Comparative Effectiveness Review
Number 220

Comparative Effectiveness of Analgesics To Reduce Acute Pain in the Prehospital Setting

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Comparative Effectiveness Review

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Key Messages

Purpose of Review
To evaluate effectiveness and harms of opioids compared to nonopioid analgesics as treatment of moderate to severe acute pain in the prehospital setting.

Key Messages

- As initial therapy in the prehospital setting:
  - Nonsteroidal anti-inflammatory drugs provide similar pain relief to opioids and may cause fewer overall side effects and less drowsiness.
  - Acetaminophen may provide similar pain relief to opioids, and may cause fewer side effects overall and less dizziness.
  - Ketamine may provide similar pain relief to opioids. Ketamine may cause more dizziness or overall side effects, while opioids may cause more respiratory depression.
    - Combining an opioid with ketamine may be more effective in reducing pain compared with opioids alone.
    - If morphine does not adequately relieve pain, changing to ketamine may be more effective and more quickly reduce pain than giving additional morphine.

Caveats

- Few studies have been conducted in the prehospital setting; we relied on evidence from the emergency department.
- Analgesics were primarily administered intravenously; this was the only route studied for acetaminophen. The intranasal route was common in studies reporting adverse events for the comparison of opioids versus ketamine.

This report is based on research conducted by the University of Connecticut Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00012-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. The National Highway Traffic Safety Administration (NHTSA) requested this report from the EPC Program at AHRQ and provided funding for the report. AHRQ assigned this report to the following EPC: University of Connecticut Evidence-based Practice Center (Contract Number 290-20-1500012-I).

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new healthcare technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for healthcare quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

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Comparative Effectiveness of Analgesics To Reduce Acute Pain in the Prehospital Setting

Structured Abstract

Objective. To assess comparative effectiveness and harms of opioid and nonopioid analgesics administered by emergency medical services for treatment of moderate to severe acute pain in the prehospital setting.

Data sources. MEDLINE®, Embase®, and Cochrane Central from earliest date through May 9, 2019; hand searches of references of relevant studies and study registries.

Review methods. Two investigators screened abstracts, reviewed full-text files, abstracted data, and assessed study-level risk of bias. We performed meta-analyses when appropriate and graded the strength of evidence (SOE) upon which conclusions were made for a priori determined comparisons and outcomes. We defined the following as clinically important differences: 2 points on a 0 to 10 pain scale; time to analgesia of 5 minutes; 10-percent absolute risk difference for any adverse event; and 5-percent absolute risk difference for hypotension, respiratory depression, and mental status changes.

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, we found no evidence of a clinically important difference in the change of pain scores with opioids versus 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), but we found no evidence of a clinically important difference at 60 minutes (low SOE). We found no evidence of a clinically important difference in time to analgesia with opioids compared with APAP, both administered IV. Opioids may cause fewer adverse events than ketamine (low SOE), 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 we found no evidence of a clinically important difference in hypotension (low SOE). Opioids may cause more adverse events and more drowsiness than NSAIDs (low SOE), administered primarily IV. Evidence on comparative effects of nitrous oxide and on harms of combined opioid and ketamine is insufficient.

For patients whose pain is not adequately reduced by IV morphine initially, we found that giving IV ketamine may reduce pain more and may be quicker than giving additional IV morphine (low SOE, insufficient evidence to determine comparative harms).

Conclusion. As initial analgesia administered primarily IV, 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, SOE is generally low, and future research in the prehospital setting is needed.

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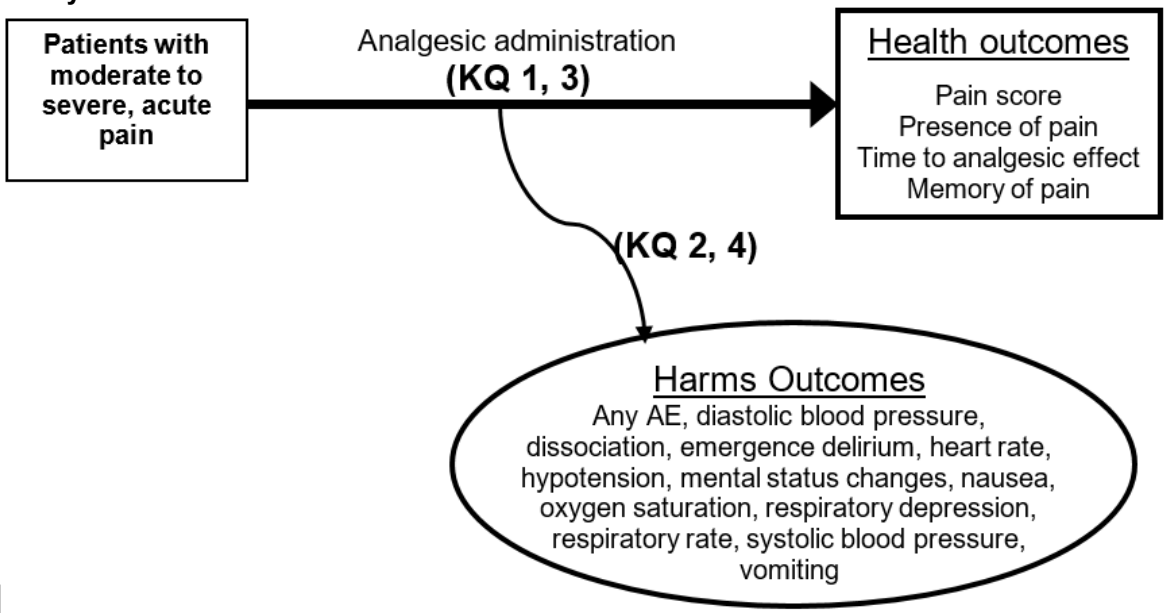
Evidence Summary

Objective and Rationale for the Review

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 20-53 percent.[1] Adequate pain relief is known to minimize anxiety and cardiac complications associated with acute pain.[2] However, as many as 43 percent of adults[3] and 85 percent of pediatric patients[4] have insufficient prehospital pain relief.

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] 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) (specifically ketorolac and ibuprofen) may provide adequate analgesia. This systematic review assesses the comparative effectiveness and harms of opioids compared to nonopioid analgesics for the prehospital management of acute pain (Figure A).

Figure A. Analytic framework



Abbreviations: AE=adverse event; KQ=Key Question

Data Sources

We searched MEDLINE®, Embase® and Cochrane Central bibliographic databases from earliest date through May 9, 2019; hand searches of references of relevant studies; www.clinicaltrials.gov and the International Controlled Trials Registry Platform. The systematic review protocol is available in the full report.

Methods

The protocol was registered in PROSPERO (CRD42018114959) and posted on the AHRQ website. The draft report will be posted for public and peer review and we will revise the report based on these comments. After input from the Technical Expert Panel (TEP), NHTSA, AHRQ and our EPC, we chose the following analgesic comparisons and outcomes upon which to formulate conclusions with graded strength of evidence (SOE): comparisons (opioids versus ketamine, opioids versus APAP, opioids versus nitrous oxide, opioids versus NSAIDs, combination opioid and ketamine versus opioids) and outcomes (pain severity, pain presence, time to analgesic effect, any adverse event, hypotension, mental status changes, and respiratory depression).

Conclusions are made in the context of clinically important differences that were established based on the input of NHTSA, AHRQ, the TEP, and our EPC. This includes 2 points on a 0 to 10 pain scale, 5 minutes for time to analgesia, 10 percent absolute difference for any adverse event and 5 percent absolute difference for hypotension, respiratory depression and mental status changes review. We judged the SOE for our conclusions in consideration of five domains: study limitations, consistency, directness, precision and reporting bias.[9] The four levels of SOE include high (+++), moderate (++), low (+), or insufficient.

The results for analgesics comparisons and outcomes that are not graded are reported in the full report.

Results

We included 52 randomized controlled trials (RCTs) and 13 observational studies, of which 37 RCTs and 4 observational studies provided evidence for graded comparisons and outcomes (Table A).[10-74] We aimed to base conclusions on direct evidence from the prehospital setting, but this was not always possible because of a lack of studies. In the absence of sufficient prehospital evidence, we used evidence from the emergency department but downgraded strength of evidence for indirectness.

Table A. Characteristics of included studies for graded comparisons, per comparison

Characteristic	Opioids Versus Ketamine	Opioid+Ketamine Versus Opioid	Opioids Versus APAP	Opioids Versus Nitrous Oxide	Opioids Versus NSAIDs
N of studies	17 RCT 3 OBS[a]	6 RCT 2 OBS[a]	10 RCT	1 RCT	3 RCT
Countries and N of studies	Afghanistan 2[b]; Australia 1; Israel 1; Iran 5; Sweden 1; 1 New Zealand; USA 8; Vietnam 1	Afghanistan 1[b]; France 1; Iran 3; Switzerland 1; USA 2	Iran 4; Turkey 4; Qatar 1; UK 1	Iran 1	Canada 1; Iran 1; USA 1
N of patients	2,484	1,566	2,001	100	474
Gender (Range of males, %)	23.3 to 100	40 to 100	43 to 83	72 to 84	56.4 to 70.5
Age (Range of means, y)	7 to 77.3	23 to 51.58	29.1 to 44.6	35.8 to 37	11.7 to 39.3
Pain Classification (N studies)	Traumatic: 13 Nontraumatic: 1 Mixed: 6	Traumatic: 3 Nontraumatic: 2 Mixed: 3	Traumatic: 4 Nontraumatic: 5; Mixed: 1	Traumatic: 1	Traumatic: 1 Nontraumatic: 1; Mixed: 1

Characteristic	Opioids Versus Ketamine	Opioid+Ketamine Versus Opioid	Opioids Versus APAP	Opioids Versus Nitrous Oxide	Opioids Versus NSAIDs
Setting (N studies)	Prehospital: 4 ED: 14 Battlefield: 2	Prehospital: 2 ED: 5 Battlefield: 1	ED: 10	ED: 1	ED: 3
Administered doses (N studies)[c]	Single: 11 Multiple: 7 NR: 2	Single: 6 NR: 2	Single: 10	Single: 1	Single: 1 Multiple: 2
Dosage forms (N of studies each)	IV vs. IV: 10 IN vs. IN: 4 IV vs. IN: 2[d] IM vs. IN: 1[d] IM vs. IV: 1 NEB vs. IV: 1 Mixed/NR: 2	IV+IV vs. IV: 6 IV+IN vs. IV: 1 NR: 1	IV vs. IV: 10	IV vs. inhaled: 1	IV vs. IV: 2 PO vs. PO: 1
Specific drugs (N studies)	Morphine: 12 Fentanyl: 6 Mixed: 2	Morphine: 6 Mixed: 2	Morphine: 9 Fentanyl: 1	Fentanyl: 1	Morphine: 3 Ketorolac: 2 Ibuprofen: 1
Risk of bias (N studies)[e]	Low: 12 Medium: 2 High: 2 Unclear: 2 Low/medium: 2	Low: 7 Medium: 1	Low: 9 Unclear: 1	Low/medium: 1	Low: 2 Medium: 1

Abbreviations: APAP=acetaminophen; ED=emergency department; IM=intramuscular; IN=intranasal; IV=intravenous; NEB=nebulized; NR=not reported; NSAIDs=nonsteroidal anti-inflammatory drugs; OBS=observational; PO=oral; RCT=randomized controlled trial; UK=United Kingdom; USA=United States of American; vs=versus

[a]Two observational studies included two comparisons: opioids vs. ketamine and morphine vs. fentanyl, one of these studies also compares opioids+ketamine vs. opioids.

[b]These studies took place in Afghanistan but were US military forces

[c]Studies were classified according to the number of doses given of the randomized analgesic. Studies either allowed one dose or multiple doses.

[d]One trial included 3 arms and thus has two comparisons: morphine IV vs. ketamine and morphine IM vs. ketamine

[e]Some studies had different risk of bias based on the individual outcome, and in these cases were listed as "low/medium" risk of bias

Initial Analgesia

Key Questions (KQ) 1 and 2 aimed to evaluate comparative effectiveness (KQ 1) and harms (KQ 2) of initial analgesics (Table B). Conclusions are based on indirect evidence from the emergency department setting. Opioids, ketamine and NSAIDs were primarily administered IV, and for APAP this was the only route studied. The IN route was also common in studies reporting adverse event outcomes for the comparison of opioids versus ketamine.

We found no evidence of clinically important differences in pain reduction between opioids and ketamine administered primarily IV, IV APAP or NSAIDs administered primarily IV. Combining opioids and ketamine may be more effective than opioids alone, administered primarily IV.

Opioids may cause fewer adverse events than ketamine, primarily administered IN. Based on subgroup analysis, this risk may be associated with age or route of administration. Opioids may cause more adverse events than NSAIDs, administered primarily IV. Opioids may cause more side effects than APAP, both administered IV.

Table B. Summary of the comparative effectiveness and harms of initial analgesics in the prehospital setting

Outcome	Opioid[a] Versus Ketamine[a]	Opioid+ketamine[a] Versus Opioid[a]	Opioid[a] Versus IV APAP	Opioid[a] Versus Nitrous Oxide	Opioid[a] Versus NSAIDs[a]
Pain severity (continuous)	No clinically important difference (+)	Combination may be more effective[b] (+)	No clinically important difference (+)	Insufficient	No clinically important difference[c] (++)
Pain presence (dichotomous)	Insufficient	Insufficient	Insufficient	No data	Insufficient
Time to analgesic effect	Insufficient	No data	No clinically important difference (+)	No data	Insufficient
Any adverse event	Fewer with opioids (+)	Insufficient	More with opioids (+)	Insufficient	More with opioids (+)
Hypotension	Insufficient	Insufficient	No clinically important difference (+)	No data	Insufficient
Mental status changes	Less dizziness with opioids[d] (+)	Insufficient[e]	More dizziness with opioids[f] (++)	Insufficient[g]	More drowsiness with opioids[h] (+)
Respiratory depression	More with opioids (+)	Insufficient	Insufficient	No data	No data

[a]Routes of administration were primarily intravenous, with exception of opioid versus ketamine for "any adverse event" where analgesics were primarily administered IN. (see table A, dosage form row).
Abbreviations: IV=intravenous
Strength of evidence: white = no evidence; yellow = insufficient; orange (+) = low; blue (++) = moderate. Conclusions of no clinically important difference are based on a priori determined thresholds of 2 points on a 0 to 10 pain scale, 5 minutes for time to analgesia, 10% absolute difference for any adverse event and 5% absolute difference for hypotension, respiratory depression and mental status changes.
[b]Change in 15 and 30 minutes; no clinically important difference at 60 min
[c]At 30 and 60 min, inconclusive at 15 min
[d]Insufficient for drowsiness, changes in RAAS, reduced GCS, sleepiness/tired, confusion, sedation, difficulty concentrating
[e]For dizziness, sedation
[f]Inconclusive for mild sedation
[g]For dizziness
[h]Insufficient for depression (as a mental status change), dizziness

Analgesia When Initial Choice Is Insufficient

KQ 3 and 4 aimed to evaluate comparative effectiveness and harms of subsequent analgesia when initial analgesia is ineffective. Giving a patient ketamine IV instead of continuing to administer morphine IV when the initial morphine IV administration does not provide the patient with pain relief may reduce pain more and may reduce pain more quickly. This is based on direct evidence from the prehospital setting. Evidence of harms was either insufficient or nonexistent.

Table C. Summary of the comparative effectiveness and harms of subsequent analgesics in the prehospital setting

Outcome	Additional Opioid Versus Switching to Ketamine
Pain severity (continuous)	Ketamine may be more effective (+)
Pain presence (dichotomous)	Insufficient
Time to analgesic effect	Ketamine may be quicker (+)
Any adverse event	Insufficient
Hypotension	Insufficient
Mental status changes	Insufficient
Respiratory depression	No data

Strength of evidence: white = no evidence; yellow = insufficient; orange (+) = low; blue (++) = moderate

Discussion

Our review found that as an initial analgesic and primarily administered IV, opioids are no different than the nonopioid analgesics ketamine, APAP and NSAIDs in reducing pain. The combination of opioids and ketamine may be more effective in reducing pain, compared with opioids alone. When initial IV morphine is not effective, switching to IV ketamine may be better in reducing pain than continuing to administer morphine.

To put these findings in context there are key parameters concerning applicability to consider. The studies that compared the efficacy of opioids with ketamine mostly compare weight-based IV morphine 0.1mg/kg with IV ketamine (variable weight-based dosing). Some studies evaluated IN fentanyl and IN ketamine, which were prepared from the IV formulations and delivered IN via an atomizer. The IN ketamine product on the US market is not approved for pain management and is specific to management of treatment-resistant depression. The doses of ketamine varied and too few studies were available to identify associations based on dose. When ketamine was studied in combination with opioids, a single IV dose was added to the opioid regimen. How administration of more than one 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 1g, 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. We were unable to draw conclusions about the efficacy of opioids compared with nitrous oxide (based on a single study with limitations).

Comparative harms of specific adverse events vary among analgesics and in the absence of clinically important differences in pain reduction, can inform individualized treatment decisions. The overall frequency of total adverse events in trials that compared opioids with ketamine suggests that at least 50 percent of treated patients will experience some type of adverse event but low-strength evidence suggests that opioids may cause fewer total adverse events than ketamine. 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 either age or route of administration. Opioids may cause more respiratory depression while ketamine causes more dizziness. In contrast to the comparison of opioids with ketamine, opioids may cause more adverse events than IV APAP or NSAIDs when used as initial analgesics. In patients who do not adequately respond to initial morphine, comparative harms of giving ketamine compared with giving additional morphine are uncertain.

