agitation in prehospital settings.

Research Questions

1. What is the comparative evidence regarding safety of ketamine administration performed in pre-hospital settings versus by a physician for pharmacological management of aggression and agitation?
2. What is the comparative safety between ketamine and lorazepam, diazepam, or haloperidol for pharmacological management of aggression and agitation in pre-hospital settings?
3. What is the comparative clinical effectiveness and safety between ketamine and lorazepam, diazepam, or haloperidol for pharmacological management of aggression and agitation in any setting?
4. What are the evidence-based guidelines regarding the pharmacological management of aggression and agitation in pre-hospital settings?

Key Findings

Low quality evidence suggests that ketamine was associated with higher intubation rate when administered by ground emergency medical services paramedics compared with services during air medical transport or services at the emergency department. In prehospital settings (i.e., care by paramedics), ketamine was associated with higher rate of intubation and frequency of complications compared with haloperidol plus benzodiazepine or haloperidol alone. In the emergency department setting, ketamine administration resulted in significantly faster sedation, but no significant difference in intubation rate compared with other pharmacological sedation. No studies conducted in the community health centre, or remote and isolated care facilities settings, where ketamine was given in the absence of a physician, were identified. No evidence-based guidelines were identified regarding the pharmacological management of aggression and agitation in prehospital settings.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type for questions 1-3. A guidelines filter was applied for question 4 only. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and April 16, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1,2,4: Patients of all ages, experiencing aggression or agitation, in pre-hospital settings (e.g., community health centre, emergency medical services, remote and isolated care facilities) Q3: Patients of all ages, experiencing aggression or agitation, in any setting
Intervention	Q1, Q2: Ketamine administration performed in pre-hospital settings Q3: Ketamine administration performed in any setting
Comparator	Q1: Ketamine administration performed by a physician Q2,3: Lorazepam (e.g., Ativan) diazepam (e.g., Valium), or haloperidol (e.g., Haldol)
Outcomes	Q1-3: Safety (e.g., side effects, adverse reactions, respiratory depression, worsening of delirium, risk of extrapyramidal symptoms, prolonged QT interval, torsades de pointes, akathisia, all-cause mortality). Q3: Clinical effectiveness (e.g., deescalating aggression or agitation, rate of onset of action, level of sedation, mood regulation) Q4: Evidence-based guidelines on appropriate use and place in therapy
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs), non-randomized studies, and evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1 and if they were published prior to 2014. Studies were excluded if ketamine was used for anesthesia, pain management, procedural sedation, asthma, or anti-depression. Guidelines with unclear methodology or that were not clearly evidence-based were also excluded.

Critical Appraisal of Individual Studies

The AMSTAR-2 checklist was used to assess the quality of SRs.[7] The critical appraisal checklists of Joanna Briggs Institute (JBI) were used to assess the quality of the included RCTs and non-randomized studies.[8] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 675 citations were identified in the literature search. Following screening of titles and abstracts, 651 citations were excluded and 24 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of the 24 potentially relevant articles, 19 publications were excluded for various reasons, while five publications including one SR,[9] and four primary studies[10-13] met the inclusion criteria and were included in this report. No relevant guidelines were identified. Appendix 1 presents the PRISMA flowchart[14] of the study selection.

Summary of Study Characteristics

The characteristics of the identified SR,[9] and primary studies[10-13] are summarized and details are presented in Appendix 2.

Study Design

The identified SR[9] included 18 non-randomized studies (retrospective, case series), many of which were uncontrolled. The literature search of 14 databases was from inception to January, February or May 2018.

Four additional primary studies were identified including one retrospective review of charts,[10] one prospective cross-over study,[11] one double-blind RCT,[12] and one prospective non-randomized study.[13]

Country of Origin and Publication Year

The SR[9] was conducted by authors from the US, and was published in 2018.

The three identified primary studies[10,11,13] were conducted by authors from the US, and one study[12] was from Iran. The studies were published in 2019,[10] 2018,[12] 2017[13] and 2016.[11]

Study Setting

The SR[9] included studies assessing the safety and effectiveness of ketamine for rapid sedation of agitated patients in the prehospital and ED settings. The prehospital settings included paramedic ground transport service and air medical transport service.

