






## Comparative Effectiveness of Analgesics to Reduce Acute Pain in the Prehospital Setting

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# SPECIAL CONTRIBUTIONS

## COMPARATIVE EFFECTIVENESS OF ANALGESICS TO REDUCE ACUTE PAIN IN THE PREHOSPITAL SETTING

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### ABSTRACT

**Objectives:** The objectives of this study were to assess comparative effectiveness and harms of opioid and non-opioid analgesics for the treatment of moderate to severe acute pain in the prehospital setting. **Methods:** We searched MEDLINE<sup>®</sup>, Embase<sup>®</sup>, and Cochrane Central

from the earliest date through May 9, 2019. Two investigators screened abstracts, reviewed full-text files, abstracted data, and assessed study level risk of bias. We performed meta-analyses when appropriate. Conclusions were made with consideration of established clinically important differences and we graded each conclusion's strength of evidence (SOE). **Results:** We included 52 randomized controlled trials and 13 observational studies. Due to the absence or insufficiency of prehospital evidence we based conclusions for initial analgesia on indirect evidence from the emergency department setting. As initial analgesics, there is no evidence of a clinically important difference in the change of pain scores with opioids vs. ketamine administered primarily intravenously (IV) (low SOE), IV acetaminophen (APAP) (low SOE), or nonsteroidal anti-inflammatory drugs (NSAIDs) administered primarily IV (moderate SOE). The combined use of an opioid and ketamine, administered primarily IV, may reduce pain more than an opioid alone at 15 and 30 minutes (low SOE). Opioids may cause fewer adverse events than ketamine (low SOE) when primarily administered intranasally. Opioids cause less dizziness than ketamine (low SOE) but may increase the risk of respiratory depression compared with ketamine (low SOE), primarily administered IV. Opioids cause more dizziness (moderate SOE) and may cause more adverse events than APAP (low SOE), both administered IV, but there is no evidence of a clinically important difference in hypotension (low SOE). Opioids may cause more adverse events and more drowsiness than NSAIDs (low SOE), both administered primarily IV. **Conclusions:** As initial analgesia, opioids are no different than ketamine, APAP, and NSAIDs in reducing acute pain in the prehospital setting. Opioids may cause fewer total side effects than ketamine, but more than APAP or NSAIDs. Combining an opioid and ketamine may reduce acute pain more than an opioid alone but comparative harms are uncertain. When initial morphine is inadequate, giving ketamine may provide greater and quicker acute pain relief than giving additional morphine, although comparative harms are uncertain. Due to indirectness, strength of evidence is generally

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The data presented in this manuscript is part of a larger report that is published in full [insert URL once AHRQ has it].

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low, and future research in the prehospital setting is needed. **Key words:** acute pain; analgesics; opioids

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## INTRODUCTION

Appropriate management of acute pain is an integral part of patient management in the prehospital setting. The prevalence of pain specifically in the prehospital setting varies, with estimates ranging from 20 to 53% (1). Adequate pain relief is known to minimize anxiety and cardiac complications associated with acute pain (2). However, as many as 43% of adults and 83% of pediatric patients have insufficient prehospital pain relief (3, 4).

For patients experiencing moderate to severe traumatic injury pain, current guidelines (based on moderate quality evidence) strongly recommend initial prehospital management with a weight-based opioid, either intravenous (IV) morphine or IV/intranasal (IN) fentanyl (5). Further complicating the appropriate use of prehospital opioids is the fear of their abuse and the resulting epidemic in the United States (6, 7). When combined with concerns of adverse events, such as vomiting and subsequent airway obstruction, respiratory depression, hypotension, and sedation (8), alternative analgesics have been sought. Nonopioid analgesics, including ketamine, acetaminophen (APAP), nitrous oxide/oxygen, and nonsteroidal anti-inflammatory drugs (NSAIDs) have been used to provide adequate analgesia. This systematic review assessed the comparative effectiveness and harms of opioids compared to nonopioid analgesics for the prehospital management of moderate to severe acute pain.

## METHODS

The systematic review was performed at the University of Connecticut Evidence-based Practice Center (EPC) through a contract with the U.S. Agency for Health-Care Research and Quality (AHRQ). With input from the National Highway Traffic Safety Administration (NHTSA), the project technical expert panel (TEP), and AHRQ, we developed and followed a protocol (9) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (10) (PROSPERO CRD42018114959). This manuscript presents the comparisons and outcomes with conclusions and graded strength of evidence (see Strength of Evidence Assessment section). Additional comparisons and outcomes are presented in the full report that is available on the AHRQ website (11).