The focus of this report is to synthesize existing evidence. We do not make clinical recommendations. We encourage application of this evidence toward future work generating evidence-based clinical guidelines.

The major limitation of this review is the indirectness of evidence, which may have significant implications and 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, including patient and drug regimen characteristics and EMS personnel training and how these characteristics may modify comparative effectiveness and harms of analgesics.

Conclusion

As initial analgesia administered primarily IV, 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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Introduction

Background

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 20-53 percent.[1] Adequate pain relief is known to minimize the anxiety and cardiac complications associated with acute pain.[2] However, as many as 43 percent of adults[3] and 85 percent of pediatric patients[4] have insufficient prehospital pain relief. Reasons for this have included fear of adverse events with analgesic administration, unwanted masking of underlying pathology, and provider indifference to pain complaints, amongst others.[5-7] Under-treatment of pain in the prehospital setting paired with the recent focus on optimizing opioid exposure creates a need for clinicians to have a thorough understanding of pain assessment tools and the comparative effectiveness and safety of analgesics for prehospital acute pain management.

Since pain cannot be adequately treated if not appropriately assessed, a careful evaluation of validated tools to measure pain in the prehospital setting is required. Current guidelines[8] for the management of prehospital trauma pain recommend specific pain scales, broken into age-related categories. However, there is a dearth of studies comparing the diagnostic accuracy of pain assessment tools in the prehospital setting particularly in the absence of a gold standard assessment tool.[9] Of particular interest is the evidence for use of these assessment tools in special populations including pediatrics, non-English speakers, and those with cognitive impairment or substance impairment.

Management of Acute Pain in the Prehospital Setting

For patients experiencing moderate to severe pain, current guidelines strongly recommend (based on moderate quality evidence) initial management with a weight-based opioid, either intravenous (IV) morphine or IV/intranasal (IN) fentanyl.[8] Complicating the appropriate use of prehospital opioids is the fear of their abuse and the resulting epidemic in the United States.[10,11] When combined with concerns of adverse events, such as vomiting and subsequent airway obstruction, respiratory depression, hypotension, and sedation,[12] alternatives to opioid analgesia have been sought. Nonopioid analgesics, including ketamine, nitrous oxide/oxygen, acetaminophen, and non-steroidal anti-inflammatory drugs (NSAIDs) may be alternates to opioids in the prehospital setting and are a focus of this review (Table 1). A variety of non-pharmacologic modalities are also available (e.g. splinting, distraction, etc.), although they are not included in the current review.

Table 1. Onset, duration, and typical initial doses for analgesics[a,13-33]

Analgesic – Route	Onset	Analgesic Duration	Typical Initial Adult Dosing for Acute Pain	Typical Initial Pediatric Dosing for Acute Pain
Acetaminophen – IV	5-10 minutes	4-6 hours	<50 kg: 12.5 mg/kg every 4 hours or 15 mg/kg every 6 hours; ≥50 kg: 650 mg every 4 hours or 1,000 mg every 6 hours	≥2y and adolescents; <50kg: refer to adult dosing; >50kg: refer to adult dosing
Acetaminophen – PO	<1 hour	4-6 hours	Regular strength: 650 mg every 4-6 hours; Extra strength: 1000 mg every 6 hours;	10-15mg/kg every 4 to 6 hours

Analgesic – Route	Onset	Analgesic Duration	Typical Initial Adult Dosing for Acute Pain	Typical Initial Pediatric Dosing for Acute Pain
Fentanyl - IV	Almost immediate	30-60 minutes	0.35-0.5 mcg/kg every 30-60 minutes as needed	Infant: 1-2 mcg/kg, may repeat at 2 to 4 hour intervals; Children: 1-2mcg/kg, may repeat at 30-60 min intervals; Adolescents<18y and <50kg: 0.5 to 1 mcg/kg, may repeat every 1 to 2 hours; Adolescents <18y and ≥50kg: 25 to 50mcg every 1 to 2 hours
Fentanyl - IM	7-8 minutes	1-2 hours	0.35-0.5 mcg/kg every 30-60 minutes as needed	NA
Fentanyl - IN	5-10 minutes	1 hour	100 mcg (one 100 mcg spray in one nostril)[b]	IV solution delivered via atomizer at doses ranging from 1-2mcg/kg has been studied.
Fentanyl -NEB	Almost immediate	30-60 minutes	Studies used IV solution delivered via nebulizer, doses were either 2mcg/kg or 4mcg/kg.	NA
Fentanyl - transmucosal lozenge	5-15 minutes	Related to blood level	200 mcg consumed over 15 minutes	NA
Ibuprofen - IV	30-60 minutes	6-8 hours	400 to 800 mg IV every 6 hours as needed	6 months to <12y: 10mg/kg every 4 to 6 hours; 12-17y: 400mg every 4 to 6 hours
Ibuprofen - PO	30-60 minutes	6-8 hours	200 to 800 mg 3-4 times daily	Infants and children <50kg: 4 to 10mg/kg every 6 to 8 hours
Ketamine – IV[c]	Within 30 seconds	5-10 minutes	0.1-0.3mg/kg IV bolus over 10-15 minutes with option of continuous infusion at 0.15 to 0.2mg/kg/hr	Doses ranging from 0.2 to 0.3mg/kg IV bolus have been studied
Ketamine - IN	Within 10 minutes	Up to 60 minutes	0.5-1mg/kg	IV solution delivered via atomizer has been studied at doses ranging from 1-1.5mg/kg
Ketorolac - IV	~30 minutes	4-6 hours	≥50kg: 30 mg IV as a single dose or 30 mg every 6 hours	<2y: 0.5mg/kg every 6 to 8 hours; ≥2y and ≤16y: 0.5mg/kg every 6 hours; ≥17y and <50kg: 15mg as a single dose or 15mg every 6 hours; ≥17y and ≥50kg: refer to adult dosing
Ketorolac - PO	30-60 minutes	4-6 hours	≥50kg: 20 mg PO, followed by 10 mg every 4-6 hours as needed	≥2y and ≤16y: 1mg/kg as a single dose; ≥17y and <50kg: 10mg, then 10mg every 4 to 6 hours; ≥17y and ≥50kg: refer to adult dosing
Morphine - IV	5-10 minutes	4-5 hours	2.5-5 mg every 3-4 hours as needed	≤6 months: 0.025 to 0.03mg/kg every 2 to 4 hours; >6 months and <50kg: 0.05mg/kg every 2 to 4 hours; >6 months and ≥50kg: 2 to 5mg every 2 to 4 hours
Morphine - IM	10-30 minutes	4-5 hours	5-10 mg every 4 hours as needed	Refer to pediatric IV morphine dosing

Analgesic – Route	Onset	Analgesic Duration	Typical Initial Adult Dosing for Acute Pain	Typical Initial Pediatric Dosing for Acute Pain
Morphine - PO	~30 minutes	3-5 hours	15-30 mg every 4 hours as needed	≤6 months: 0.08 to 0.1mg/kg every 3 to 4 hours; >6 months and <50kg: 0.2 to 0.5mg/kg every 3 to 4 hours; >6 months and ≥50kg: 15 to 20mg every 3 to 4 hours
Nitrous Oxide	2-5 minutes	N/A	25% to 50% nitrous oxide with oxygen	Refer to adult dosing

Abbreviations: IM=intramuscular; IN=intranasal; IV=intravenous; kg=kilogram; mcg=microgram; mg=milligram; NA=not applicable; NEB=nebulizer; PO=by mouth

[a]This table should be used in the context of understanding the findings of the report, as it relates to applicability of evidence. Please refer to drug dosing reference for maximal doses and additional clinical considerations when prescribing analgesics to treat acute pain, particularly because some routes for some analgesics are used off-label and established doses may be less clear.

[b]Per FDA label for intranasal fentanyl approved for cancer breakthrough pain.

[c]Ketamine is used off-label for acute pain management and doses may vary although use of sub-dissociative doses are general suggested for acute pain management.

Impetus for the Review

This systematic review will assess the comparative effectiveness and harms of opioid and nonopioid analgesics for the prehospital management of acute pain to support future work sponsored by the National Highway Traffic Safety Administration (NHTSA). The scope and Key Questions (KQs) for this topic were developed by the Agency for Healthcare Research and Quality in conjunction with the NHTSA and University of Connecticut Evidence-based Practice Center.

Key Questions

KQ1. What is the comparative effectiveness of the initial analgesic agent treatment for achieving reduction in moderate-to-severe acute-onset pain level when administered by emergency medical services (EMS) personnel in the prehospital setting?

KQ 1a. How does effectiveness vary by patient characteristics?

KQ 1b. How does effectiveness vary by routes of administration, dosing, and timing?

KQ 2. What are the comparative harms of analgesic agents when administered by EMS personnel to control moderate-to-severe pain in the prehospital setting?

KQ 2a. How do harms vary by patient characteristics?

KQ 2b. How do harms vary by routes of administration, dosing, and timing?

KQ 2c. What are the comparative harms to EMS personnel who

administer analgesics to patients for the control of moderate-to-severe pain in the prehospital setting?

KQ 3. In patients whose moderate-to-severe acute-onset pain level is not controlled following initial analgesic treatment, what is the comparative effectiveness of switching the analgesic regimen compared to repeating the initial treatment?

KQ 3a. How does effectiveness vary by patient characteristics?

KQ 3b. How does effectiveness vary by timing of the second treatment administration?

KQ 4. In patients whose moderate-to-severe acute-onset pain level is not controlled following initial analgesic treatment, what are the comparative harms of switching to another analgesic agent?

KQ 4a. How do harms vary by patient characteristics?

KQ 4b. How do harms vary by routes of administration, dosing, and timing?

Population, Intervention, Comparator, Outcome, Timing, Setting

For this systematic review, the following population, intervention, comparator, outcome, timing, and setting (PICOTS) applies.

Populations: The population of interest is people with acute onset pain, moderate to severe in intensity, without restrictions on age. We determined pain intensity by 1) study inclusion/exclusion 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 studies 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.

KQ 3 and 4 required patients to have had an inadequate responsive to a first analgesic. The definition of "inadequate response" was based on what was used in the study. We did not exclude studies based on the threshold or tool used by the study to determine adequacy of response.

Sub-KQ 1a, 2a, 3a and 4a targeted population characteristics that were potential modifiers of the original KQ including age, source of pain, severity of pain, medical condition (including chronic pain, chronically painful conditions or chronic opioid users), location of the pain, and vital signs.

Sub-KQ 2c was specific to the population of EMS personnel that administer or handle analgesics in the care of patients with acute onset, moderate to severe pain, including emergency medical technicians, advanced emergency medical technicians, and paramedics.

Interventions: Interventions included in this report are listed in Table 2. We included studies regardless of the studied dose, frequency or route of administration (oral, subcutaneous, intravenous, intramuscular, intraosseous, intranasal, inhaled, or transdermal). We excluded other interventions such as nonpharmacologic treatments, placebo, no treatment, other combinations of interventions or complimentary/alternative medicine.

Table 2. Included analgesics

Class	Analgesics
Opioid	Fentanyl, morphine
Nonopioid	Acetaminophen, ketamine, nitrous oxide/oxygen, NSAIDs (ketorolac or ibuprofen)
Combinations	Opioid (fentanyl or morphine) + ketamine

Abbreviations: NSAIDs=nonsteroidal anti-inflammatory drugs

KQ 3 and 4 also evaluated the interventions in Table 2 but at a different dose that initially used or a different analgesic than the first, ineffective analgesic.

Sub-KQb 1-4 targeted characteristics of the analgesic regimen or training and background of the personnel that were potential modifiers of the original KQ. KQ 1b, 2b, 4b explore route of administration, dose of analgesic and frequency of dose, EMS personnel training/background. KQ 3b explored timing of the second analgesic.

Comparators: We were interested in comparing 1) opioid to nonopioid analgesics, 2) the combination of opioid plus ketamine to ketamine alone, 3) nonopioid to a different nonopioid analgesic, and 4) opioid to a different opioid analgesic (Table 2). We included studies regardless of the studied dose, frequency or route of analgesic administration (oral, subcutaneous, intravenous (IV), intramuscular (IM), intraosseous, intranasal (IN), inhaled, or transdermal). We excluded studies that did not have at least one comparator in Table 2.

KQ 3 and 4 required the study comparator to be the initial drug regimen studied to which the patient was determined to be inadequately responsive to.

Outcomes:

- KQ 1,3:
  - Pain severity scores (continuous) and presence of pain (dichotomous), as defined by the tools and thresholds used in the included studies
  - Time to analgesic effect
  - Self-reported recall of pain episode
- KQ 2,4:
  - Any adverse event (as in the total number of subjects that experienced an adverse event during the study)
  - Blood pressure (systolic and diastolic)
  - Dissociative experiences scale response
  - Emergence delirium
  - Heart rate
  - Hypotension
  - Mental status changes

    - Nausea
    - Oxygen saturation
    - Respiratory depression
    - Respiratory rate
    - Vomiting
- KQ 2c:
    - Diversion
    - Future risk of substance abuse or misuse
    - Needle sticks

Timing: There were no restrictions based on timing aside from studies from the ED setting for which we included pain related outcomes through 60 minutes.

Settings: The primary setting of interest was prehospital, and studies from the prehospital setting were considered to provide direct evidence. We also included studies from the ED and battlefield but these settings were considered to provide indirect evidence to the prehospital setting. See the methods section regarding the impact of evidence from indirect settings on strength of evidence grading.

Study Designs: We included randomized controlled trials, case-control, and cohort studies.

Contextual Questions

Two Contextual Questions (CQ) are addressed within this report. The intent of CQs is to enhance findings of the review and to ensure the findings are put into appropriate clinical or policy context. Contextual Questions are not systematically reviewed, and use a "best evidence" approach. Findings related to the CQs are presented in the Discussion chapter, within the Applicability subsection.

CQ 1: Which treatments are contraindicated for specific medical conditions or patient characteristics (e.g., dental pain, abdominal pain, depressed blood pressure, heart rate, and/or respiratory rate, altered mental status, agitation)?

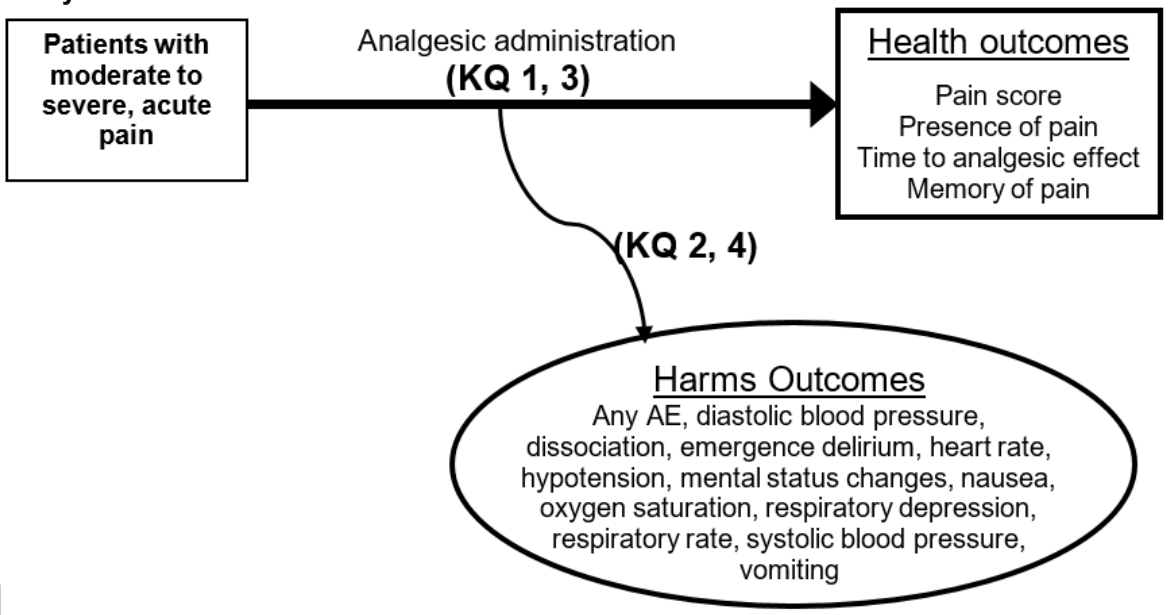
CQ 2: What is the evidence regarding use of pain assessment tools in the prehospital setting for special populations including children, individuals with cognitive impairment, substance impaired individuals, and non-English speakers?

Methods

The scope and Key Questions (KQs) for this topic were developed by the Agency for Healthcare Research and Quality (AHRQ) in conjunction with the National Highway Traffic Safety Administration (NHTSA) and the University of Connecticut Evidence-based Practice Center (UConn EPC). We (the UConn EPC) then drafted a protocol for the systematic review and recruited a panel of technical expert panelists (TEP) to provide high-level content and methodological expertise throughout the development of the review. The finalized protocol is posted on the Effective Health Care website at https://effectivehealthcare.ahrq.gov/topics/acute-pain-ems/protocol. The PROSPERO registration is CRD42018114959.