Two primary studies[10,11] were conducted in the prehospital settings (i.e., hospital-based emergency medical services [paramedics]) and two primary studies[12,13] were in the ED settings.

Population

Participants were adult patients (aged 18 years or older) with severe acute undifferentiated agitation. Patients with altered mental status score (AMSS) of +3 or +2 were included in two primary studies.[11,12] Patients with AMSS score of +4 or AMSS ≤ +1 were excluded. One primary study[13] included patients with agitation scores ≥ 4 on a validated 6-point sedation scale. The SR[9] and one identified primary study[10] did not report the agitation scores of the included participants.

Interventions and Comparators

The SR[9] compared the safety of IM ketamine (4.9 ± 2.4 mg/kg) or IV ketamine (0.94 ± 0.74 mg/kg) for rapid sedation of agitated patients among three settings, i.e., paramedic ground transport, air medical transport and ED. This study provided answer to research question 1.

Two primary studies[10,11] were identified that provided answer to research question 2 (prehospital setting). One compared the complications and outcomes between IM ketamine (4 mg/kg) and IM haloperidol (5 mg) plus benzodiazepine (between 2 mg and 4 mg of midazolam or lorazepam),[10] while the other compared the effectiveness and safety between IM ketamine (5 mg/kg) and IM haloperidol (10 mg).[11]

Two additional primary studies[12,13] were identified that provided answer to research question 3 (ED setting). One study[12] compared efficacy and safety between IM ketamine (4 mg/kg) and IM haloperidol (5 mg), while the other study[13] examined the effectiveness and safety between treatment groups such as ketamine (4 to 6 mg/kg IM or 1 to 2 mg/kg IV), midazolam (5 to 10 mg IM or 5 mg IV), lorazepam (1 to 2 mg IM or IV), haloperidol (5 to10 mg IM) and combination of haloperidol and benzodiazepine.

Outcomes

Only outcomes relevant to the research questions were presented in this report.

The SR[9] compared endotracheal intubation rates after receiving ketamine in different settings (i.e., by ground transport, by air medical transport, and in the ED).

The safety outcomes evaluated in the two primary studies[10,11] relevant to the research question 2 included intubation rates, requirement of additional sedation, and complications (e.g., hypersalivation, emergence reaction, vomiting, dystonia, laryngospasm, akathisia and deaths).

The clinical effectiveness outcomes investigated in the primary studies[12,13] relevant to the research question 3 included time to adequate sedation, proportion of patients achieving adequate sedation, and requirement for subsequent redosing of sedative medication. The safety outcomes were intubation rates and incidence of complications (e.g., hypersalivation, emergence reaction and laryngospasm).

Treatment Duration

In all studies, ketamine or other sedative medications were used for sedation of acutely agitated patients for a short period of time.

Quality Appraisal Tools

The authors of the SR[9] assessed the quality of the included studies using the Methodological Index for Non-Randomized Studies (MINORS), a validated 14-point scale that was designed to assess methodological quality of non-randomized studies, whether comparative or non-comparative.

Data Analysis and Synthesis

Due to the lack of RCTs and only few comparative observational studies, the authors of the SR[9] used proportional meta-analysis to provide estimates of intubation rates in each setting, without producing relative association measures such as odds ratios or relative risks.

Appropriate comparative statistics were used in all identified primary studies. Only one study[13] provided sample size calculation, while the other three[10-12] did not.

Funding

The sources of funding were not reported in the SR[9] and the two primary studies.[11,12] One study[10] reported that it did not receive any specific grant from funding agencies, and one study[13] was supported by an university grant.

Summary of Critical Appraisal

The quality assessment of the SR[9] (Table 4), RCT[12](Table 5), and non-randomized studies[10,11,13] (Table 6) are presented in Appendix 3.