## Search Strategy

We searched MEDLINE, MEDLINE In-Process and Other Nonindexed Citations, EMBASE and Cochrane Central Register of Controlled Trials via OVID from earliest date through May 9, 2019 (Supplemental Appendix A). We supplemented the bibliographic database searches with backward citation tracking of relevant citations. We searched <http://www.clinicaltrials.gov> and the International Controlled Trials Registry Platform for ongoing studies and completed studies that reported results. There were no limits placed on publication date or language.

## Study Selection

We included randomized controlled trials (RCTs), prospective or retrospective controlled cohort studies and case-control studies of patients with moderate to severe acute pain, without restrictions on age. We determined pain intensity by reviewing 1) study inclusion criteria, 2) reported baseline pain scores, or 3) in the absence of 1 or 2, we assumed pain to have been at least moderate for trials studying opioids or ketamine. We did not exclude based on the specific tool or threshold used by the study to define moderate or severe pain. Studies that targeted patients with mild pain, non-zero pain or labor and delivery pain were excluded. We also included studies of patients with acute onset pain, moderate to severe in intensity, who had an inadequate response to the first analgesic. These studies were evaluated separately from those studying initial analgesia.

We included studies that compared two of the following analgesics, regardless of dose, route or frequency of administration: opioids (fentanyl or morphine) and nonopioids (acetaminophen, ketamine, nitrous oxide/oxygen, or nonsteroidal anti-inflammatory drugs [NSAIDs; ketorolac or ibuprofen]). The combination of an opioid with ketamine compared with an opioid alone was also included.

Outcomes included pain (continuous and dichotomous), time to analgesic effect, memory of pain, "any adverse event" (as in total number of subjects with an adverse event), hypotension, respiratory depression, mental status changes, blood pressure, heart rate, respiratory rate, oxygen saturation, nausea, vomiting, and emergence delirium.

Studies were required to be conducted in the prehospital setting and in the absence of sufficient prehospital data, we allowed inclusions of studies from the emergency department (ED) to provide indirect evidence. There were no restrictions based on timing aside from studies from the ED setting for which we included pain related outcomes through 60 minutes.

EPC reviewers screened titles and abstracts using two independent investigators to identify citations that met eligibility criteria. We reviewed full-text publications when both reviewers agreed that a citation was eligible; if needed, a third reviewer was consulted to resolve any disagreement until consensus was reached. Finally, we contacted corresponding authors, when needed, to assess the study for inclusion.

## Data Extraction and Study Quality Assessment

One investigator abstracted data into a standardized online form and into evidence tables while a second investigator verified entries. Two independent investigators assessed the quality of each included study using the Cochrane Risk of Bias Tool (12) for RCTs and the Newcastle Ottawa Scale (13) for observational studies. The overall study risk of bias was classified for each included study as “low,” “moderate,” “high,” or “unclear.”

## Data Synthesis and Statistical Analysis

Pain was classified as traumatic, nontraumatic or mixed. We synthesized all pain classifications together and when possible, we analyzed and reported results for traumatic pain separately. Additional subgroup analyses that were possible included subject age, pain location, analgesic route and timing of administration. We collected and analyzed three time points: 15 minutes (post-drug administration through 15 minutes), 30 minutes (20 to 30 minutes) and 60 minutes (40 to 60 minutes). We did not combine prehospital and ED study data together in meta-analyses and instead we reported results separately when applicable.

When there were two or more trials of similar pharmacologic comparisons and outcomes, we performed random-effects meta-analysis using inverse-variance weighting. Between-study variance was estimated using the Paule-Mandel estimator (14). The Hartung-Knapp method was used to adjust 95% confidence intervals (CI) when three or more studies were meta-analyzed (15, 16); otherwise, a traditional DerSimonian-Laird random-effects model was used (17). Continuous outcomes are reported as mean differences and 95% CI. For continuous pain scales, we converted scores (e.g., 0–100 scale) to a 10-point scale using the methods of Thorlund et al. (18). For binary outcomes, risk differences (RD) are reported with corresponding 95% CI. For outcomes with zero events in one or both study arms, continuity correction was used (19, 20).