We developed an a priori analytic framework to guide the systematic review process (Figure 1). The details of the analytic framework were determined in consultation with NHTSA and the TEP. We identified relevant literature by searching Ovid MEDLINE, Ovid MEDLINE In-Process & Other Nonindexed Citations, EMBASE via Ovid and Cochrane Central Register of Controlled Trials from earliest date through May 9, 2019 using subject headings and natural language terms reflecting the settings and analgesics of interest (Appendix A). We supplemented the bibliographic database searches with backwards citation tracking of relevant publications. We searched the clinicaltrials.gov website and the World Health Organization International Controlled Trials Registry Platform for ongoing studies and those completed with reported results.

Figure 1. Analytic framework



Abbreviations: AE=adverse event; KQ=Key Question

We managed citations using DistillerSR®. We screened titles and abstracts using two independent reviewers to determine if the citation met inclusion/exclusion criteria (Table 3). When both reviewers agreed that a citation met inclusion criteria, we reviewed the full text for inclusion into the review. A third reviewer resolved disagreements.

Table 3. Inclusion and exclusion criteria for Key Questions

Category	Inclusion Criteria	Exclusion Criteria
Population	KQ 1-4: Any age with acute onset, moderate to severe pain.[a] KQ 3, 4: Above criteria plus considered inadequately responsive to the initial analgesic.	KQ 1-4: Pain associated with labor and delivery; mild or non-zero pain severity
Intervention	KQ 1-4: Opioids (morphine or fentanyl); Nonopioids [ketamine, nitrous oxide/oxygen, NSAIDs (ketorolac or ibuprofen), APAP]; Opioids + ketamine KQ 3, 4: Above criteria plus the analgesic must vary in dose or drug, from the initial analgesic the patient was determined inadequately responsive to.	KQ 1-4: Any other combination or single interventions such as other analgesics, nonpharmacological, placebo, no treatment or complimentary alternative medicine. KQ 3, 4: Administration of the same drug and dose as the initial analgesic, which the patient was determined to be inadequately responsive to.
Comparator	KQ 1-4: Opioids (morphine or fentanyl); Nonopioids [ketamine, nitrous oxide/oxygen, NSAIDs (ketorolac or ibuprofen), APAP]; Opioids + ketamine KQ 3, 4: The initial analgesic regimen studied to which the patient was inadequately responsive.	KQ 1-4: Any other single interventions such as other analgesics, nonpharmacological, placebo, no treatment or complimentary alternative medicine. Any combinations of treatments that are not specified in the inclusion criteria. KQ 3, 4: Comparisons to analgesic regimens other than the initial regimen to which the patient was determined to be inadequately responsive.
Outcomes	At least one outcome listed in PICOTS (see Outcomes section above)	Studies that do not include at least one outcome
Timing	All study durations and follow-ups	None
Setting	Prehospital, battlefield, ED	All other settings.
Study Design	RCTs, nonrandomized controlled trials, prospective or retrospective controlled cohort studies, case-controlled studies	Case series, case reports, studies without an active comparator or non-active control group
Publication Language, Dates	No limits on publication date or language[b]	Abstracts without published study manuscripts.

Abbreviations: APAP=acetaminophen; ED=emergency department; KQ=Key Question; NSAIDs=nonsteroidal anti-inflammatory drugs; PICOTS=population, intervention, comparator, outcomes, timing, setting; RCT=randomized controlled trial

[a]Severity of pain was determined by study inclusion criteria, baseline pain scores, or if these data were not available severity was assumed to be moderate to severe in studies of opioids or ketamine.

[b]English language abstracts of non-English language articles will be reviewed at the abstract stage consistent with the process described by the Methods Guide.[34]

We contacted corresponding authors when needed for clarification related to inclusion criteria and to solicit data for outcomes that were reported in the methods of the paper but not reported as a numerical result. All authors were given a minimum of 7 days to acknowledge queries. We matched results posted in clinical trial registries, abstracts and meeting presentations to their corresponding full text publication, which was always used as the primary data source, and reviewed for supplemental data. We considered post-hoc and subgroup analyses of included studies when they provide data on the outcomes of interest.

One investigator extracted data into standardized collection forms and evidence and outcomes tables, followed by verification by a second investigator. Two independent reviewers assessed risk of bias using the Cochrane Collaboration's Risk of Bias Tool[35] for randomized controlled trials (RCTs) and Newcastle Ottawa Scale[36] for observational studies. We classified overall risk of bias for each study as low, moderate or high, according to the collective risk of bias per evaluated domain and the investigator's confidence in the study results given the identified limitations.[37] A low rating implies lack of major or minor sources of bias that were

likely to have influenced results. A medium rating implies some confidence that the results represented true treatment effect and although the study was susceptible to some bias, it was not sufficient to invalidate results. A high rating implies low confidence that results represented true treatment effects, due to significant flaws that implied biases of various types. Risk of bias was considered unclear if the majority of domains evaluated were unclear, meaning information was missing to permit judgements of possible bias. Studies with high risk of bias were not excluded from analyses rather their contribution to the evidence base was considered when grading strength of evidence for our conclusions.

To characterize the population, we classified the type of pain for each study as traumatic, nontraumatic or mixed. We synthesized all pain classifications together and when possible, we also analyzed and reported results for traumatic pain. We based synthesis on specific analgesic comparisons (i.e. opioid versus ketamine, opioid versus acetaminophen [APAP] etc.) and regimen characteristics including route, dose and frequency, were explored in subgroup analyses. Some studies, almost exclusively from the emergency department (ED) setting, reported outcomes at multiple specific time points over the course of the study. We collected and analyzed three times points: 15 minutes (post-drug administration through 15 min), 30 minutes (20 to 30 minutes) and 60 minutes (40 to 60 minutes). These time points were selected in consideration of the pharmacokinetic profiles of the analgesics studied and time points that were decided to be most informative to the prehospital setting. When the time point of an outcome was not at 15, 30 or 60 minutes but fell within the given range of values considered acceptable for that time point, we included the data in our analysis (i.e. if a study reported pain at 20 minutes but not 30 minutes, we used the data from 20 minutes in the analysis of 30 minutes).

This review sought to address prehospital pain management although given the scarcity of studies, battlefield and ED settings were included to provide indirect evidence. We did not use meta-analysis across the three settings, only within each setting when applicable. However, when synthesizing the evidence we did consider data from the various settings. Battlefield data were qualitatively described and did not contribute to our conclusions.

We assessed clinical and methodological heterogeneity to determine appropriateness of meta-analysis. 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.[38] The Hartung-Knapp method was used to adjust 95 percent confidence intervals (CI) when three or more studies were meta-analyzed;[39,40] otherwise, a traditional DerSimonian-Laird random-effects model was used.[41] Continuous outcomes are reported as mean differences and 95 percent CI. We pooled either mean change in continuous parameters from baseline (also referred to as the change score) for each arm or a difference in change scores, depending on what was reported in the studies. When necessary for parallel trials that did not report change scores individually for each arm, we calculated it from the available baseline and end-point values, as suggested by Follman et al.[42] For continuous pain scales, we converted scores (e.g. 0-100 scale) to a 10-point scale using the methods of Thorlund, et al.[43] When studies reported continuous parameters as medians and related variances, we converted the data to means and standard deviations according to the methods of Wan et al.[44] For binary outcomes, risk differences (RD) and risk ratios (RR) are reported with corresponding 95 percent CI. For outcomes with zero events in one or both study arms, continuity correction was used.[45,46] All studies, including those that were not amenable to pooling, are qualitatively summarized.

When quantitative pooling of studies was possible, 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 percent) of variability in the treatment estimate that is attributable to heterogeneity.[47] 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.[48] We conducted subgroup analyses to evaluate for the presence of effect modifiers. Analyses were done for graded comparisons and outcomes, as previously specified. For individual outcomes, analyses were either stratified according to the subgroup or, when available, results from subgroup analyses reported in individual trials are summarized. All analyses were performed using the 'meta' package (version 4.9-4) in R (version 3.5.2; the R Project for Statistical Computing).

At the completion of the review, two reviewers independently constructed conclusions and graded each conclusion's strength of evidence (SOE). Conflicts were resolved either through consensus or third-party adjudication. Input from NHTSA, the TEP, AHRQ and our EPC led to a prioritized list of comparisons and outcomes for which conclusions were constructed and graded. Prioritized comparisons were opioids versus ketamine, opioids plus ketamine versus opioids, opioids versus APAP, opioids versus nitrous oxide and opioids versus nonsteroidal anti-inflammatory drugs (NSAIDs). Prioritized outcomes were pain severity (continuous measures), presence of pain (dichotomous measures), time to analgesic effect, respiratory depression, hypotension, change in mental status, and "any adverse event".

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 (Table 4). These CIDs reflect input from our EPC and consultant experts, NHTSA, and the TEP. When the body of evidence generated a point estimate and confidence interval that exceeded the CID in one direction we concluded a difference exists between the analgesics compared for that outcome. When the point estimate and confidence interval suggested a CID may exist (confidence interval included both a CID and also a smaller difference, but overall was shifted towards a CID) we concluded there "may" be a difference between the two analgesics for that outcome. When the point estimate and confidence interval were entirely within the CID such that a CID in either direction was ruled out, we concluded "there was no evidence of a clinically important difference" for that analgesic comparison and outcome. We reserved use of "inconclusive" for when the confidence interval of the absolute measure was uninformative and included possibility of a CID in either direction or when the evidence base had multiple downgraded domains such that we were uncertain what the true effect was.

Table 4. Clinically important differences for graded outcomes

Outcome	Clinically Important Difference
Pain score	2 points on a continuous scale from 0 to 10
Presence of pain, hypotension, respiratory depression, mental status changes	ARD of 5%
Time to analgesic effect	5 minutes on a continuous scale
Any adverse events	ARD of 10%

Abbreviations: ARD=absolute risk difference

The SOE of these conclusions was judged to be one of four levels (Table 5), in consideration of 5 domains: study limitations, consistency, directness (prehospital setting versus ED setting, the latter which is indirect evidence), precision and reporting bias.[49] Conclusions based on RCTs

started with a high SOE which could be downgraded based on the assessment of the 5 domains. Conclusions based on observational data began with a grade of low and may have been upgraded based on assessment of the 5 domains.

Table 5. Strength of evidence (SOE) levels[49]

SOE	Explanation
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of the effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

We assessed applicability of studies using the population, intervention, comparator, outcomes, timing, setting (PICOTS) framework.[50] Characteristics that may have influenced applicability included but are not limited to age of patients, severity and type of pain, analgesic regimen characteristics (i.e. dose, route, frequency) and the timing of and definitions used for outcomes.

The Contextual Questions (CQ) were not based on a systematic review as the aim of the CQ were to provide a qualitative overview using the best evidence approach, without formal systematic review or analytic plans. Findings related to the CQs in this report are presented in the Discussion.

Experts in emergency medicine services, pain management and individuals representing stakeholder and user communities were invited to provide external peer review of this systematic review; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ website for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documenting everything in a disposition of comments report to be made available three months after the Agency posts the final systematic review on the Effective Health Care website.

Results

Organization of the Report

We begin by presenting the results of our literature search and citation screening. We provide an overview of study characteristics organized by unique analgesic comparisons.

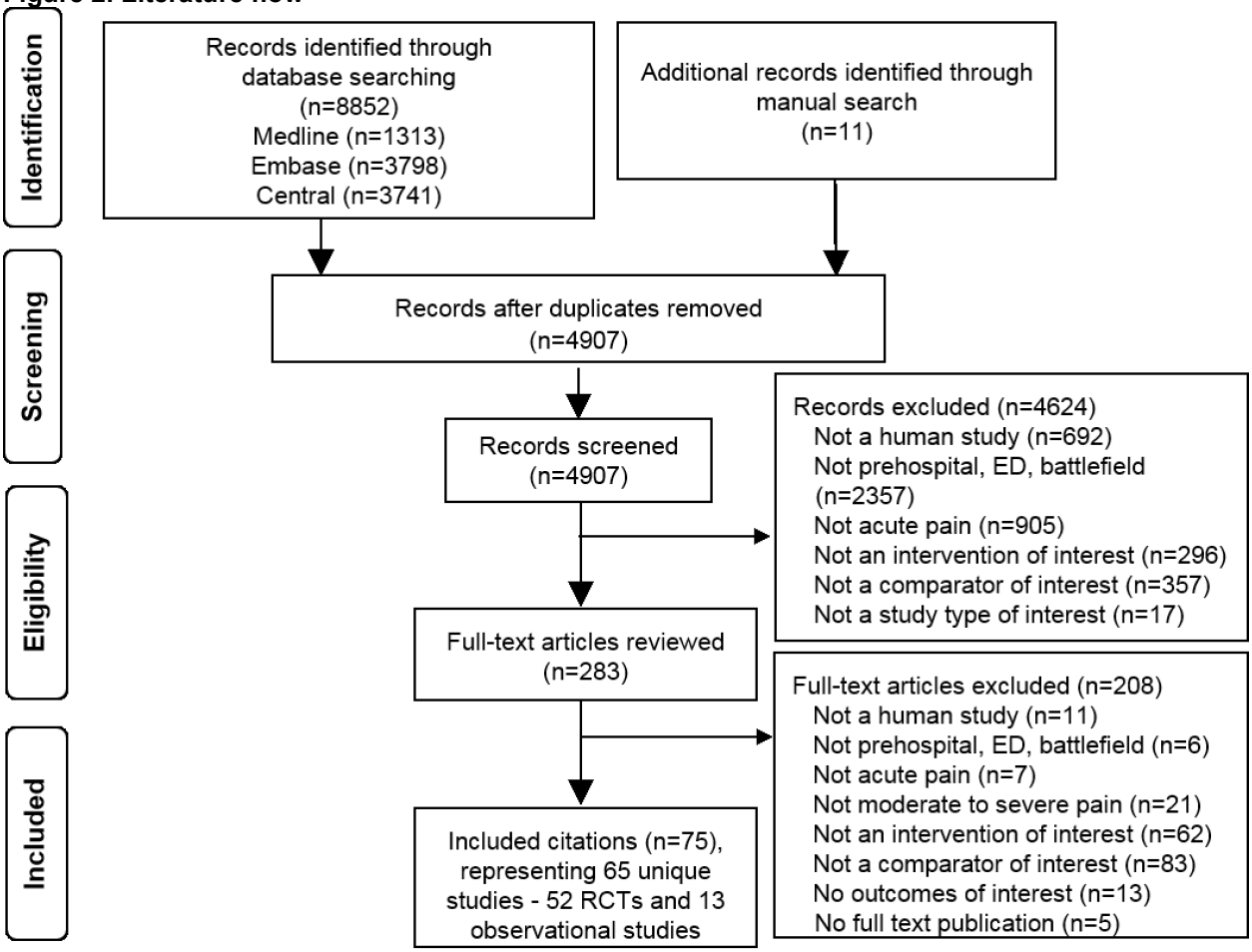
Next we present the results for each Key Question (KQ). Results are organized by unique analgesic comparisons starting with graded comparisons (opioid versus ketamine, combination opioid and ketamine versus opioid, opioid versus acetaminophen [APAP], opioid versus nitrous oxide, opioid versus nonsteroidal anti-inflammatory drugs [NSAIDs]). Under the analgesic comparison, we present key messages followed by results and conclusions for the graded outcomes first, then results from subgroups of interest (the sub-KQs). After we conclude presentation of graded outcomes we provide "Additional Findings" which reflect results from outcomes that are not graded.

Supporting tables and figures relevant to the results appear in Appendixes C-F, including study and population characteristics, study level outcomes data, study risk of bias assessments, details regarding the strength of evidence (SOE) grading and forest plots.

Search Results

Our search identified 4907 nonduplicate records, of which 283 required full-text review after title and abstract screening, and 75 met eligibility criteria for inclusion in this review (Figure 2). These 75 citations reported results for 65 unique studies;[16,17,19-21,27-30,51-106] 52 randomized controlled trials (RCTs) and 13 observational studies. Citations excluded at the full text review stage are presented in Appendix B. As a result of searching trial registries, we found one study[28] with results posted that has not been published in the peer reviewed literature. In addition, we received additional outcomes data from authors of 5 included studies.[58,66,74,90,93]

Figure 2. Literature flow



Characteristics of Included Studies

The distribution of studies per KQ, organized by comparison and study design, is presented in Table 6. Most of the literature answers KQ 1 and 2, whereas only 2 RCTs answer KQ 3 and 4. We present a summary of the characteristics of included studies in Table 7-8, followed by further details in the text, organized by comparison group.