The SR[9] was explicit in terms of research questions, a protocol prior to conduct of the review, explanations for selection of the study designs for the inclusion, comprehensive literature search strategies, description of the included studies in, techniques for assessing the risk of bias in individual studies included in the review, methods for statistical combining of results, description of the risk of bias and clinical heterogeneity in individual studies in the discussion and interpretation of the results, satisfactory explanation for, and discussion

of, any heterogeneity observed in the results, and investigation of publication bias. The SR[9] had several methodological limitations in that the review authors did not perform study selection and data extraction in duplicate, did not report the sources of funding of the cited studies, did not assess the potential impact of risk of bias in the individual studies on the results of the meta-analysis, and did not report potential sources of conflict of interest.

The RCT[12] was explicit in terms of randomization, similarity in baseline characteristics between groups, blinding to participants and treatment providers, identical in treatment between groups other than the intervention of interest, completion of follow-up, similar outcome measurement for treatment groups using reliable method and appropriate statistical analysis. It was unclear if allocation concealment and blinding of outcome assessors were adequately performed.

All three non-randomized studies[10,11,13] provided appropriate research questions and objectives, have a control group, measured the outcomes of participants in the same and reliable way, and used appropriate statistical analysis. In all studies, it was unclear if participants between treatment groups were similar in characteristics, and received similar treatment and care other than the exposure or intervention of interest. Hence, it is possible, that the effect may be explained by the differences between participants or by other exposures or treatments, rather than the intervention of interest. It was also unclear if patients were lost to follow-up.

Summary of Findings

Clinical Effectiveness and Safety

The main findings and conclusions of the SR[9] (Table 7), and the additional primary studies[10-13] (Table 8) are presented in Appendix 4.

Safety of ketamine administered in prehospital settings versus a setting having a physician (for research question 1)

The SR found that patients receiving ketamine by ground transport (11 studies) or by air medical transport (3 studies) paramedics were intubated 40.4% or 4.9% of the time, respectively, while only 1.8% of patients, who were administered ketamine in the ED (4 studies) in the presence of a physician, were intubated. The difference in intubation rates between settings was statistically significant ($P < 0.00001$).

Comparative safety between ketamine and other chemical sedation in a pre-hospital setting (for research question 2)

Intubation

In the emergency medical services (paramedics) setting, patients who received ketamine had significantly higher rate of intubation compared to those receiving haloperidol plus benzodiazepine (11.6% versus 5%; OR 8.77; 95% CI 1.10 to 69.68)[10] or haloperidol alone (39% versus 4%; $P < 0.0001$).[11] The majority of intubation occurred upon arrival in the ED.

Complications

Compared to haloperidol, ketamine administration had higher rates of hypersalivation (38% versus 0%), emergence reaction (10% versus 0%), vomiting (9% versus 3%) laryngospasm (5% versus 0%), and akathisia (2% versus 0%).[11]

Comparative clinical effectiveness and safety between ketamine and other chemical sedation in any setting (for research question 3)

Time to adequate sedation

In an RCT[12] comparing ketamine and haloperidol in an ED setting, the mean time to adequate sedation (AMSS ≤ +1) in the ketamine group was significantly lower than that in the haloperidol group (7.7 minutes versus 11.4 minutes; $P < 0.01$). One non-randomized controlled study[13] that allowed physicians in the ED to choose among ketamine, midazolam, lorazepam, haloperidol or combination of benzodiazepine and haloperidol found that the mean time (minutes) to adequate sedation was numerically lower in ketamine group compared to others (6.57 versus 14.95, 17.73, 13.43, and 23.30, respectively). However, there was no statistically significant difference between the groups ($P = 0.107$).

Proportion of patients achieving adequate sedation

The proportion of patients achieving adequate sedation was significantly higher in the ketamine group compared to other medication groups in an ED setting. In the RCT,[12] 93.3% of patients in the ketamine group were no longer agitated compared to 71.1% of patients in the haloperidol group; $P < 0.0001$. In the non-randomized controlled study[13], significantly more patients in the ketamine groups were no longer agitated compared to other medication groups at 5 minutes ($P = 0.001$), 10 minutes ($P \leq 0.001$), and 15 minutes ($P = 0.032$).

Requirement for repeated doses of sedative medication

One RCT[12] and one non-randomized study[13] showed no significant difference between ketamine and other medication groups in the requirement for repeated doses of sedative medication.