We assessed presence of statistical heterogeneity using the Cochrane  $p$ -value ( $p < 0.10$  significant) and

the  $I^2$  statistic which represents the percentage (0–100%) of variability in the treatment estimate that is attributable to heterogeneity (21). Small study effects were evaluated for through visual inspection of funnel plots. Tests for funnel plot asymmetry were conducted when 10 or more studies reported a given outcome (22). We conducted subgroup analyses to evaluate for the presence of effect modifiers. All analyses were performed using the “meta” package (version 4.9-4) in R (version 3.5.2; the R Project for Statistical Computing).

## Strength of Evidence (SOE) Assessment

We prioritized comparisons and outcomes upon which to construct conclusions with input from NHTSA, the project TEP and AHRQ. These included the comparisons of opioid to nonopioid or combined administration of opioid and ketamine to opioid alone. The prioritized outcomes include changes in pain severity (continuous measures), presence of pain (dichotomous measures), time to analgesic effect, respiratory depression, hypotension, change in mental status, and “any adverse event.” Other comparisons and outcomes do not have an accompanying conclusion with SOE and are reported in the full report (11).

Conclusions were constructed with consideration of the absolute effect estimates and their corresponding confidence intervals compared to clinically important differences (CID) established for this review; details of the chosen thresholds and how conclusions were made are found in Supplemental Appendix B. We graded the SOE for each conclusion using established guidance (23), two independent senior investigators evaluated SOE for each prioritized comparison and outcome. The SOE was judged to be one of four levels (high, moderate, low, or insufficient), in consideration of five domains: study limitations, consistency, directness (prehospital setting vs. ED setting, the latter which is indirect evidence), precision, and reporting bias.

## RESULTS

Our search identified 4,907 nonduplicate records, of which 283 required full-text review after title and abstract screening, resulting in 65 unique studies; 52 RCT and 13 observational studies (Figure 1). Of these 65 studies, 37 RCTs (24–60) and 4 observational studies (61–64) contributed data to graded comparisons and are described in Supplemental Appendix C Tables 2–5. Most evidence was studying initial analgesia and comparing opioids with ketamine, followed by opioids with APAP and the combination of opioids and ketamine with opioids