Table 6. Number of studies included in each Key Question, by comparison and study design

	Comparison	Overall N Studies	KQ 1	KQ 2	KQ 3	KQ 4
Graded Strength of Evidence	Opioids vs. Ketamine	17 RCT 3 OBS[a]	14 RCT 2 OBS	14 RCT 3 OBS	2 RCT	2 RCT
	Opioid + Ketamine vs. Opioid	6 RCT 2 OBS[a]	6 RCT 1 OBS	6 RCT 1 OBS	None	None
	Opioid vs. APAP	10 RCT	9 RCT	10 RCT	None	None
	Opioid vs. Nitrous Oxide	1 RCT	1 RCT	1 RCT	None	None
	Opioid vs. NSAID	3 RCT	3 RCT	3 RCT	None	None

	Comparison	Overall N Studies	KQ 1	KQ 2	KQ 3	KQ 4
Strength of Evidence Not Graded	APAP vs. NSAID	3 RCT	3 RCT	2 RCT	None	None
	Ketamine vs. NSAID	1 RCT	1 RCT	1 RCT	None	None
	Morphine vs. Fentanyl	11 RCT 10 OBS[a]	9 RCT 8 OBS	11 RCT 7 OBS	None	None
	Opioid + Ketamine vs. Ketamine	1 OBS	None	1 OBS	None	None

Abbreviations: APAP=acetaminophen; ED=emergency department; KQ=Key Question; NSAIDs= nonsteroidal anti-inflammatory; OBS=observational; RCT=randomized controlled trial; vs=versus

[a]Two observational studies include two comparisons: opioids vs. ketamine and morphine vs. fentanyl, one of these studies also compared opioid+ketamine vs. opioid

Table 7. Characteristics of included studies for graded comparisons, per comparison

Characteristic	Opioids Versus Ketamine	Opioids + Ketamine Versus Opioid	Opioids Versus APAP	Opioids Versus Nitrous Oxide	Opioids Versus NSAIDs
N of studies	17 RCT 3 OBS[a]	6 RCT 2 OBS[a]	10 RCT	1 RCT	3 RCT
Countries (N studies)	Afghanistan 2[b]; Australia 1; Israel 1; Iran 5; Sweden 1; 1 New Zealand; USA 8; Vietnam 1	Afghanistan 1[b]; France 1; Iran 3; Switzerland 1; USA 2	Iran 4; Turkey 4; Qatar 1; UK 1	Iran 1	Canada 1; Iran 1; USA 1
N of patients	2,484	1,566	2,001	100	474
Gender (Range of males, %)	23.3 to 100	40 to 100	43 to 83	72 to 84	56.4 to 70.5
Age (Range of means, years)	7 to 77.3	23 to 51.6	29.1 to 44.6	35.8 to 37	11.7 to 39.3
Pain Classification (N studies)	Traumatic: 13 Nontraumatic: 1 Mixed: 6	Traumatic: 3 Nontraumatic: 2 Mixed: 3	Traumatic: 4 Nontraumatic: 5 Mixed: 1	Traumatic: 1	Traumatic: 1 Nontraumatic: 1 Mixed: 1
Setting (N studies)	Prehospital: 4 ED: 14 Battlefield: 2	Prehospital: 2 ED: 5 Battlefield: 1	ED: 10	ED: 1	ED: 3
Administered doses (N studies)[c]	Single: 11 Multiple: 7 Unknown: 2	Single: 6 Unknown: 2	Single: 10	Single: 1	Single: 1 Multiple: 2
Dosage forms (N of studies each)	IV vs. IV: 10 IN vs. IN: 4 IV vs. IN: 2[d] IM vs. IN: 1[d] IM vs. IV: 1 NEB vs. IV: 1 Mixed/Unknown: 2	IV+IV vs. IV: 6 IV+IN vs. IV: 1 Unknown: 1	IV vs. IV: 10	IV vs. inhaled: 1	IV vs. IV: 2 PO vs. PO: 1
Specific drugs (N studies)	Morphine: 12 Fentanyl: 6 Mixed: 2	Morphine: 6 Mixed: 2	Morphine: 9 Fentanyl: 1	Fentanyl: 1	Morphine: 3 Ketorolac: 2 Ibuprofen: 1
Risk of bias (N studies)[e]	Low: 12 Medium: 2 High: 2 Unclear: 2 Low/medium: 2	Low: 7 Medium: 1	Low: 9 Unclear: 1	Low/medium: 1	Low: 2 Medium: 1

Abbreviations: APAP=acetaminophen; ED=emergency department; IM=intramuscular; IN=intranasal; IV=intravenous; NEB=nebulized; NSAIDs=nonsteroidal anti-inflammatory drugs; OBS=observational; PO=oral; RCT=randomized controlled trial; UK=United Kingdom; USA=United States of American; vs=versus

[a]Two observational studies included two comparisons: opioids vs. ketamine and morphine vs. fentanyl, one of these studies also compares opioids+ketamine vs. opioids.

[b]These studies took place in Afghanistan but were US military forces

[c]Studies were classified according to the number of doses given of the randomized analgesic. Studies either allowed one dose or multiple doses.

[d]One trial included 3 arms and thus has two comparisons: morphine IV vs. ketamine and morphine IM vs. ketamine

[e]Some studies had different risk of bias based on the individual outcome, and in this case were listed as "low/medium" risk of bias

Table 8. Characteristics of included studies for comparisons not graded, per comparison

Characteristic	APAP Versus NSAIDs	Ketamine Versus NSAIDs	Morphine Versus Fentanyl	Opioid + Ketamine Versus Ketamine
N of studies	3 RCT	1 RCT	11 RCT 10 OBS[a]	1 OBS
Countries (N studies)	Canada 1; Italy 1; Turkey 1	Iran	Afghanistan 2[b]; Australia 5; Canada 2; France 1; Germany 1; Iran 2; USA 8	Australia
N of patients	564	141	4,121	37
Gender (Range of males, %)	30 to 66.4	71 to 81.2	38 to 100	NR
Age (Range of means, years)	11.8 to 36	34.2 to 37.9	6.6 to 66.5	NR
Pain Classification (N studies)	Traumatic: 1 Nontraumatic: 1 Mixed: 1	Nontraumatic: 1	Traumatic: 12 Nontraumatic: 2 Mixed: 7	Traumatic: 1
Setting (N studies)	ED: 3	ED: 1	Prehospital: 8 ED: 11 Battlefield: 2	EMS: 1
Administered doses (N studies)[c]	Single: 3	Single: 1	Single: 7 Multiple: 10 Unknown: 4	Unknown: 1
Dosage forms (N of studies each)	IV vs. IV: 1 SL vs. melt away: 1 PO vs. PO: 1	IV vs. IV: 1	IV vs. IV: 7 IV vs. NEB: 3 IV vs. IN: 4 IV vs. oral lozenge: 1 IM vs. IN: 1 Unknown: 3 Mixed: 2	Unknown: 1
Specific drugs (N studies)	Ibuprofen: 2 Ketorolac: 1	Ketorolac: 1	NA	Morphine or Fentanyl: 1
Risk of bias (N studies)[d]	Low: 3	Low: 1	Low: 9 Medium: 7 High: 3 Low/medium: 2	Medium: 1

Abbreviations: APAP=acetaminophen; ED=emergency department; IM=intramuscular; IN=intranasal; IV=intravenous; NA=not applicable; NEB=nebulized; NSAIDs=nonsteroidal anti-inflammatory drugs; NR=not reported; OBS=observational; PO=oral; RCT=randomized controlled trial; SL=sublingual; USA=United States of American; vs=versus

[a]Two observational studies included two comparisons: opioids vs. ketamine and morphine vs. fentanyl, one of these studies also compares opioids+ketamine vs. opioids.

[b]These studies took place in Afghanistan but were US military forces

[c]Studies were classified according to the number of doses given of the randomized analgesic. Studies either allowed one dose or multiple doses.

[d]Some studies had different risk of bias based on the individual outcome, and in this case were listed as "low/medium" risk of bias

Opioids Versus Ketamine

We included 17 RCTs (n=1831) and 3 observational studies (n=653) that compared opioids with ketamine.[17,27-30,51-65]

Effectiveness and Harms of Initial Analgesia (KQ 1 and 2)

Fifteen RCTs (n=1669)[17,27-30,51-60] and 3 observational studies (n=653)[61-63] answer KQ 1 and 2. Two studies were in the emergency medical services (EMS) setting,[27,61] 14 were in the emergency department (ED) setting,[17,28-30,51-60] and 2 were in the battlefield setting.[62,63] One of

these studies was only identified through a search on www.clinicaltrials.gov with posted results but has not been published in the peer reviewed literature; thus, it was not pooled with other studies.[28] The mean age ranged from 7 to 77 years. Five studies exclusively enrolled subjects under the age of 18 years, with lower age limits of 3, 4 and 8 years. In these trials mean or median age ranged from 7 to 13.3 years. One study exclusively enrolled older aged subjects, 65 years and older (mean age was 77 years). Baseline pain scores (mean or median) ranged from 7.4 to 9.2 on a 0 to 10 scale. Pain was classified as traumatic in 11 studies (road traffic injuries, blunt trauma, falls, assault, extremity fractures and soft tissue injuries, battlefield),[17,27,29,53,56,59,60,62,63] nontraumatic in 1 study (renal colic),[54] and mixed in 6 studies.[28,52,55,57,58,61]

Six studies compared fentanyl with ketamine,[17,29,30,51,52,61] either as a single dose of analgesic[17,30,51,52] or allowing multiple doses.[29,61] Fentanyl intranasal (IN) was compared with ketamine IN in 4 studies; fentanyl doses were either 1.5mcg/kg or 2mcg/kg and ketamine doses were ether 1mg/kg or 1.5mg/kg.[17,29,51,52] One study compared fentanyl 2mcg/kg intravenous (IV) with ketamine 0.3mg/kg IV.[61] One study compared nebulized fentanyl 4mcg/kg with ketamine 0.4mg/kg IV.[51]

Ten studies compared morphine with ketamine,[27,28,53-60] either as a single dose[28,52,53-57] of analgesic or allowing multiple doses.[58-60] Seven of these studies compared morphine 0.1mg/kg IV to ketamine; ketamine was administered IV at a dose of 0.2mg/kg in 1 study,[56] 0.3mg/kg in 3 studies,[55,57,58] or 0.5mg/kg in 2 studies;[59,60] ketamine was administered IN at a dose of 1mg/kg in 1 study.[54] One study compared morphine 0.05mg/kg with ketamine 0.3mg/kg IV.[28] One study compared age-based dosing of morphine 5 to 10mg IM with ketamine 0.2 to 0.3mg/kg IV.[27] One study had 3 arms and compared morphine 0.1mg/kg IV, morphine 0.15mg/kg IM and ketamine 1mg/kg IN.[53]

Two studies compared either morphine or fentanyl with ketamine.[62,63] One study did not report route or dose[62] and the other did not report dose but included IV and IM routes for opioids and ketamine.[63]

Effectiveness and Harms of Subsequent Analgesia (KQ 3 and 4)

The body of evidence for KQ 3 and 4 include 2 RCTs (n=162) from the EMS setting,[64,65] both evaluating continued titration of morphine IV versus switching to titrated ketamine IV in subjects inadequately responsive to initial morphine IV. These are the only two studies that qualify for KQ 3 and 4 in this review.

The mean age ranged from 41 to 74 years. Baseline pain scores (mean or median) ranged from 7.4 to 8.5 on a 0 to 10 scale and pain was classified as traumatic in both trials. One trial[64] enrolled subjects whose pain score remained ≥5/10 after morphine 5mg IV. Subjects received either titrated ketamine IV (10 to 20mg bolus, 10mg repeated every 3 minutes) or titrated morphine IV (5mg bolus repeated every 5 min). The second trial[65] enrolled subjects whose pain score was ≥4/10 after morphine 0.1mg/kg IV. Subjects received either ketamine 0.2mg/kg or morphine 0.1mg/kg.

Combination of an Opioid and Ketamine Versus Opioid

We included 6 RCTs (n=579) and 2 observational study (n=987). Two studies were in the EMS setting,[66,67] 5 studies in the ED setting,[68-72] and 1 study in the battlefield setting.[62] The mean age ranged from 23 to 51.58 years. One study enrolled subjects as young as 15 years but the other studies used a lower limit of 18 years for enrollment. Baseline pain scores (mean or median) ranged from 7.5 to 8.7 on a 0 to 10 scale. Pain was classified as traumatic in 3 studies

(traumatic limb, fracture, battlefield),[62,66,72] nontraumatic in 2 studies (renal colic),[68,71] and mixed in 3 studies.[67,69,70] The trial by Beaudoin et al. was not pooled in meta-analysis of results related to this comparison.[70] Unlike the other studies, this trial allowed enrollment of subjects that had previously failed analgesia for the acute pain episode, which reached 80 percent of the studied population.

In this body of evidence, all 6 RCTs added a single dose of ketamine to an initial dose of morphine IV and compared the combination to morphine alone. All trials also allowed titration of morphine IV after the initial dose but ketamine was not re-dosed. Morphine was dosed as 0.1mg/kg in 5 trials and compared to IV ketamine.[66,68-71] The doses of IV ketamine studied in these 5 trials were 0.15mg/kg in 2 trials,[70,71] 0.2mg/kg in 2 trials,[66,68] and 0.3mg/kg in 2 trials.[69,70] One trial had 3 arms such that two ketamine doses were evaluated.[70] Morphine was dosed as 0.05mg/kg IV in 1 trial and compared to ketamine 1mg/kg IN.[72]

The 2 observational studies[62,67] did not specify dosing strategies. One study evaluated either fentanyl or morphine in combination with ketamine, all delivered IV.[67] One study from the battlefield setting did not report routes of administration for the opioids (morphine or fentanyl) or for ketamine.[62]

Opioids Versus Acetaminophen

We included 10 RCTs (n=2,001), all of which were in the ED setting.[73-82] The mean age ranged from 29.1 to 44.6 years old. All studies required subjects to be either 18 or 21 years of age for inclusion. All but 1 trial[74] applied an upper age limit, which was 55 to 65 years of age. Baseline pain scores (mean or median) ranged from 7.4 to 9.14 on a 0 to 10 scale. Pain was classified as traumatic in 4 trials (2 trials on fractures,[79,81] 1 on acute limb trauma,[74] and 1 on post-trauma headache[73]), nontraumatic in 5 trials (4 renal colic,[75,78,80,82] 1 sciatic nerve pain[76]) and 1 mixed population.[77]

Nine trials compared single doses of morphine 0.1mg/kg IV with APAP 1 gm IV.[73-79,81,82] One trial compared a single dose of fentanyl 2mcg/kg IV with APAP 10mg IV.[80]

Opioids Versus Nitrous Oxide/Oxygen

One RCT (n=100) compared opioids with nitrous oxide/oxygen and this trial was in the EMS setting.[83] The study enrolled subjects aged 15 to 85 years and the mean age was 35.8 to 37 years. Baseline pain scores (mean or median) were 9.0 on a 0 to 10 scale and the pain was classified as traumatic pain (isolated limb trauma). This trial compared fentanyl 2mcg/kg IV with self-administered nitrous oxide mixed with oxygen in a 50:50 ratio.

Opioids Versus Nonsteroidal Anti-Inflammatory Drugs

We included 3 RCTs (n=564), all of which were in the ED setting.[84-86] The mean age ranged from 11.7 to 39.3 years. One trial[86] enrolled subjects 6-17 years of age while the other 2 trials[84,85] enrolled subjects at least 18 years of age. Baseline pain scores (mean or median) ranged from 7.6 to 10.0 on a 0 to 10 scale. Pain was classified as traumatic in 1 trial[84] (long bone fracture), nontraumatic in 1 trial[85] (renal colic) and mixed in 1 trial.[86] Two trials[84,85] compared morphine 5mg IV bolus with ketorolac (10mg or 15mg IV bolus) with second doses of morphine 5mg and ketorolac 5mg or 15mg if pain remained elevated. One trial compared a single dose of morphine 0.2mg/kg by mouth with ibuprofen 10mg/kg by mouth.[86]

Acetaminophen Versus Nonsteroidal Anti-Inflammatory Drugs

We included 3 RCTs (n=564), all of which we in the ED setting.[87-89] The mean age ranged from 11.6 to 36 years. One trial[87] enrolled subjects age 18 years and older while the other two trials enrolled children; 6 to 17 years old[89] and 4 to 18 years old.[88] Baseline pain scores (mean or median) ranged from 7 to 8 on a 0 to 10 scale. Pain was classified as traumatic in 1 trial (fractures),[89] nontraumatic in 1 trial (renal colic),[87] and mixed in 1 trial.[88] APAP 1g IV was compared to ibuprofen 800mg IV in 1 trial;[87] acetaminophen 15mg/kg by mouth was compared with ibuprofen 10mg/kg by mouth in 1 trial;[89] and ketorolac 0.5mg/kg sublingual was compared with APAP 20mg/kg melt away powder in 1 trial.[88]

Ketamine Versus Nonsteroidal Anti-Inflammatory Drugs

One RCT[90] (n=141) compared ketamine with ketorolac in the ED setting. The study enrolled subjects over the age of 18 years, the mean was 34.2 to 37.9 years. Baseline pain scores (mean) were 8.4 to 8.7 on a 0 to 10 scale and the pain was classified as nontraumatic pain (renal colic). This trial compared ketamine 0.6mg/kg IV with ketorolac 30mg IV.