Intubation

In the ED setting, both studies[12,13] showed no significant difference between ketamine and other medication groups in the intubation rate.

Complications

In the RCT,[12] the incidence of complications was numerically higher, but not significantly different, in the ketamine group (35.6%) than in the haloperidol group (17.8%); $P = 0.094$. In the ketamine group, common complications included hypersalivation (13.3%), laryngospasm (4.4%), and emergence phenomena (6.7%). In the haloperidol group, complications included vomiting (2.2%), dystonia (4.4%), akathisia (8.9%), and hypoxia (2.2%).

Guidelines

No evidence-based guidelines regarding the pharmacological management of aggression and agitation in prehospital settings were identified; therefore, no summary can be provided.

Limitations

No study that was conducted in the community health centre, or remote and isolated care facilities settings, where ketamine was administered in the absence of a physician, was identified. The prehospital settings of all the identified relevant studies were mainly

hospital-based emergency medical services providers (paramedics). In addition, no evidence-based guidelines were identified regarding the pharmacological management of aggression and agitation in prehospital settings.

There were several limitations with respect to the quality of evidence of the SR. First, all the cited studies were non-randomized studies, including retrospective studies and case series, which have major risk of bias. Second, as few studies had comparators and no studies directly compared prehospital settings versus facilities having physicians, relative association measures such as odds ratios or relative risks that provide direct comparisons between settings could not be produced; instead, estimates of intubation rates in each setting were provided. Statistical methods were then used to compare among settings without controlling for confounding variables including route of ketamine administration (IM and IV), patient weights and dose calculation of ketamine (usually by estimation), degree of agitation, and history of mental illness. Third, reporting bias may exist regarding ketamine-related complications and intubation, as the majority of patients who were administered with ketamine and transferred by ground emergency medical services were intubated, and the intubations were mostly performed upon arrival to ED.

As the three included studies[10,11,13] were non-randomized and non-blinded, there is potential for selection, performance and detection biases. . In the ED setting,[12,13] the non-significant difference between ketamine and other medication groups, with respect to intubation and complication rates could be due to the relatively small sample size and lack of power to detect differences.

Conclusions and Implications for Decision or Policy Making

One systematic review,[9] one RCT,[12] and three non-randomized studies,[10,11,13] that were relevant for this report, were identified. No evidence-based guidelines were identified regarding the pharmacological management of aggression and agitation in prehospital settings.

Low quality evidence suggests that patients who received ketamine by ground emergency medical services paramedics had higher intubation rates compared to those presented to the ED or transported by air medical paramedics. In prehospital settings (i.e., care by paramedics), ketamine was associated with higher rate of intubation compared with haloperidol plus benzodiazepine or haloperidol alone. Compared to haloperidol, ketamine administration had higher frequency of complications including hypersalivation, emergence reaction, vomiting, laryngospasm, and akathisia in the prehospital environment (i.e., care by paramedics). In the ED setting, ketamine administration resulted in faster sedation than haloperidol, benzodiazepine, or combination of haloperidol and benzodiazepine. However, there was no significant difference between ketamine and other chemical sedations in the intubation rate or frequency of complications when administered in the ED. Given the aforementioned limitations of the included studies, the findings should be interpreted with cautions. Future controlled trials with high degree of internal validity and adequate power are warranted.