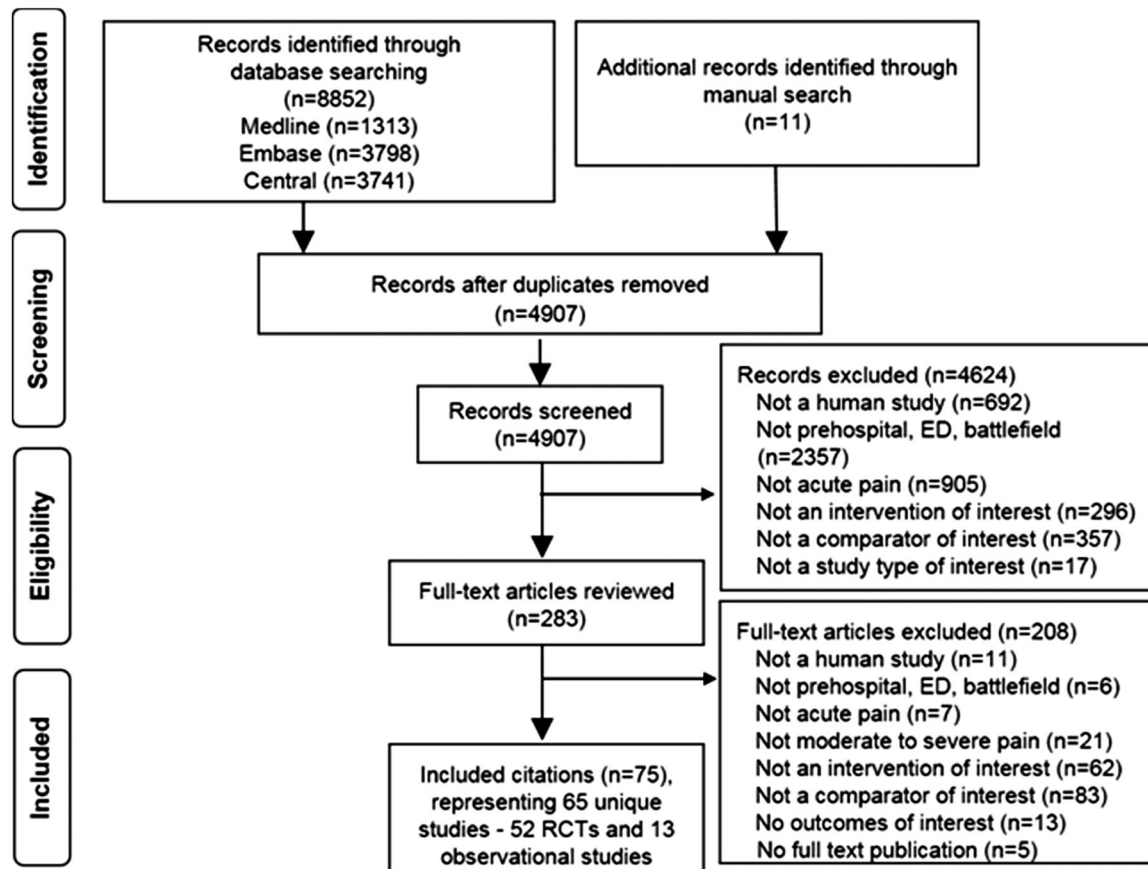


FIGURE 1. Identification and screening of citations. Abbreviations: ED=emergency department; OBS=observational; RCT=randomized controlled trial.

alone. The majority of studies were of adults with a mean age in the second to fourth decades. Source/etiology of pain was mixed; the most common cause for traumatic pain was extremity injuries/fractures. Most often, analgesics were administered intravenously (IV); there were also several trials studying intranasal (IN) administration of ketamine and fentanyl using an atomizer to deliver the IV solution IN. The majority of studies were conducted in the ED setting.

### Risk of Bias

Risk of bias of individual studies are shown in Supplemental Appendix C Tables 6 and 7. Most RCTs (31/37, 83.8%) were rated with low or unclear risk of bias. Two RCTs (5.4%) were rated with medium risk of bias due either to inadequate randomization procedures or an open label design. Three RCTs (8.1%) were rated as low risk of bias for objective outcomes but medium risk of bias for subjective outcomes due to an open-label design. Two (50%) observational studies were rated as low risk of bias. One RCT (1.9%) was rated with high risk of

bias due to its open-label design, inappropriate sequence generation and allocation concealment, and high differential attrition between groups. One observational study (25%) was rated as medium risk of bias attributed to a select group of users (battlefield), controlling for a single factor and unknown follow-up. One (25%) observational studies was rated as high risk of bias attributed to a select group of users (battlefield), uncontrolled analyses and inadequate cohort follow-up.

### Opioids versus Ketamine

Direct evidence from the prehospital setting is insufficient to conclude comparative effectiveness of opioids and ketamine in reducing pain (25, 62). Using indirect evidence from the ED, we found no evidence of a clinically important difference in the reduction of pain scores when opioids are compared with ketamine at 15, 30, and 60 minutes (all low SOE) (Table 1, Supplemental Appendix D Figure 1). There is insufficient evidence for the outcome of pain presence and time to analgesic effect (Supplemental C Appendix Table 8).

TABLE 1. Conclusions and strength of evidence for the comparison of opioids vs. ketamine as initial analgesics