Morphine Versus Fentanyl

We included 11 RCTs[16,19-21,91-97] (n=1405) and 10 observational studies[62,63,98-105] (n=2716). Eight studies[92-95,98,102-104] were in EMS, 11 studies[16,19-21,96,97,99-101] were in the ED and 2 studies[62,63] were in battlefield settings. The mean age ranged from 6.6 to 66.5 years. Five studies[16,21,96,97,102] exclusively enrolled children, with inclusion criteria as young as 3 years and as old as 18 years. One study enrolled patients 6 months or older,[103] and 1 study enrolled subjects 3 to 21 years old.[100] The remaining trials enrolled subjects aged 15 years through adulthood. Baseline pain scores (mean or median) ranged from 5 to 10 on a 0 to 10 scale. Pain was classified as traumatic in 12 studies (blunt trauma, wound/soft tissue, fractures and battlefield),[16,20,21,62,63,94,96,97,100,101] nontraumatic in two studies (ischemic chest pain, ab pain),[19,92] and mixed in 7 studies.[93,95,98,99,102-104]

In this body of evidence, morphine was administered IV in 16 studies,[19-21,92-98,100-102,104] IM in 1 study,[16] and mixed or unknown route in 4 studies.[62,63,99,103] Fentanyl was administered IV in 8 studies,[92-94,98,101,104] IN in 5 studies,[95,97,16,100,102] nebulized IV solution in 3 studies,[19-21] transmucosal lozenge in 1 study,[96] and mixed or unknown routes in 4 studies.[62,63,99,103]

Eight studies compared single doses of morphine with fentanyl.[16,19-21,96,101] Three studies compared a single dose of morphine 0.1mg/kg IV with fentanyl delivered via nebulizer, at a dose of 4mcg/kg[20,21] or 2mcg/kg.[19] One study compared a single dose of morphine 0.1mg/kg IV with fentanyl 10-15mcg/kg oral transmucosal lozenge.[96] One study compared a single dose of morphine 0.2mg/kg IM with fentanyl 1mcg/kg IN.[16] One study compared a single dose of morphine 4mg IV with fentanyl 50mcg IV.[101] One study compared morphine 0.1mg/kg IV with fentanyl 1mcg/kg IV.[91]

Nine studies compared multiple doses of morphine with fentanyl.[92-95,97,102-104] One study compared weight and age based doses of morphine 2.5 to 5mg IV with fentanyl 25 to 50mcg IV.[92] One study compared morphine 4mg IV with fentanyl 50mcg IV.[94] Two studies compared age-based dosing of morphine IV with age-based dosing of fentanyl, IN in one study[102] and IV in one study.[104] One study compared morphine 2.5 to 5mg IV with fentanyl 180mcg IN.[95] Two studies compared morphine 0.1mg/kg IV with fentanyl, 1mcg/kg IV in 1 study[93] and 1.4mcg/kg IN in 1 study.[97] One study compared fixed doses of morphine IV or IM with weight-based

fentanyl IV or IM.[103] One study compared morphine IV, without a specified dose, with fentanyl 1.5mg/kg IN.[100]

In three studies dose of morphine was not specified[62,63,99] and in 2 of these studies the route was not specified.[62,99] In one study the dose and frequency of morphine and fentanyl were not specified.[105]

Combination of Opioid and Ketamine Versus Ketamine

We included one observational study (n=37) from the EMS setting studying traumatic pain.[106] The age and gender for the cohort treated with analgesics was not reported in this study. Morphine plus ketamine, fentanyl plus ketamine, and ketamine alone were studied, although routes and doses were not provided.

Key Question (KQ) 1. What is the comparative effectiveness of the initial analgesic agent treatment for achieving reduction in moderate-to-severe acute-onset pain level when administered by EMS personnel in the prehospital setting?

KQ 1a. How does effectiveness vary by patient characteristics?

KQ 1b. How does effectiveness vary by routes of administration, dosing, and timing?

Opioids Versus Ketamine

Key Messages

- There is no evidence of a clinically important difference between opioids and ketamine in the change of pain scores in 15, 30, or 60 minutes (low SOE). This conclusion is based on indirect evidence from the ED setting and primarily weight-based IV doses of morphine and ketamine.
- Evidence is insufficient for outcomes measuring full or partial resolution of pain or time to analgesic effect.

Detailed Results

We present the conclusions for the comparative effectiveness of opioids versus ketamine as initial analgesics in Table 9. The majority of this evidence base is indirect data from the ED setting and compares weight-based doses of morphine IV with ketamine IV.

Table 9. Conclusions and strength of evidence for the comparison of opioids versus ketamine, Key Question 1

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates and 95% Confidence Intervals)	Strength of Evidence (Limitations)
Pain severity – 15 min	12 RCTs[17,29,30,51,52-59] (n=1128)	**There is no evidence of a clinically important difference between opioids and ketamine in the change of pain scores in 15 min.** ED: Meta-analysis of 12 RCTs found MD 0.35 (-0.36 to 1.06) at 15 min	Low (Inconsistent, indirect)

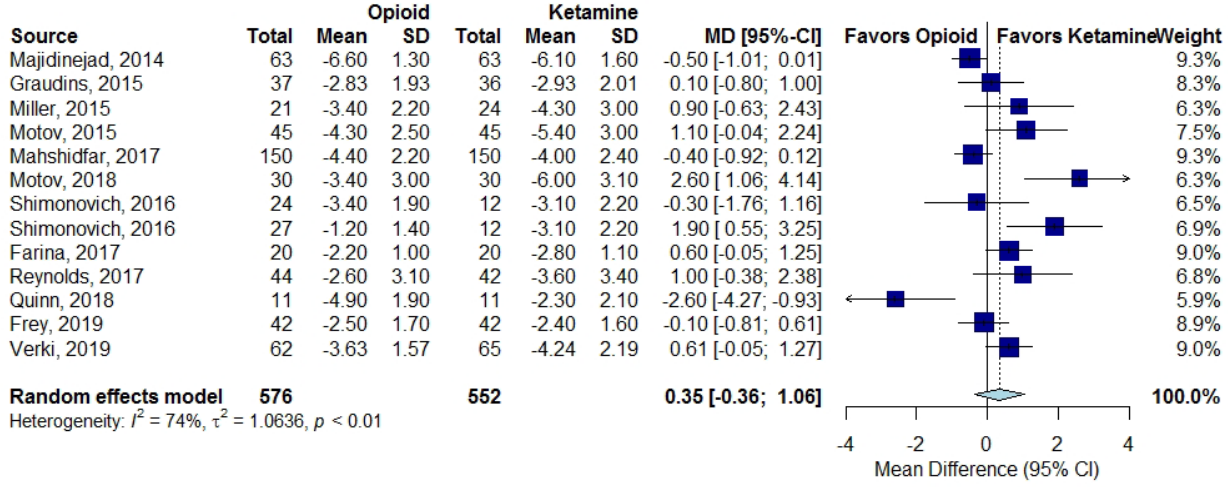
Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates and 95% Confidence Intervals)	Strength of Evidence (Limitations)
Pain severity –30 min	12 RCTs[17,29,30,51-58,60] (n=1153)	**There is no evidence of a clinically important difference between opioids and ketamine in the change of pain scores in 30 min.** 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[17,27,29,30,51-53,55-58,60] (n=1409) 1 OBS[61] (n=158)	**There is no evidence of a clinically important difference between opioids and ketamine in the change of pain scores in 60 min.** EMS: One trial[27] over prehospital period, MD -0.4 (-0.8 to 0.09). One observational study[61] favored ketamine vs. morphine over the prehospital period [-5.5(3.1) vs. -2.5 (2.4), p<0.001] ED: Meta-analysis of 11 RCTs[17,29,30,51-53,55-58,60] found MD -0.36 (-0.94 to 0.23) at 60 min.	Low (Inconsistent, indirect)
Pain presence – full resolution 15 min	1 RCT (n=60)[55]	**Inconclusive.** ED: 1 RCT found AR 16.7% vs. 50%; RD -33% (-53 to -9)	Insufficient (Unknown consistency, indirect)
Pain presence – full resolution 30 min	3 RCT[52,55,57] (n=172)	**Inconclusive.** ED: Meta-analysis of 3 RCTs found AR 26.7% vs. 27.9%; RD -1% (-39 to 38)	Insufficient (Indirect, very imprecise)
Pain presence – full resolution 60 min	2 RCT[55,57] (n=146)	**Inconclusive**. ED: Meta-analysis of 2 RCTs found AR 23.3% vs. 21.9%; RD 1% (-13 to 14)	Insufficient (Indirect, very imprecise)
Pain presence-partial resolution - 15 min	5 RCT[30,52,55,57,59] (n=369)	**Inconclusive.** ED: Meta-analysis of 5 RCTs found AR 76.1% vs. 77.3%; RD 2% (-25 to 28)	Insufficient (Inconsistent, indirect, very imprecise)
Pain presence-partial resolution - 30 min	4 RCT[29,30,55,57] (n=301)	**Inconclusive.** ED: Meta-analysis of 4 RCTs found AR 74.5% vs. 75.7%; RD -1% (-6 to 4)	Insufficient (Indirect, imprecise)
Pain presence-partial resolution - 60 min	3 RCT[30,55,57] (n=208) 1 OBS[61] (n=158)	**Inconclusive.** EMS: One observational study[61] found more patients to have partial resolution of pain with ketamine over the prehospital period. ED: Meta-analysis of 3 RCTs[30,55,57] found AR 76.9% vs. 74.0%; RD 1% (-38 to 39)	Insufficient (Inconsistent, indirect, very imprecise)
Time to analgesic effect – onset	1 RCT[53] (n=48)	**Inconclusive**. ED: 1 3-arm trial found time to onset (min) favored IN ketamine vs. IM morphine but was not different compared with IV morphine.	Insufficient (High study limitations, inconsistent, indirect, imprecise)
Time to analgesic effect – max effect	1 RCT[53] (n=48)	**Inconclusive.** ED: 1 3-arm trial found time to max effect (min) was not different between IV morphine, IM morphine and IN ketamine.	Insufficient (High study limitations, 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

There is 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) (Figure 3-Figure 5). These conclusions are each based on meta-analysis of the change in pain scores using indirect evidence from the ED setting and a clinically important difference of 2 points on a 0 to 10 scale. One RCT and one observational study from the EMS setting reported pain scores over the prehospital period. We considered these two studies in the conclusion for pain severity at 60 min. because they did not report transport times and for studies that do, the majority of transport times exceed 30 minutes.

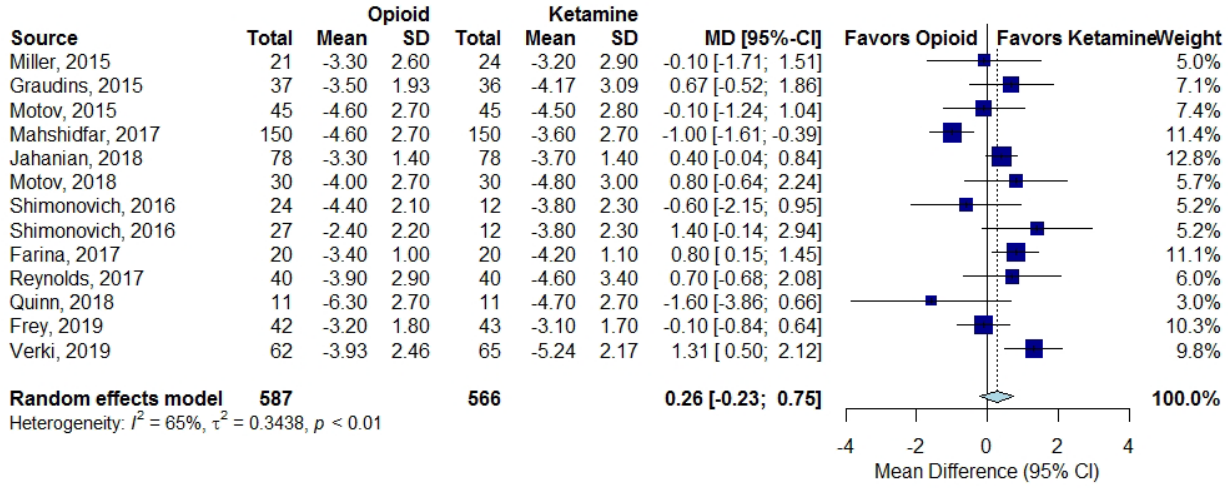
One observational study from the battlefield setting reported change in pain scores from 0 to 10 during the tactical evacuation period.[63] We did not consider battlefield data in formulating conclusion because the population and setting is too unlike the civilian population expected to access EMS services. This study found median (interquartile range) change in pain scores to be -3 (-5 to -1) with morphine, -3 (-4 to -2) with fentanyl, and -4 (-6 to -2) with ketamine in 144 subjects.

Figure 3. Change in pain scores at 15 minutes, opioids versus ketamine



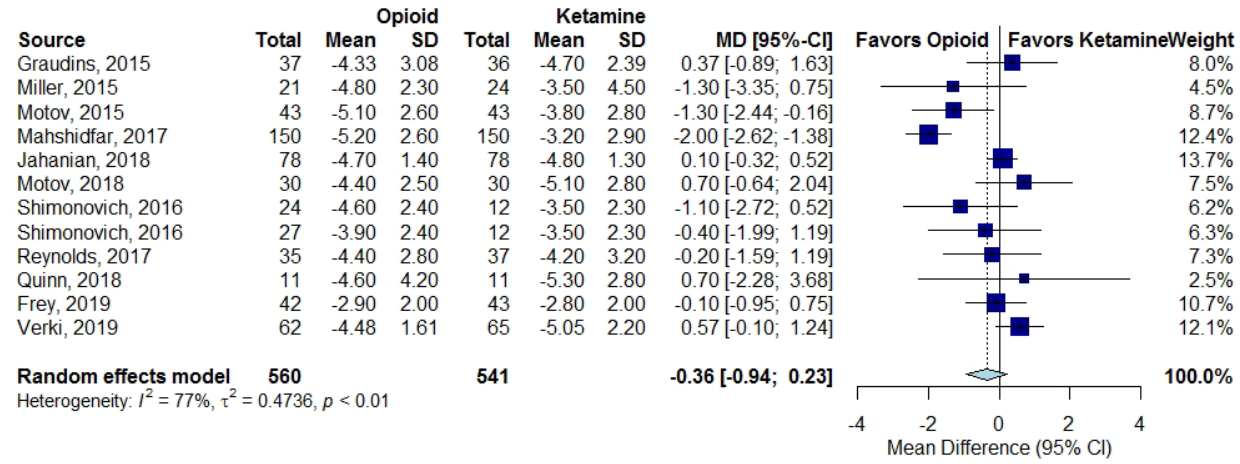
Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation

Figure 4. Change in pain scores at 30 minutes, opioids versus ketamine



Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation

Figure 5. Change in pain scores at 60 minutes, opioids versus ketamine



Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation

There was insufficient evidence to conclude comparative effectiveness of opioids versus ketamine for the outcome of pain presence, either partial or full resolution of pain. In addition to indirectness of the data, effect estimates were very imprecise and included the possibility of clinically important differences favoring either analgesic. The single study[61] from the EMS setting was observational and found more patients to achieve at least a 50 percent reduction in Numeric Rating Scale score with ketamine IV versus fentanyl IV (67 percent versus 19 percent, p=NR), after propensity score matching.

There was insufficient evidence to conclude comparative effectiveness of opioids versus ketamine on the time to analgesic effect. The single trial[53] for this outcome had a high risk of bias because of inadequate randomization and allocation procedures, lack of blinding and high differential attrition between the morphine and ketamine arms.

No studies reported measures of the memory of a pain episode.

Subgroups

Age

Age (<18 years old, ≥18 years old) did not appear to be associated with differing effects of opioids versus ketamine for the outcome of change in pain at 15, 30 or 60 minutes (Appendix Figures F-6 to F-8).

Type of Pain

We analyzed studies that included traumatic pain only. Change in pain scores at 15, 30 and 60 minutes were similar to the main conclusion that there is no evidence of a clinically important difference in change of pain scores between opioids and ketamine (Appendix Figures F-9 to F-11).

Location of Pain

We performed subgroup analysis by location of pain (extremity versus mixed/not reported). Location did not appear to be associated with differing effects of opioids versus ketamine for the outcome of change in pain at 15, 30 or 60 minutes (Appendix Figures F-12 to F-14).

Route of Analgesic Administration

We performed a subgroup analysis of RCTs according to route of administration of opioid versus ketamine (IN versus IN, IV versus IN and IV versus IV). These route combinations did not appear to be associated with differing effects of opioids versus ketamine for the outcome of change in pain in 15, 30 or 60 minutes (Appendix Figures F-15 to F-17).

One 3-arm RCT[53] was designed to route of morphine administration (IV vs IM) to ketamine IN. Time to onset was significantly faster with IN ketamine versus IM morphine (14.3 minutes [95 percent confidence interval 9.8 to 18.8) versus 26.0 minutes [20.3 to 31.7], p=0.003), but not compared to IV morphine [14.3 minutes [9.8 to 18.8] vs 8.9 minutes [6.6 to 11.2], p=0.30). Time to maximal pain reduction and proportion of non-responders did not differ statistically.

Frequency of Analgesic Administration

Regardless of whether studies were comparing a single dose of opioids versus a single dose of ketamine or multiple doses of opioids versus multiple doses of ketamine, changes in pain scores at 15, 30 or 60 minutes were similar between opioids and ketamine (Appendix Figures F-18 to F-20).

Combination of Opioid and Ketamine Versus Opioid

Key Messages

- Combining an opioid and ketamine may reduce pain more than an opioid alone in 15 and 30 minutes (low SOE) but there is no evidence of a clinically important difference at 60 minutes (low SOE). This is based mostly on indirect evidence from the ED setting comparing IV morphine and IV ketamine, where a single dose of ketamine was added to weight-based morphine.
- Evidence is insufficient for outcomes measuring pain presence or time to analgesic effect.

Detailed Results

We present the conclusions for the comparative effectiveness of the combination of an opioid and ketamine versus an opioid alone as initial analgesics in Table 10. The majority of this evidence base is indirect data from the ED setting and compares the combination of weight-based doses of morphine IV with a single weight-based dose of ketamine IV to weight-based morphine IV alone.