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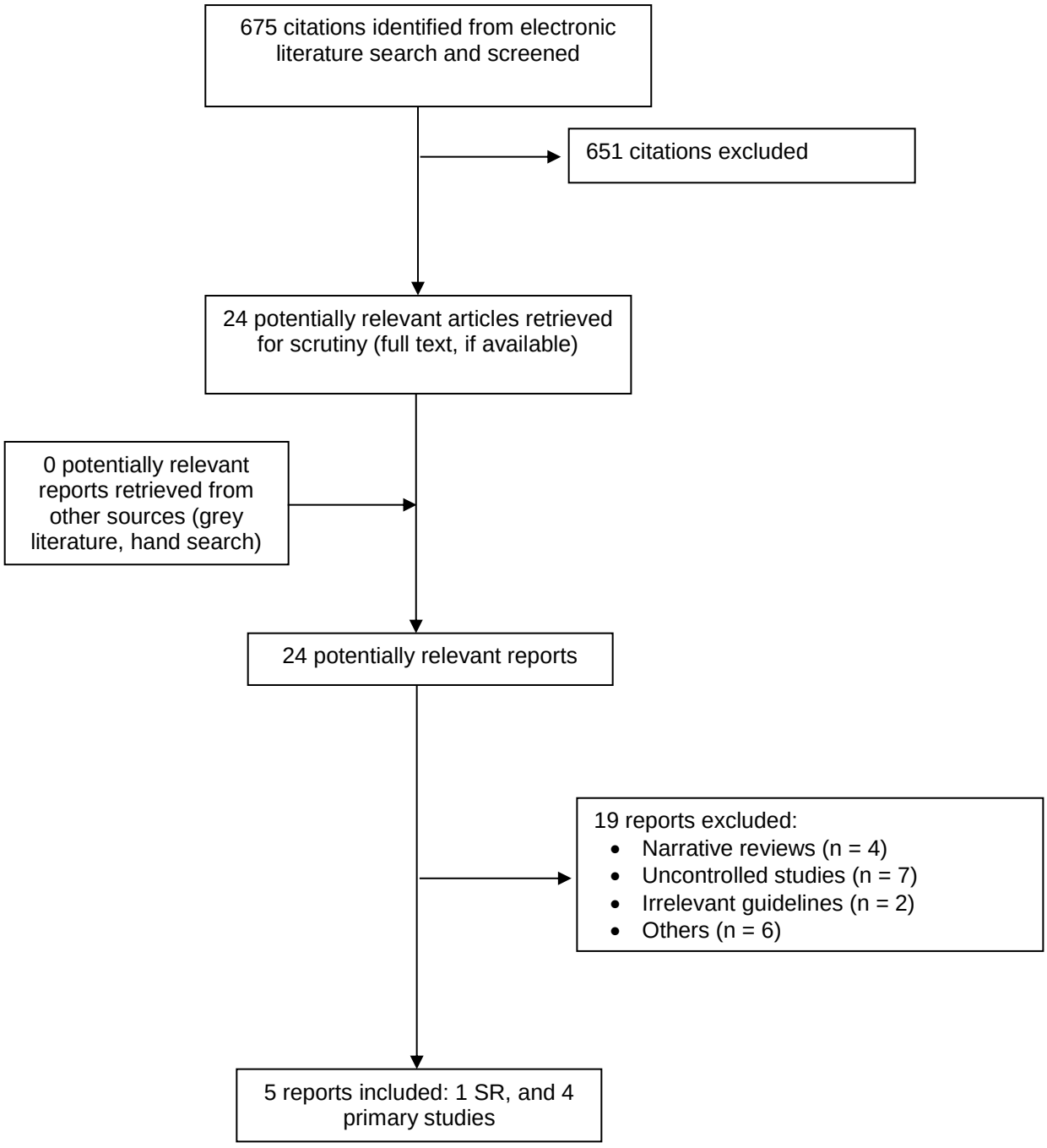
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date, Analysis	Characteristics	Interventions and Comparisons	Outcomes
Mankowitz et al., 2018[9] USA Funding: Not reported	Objectives: To determine the safety and effectiveness of ketamine for rapid sedation of agitated patients in the pre-hospital and emergency department settings. 18 observational studies included (retrospective, case series) Study quality was assessed using the Methodological Index for Non-Randomized Studies (MINORS). Literature searches were conducted in 14 databases (submitted to Prospero). Search date: From inception to January, February, or May 2018 Analysis: Proportional meta-analysis to quantitatively analyze non-comparative series, which does not produce relative association measures such as odds ratios or relative risks, but can give estimates of event rates.	Settings: • Pre-hospital – Paramedic ground transport – Air medical transport • Emergency department Participants presented with undifferentiated agitation	Interventions: IM or IV ketamine (4.9 ± 2.4 mg/kg IM or 0.94 ± 0.74 mg/kg IV) Comparisons: Few studies have comparators. Some used antipsychotics and benzodiazepines	• Dosage • Effectiveness of ketamine (Time to adequate sedation) • Adverse effects • Endotracheal intubation