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates)	Strength of Evidence (Limitations)
Pain severity – 15 min	12 RCTs (24, 27–37) (n = 1128)	<b>There is no evidence of a clinically important difference between opioids and ketamine in the change of pain scores in 15 min.</b> ED: Meta-analysis of 12 RCTs found MD 0.35 (–0.36 to 1.06) at 15 min	Low (Inconsistent, indirect)
Pain severity –30 min	12 RCTs (24, 27–36, 38) (n = 1153)	<b>There is no evidence of a clinically important difference between opioids and ketamine in the change of pain scores in 30 min.</b> ED: Meta-analysis of 12 RCTs found MD 0.26 (–0.23 to 0.75) at 30 min	Low (Inconsistent, indirect)
Pain severity – 60 min	12 RCTs (24, 25, 27–31, 33–36, 38) (n = 1409) 1 OBS (62) (n = 158)	<b>There is no evidence of a clinically important difference between opioids and ketamine in the change of pain scores in 60 min.</b> EMS: One trial (25) over prehospital period, MD –0.4 (–0.8 to 0.09). One observational study (62) favored ketamine vs. morphine over the prehospital period [–5.5(3.1) vs. –2.5 (2.4), <i>p</i> < 0.001] ED: Meta-analysis of 11 RCTs (24, 27–31, 33–36, 38) found MD –0.36 (–0.94 to 0.23) at 60 min.	Low (Inconsistent, indirect)
Any adverse event	8 RCTs (24, 27, 28, 30, 32, 33, 35, 36) (n = 398)	<b>Opioids may cause fewer total adverse events than ketamine.</b> ED: Meta-analysis of 6 RCTs (24, 27, 28, 30, 32, 36) over the study period found AR 50.0% vs. 82.4%; RD –30% (–56 to –4). Two RCTs (33, 35) reported AEs at 15 and at 30 min are generally in agreement.	Low (Inconsistent, indirect, imprecise)
Mental status changes - dizziness	9 RCTs (n = 723) (27, 28, 30, 31–36)	<b>Opioids cause less dizziness than ketamine.</b> ED: Meta-analysis of 7 RCTs (27, 28, 30, 31, 32, 34, 36) over the study period found AR 25.4% vs. 43.5%; RD –29% (–52 to –6). Two RCTs (33, 35) reported dizziness at 15 and 30 min and are generally in agreement.	Low (Inconsistent, indirect)
Respiratory depression	4 RCTs (24, 33, 34, 36) (n = 491) 1 OBS (62) (n = 158)	<b>Opioids may cause more respiratory depression than ketamine.</b> EMS: One OBS study (62) found 2 vs. 0 cases of respiratory compromise that needed oxygen supplementation – insufficient data, conclusion based on ED data ED: Meta-analysis of 4 RCTs (24, 33, 34, 36) over the study period found AR 11.5% vs. 2.4%, RD 4% (–2 to 11)	Low (Inconsistent, indirect, imprecise)

Abbreviations: AR = absolute risk; ED = emergency department; EMS = emergency medical services; IM = intramuscular; IN = intranasal; IV = intravenous; MD = mean difference; min = minutes; OBS = observational; RCT = randomized controlled trial; RD = risk difference.

Based on indirect evidence from the ED, opioids may cause fewer total adverse events than ketamine (low SOE), less dizziness than ketamine (low SOE), and may cause more respiratory depression than ketamine (low SOE). Dizziness may be associated with an age less than 18 years old or with the intranasal route of administration (Supplemental Appendix D Figures 2 and 3) although this interaction is unclear because these two subgroups were represented by the same

trials. Evidence is insufficient for the outcomes of hypotension and other measures of mental status changes.

In patients with an inadequate response to initial analgesia with IV morphine, giving IV ketamine may reduce pain more than giving additional opioids (low SOE) and may be quicker to reduce pain to a clinically important difference compared to giving additional opioids (low SOE) (Table 2, Supplemental Appendix D Figure 4). These

TABLE 2. Conclusions and strength of evidence for the comparison of opioids vs. ketamine in patients with inadequate response to initial analgesia

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates)	Strength of Evidence (Limitations)
Pain severity	2 RCT (39, 40) (n = 162)	<b>Giving ketamine may reduce pain more than giving additional opioids.</b> EMS: Meta-analysis of 2 RCTs found MD 1.99 (0.95 to 3.03) over the prehospital period.	Low (Medium study limitations, imprecise)
Time to analgesic effect	1 RCT (39) (n = 135)	<b>Giving ketamine may be quicker to reduce pain to a clinically important difference compared to giving additional opioids.</b> EMS: 1 RCT found the median difference in the change of pain score per minute to be -2.5 points per minute (-3.9 to -1.1) in favor of ketamine compared to opioids.	Low (Medium study limitations, unknown consistency)

Abbreviations: EMS = emergency medical services; MD = mean difference; OBS = observational; RCT = randomized controlled trial.