Table 10. Conclusions and strength of evidence for the comparison of combining an opioid and ketamine versus an opioid, Key Question 1

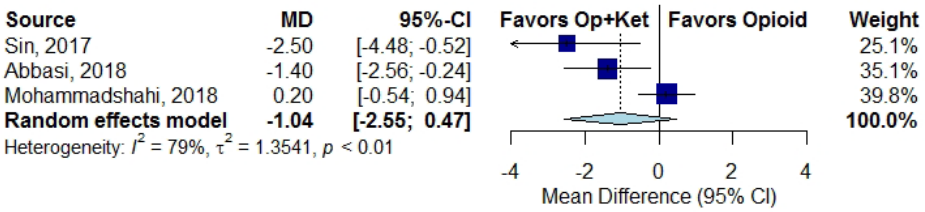
Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates and 95% Confidence Interval)	Strength of Evidence (Limitations)
Pain severity – 15 min	4 RCT[66,69,71,72] (n=336)	**Combining an opioid and ketamine may reduce pain more than an opioid alone at 15 min.** EMS: 1 RCT[66] found MD -1.3 (-2.6 to 0.02) at 15 min. ED: Meta-analysis of 3 RCT[69,71,72] found MD -1.04 (-2.55 to 0.47).	Low (Inconsistent, indirect, imprecise)
Pain severity –30 min	5 RCT[66,68,69,71,72] (n=545)	**Combining an opioid and ketamine may reduce pain more than an opioid alone at 30 min.** EMS: 1 RCT[66] 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[68,69,71,72] found MD -0.59 (-2.24 to 1.06).	Low (Inconsistent, indirect, imprecise)

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates and 95% Confidence Interval)	Strength of Evidence (Limitations)
Pain severity – 60 min	3 RCT[69,71,72] (n=241)	**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.** ED: Meta-analysis of 3 RCT found MD -0.07 (-1.14 to 1.00).	Low (Inconsistent, indirect)
Pain presence-partial resolution	1 RCT[66] (n=65) 1 OBS[67] (n=606)	**Inconclusive.** EMS: 1 RCT found partial response in 60.6% vs. 40.6% of patients, RD 20% (-4 to 41). 1 OBS study found the proportion of sufficient response was 69% vs. 70.9%, p=NR.	Insufficient (Inconsistent, imprecise)

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

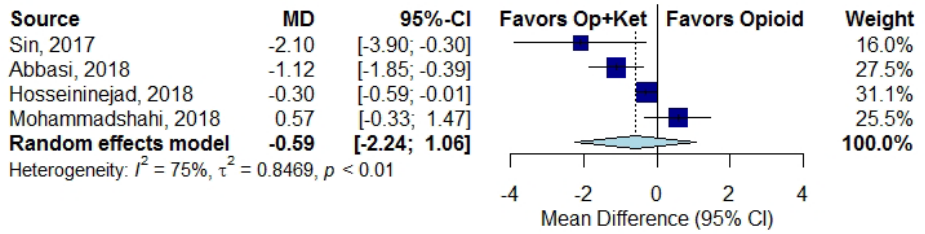
Combining an opioid and ketamine compared with an opioid alone may reduce pain more than opioids alone, at 15 and 30 minutes (low SOE) (Figure 6-Figure 7). The clinically important difference was 2 points on a 0 to 10 scale. Data from the single trial[66] in the EMS setting and from the meta-analyses of ED data agreed that a clinically important difference favoring the combination of analgesics was possible at both 15 and 30 minutes. At 60 minutes, there was no evidence of a clinically important difference between the combination of an opioid and ketamine and an opioid alone in the change in pain scores, based entirely in indirect evidence from the ED (low SOE) (Figure 8).

Figure 6. Change in pain scores at 15 minutes, combination of an opioid and ketamine versus opioid



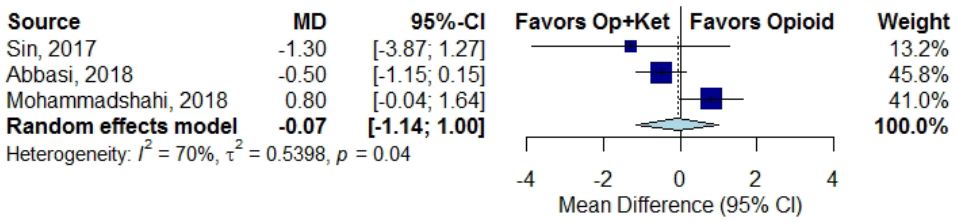
Abbreviations: CI=confidence interval; MD=mean difference; Op+Ket= opioid plus ketamine

Figure 7. Change in pain scores at 30 minutes, combination of an opioid and ketamine versus opioid



Abbreviations: CI=confidence interval; MD=mean difference; Op+Ket= opioid plus ketamine

Figure 8. Change in pain scores at 60 minutes, combination of an opioid and ketamine versus opioid



Abbreviations: CI=confidence interval; MD=mean difference; Op+Ket= opioid plus ketamine

There is insufficient evidence to conclude the comparative effectiveness of combined opioid and ketamine versus opioid alone for the outcome of partial resolution of pain. Trial[66] and observational study data[67] were inconsistent and results from the trial did not exclude the possibility of no difference or a difference favoring the opioid alone. The 3-arm study by Beaudoin et al. was not pooled with others or considered in the conclusions made because 80 percent of the population enrolled had previously failed an analgesic; thus, this study was not answering comparative effectiveness of initial analgesia.[70] The study used a summed pain-intensity difference (SPID) over 2 hours to measure changes in pain scores and the proportion achieving a SPID reduction of 33 percent or more were considered responders. There were more responders in the combination arm (morphine+ketamine 0.15mg/kg versus morphine alone, 50 percent versus 25 percent p=0.19; morphine+ketamine 0.3mg/kg versus morphine alone, 70 percent versus 25 percent, p=0.01).

No studies reported time to analgesic effect (insufficient SOE) or measures of the memory of pain.

Subgroups

Analgesic Dose

One RCT[70] included 3 arms to compare two different doses of ketamine (0.15mg/kg or 0.3mg/kg) when added to morphine (0.1mg/kg), versus morphine 0.1mg/kg alone. The proportion achieving a SPID reduction of 33 percent or more were considered responders. The difference between the ketamine groups was not significant (50 percent versus 70 percent, p=0.33).

Opioids Versus Acetaminophen

Key Messages

- There is no evidence of a clinically important difference between IV opioids and IV APAP in the change of pain scores in 15, 30 or 60 minutes (low SOE), or in the time to analgesic effect (low SOE).
- These conclusions are based on indirect evidence from the ED setting comparing weight-based doses of morphine IV with fixed doses of APAP IV.

Detailed Results

We present the conclusions of the comparative effectiveness of opioids versus APAP in Table 11. This evidence base is entirely indirect from the ED setting and compares morphine IV to APAP IV.

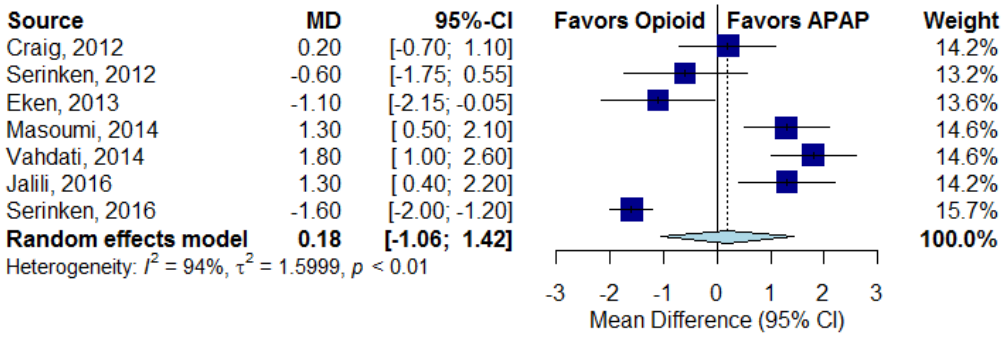
Table 11. Conclusions and strength of evidence for the comparison of opioids versus acetaminophen, Key Question 1

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates and 95% Confidence Intervals)	Strength of Evidence (Limitations)
Pain severity – 15 min	7 RCT[73,74,76-79,82] (n=647)	**There is no evidence of a clinically important difference between IV opioids and IV APAP in the change of pain scores in 15 min.** ED: Meta-analysis of 7 RCTs found MD 0.18 (-1.06 to 1.42).	Low (Inconsistent, indirect)
Pain severity – 30 min	9 RCT[73-79,81,82] (n=1795)	**There is no evidence of a clinically important difference between IV opioids and IV APAP in the change of pain scores in 30 min.** ED: Meta-analysis of 9 RCTs found MD 0.30 (-0.84 to 1.44).	Low (Inconsistent, indirect)
Pain severity – 60 min	3 RCT[75,79,82] (n=1260)	**There is no evidence of a clinically important difference between IV opioids and IV APAP in the change of pain scores in 60 min.** ED: Meta-analysis of 3 RCT found MD 0.40 (-1.01 to 1.81).	Low (Inconsistent, indirect)
Pain presence-partial resolution - 30 min	1 RCT[75] (n=996)	**Inconclusive.** ED: 1 RCT found a partial response in 81.8% vs. 78.1% of patients, RD -4% (-8 to 1)	Insufficient (Unknown consistency, indirect, imprecise)
Time to analgesic effect	1 RCT[75] (n=1097)	**There is no evidence of a clinically important difference in the time to analgesia with IV opioids compared with IV APAP.** ED: Median time to NRS<2 was 60 min in both arms, IQR 30 to 90 min.	Low (Unknown consistency, indirect)

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

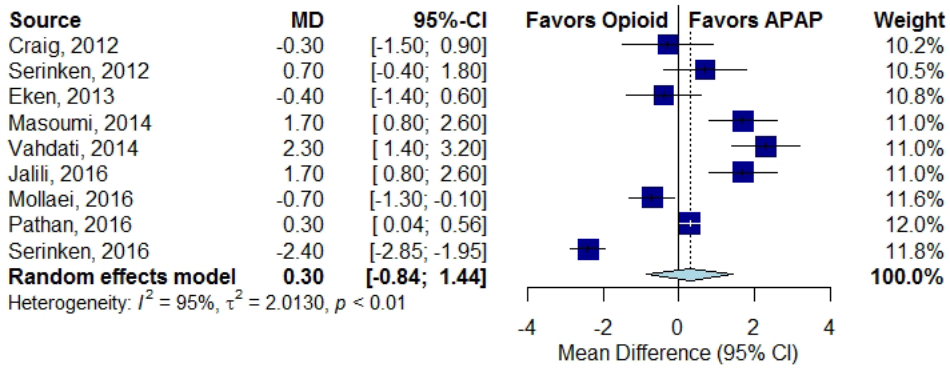
There is no evidence of a clinically important difference in the reduction of pain scores when IV opioids are compared to IV APAP at 15, 30 and 60 minutes (all low SOE) (Figure 9-Figure 11). These conclusions are each based on meta-analysis of the change in pain scores using indirect evidence from the ED setting and a clinically important difference of 2 points on a 0 to 10 scale.

Figure 9. Change in pain scores at 15 minutes, opioids versus acetaminophen



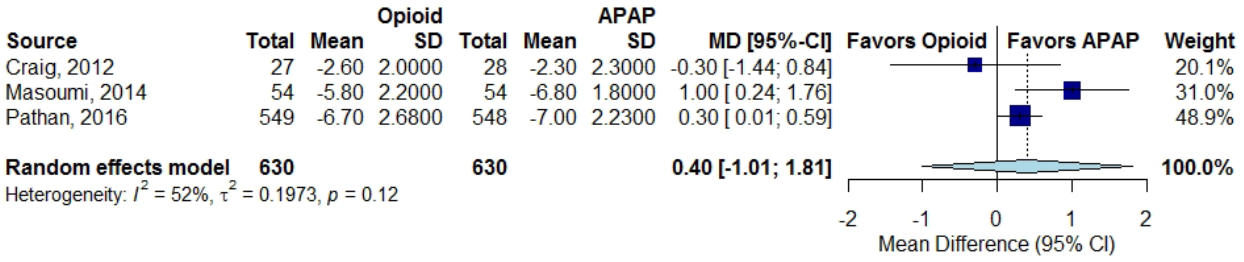
Abbreviations: CI=confidence interval; MD=mean difference

Figure 10. Change in pain scores at 30 minutes, opioids versus acetaminophen



Abbreviations: CI=confidence interval; MD=mean difference

Figure 11. Change in pain scores at 60 minutes, opioids versus acetaminophen



Abbreviations: CI=confidence interval; MD=mean difference

There is insufficient evidence to conclude the comparative effectiveness IV opioids versus IV APAP on the outcome of partial responders at 30 minutes. One RCT found more patients achieved a reduction of 3 or more on the NRS with IV APAP versus IV opioids at 30 minutes.[75] The confidence interval did not exclude the possibility of a clinically important difference of 5 percent in favor of opioids; thus, this estimate was imprecise as well as indirect. We were unable to judge consistency with only one study and given additional downgraded domains, SOE was judged to be insufficient.

There is no evidence of a clinically important difference in the time to analgesia with IV opioids compared with IV APAP (low SOE). One trial[75] reported the median time to NRS less than 2, as 60 minutes (IQR 30 to 90 min) in both arms, suggesting no difference between these analgesics. We were unable to judge consistency with only one study and data were also indirect.

No studies reported measures of the memory of pain.

Subgroups

Type of Pain

We analyzed studies that included traumatic pain only. Change in pain scores at 15 and 30 minutes were similar to the main conclusion that there is no evidence of a clinically important difference in change of pain scores between IV opioids and IV APAP (Appendix Figures F-21 and F-22).

Opioids Versus Nitrous Oxide

Key Messages

- Evidence is insufficient for the comparison of IV opioids with inhaled nitrous oxide, for outcomes measuring pain severity. No studies reported pain presence or time to analgesic effect.

Detailed Results

We present the conclusions of the comparative effectiveness of opioids versus nitrous oxide in Table 12. This evidence base included a single trial from the EMS setting comparing morphine IV with self-administered nitrous oxide/oxygen (50:50).[83] This study had a medium risk of bias as it was open-label and we were unable to determine consistency without another study. Thus, evidence is insufficient to make conclusions regarding this comparison. No studies reported presence of pain or time to analgesic effect (insufficient SOE).

Table 12. Conclusions and strength of evidence for the comparison of opioids versus nitrous oxide, Key Question 1

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates and 95% Confidence Intervals)	Strength of Evidence (Limitations)
Pain severity – 15 min	1 RCT[83] (n=100)	**Inconclusive.** EMS: 1 RCT found MD 0.8 (0.0 to 1.6)	Insufficient (Medium study limitations, unknown consistency)
Pain severity – 60 min	1 RCT[83] (n=100)	**Inconclusive.** EMS: 1 RCT found MD 0.1 (-0.6 to 0.8)	Insufficient (Medium study limitations, unknown consistency)

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

Opioids Versus Nonsteroidal Anti-Inflammatory Drugs

Key Messages

- There is no evidence of a clinically important difference between opioids and NSAIDs administered IV and orally, in the change of pain scores in 30 or 60 minutes (moderate SOE).
- Evidence is insufficient for outcomes measuring pain severity at 15 minutes, partial or full resolution of pain, and time to analgesic effect.

Detailed Results

We present the conclusions of the comparative effectiveness of opioids versus NSAIDs in Table 13. This evidence base was entirely indirect evidence from the ED setting. Morphine IV was compared with ketorolac IV in two studies and oral morphine was compared to oral ibuprofen in one study.