IM = intramuscular; IV = intravenous

Table 3: Characteristics of Included Primary Studies

First Author, Publication Year, Country, Funding	Study Setting, Design, Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes
Randomized controlled trial					
Heydari et al., 2018[12] Iran Funding: NR	Setting: ED Design: Double-blind, RCT Sample size calculation: No Analysis: Chi-square test and Fisher's exact test	Patients with severe acute agitated and aggressive behavior AMSS: +3 or +2 Mean age: 30 years Sex: 74% male	Ketamine (4 mg per kg IM) (n = 45)	Haloperidol (5 mg IM) (n = 45)	• Time to adequate sedation • Proportion of patients achieved adequate sedation • Additional sedation • Complications • Intubation rate • Satisfaction of physicians
Non-randomized studies					
O'Connor et al., 2019[10] USA Funding: No specific funding	Setting: Hospital-based emergency medical services (paramedics) Design: Retrospective review of charts between January 2014 and February 2018 Sample size calculation: No Analysis: Comparative statistics were performed including odds ratios, and *P* values	Patients with combative or agitated behavior AMSS: not defined Age: Ranging from 18 to 86 years Sex: 61.6% male	Ketamine (4 mg per kg IM based on estimated weight) (n = 95)	• Physical restraint (n = 51) • Haloperidol and benzodiazepine (IM haloperidol 5 mg and between 2 and 4 mg of midazolam or lorazepam) (n = 68)	• Intubation • Additional chemical restraints • Additional restraints (any type) • Staff injury • ED length of stay
Riddle et al., 2017[13] USA Funding: University	Setting: ED Design: Single-center, prospective, observational study Sample size calculation: Yes Analysis: Chi-square statistics	Patients with acute agitation Agitation scores: ≥ 4 on a validated 6-point sedation scale Age: Ranging from 18 to 63 years Sex: Varied among	Ketamine (4 to 6 mg per kg IM or 1 to 2 mg/kg IV) (n = 24)	• Midazolam (5 to 10 mg IM or 5 mg IV) (n = 19) • Lorazepam (1 to 2 mg IM or IV) (n = 33) • Haloperidol (5 to 10 mg IM) (n = 14) • Combo (Benzodiazepine +	• Time to adequate sedation • Additional sedation • Pulse rate reduction • Intubation

First Author, Publication Year, Country, Funding	Study Setting, Design, Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes
		groups, but mostly male		haloperidol) (n = 10) Benzodiazepine comprised of midazolam or lorazepam	
Cole et al., 2016[11] USA Funding: NR	Setting: Hospital-based emergency medical services (paramedics) Design: 12-month prospective cross-over study (First 3 months with haloperidol, nest 6 months with ketamine, final 3 months with haloperidol) Sample size calculation: No Analysis: Percentile difference and 95% CI, Chi-square test	Patients with severe acute undifferentiated agitation AMSS: +3 or +2 +3: 89% in ketamine, 73% in Haloperidol +2: 11% in ketamine, 27% in Haloperidol Age: Ranging from 18 to 69 years Sex: 56% male	Ketamine (5 mg per kg IM) (n = 64)	Haloperidol (10 mg IM) (n = 82)	• Time to adequate sedation • Proportion of patients achieved adequate sedation • Additional sedation • Complications • Intubation rate

AMSS = Altered Mental Status Scale; CI = confidence interval; ED = emergency department; IM = intramuscular; IV = intravenous; NR = not reported

Appendix 3: Quality Assessment of Included Studies

Table 4: Quality Assessment of Systematic Reviews

AMSTAR 2 Checklist[7]	Mankowitz et al., 2018[9]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes
5. Did the review authors perform study selection in duplicate?	No
6. Did the review authors perform data extraction in duplicate?	No
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No

AMSTAR = Assessing the Methodological Quality of Systematic Reviews; RoB = risk of bias