TABLE 3. Conclusions and strength of evidence for the comparison of combining an opioid and ketamine vs. an opioid

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates)	Strength of Evidence (Limitations)
Pain severity – 15 min	4 RCT (41, 43, 45, 46) (n = 336)	<b>Combining an opioid and ketamine may reduce pain more than an opioid alone at 15 min.</b> EMS: 1 RCT (41) found MD -1.3 (-2.6 to 0.02) at 15 min. ED: Meta-analysis of 3 RCT (43, 45, 46) found MD -1.04 (-2.55 to 0.47).	Low (Inconsistent, indirect, imprecise)
Pain severity –30 min	5 RCT (41–43, 45, 46) (n = 545)	<b>Combining an opioid and ketamine may reduce pain more than an opioid alone at 30 min.</b> EMS: 1 RCT (41) found mean difference in the change of pain scores to be MD -1 (-2.2 to 0.2) at 30 min. ED: Meta-analysis of 4 RCT (42, 43, 45, 46) found MD -0.59 (-2.24 to 1.06).	Low (Inconsistent, indirect, imprecise)
Pain severity – 60 min	3 RCT (43, 45, 46) (n = 241)	<b>There is no evidence of a clinically important difference between combining opioid and ketamine and opioid alone in the change of pain scores in 60 min.</b> ED: Meta-analysis of 3 RCT found MD -0.07 (-1.14 to 1.00).	Low (Inconsistent, indirect)

Abbreviations: ED = emergency department; EMS = emergency medical services; MD = mean difference; NR = not reported; OBS = observational; RCT = randomized controlled trial.

conclusions are based on direct evidence from the prehospital setting. Evidence is insufficient for the outcomes of any adverse event, hypotension, and mental status changes (Supplemental Appendix C Table 9).

### Opioids + Ketamine vs. Opioid

Combining an opioid and ketamine may reduce pain more than opioids alone, at 15 and 30 minutes (low SOE) (Table 3, Supplemental Appendix D Figure 5), but not at 60 minutes (low SOE). A single

trial (41) in the prehospital setting agreed that a clinically important difference favoring the combination of analgesics was possible at both 15 and 30 minutes. There is insufficient evidence for the outcomes of pain presence, any adverse events, hypotension, mental status changes, and respiratory depression (Supplemental Appendix C Table 10).

### Opioids vs. Acetaminophen

Based on indirect evidence from the ED, we found no evidence of a clinically important difference in

TABLE 4. Conclusions and strength of evidence for the comparison of opioids vs. acetaminophen

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates)	Strength of Evidence (Limitations)
Pain severity – 15 min	7 RCT (47,48,50–53,56) (n = 647)	<b>There is no evidence of a clinically important difference between IV opioids and IV APAP in the change of pain scores in 15 min.</b> ED: Meta-analysis of 7 RCTs found MD 0.18 (–1.06 to 1.42).	Low (Inconsistent, indirect)
Pain severity –30 min	9 RCT (47–53, 55, 56) (n = 1795)	<b>There is no evidence of a clinically important difference between IV opioids and IV APAP in the change of pain scores in 30 min.</b> ED: Meta-analysis of 9 RCTs found MD 0.30 (–0.84 to 1.44).	Low (Inconsistent, indirect)
Pain severity – 60 min	3 RCT (49, 53, 56) (n = 1260)	<b>There is no evidence of a clinically important difference between IV opioids and IV APAP in the change of pain scores in 60 min.</b> ED: Meta-analysis of 3 RCT found MD 0.40 (–1.01 to 1.81).	Low (Inconsistent, indirect)
Time to analgesic effect	1 RCT (49) (n = 1097)	<b>There is no evidence of a clinically important difference in the time to analgesia with IV opioids compared with IV APAP.</b> ED: Median time to NRS < 2 was 60 min in both arms, IQR 30 to 90 min.	Low (Unknown consistency, indirect)
Any adverse event	6 RCTs (47, 49, 51–53, 56) (n = 1,484)	<b>Opioids may cause more adverse events than APAP.</b> ED: Meta-analysis of 5 RCTs (47, 51–53, 56) over the study period found AR 35.4% vs. 5.6%, RD 30% (–1 to 62). 1 RCT (49) reporting total AEs “during acute” management found 3.5% vs. 1.3%, RD 2% (0.4 to 4).	Low (Inconsistent, indirect, imprecise)
Hypotension	5 RCTs (47, 50–52, 54) (n = 624)	<b>There is no evidence of a clinically important difference in hypotension with opioids compared to APAP.</b> ED: Meta-analysis of 5 RCTs found AR 2.6% vs. 0%, RD 2% (0.00 to 4%).	Low (Indirect, imprecise)
Mental status changes - dizziness	6 RCTs (47, 48, 51, 52, 54, 55) (n = 539)	<b>Opioids cause more dizziness than APAP.</b> ED: Meta-analysis of 6 RCTs found, AR 7.8% vs. 0.3%, RD 7% (5 to 9)	Moderate (Indirect)