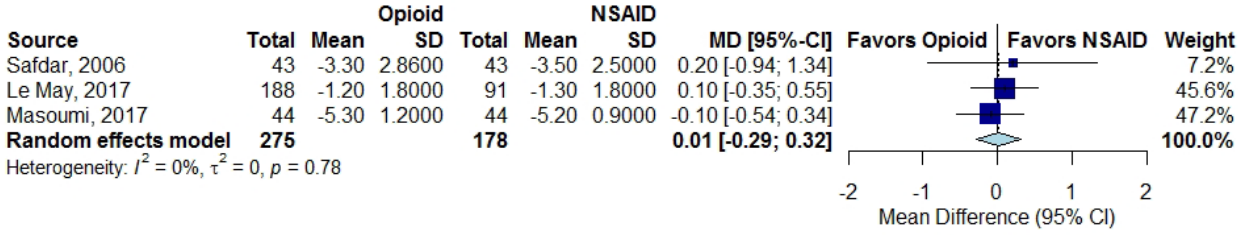
Table 13. Conclusions and strength of evidence for the comparison of opioids versus nonsteroidal anti-inflammatory drugs, Key Question 1

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates and 95% Confidence Intervals)	Strength of Evidence (Limitations)
Pain severity – 15 min	1 RCT[84] (n=88)	**Inconclusive.** ED: 1 RCT found MD 0.2 (-0.4 to 0.8)	Insufficient (Medium study limitations, unknown consistency, indirect)
Pain severity – 30 min	3 RCT[84-86] (n=453)	**There is no evidence of a clinically important difference between opioids and NSAIDs in the change of pain scores in 30 min.** ED: Meta-analysis of 3 RCT found MD 0.01 (-0.29 to 0.32)	Moderate (Indirect)
Pain severity – 60 min	3 RCT[84-86] (n=453)	**There is no evidence of a clinically important difference between opioids and NSAIDs in the change of pain scores in 60 min.** ED: Meta-analysis of 3 RCT found MD 0.21 (-0.10 to 0.51)	Moderate (Indirect)
Pain presence-partial resolution - 30 min	1 RCT[86] (n=227)	**Inconclusive.** ED: 1 RCT found partial response in 20.7% vs. 19.8%, RD 1% (-10 to 10)	Insufficient (Unknown consistency, indirect, very imprecise)
Pain presence-partial resolution - 60 min	1 RCT[86] (n=243)	**Inconclusive.** ED: 1 RCT found partial response in 29.3% vs. 33.0%, RD -4% (-16 to 7)	Insufficient (Unknown consistency, indirect, very imprecise)
Pain presence-full resolution - 30 min	1 RCT[85] (n=86)	**Inconclusive.** ED: 1 RCT found 16.3% vs. 11.6%, RD 5% (-11 to 20)	Insufficient (Unknown consistency, indirect, very imprecise)

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

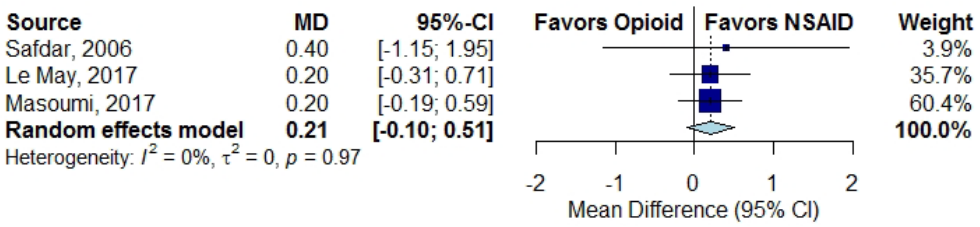
There is no evidence of a clinically important difference in the reduction of pain scores when opioids are compared with NSAIDs at 30 and 60 minutes (all moderate SOE) (Figure 12-Figure 13). These conclusions are each based on meta-analysis of the change in pain scores using indirect evidence from the ED setting and a clinically important difference of 2 points on a 0 to 10 scale. Evidence is insufficient to conclude effects at 15 minutes. The single trial[84] reporting 15 minutes data had a medium risk of bias due to inadequate randomization and allocation concealment procedures, we were unable to judge consistency with only 1 study, and data were indirect from the ED setting.

Figure 12. Change in pain scores at 30 minutes, opioids versus nonsteroidal anti-inflammatory drugs



Abbreviations: CI=confidence interval; MD=mean difference; NSAID=nonsteroidal anti-inflammatory drug; SD=standard deviation

Figure 13. Change in pain scores at 60 minutes, opioids versus nonsteroidal anti-inflammatory drugs



Abbreviations: CI=confidence interval; MD=mean difference; NSAID=nonsteroidal anti-inflammatory drug; SD=standard deviation

Evidence is insufficient to conclude comparative effectiveness of opioids versus NSAIDs on the outcomes of partial or full response because of very imprecise estimates that included a clinically important difference in favor of either analgesic.

No studies reported time to analgesic effects (insufficient SOE) or measures of memory of pain.

Acetaminophen Versus Nonsteroidal Anti-Inflammatory Drugs

We present results from studies that compared APAP versus NSAIDs in Table 14. This evidence base was entirely indirect evidence from the ED setting. One trial found pain to decrease less with APAP versus NSAIDs at 15 minutes. Otherwise, findings did not favor either analgesic significantly. No studies reported time to analgesic effect or memory of pain.

Table 14. Findings for the comparison of acetaminophen with nonsteroidal anti-inflammatory drugs, Key Question 1

Outcome	Study Design and Sample Size	Findings (Setting: Effect estimates and 95% Confidence Interval)
Pain severity – 15 min	1 RCT[87] (n=199)	ED: MD 1.0 (0.5 to 1.4), p=0.000
Pain severity – 30 min	3 RCT[87-89] (n=542)	ED: Meta-analysis of 3 RCTs MD 0.63 (-0.62 to 1.88)
Pain severity - 60 min	2 RCT[88-89] (n=340)	ED: Meta-analysis of 2 RCTs MD 0.53 (-0.87 to 1.92)
Pain presence – partial resolution 30 min	1 RCT[88] (n=92)	ED: AR 31.4% vs. 30.0%; RD 1% (-14 to 16)
Pain presence – partial resolution 60 min	2 RCT[88,89] (n=340)	ED: Meta-analysis of 2 RCTs, AR 44.7% vs. 52.4%; RD -6% (-26 to 13)

Abbreviations: AR=absolute risk; ED=emergency department; MD=mean difference; RCT=randomized controlled trial; RD=risk difference

Ketamine Versus Nonsteroidal Anti-Inflammatory Drugs

We present results from a single trial that compared ketamine versus NSAIDs (ketorolac) in Table 15. The evidence base is indirect from the ED setting. Findings did not suggest a statistically significant difference in favor of either analgesic at 15 or 60 mins, but at 30 minutes the change in pain score was greater in subjects randomized to ketorolac. No studies reported presence of pain, time to analgesic effect or memory of pain.

Table 15. Findings for the comparison of ketamine with nonsteroidal anti-inflammatory drugs, Key Question 1

Outcome	Study Design and Sample Size	Findings (Setting: Effect estimates and 95% Confidence Intervals)
Pain severity – 15 min	1 RCT (n=126)[90]	ED: 1 RCT MD 0.2 (-0.8 to 1.2)
Pain severity – 30 min	1 RCT (n=126)[90]	ED: 1 RCT MD 1.3 (0.4 to 2.2)
Pain severity - 60 min	1 RCT (n=126)[90]	ED: 1 RCT MD 0.7 (-0.1 to 1.5)

Abbreviations: ED=emergency department; MD=mean difference; RCT=randomized controlled trial

Morphine Versus Fentanyl

We present results from RCTs that compared morphine versus fentanyl in Table 16 followed by a summary of findings from observational studies. Three trials are in the EMS setting[93-95] and 5 trials[19-21,91,97] are from the ED setting. Findings from the RCTs are not significant in favor of either analgesic (Table 16).

Table 16. Findings for the comparison of morphine versus fentanyl, Key Question 1

Outcome	Study Design and Sample Size	Findings (Setting: Effect estimates and 95% Confidence Intervals)
Pain severity – 15 min	6 RCT[19-21,91,93,97] (n=622) 1 OBS[102] (n=612)	EMS: 1 RCT[93] MD 0.5 (-0.7 to 1.7), 1 OBS see text[102] ED: Meta-analysis of 5 RCTs[19-21,91,97] MD 0.25 (-0.19 to 0.69)
Pain severity – 30 min	8 RCT[19-21,91,93-95,97] (n=1049)	EMS: Meta-analysis of 3 RCTs[93-95] MD -0.17 (-1.49 to 1.15) ED: Meta-analysis of 5 RCTs[19-21,91,97] MD 0.64 (-0.51 to 1.78)
Pain severity - 60 min	3 RCT[19,20,91] (n=429) 3 OBS[98,103,104] (n=1036)	EMS: 3 OBS see text[98,103,104] ED: Meta-analysis of 3 RCTs[19,20,91] MD 1.10 (-2.43 to 4.64)
Pain presence – partial resolution 15 min	1 RCT[93] (n=54) 1 OBS[102] (n=612)	EMS: 1 RCT[93] AR 30.8% vs. 39.3%; RD -9% (-32 to 16), 1 OBS see text[102]
Pain presence – partial resolution 30 min	2 RCT[93,94] (n=163)	EMS: Meta-analysis of 2 RCTs AR 62% vs. 66.4%; RD -4% (-18 to 10)
Time to analgesic effect	3 OBS[100,101,103] (n=419)	EMS: 1 OBS see text[98] ED: 2 OBS see text[95,96]

Abbreviations: AR=absolute risk; ED=emergency department; EMS=emergency medical services; MD=mean difference; OBS=observational; RCT=randomized controlled trial; RD=risk difference

Eight observational studies[63,98,100-105] compared efficacy of morphine with fentanyl. Four studies are in the EMS setting. Bendall et al.[102] found no difference in reduction of pain scores between morphine [median 5 (IQR 4 to 7)] and fentanyl [median 5 (IQR 3 to 7), p=not reported, stated no difference] or in the adjusted odds of a ≥30 percent reduction in pain score comparing morphine to fentanyl [adjust odds ratio 0.85 (95 percent confidence interval 0.50 to 1.35]. Fleischman et al.[104] found no difference in the adjusted change in pain scores on a 0 to 10 scale comparing morphine with fentanyl [0.23 points (-0.24 to 0.71)]. Sharnow et al.[98] found no significant difference in the decrease of pain scores between morphine and fentanyl (baseline and final mean scores, respectively, morphine 7.6 to 3.4, fentanyl 8 to 3.3). Garrick et al.[103] found the average decrease in pain score was greater with fentanyl (3.62 points) versus morphine (2 points, p=NR) and that pain relief was more rapid with fentanyl based on the percent of subjects reporting pain relief within 1 minute (16.6 percent versus 2.0 percent), 1-2 minutes (47.0 percent versus 14.0 percent), 2-3 minutes (19.9 percent versus 36.0 percent) and more than 3 minutes (16.6 percent versus 48 percent), p=NR.

Three studies were in the ED setting. Schacherer et al.[100] reported nonsignificant findings for the number of patients with a pain score decrease by at least 2 point within 20 minutes of drug administration (morphine 14 percent versus fentanyl 26 percent, p=0.45), the number of patients with a pain score decrease to 0 (morphine 45 percent versus 43 percent, p=0.89) or for time to analgesic effect [morphine median 48 (IQR 20 to 65) versus fentanyl median 38 (IQR 15 to 100), p=0.99]. Wenderoth et al.[101] reported a nonsignificant difference in reduction of pain scores [morphine median -2 (IQR 1 to 4) versus fentanyl median -2 (IQR 1 to 4), p=0.76] but found a

significant difference in the time to lowest pain score favoring fentanyl [morphine median 47 minutes (IQR 25 to 57) versus fentanyl median 22 minutes (IQR 12 to 34), p<0.001]. Griffioen et al. reported the percent improvement in pain scores from pre- to post-analgesia administration to be 35 percent for fentanyl users versus 32 percent for morphine users, a finding stated to be not statistically significant (p=NR).[105]

One study was in the battlefield setting and reported change in pain scores from 0 to 10 during the tactical evacuation period.[63] The median (interquartile range) change in pain scores were -3 (-5 to -1) with morphine and -3 (-4 to -2) with fentanyl.

KQ 2. What are the comparative harms of analgesic agents when administered by EMS personnel to control moderate-to-severe pain in the prehospital setting?

KQ 2a. How do harms vary by patient characteristics?

KQ 2b. How do harms vary by routes of administration, dosing, and timing?

KQ 2c. What are the comparative harms to EMS personnel who administer analgesics to patients for the control of moderate-to-severe pain in the prehospital setting?

Opioids Versus Ketamine

Key Messages

- Opioids may cause fewer total adverse events than ketamine (low SOE), primarily administered IN. Differences in adverse events may be associated with age, route, or type of pain.
- Opioids cause less dizziness than ketamine (low SOE), primarily administered IV. Differences in dizziness may be associated with age or route.
- Opioids may cause more respiratory depression than ketamine (low SOE), primarily administered IV.
- Evidence is insufficient for the outcome of hypotension and measures of mental status changes other than dizziness.
- Results from outcomes that were not graded for SOE suggest opioids lead to statistically lower values for heart rate, respiratory rate and systolic blood pressure compared with ketamine in 15 minutes; statistically lower systolic blood pressure versus ketamine in 30 minutes; statistically greater nausea/vomiting versus ketamine, administered primarily IV. Clinical relevance of these results is uncertain.

Detailed Results

We present the conclusions for the comparative harms of opioids versus ketamine as initial analgesics in Table 17. The majority of this evidence base is indirect data from the ED setting and compares weight-based doses of morphine IV or fentanyl IN with weight-based doses of ketamine IV or IN.

Table 17. Conclusions and strength of evidence for the comparison of opioids versus ketamine, Key Question 2

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates and 95% Confidence Intervals)	Strength of Evidence (Limitations)
Any adverse event	8 RCTs[17,29,30,52,54,55,57,58] (n=398)	**Opioids may cause fewer total adverse events than ketamine.** ED: Meta-analysis of 6 RCTs[17,29,30,52,54,58] over the study period found AR 50.0% vs. 82.4%; RD -30% (-56 to -4). Two RCTs[55,57] reported AEs at 15 and at 30 min are generally in agreement.	Low (Inconsistent, indirect, imprecise)
Hypotension	4 RCTs[17,29,54,56] (n=508)	**Inconclusive.** ED: Meta-analysis of 4 RCTs over the study period found AR 3.6% vs. 0%; RD 8% (-20 to 37)	Insufficient (Inconsistent, indirect, very imprecise)
Mental status changes - dizziness	9 RCTs[29,30,52,53-58] (n=723)	**Opioids cause less dizziness than ketamine.** ED: Meta-analysis of 7 RCTs[29,30,52-54,56,58] over the study period found AR 25.4% vs. 43.5%; RD -29% (-52 to -6). Two RCTs[55,57] reported dizziness at 15 and 30 min and are generally in agreement.	Low (Inconsistent, indirect)
Mental status changes - drowsiness	4 RCTs[29,30,58,60] (n=356)	**Inconclusive.** ED: Meta-analysis of 4 RCTs over the study period found AR 8.5% vs. 11.2%; RD -2% (-19 to 15)	Insufficient (Indirect, very imprecise)
Mental status changes - GCS	1 OBS[61] (n=158)	**Inconclusive.** EMS: One OBS study found no difference in change in GCS score 0.03 (0.4) vs. -0.1 (0.8), p=0.16	Insufficient (Unknown consistency, imprecise)
Mental status changes - sedation	2 RCT[30,52] (n=95)	**Inconclusive.** ED: 1 RCT found sedation over the study period in 18.2% vs. 63.6% of patients, RD -45% (-70 to -5). A second trial found sedation scores to be similar between groups.	Insufficient (Inconsistent, indirect, imprecise)
Mental status changes - confusion	1 RCT[53] (n=75)	**Inconclusive.** ED: One 3-arm trial found confusion over the study period in 33.3% vs. 50% of patients; morphine IV RD -38% (-58 to -11), morphine IM RD -31% (-53 to -5)	Insufficient (High ROB, unknown consistency, indirect)
Mental status changes - difficulty concentrating	1 RCT[53] (n=75)	**Inconclusive.** ED: One 3-arm trial found difficulty concentrating over the study period in 21.6% vs. 58.3% of patients; morphine IV RD -38% (-58 to -10); morphine IM RD -36% (-57 to -9)	Insufficient (High ROB, unknown consistency, indirect)
Mental status changes - sleepiness/tired	1 RCT[29] (n=82)	**Inconclusive.** ED: 1 RCT found sleepiness/tired to occur in 36.6% vs. 46.3% of patients, RD -2% (-22 to 18)	Insufficient (Unknown consistency, indirect, very imprecise)
Mental status changes - RASS	1 RCT[58] (n=36)	**Inconclusive.** ED: 1 RCT evaluated RASS scores at various times throughout the trial and found no significant differences between groups. Median scores were 0 in both arms at all evaluated times.	Insufficient (unknown consistency, indirect, imprecise)
Respiratory depression	4 RCTs[17,55,56,58] (n=491) 1 OBS[61] (n=158)	**Opioids may cause more respiratory depression than ketamine.** EMS: One OBS study[61] 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[17,55,56,58] 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; GCS=Glasgow Comas Scale; IM=intramuscular; IV=intravenous; MD=mean difference; min=minutes; OBS=observational; RASS=Richmond Agitations Sedation Scale; RCT=randomized controlled trial; RD=risk difference

Opioids may cause fewer total adverse events than ketamine (low SOE). This conclusion is based on meta-analysis of indirect data from the ED setting and using the clinically important differences of 10 percent. The confidence interval included possibility of a difference less than clinically important; thus, this estimate is imprecise. Two trials by Motov et al.[55,57] reported adverse events at 15 and 30 minutes and were not pooled with the other studies that reported adverse events over the study period. Risk differences for any adverse event at 15 and 30 minutes, using these two trials, were -39 percent (-53 to -24) and -19 percent (-53 to 15), respectively, and were considered to be in agreement with the overall analysis.

Opioids cause less dizziness than ketamine (low SOE). This conclusion is based on meta-analysis of indirect data from the ED setting and using the clinically important differences of 5 percent. Two trials by Motov et al.[55,57] reported dizziness at 15 and 30 minutes and were not pooled with the other studies that reported dizziness over the study period. Risk differences for dizziness at 15 and 30 minutes, using these two trials, were -25 percent (-40 to -10) and -20 percent (-63 to 23), respectively, and were considered to be in agreement with the overall analysis.

Opioids may cause more respiratory depression than ketamine (low SOE). One observational study[61] from the EMS setting reported 2 versus 0 cases of respiratory depression in morphine versus ketamine treated subjects, both of which required oxygen supplementation. Data were considered insufficient to conclude comparative harms. Thus we considered meta-analysis of indirect data from the ED setting. Results did not rule out the possibility of a clinically important difference of respiratory depression, in favor of ketamine.