Table 5: Quality Assessment of Randomized Controlled Trials

JBI Critical Appraisal Checklist for RCT[8]	Heydari et al., 2018[12]
1. Was true randomization used for assignment of participants to treatment groups?	Yes
2. Was allocation to treatment groups concealed?	Unclear
3. Were treatment groups similar at the baseline?	Yes
4. Were participants blind to treatment assignment?	Yes
5. Were those delivering treatment blind to treatment assignment?	Yes
6. Were outcomes assessors blind to treatment assignment?	Unclear
7. Were treatment groups treated identically other than the intervention of interest?	Yes
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Yes
9. Were participants analyzed in the groups to which they were randomized?	Yes
10. Were outcomes measured in the same way for treatment groups?	Yes
11. Were outcomes measured in a reliable way?	Yes
12. Was appropriate statistical analysis used?	Yes
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Yes

JBI = Joanna Briggs Institute; RCT = randomized controlled trial

Table 6: Quality Assessment of Non-Randomized Studies

JBI Critical Appraisal Checklist for Non-Randomized Studies[8]	O'Connor et al., 2019[10]	Cole et al, 2016[11]	Riddell et al., 2017[13]
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	Yes	Yes	Yes
2. Were the participants included in any comparisons similar?	No	Yes	No
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Unclear	Unclear	Unclear
4. Was there a control group?	Yes	Yes	Yes
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	NA	NA	NA
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Unclear	Unclear	Unclear
7. Were the outcomes of participants included in any comparisons measured in the same way?	Yes	Yes	Yes
8. Were outcomes measured in a reliable way?	Yes	Yes	Yes
9. Was appropriate statistical analysis used?	Yes	Yes	Yes

JBI = Joanna Briggs Institute; NA = not applicable

Appendix 4: Main Study Findings and Author's Conclusions

Table 7: Summary of Findings of Systematic Reviews

Main Study Findings	Author's Conclusions
Mankowitz et al., 2018[9]	
Time to adequate sedation: 7.21 min ± 4.89 Proportion of patients achieved sedation within 5 minutes: 68.5% (95% CI 61.7 to 75.3%) Endotracheal intubation rates after receiving ketamine: • Total cohort: 30.5% (95% CI 27.0 to 34.1%) • By ground transport: 40.4% (95% CI 36.0 to 44.8%) were intubated in the field or upon arrival to the ED • By air medical transport: 4.9% (95% CI 0.0 to 10.3%) • In the ED: 1.8% (95% CI 0.0 to 4.4%) • The difference in intubation rates between ground transport and air medical transport or between ground transport and in ED was statistically significant ($P < 0.00001$) Ketamine side effects of total cohort: • Laryngospasm: 1.3% (95% CI 0.3 to 2.3%) • Hypoxia (not intubated): 1.8% (95% CI 0.1 to 3.6%) • Vomiting: 5.2% (95% CI 2.3 to 8.1%) • Emergence: 3.5% (95% CI 1.4 to 5.6%) • Hypertension: 12.1% (95% CI 5.7 to 18.6%) • Hypersalivation: 18.8% (95% CI 12.9 to 24.7%) • Required additional sedation: 24.4% (20.5 to 28.3%)	*"Ketamine provides rapid sedation for undifferentiated agitated patients and is associated with higher intubation rates when used by ground Emergency Medical Services paramedics, compared with ED or air medical transport patients. Other side effects are common but usually self-limiting."*[9] p.670