Abbreviations: ED = emergency department; IQR = interquartile range; MD = mean difference; min = minutes; NRS = Numeric Rating Scale; RCT = randomized controlled trial; RD = risk difference.

the reduction of pain scores with IV opioids compared to IV APAP at 15, 30, and 60 minutes (all low SOE) (Table 4, Supplemental Appendix D Figure 6). We found no evidence of a clinically important difference in the time to analgesia with IV opioids compared with IV APAP (low SOE) (49). There is insufficient evidence for the outcome of pain presence (Supplemental Appendix C Table 11).

Opioids may cause more adverse events than APAP (low SOE). We found no evidence of a clinically important difference in hypotension with opioids compared to APAP (low SOE). No subjects had hypotension in the APAP group and 8 (2.6%) had hypotension in the opioid group. Opioids cause more dizziness than APAP (moderate SOE). Evidence is insufficient for the outcomes of “mild” sedation and respiratory depression.

## Opioids versus Nitrous Oxide

A single RCT compared opioids to nitrous oxide/oxygen and evidence was insufficient to conclude comparative effects (Supplemental Appendix C Table 12) (57).

## Opioids versus Nonsteroidal Anti-Inflammatory Drugs

We found no evidence of a clinically important difference in the reduction of pain scores when opioids are compared with NSAIDs at 30 and 60 minutes (all moderate SOE) (Table 5, Supplemental Appendix D Figure 7). Evidence is insufficient to conclude effects at 15 minutes and for pain presence (Supplemental Appendix C Table 13). Opioids may cause more adverse events and

TABLE 5. Conclusions and strength of evidence for the comparison of opioids vs. nonsteroidal anti-inflammatory drugs

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates)	Strength of Evidence (Limitations)
Pain severity –30 min	3 RCT (58–60) ( <i>n</i> = 453)	<b>There is no evidence of a clinically important difference between opioids and NSAIDs in the change of pain scores in 30 min.</b> ED: Meta-analysis of 3 RCT found MD 0.01 (–0.29 to 0.32)	Moderate (Indirect)
Pain severity – 60 min	3 RCT (58–60) ( <i>n</i> = 453)	<b>There is no evidence of a clinically important difference between opioids and NSAIDs in the change of pain scores in 60 min.</b> ED: Meta-analysis of 3 RCT found MD 0.21 (–0.10 to 0.51)	Moderate (Indirect)
Any adverse event	2 RCT (58, 60) ( <i>n</i> = 367)	<b>Opioids may cause more adverse events than NSAIDs.</b> ED: Meta-analysis of 2 RCTs found AR 24.6% vs. 7.4%, RD 21% (4 to 38)	Low (Inconsistent, indirect, imprecise)
Mental status changes – drowsiness	2 RCT (58, 60) ( <i>n</i> = 367)	<b>Opioids may cause more drowsiness than NSAIDs.</b> ED: Meta-analysis of 2 RCTs found AR 3.9% vs. 0.7%, RD 3% (0 to 6%)	Low (indirect, imprecise)

Abbreviations: ED = emergency department; MD = mean difference; NSAIDs = nonsteroidal anti-inflammatory drugs; RCT = randomized controlled trial; RD = risk difference.

may cause more drowsiness than NSAIDs (low SOE). Evidence is insufficient for the outcomes of hypotension and other measures of mental status changes.

## DISCUSSION

As initial analgesics for acute pain in the prehospital setting, we found no evidence of clinically important differences of pain reduction when opioids are compared with ketamine, APAP or NSAIDs. Combined administration of an opioid and ketamine may be more effective in reducing pain than opioids alone. These conclusions are all graded with a low strength of evidence, primarily due to inconsistency and reliance on indirect evidence from the ED setting. There are also important considerations for applicability of this evidence. Studies comparing efficacy of opioids with ketamine mostly compared weight-based IV morphine 0.1 mg/kg with IV ketamine (variable weight-based dosing). Some studies evaluated IN fentanyl and IN ketamine by administering the IV solution via an atomizer. The doses of ketamine were primarily sub-dissociative, although too few studies were available to conduct dose-related subgroup analysis. When ketamine was studied in combination with opioids, a single IV dose was added to the opioid regimen; how administration of multiple ketamine dose impacts outcomes is unknown. Nine of the 10 trials that compared opioids with APAP compared IV morphine 0.1 mg/kg with IV APAP 1 gm, thus results cannot be extrapolated to other routes or doses.