CI = confidence interval; ED = emergency department

Table 8: Summary of Findings of Included Primary Studies

Main Study Findings	Author's Conclusions
Randomized controlled trial	
Heydari et al., 2018[12]	
Ketamine versus haloperidol (at ED) • Median time to adequate sedation (AMSS ≤ +1): 7.7 minutes (range 1 to 20) versus 11.4 minutes (range 3 to 34); difference 3.7 minutes (95% CI 2.1 to 5.5); *P* < 0.01 • Proportion of patients achieved adequate sedation at 15 min: 93.3% versus 71.1%; difference 22% (95% CI 11 to 33); *P* < 0.0001 • Required repeated doses: 64.4% versus 51.1%; *P* = 0.289 • Required additional drug (midazolam): 24.4% versus 17.8%; *P* = 0.606 • Incidence of complications: 35.6% versus 17.8%; difference 17% (95% CI 11 to 22); *P* = 0.094 – Ketamine: Hypersalivation (13.3%), laryngospasm (4.4%), and emergence phenomena (6.7%) – Haloperidol: vomiting (2.2%), dystonia (4.4%), akathisia (8.9%), and hypoxia (2.2%) • Intubation rate: 13.3% versus 6.7%; *P* = 0.485 • Indications for intubations – Ketamine: refractory agitation, hypersalivation, hypoxia – Haloperidol: refractory agitation, hypoxia • Physician satisfaction: 80% versus 57.8%; *P* = 0.011	*"These data suggest ketamine may be used for short-term control of agitated patients, additional studies are needed to confirm if ketamine is safe in this patient population. Given rapid effective sedation and the higher physician satisfaction of ketamine in comparison to haloperidol, it may be considered as a safe and appropriate alternative to haloperidol."*[12] p.292
Non-randomized studies	
O'Connor et al., 2019[10]	
Ketamine versus haloperidol + benzodiazepine (prehospital) • Intubation: OR 8.77 (95% CI 1.10 to 69.68) • Additional chemical restraint: OR 2.94 (95% CI 1.49 to 5.80) • Additional restraint (any type): OR 2.19 (95% CI 1.15 to 4.15) • Admission: OR 1.97 (95% CI 0.84 to 4.61) • Staff injury (before or after medication given): OR 1.94 (95% CI 0.71 to 5.28) • ED length of stay: 9.46 hours versus 9.42 hours; *P* = 0.857	*"This study demonstrates a lower intubation rate in patients administered ketamine than prior literature in association with a lower weight-based dosing regimen. Ketamine use was correlated with a higher frequency of intubation and a greater need for additional chemical restraint when compared with other restraint modalities, though exogenous factors such as provider preference may have impacted this result. There was no difference in ED length of stay or admission rate between the ketamine and haloperidol plus benzodiazepine groups."*[10] p.201
Riddell et al., 2017[13]	
Ketamine versus midazolam, lorazepam, haloperidol or combination of haloperidol plus benzodiazepine (at ED)	*"In highly agitated and violent emergency department*

Main Study Findings	Author's Conclusions
• Mean time to adequate sedation (mean ± SD): 6.57 ± 8.65 versus 14.95 ± 10.47, 17.73 ± 24.78, 13.43 ± 15.36, 23.30 ± 25.12; *P* = 0.107 • Proportion of patients achieved adequate sedation: Significantly more patients in the ketamine groups achieved adequate sedation compared to other groups at 5 minutes (*P* = 0.001), 10 minutes (*P* ≤ 0.001), and 15 minutes (*P* = 0.032) • Requirement for subsequent redosing of sedative medication: No significant difference between groups • Intubation: ketamine (n = 2), midazolam (n = 1), lorazepam (n = 1), haloperidol (n = 1), combo (n = 1)	*patients, significantly fewer patients receiving ketamine as a first time sedating agent were agitated at 5-, 10-, and 15-min. Ketamine appears to be faster at controlling agitation than standard emergency department medications."*[13] p.1000
Cole et al., 2016[11]	
Ketamine versus haloperidol (prehospital) • Median time to adequate sedation: 5 minutes (range 0.4 to 23) versus 17 minutes (range 2 to 84) • Proportion of patients achieved adequate sedation pre-hospital: 95% versus 65%; difference 30% (95% CI 18 to 42); *P* < 0.0001 • Required additional sedation prehospital: 5% versus 20% • Complications – Hypersalivation: 38% versus 0% – Emergence reaction: 10% versus 0% – Vomiting: 9% versus 3% – Dystonia: 5% versus 3% – Laryngospasm: 5% versus 0% – Akathisia: 2% versus 0% – Deaths: 0% versus 1% • Intubation rate: 39% versus 4%; difference 35% (95% CI 23 to 48); *P* < 0.0001. All intubations occurred upon arrival to ED	*"Ketamine is superior to haloperidol in terms of time to adequate sedation for severe prehospital acute undifferentiated agitation, but is associated with more complications and a higher intubation rate."*[11] p.556

AMSS = Altered Mental Status Scale; CI = confidence interval; ED = emergency department; OR = odds ratio