There were only three studies comparing opioids with NSAIDs with a mixed representation of oral and IV dosage forms.

Although we found opioids may cause fewer total adverse events than ketamine, the cumulative frequency of events in both groups was at least 50%, suggesting most patients will experience an event regardless. These trials studied primarily IN analgesic administration and based on our subgroup analyses, the lower overall adverse event risk with opioids may be associated with the IN route or with younger age (<18 years). In contrast, we found opioids may cause more adverse events than IV APAP or NSAIDs when used as initial analgesics. Evidence to evaluate specific harms was often insufficient but importantly, we found opioids to be associated with more respiratory depression than ketamine. This is a potentially fatal complication of opioid use for either acute or chronic pain management. Findings of dizziness and drowsiness with ketamine and opioids, although bothersome to patients, are less concerning and are expected side effects of these analgesics.

Current guidelines strongly recommend (based on moderate quality evidence) initial prehospital management of moderate to severe traumatic pain with a weight-based opioid, either intravenous (IV) morphine or IV/intranasal (IN) fentanyl (5). National model guidelines for pain management in the prehospital setting recommend either opioid or nonopioid analgesics but the specific drug and route of administration differs based on whether treatment is for moderate or severe pain (65). Our results are in

support of the option of both opioid and nonopioid analgesics for patients with moderate to severe pain. Importantly, we found no evidence that opioids are better at reducing pain in this setting but are associated with more side effects than APAP or NSAIDs. Although we do not make clinical recommendations, we encourage the application of this evidence in future guideline development.

With the current opioid overdose epidemic and concerns about potential misuse of and addiction to opioids, recent interest in nonopioid alternatives has grown. Support for the use of sub-dissociative doses of IV ketamine for acute pain management is growing nationally (66, 67). Our conclusions support the efficacy of ketamine, and when compared to opioids there was no evidence of a clinically important differences in reducing pain. Elevations in blood pressure and heart rate with ketamine may be common (68), but we did not formulate conclusions for outcomes concerning changes in blood pressure, heart rate or respiratory rate. Similarly, we did not grade SOE for emergence reactions and although reported to be uncommon with sub-dissociative ketamine doses (66); cumulatively 8.4% (12 of 143 subjects) of ketamine treated subjects from the included studies experienced this effect.

### Limitations

The major limitation of this review is the indirectness of evidence, which led to our downgrading of conclusions. We believe the single most important future research need is addressing this evidence gap with pain management studies set in the prehospital environment. In addition, research is needed to explore subgroups further, including patient and drug regimen characteristics and EMS personnel training and how these characteristics may modify comparative effectiveness and harms of analgesics. Use of ED data was associated with addition challenges. Pain, and usually cardiorespiratory monitoring parameters, were measured multiple times throughout the study period. We chose to evaluate these outcomes at 15, 30, and 60 minutes to balance clinical applicability and multiple hypothesis testing. Assessment of mental status changes was challenging because this outcome can be described in many ways. While we were quite liberal in what we allowed as a mental status change, we separately analyzed each distinct “symptom” since within a study these outcomes may not have been mutually exclusive. Similarly, the assessment of emergence delirium posed a challenge since several signs or symptoms may be associated with this phenomenon. We were strict in collecting data explicitly reported by the authors as emergence reactions,

delirium or phenomenon rather than assuming a vaguely reported symptom may have been emergence delirium.

### CONCLUSION

As initial analgesia, opioids are no different than ketamine, APAP and NSAIDs in reducing acute pain in the prehospital setting. Opioids may cause fewer total side effects than ketamine, but more than APAP or NSAIDs. Differences in specific side effects vary between analgesics and can further inform treatment decisions. Combined administration of an opioid and ketamine may reduce acute pain more than an opioid alone but comparative harms are uncertain. When initial morphine is inadequate in reducing pain, giving ketamine may provide greater and quicker acute pain relief than giving additional morphine, although comparative harms are uncertain. Due to indirectness, strength of evidence is generally low, and future research in the prehospital setting is needed.

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