Evidence is insufficient for the outcomes of hypotension and other measures of mental status changes. One observational study[62] from the battlefield setting was not considered in the conclusion of mental status changes because the population and setting were too unlike civilians expected to access EMS. This study reported Glasgow Coma Scale scores at (median, IQR) at the point of hospital admission for morphine (15, 15 to 15), fentanyl (15, 14 to 15) and ketamine (15, 10 to 15).

Subgroups

Age

We performed a subgroup analysis of RCTs according to age (≥18 years, <18 years). The comparative difference in dizziness between morphine and ketamine may be associated with age (Appendix Figure F-40). A greater difference in dizziness, favoring opioids, was found in subjects less than 18 years of age compared to 18 years of age and older [<18 years: risk difference (RD) -53 percent (-72 to -33); ≥18 years of age RD -15 percent (-47 to 17). However, the 3 RCTs in the <18 years group are also the same 3 RCTs that represent the IN route subgroup so it is unclear if age, route or both are potential modifiers of effect.

Age (≥18 years, <18 years) did not appear to be associated with differing effects of opioids versus ketamine for the outcome of hypotension (Appendix Figure F-41).

Type of Pain

We analyzed studies that included traumatic pain only. These results were in agreement with the main conclusions for the outcomes of dizziness, drowsiness, hypotension and respiratory

depression (Appendix Figures F-42 to F-45). The analysis for any adverse event suggests that in traumatic pain, the difference between opioids and ketamine was greater than in the main analysis, favoring opioids (Main analysis RD -30 percent [-56 to -4], traumatic pain only RD -41 percent [-52 to -30] (Appendix Figure F-46).

Location of Pain

We performed subgroup analysis by location of pain (extremity versus mixed/not reported). Location did not appear to be associated with differing effects of opioids versus ketamine for the outcome of any adverse event, dizziness, or respiratory depression (Appendix Figures F-47 to F-49).

One RCT in the EMS setting reported the level of consciousness in a subset of head trauma patients to be similar before and after analgesia with opioids versus ketamine (96.4 percent versus 89.7 percent, p=NR).

Route

We performed a subgroup analysis of RCTs according to route of administration of opioid versus ketamine (IN versus IN, IV versus IN and IV versus IV). The comparative difference in dizziness between opioids and ketamine may be associated with route (Appendix Figure F-50). The difference in dizziness was more pronounced for the IN route, favoring opioids, (RD -53 percent [-65 to -41]) compared to the two other route combinations (IV versus IN: RD -9 [-47 to 29] and IV versus IV: RD -3 [-11 to 6]). However, the 3 RCTs in the IN vs IN group are also the same 3 RCTs that represent subjects <18 years of age so it is unclear if age, route or both are potential modifiers of effect.

One 3-arm RCT[53] was designed to route of morphine administration (IV vs IM) to ketamine IN. Dizziness was more frequent with IN ketamine versus IM morphine (79.2 percent versus 22.2 percent, p<0.000) but not compared with IV morphine (79.2 percent versus 50 percent, p=0.092). Confusion was more frequent with IN ketamine versus IV morphine (50 percent versus 12.5 percent, p=0.027) but not compared with IM morphine (50 percent versus 18.5 percent, p=0.061). Difficulty concentrating was more frequent with ketamine IN compared to both IV morphine (58.3 percent versus 20.8 percent, p=0.034) and IM morphine (58.3 percent versus 22.2 percent, p=0.027).

Frequency of Analgesic Administration

Regardless of whether studies were comparing a single dose of opioids versus a single dose of ketamine or multiple doses of opioids versus multiple doses of ketamine, frequency of dizziness (Appendix Figure F-51) or risk of having an adverse event (Appendix Figure F-52) was similar to the main conclusion.

Additional Findings

Additional findings for outcomes that are not graded with strength of evidence are in Table 18. Based on indirect data from the ED setting, vital sign changes at 15 minutes suggest statistically significant differences, including a lower heart rate with opioids versus ketamine [mean difference (MD) -3.08 (-5.23 to -0.92)], a lower respiratory rate with opioids versus ketamine [MD -1.88 (-2.39 to -1.38)] and a lower systolic blood pressure with opioids versus ketamine [MD -8.26 (-16.22 to -0.31)]. The change in systolic blood pressure in 30 minutes was also significant, with a lower value in opioids versus ketamine [MD -6.26 (-11.28 to -1.23)]. One

RCT from the EMS setting found a significantly higher number of patients experiencing nausea and/or vomiting with opioids versus ketamine [RD 15 percent (8 to 22)].

Table 18. Findings for the comparison of opioids versus ketamine, Key Question 2

Outcome	Study Design and Sample Size	Findings (Setting: Effect Estimates and 95% Confidence Intervals)
Diastolic blood pressure – 15 min	3 RCT[17,57,60] (n=221)	ED: Meta-analysis of 3 RCT MD -4.24 (-12.56 to 4.08)
Diastolic blood pressure – 30 min	3 RCT[17,57,59] (n=221)	ED: Meta-analysis of 3 RCT MD -0.30 (-4.76 to 4.16)
Diastolic blood pressure – 60 min	2 RCT[17,58] (n=131) 1 OBS[61] (n=158)	EMS: 1 OBS[61] mean (SD): -2.6 (14.7) vs. -1.6 (15.0), p=0.73 ED: Meta-analysis of 2 RCT[17,58] MD 4.57 (-0.29 to 9.43)
Dissociation – 15 min	1 RCT[17] (n=86)	ED: 1 RCT AR 0% vs. 2.3%; RD -2% (-12 to 7)
Dissociation – study duration	3 RCT[17,29,58] (n=213)	ED: Meta-analysis of 3 RCT AR 0% vs. 0.9%; RD -1% (-4 to 3)
Emergence delirium	4 RCT[30,54,58,59] (n=287)	ED: Meta-analysis of 4 RCT AR 0% vs. 8.4%; RD -7% (-27 to 12)
Heart rate – 15 min	3 RCT[17,57,58] (n=221)	ED: Meta-analysis of 3 RCT MD -3.08 (-5.23 to -0.92)
Heart rate – 30 min	3 RCT[17,57,58] (n=221)	ED: Meta-analysis of 3 RCT MD 0.65 (-3.80 to 5.10)
Heart rate – 60 min	2 RCT[17,58] (n=131) 1 OBS[61] (n=158)	EMS: 1 OBS mean (SD) -5.7 (16.0) vs. -3.0 (16.0), p=0.26 ED: Meta-analysis of 2 RCT MD -0.06 (-5.24 to 5.12)
Nausea – 15 min	2 RCT[55,57] (n=150)	ED: Meta-analysis of 2 RCT AR 8% vs. 16%; RD -8% (-18 to 2)
Nausea – 30 min	2 RCT[55,57] (n=150)	ED: Meta-analysis of 2 RCT AR 14.7% vs. 10.7%; RD 3% (-7 to 12)
Nausea – 60 min	1 RCT[55] (n=60)	ED: 1 RCT AR 6.7% vs. 20%; RD -13% (-31 to 5)
Nausea – study period	5 RCT[29,30,54,56,58] (n=540)	ED: Meta-analysis of 5 RCT AR 14.1% vs. 16.2%; RD -2% (-9 to 5)
Nausea and/or vomiting	3 RCT[17,27,60] (n=527)	EMS: 1 RCT[27] AR 19.4% vs. 4.7%; RD 15% (8 to 22) ED: 2 RCTs[17,60] found no difference; RD 3 (-9 to 16) and 4 (-7 to 15)
Oxygen saturation – 15 min	3 RCT[17,57,58] (n=221)	ED: Meta-analysis of 3 RCT MD -0.19 (-0.48 to 0.11)
Oxygen saturation – 30 min	3 RCT[17,57,58] (n=221)	ED: Meta-analysis of 3 RCT MD 0.08 (-0.21 to 0.37)
Oxygen saturation – 60 min	2 RCT[17,58] (n=131)	ED: Meta-analysis of 2 RCT MD 0.18 (-0.16 to 0.52)
Respiratory rate – 15 min	3 RCT[17,57,58] (n=221)	ED: Meta-analysis of 3 RCT MD -1.88 (-2.39 to -1.38)
Respiratory rate – 30 min	3 RCT[17,57,58] (n=221)	ED: Meta-analysis of 3 RCT MD -1.52 (-4.13 to 1.08)
Respiratory rate – 60 min	2 RCT[17,58] (n=131) 1 OBS[61] (n=158)	EMS: 1 OBS[61] mean (SD) -0.9 (2.8) vs. -1.8 (4.3), p=0.13 ED: Meta-analysis of 2 RCT[17,58] MD -1.97 (-4.21 to 0.27)
Systolic blood pressure – 15 min	3 RCT[17,57,58] (n=221)	ED: Meta-analysis of 3 RCT MD -8.26 (-16.22 to -0.31)
Systolic blood pressure – 30 min	3 RCT[17,57,58] (n=221)	ED: Meta-analysis of 3 RCT MD -6.26 (-11.28 to -1.23)
Systolic blood pressure – 60 min	2 RCT[17,58] (n=131) 1 OBS[61] (n=158)	EMS: 1 OBS[61] mean (SD) -3.6 (23.1) vs. -4.2 (22.7), p=0.87 ED: Meta-analysis of 2 RCT[17,58] MD -1.76 (-8.58 to 5.05)
Vomiting	1 RCT[58] (n=45)	ED: 1 RCT AR 4.8% vs. 4.2%; RD 1% (-16 to 19)

Abbreviations: AR=absolute risk; ED=emergency department; EMS=emergency medical services; MD=mean difference; RCT=randomized controlled trial; RD=risk difference

Two studies from the battlefield setting reported additional outcomes.[62,63] Schauer et al.[62] reported values at the point of admission comparing morphine, fentanyl and ketamine [median (IQR)]: systolic blood pressure [130 (106 to 144), 131 (114 to 143), 120 (91 to 140)], heart rate [93 (76 to 120), 90 (72 to 108), 108 (85 to 131)], respiratory rate [18 (16 to 22), 18 (14 to 22), 20 (16 to 25)], and oxygen saturation [99 (96 to 100), 97 (94 to 99), 99 (95 to 100)]. Shackelford et al.[63] reported change in vital signs during tactical evacuation for morphine, fentanyl and ketamine treated subjects [mean change (SD)]: systolic blood pressure [-3 (13) versus 0 (14) versus 7 (17)], heart rate [-3 (23) versus -3 (14) versus -5 (20)], respiratory rate [-1 (2) versus -1 (2) versus -1 (4)], and oxygen saturation [4 (2) versus 1 (2) versus 2 (4)].

Combination of Opioids and Ketamine Versus Opioids

Key Messages

- Evidence is insufficient for the comparison of combination opioids and ketamine versus opioids alone, for the outcomes of any adverse event, hypotension, mental status changes and respiratory depression.
- Results from outcomes that were not graded for SOE suggest combination opioid and ketamine therapy leads to a statistically higher value for oxygen saturation and respiratory rate in 30 minutes and statistically less vomiting, compared to opioids alone, but clinical relevance is uncertain. Analgesics were administered primarily IV.

Detailed Results

We present the conclusions for the comparative harms of combination opioids and ketamine versus opioids as initial analgesics in Table 19. This evidence base includes data from both EMS and ED settings mostly comparing weight-based doses of morphine IV with ketamine IV. Evidence was insufficient for the outcomes of any adverse events, hypotension, mental status changes and respiratory depression. For some of these outcomes single studies didn't allow judging consistency and additional domains had limitations that led to downgrading. In other cases estimates are very imprecise where the confidence interval included the possibility of a clinically important difference in favor of either analgesic.

One observational study[62] from the battlefield setting was not considered in the conclusion of mental status changes because the population and setting was too unlike civilians expected to access EMS. This study reported GCS scores (median, IQR) at the point of hospital admission for opioids plus ketamine (13, 8 to 14), morphine (15, 15 to 15) and fentanyl (15, 14 to 15).

Table 19. Conclusions and strength of evidence for the comparison of combination opioids and ketamine versus opioids, Key Question 2

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates and 95% Confidence Intervals)	Strength of Evidence (Limitations)
Any adverse event	1 RCT[72] (n=80)	**Inconclusive.** ED: 1 RCT found adverse events to occur in 22.5% vs. 17.5% of patients, RD 5% (-13 to 22)	Insufficient (Unknown consistency, indirect, very imprecise)
Hypotension	1 RCT[71] (n=106)	**Inconclusive.** ED: 1 RCT found hypotension to occur in 0% vs. 3% of patients, RD -6% (-16 to 3)	Insufficient (Unknown consistency, indirect, imprecise)

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates and 95% Confidence Intervals)	Strength of Evidence (Limitations)
Mental status changes - dizziness	2 RCTs[66,68] (n=265)	**Inconclusive.** EMS: 1 RCT[66] found dizziness in 18.2% vs. 0% of patients 30 min after the dose, RD 18% (3 to 34). ED: 1 RCT[68] found dizziness in 22% vs. 11% at 20 mins [RD 11% (1 to 21)] and 42% vs. 45% at 40 min [RD -3% (-16 to 11).	Insufficient (Inconsistent, indirect, imprecise)
Mental status changes - sedation	1 RCT[66] (n=65)	**Inconclusive.** EMS: 1 RCT found sedation in 21.2% vs. 6.3% of patients 30 min after the dose. RD 15% (-2 to 32)	Insufficient (Unknown consistency, imprecise)
Respiratory depression	3 RCTs[66,69,71] (n=231)	**Inconclusive.** EMS: 1 RCT[66] found respiratory depression to occur in 0% vs. 3.1% of patients, RD -3% (-16 to 9) ED: Meta-analysis of 2 RCTs[69,71] found AR 1.2% vs. 6.0%, RD -3% (-10 to 4)	Insufficient (Indirect, very imprecise)

Abbreviations: AR=absolute risk; EMS=emergency medical services; min=minutes; OBS=observational; RCT=randomized controlled trial; RD=risk difference; vs=versus

Subgroups

Analgesic Dose

One RCT[70] included 3 arms to compare two different doses of ketamine (0.15mg/kg or 0.3mg/kg) when added to morphine (0.1mg/kg), versus morphine 0.1mg/kg alone. Dizziness was more common with ketamine 0.3mg/kg (45 percent versus 0 percent, $p<0.01$). Nausea occurred in 15 percent of both ketamine groups, and 2 subjects vomited in the ketamine 0.3mg/kg group while none vomited in the 0.15mg/kg group.

Additional Findings

Additional findings for outcomes that are not graded with strength of evidence are in Table 20. One RCT from the EMS setting found a statistically significant difference in the change of oxygen saturation in 30 minutes, suggesting a higher oxygen saturation with combination therapy versus opioids alone [MD 1 (0.2 to 1.8)]. Indirect evidence from RCTs in the ED setting found statistically significant difference in the change in respiratory rate in 30 minutes, suggesting a higher value with combination therapy versus opioids alone [MD 0.6 (0.3 to 0.9)]. Combination therapy was also found to have significantly less vomiting at 30 minutes compared with opioids alone [RD -10 percent (-18 to -2)]. No other findings were significant.

Table 20. Findings for the comparison of combination opioids and ketamine versus opioids, Key Question 2

Outcome	Study Design and Sample Size	Findings (Setting: Effect Estimates and 95% Confidence Intervals)
Diastolic blood pressure – 30 min	1 RCT[68] (n=200)	ED: 1 RCT MD 1.2 (-0.6 to 3)
Diastolic blood pressure – 60 min	1 RCT[68] (n=200)	ED: 1 RCT MD -1 (-4.6 to 2.5)
Dissociation	1 [RCT69] (n=60)	ED: No events occurred
Emergence delirium	1 RCT[69] (n=60)	ED: No events occurred
Heart rate – 15 min	1 RCT[72] (n=80)	ED: 1 RCT MD 3.07 (-3.82 to 9.96)
Heart rate – 30 min	2 RCT[67,72] (n=145)	EMS: 1 RCT[67] MD -2 (-9.74 to 5.74) ED: 1 RCT[72] MD 4.88 (-2.01 to 11.77)
Heart rate – 60 min	1 RCT[72] (n=80)	EMS: 1 RCT MD 4.82 (-2.17 to 11.81)
Nausea – 30 min	1 RCT[68] (n=200)	ED: 1 RCT AR 30% versus 34%; RD -4% (-17 to 9)

Outcome	Study Design and Sample Size	Findings (Setting: Effect Estimates and 95% Confidence Intervals)
Nausea – 60 min	1 RCT[68] (n=200)	ED: 1 RCT AR 43% vs. 45%; RD -2% (-15 to 12)
Nausea – study period	1 RCT[69] (n=60)	ED: 1 RCT AR 10% vs. 3.3%; RD 7% (-8 to 23)
Nausea and/or vomiting – 30 min	1 RCT[66] (n=65)	EMS: 1 RCT AR 24.2% vs. 12.5%; RD 12% (-8 to 30)
Nausea and/or vomiting – study period	1 RCT[71] (n=106)	ED: 1 RCT AR 7.5% vs. 13.2%; RD -6% (-18 to 7)
Oxygen saturation – 15 min	1 RCT[72] (n=80)	ED: 1 RCT 0.7 (-8.1 to 9.5)
Oxygen saturation – 30 min	2 RCT[66,72] (n=145)	EMS: 1 RCT[66] MD 1 (0.2 to 1.8) ED: 1 RCT[72] MD 0.8 (-8 to 9.6)
Oxygen saturation – 60 min	1 RCT[72] (n=80)	ED: 1 RCT MD 0.8 (-8 to 9.6)
Respiratory rate – 30 min	1 RCT[68] (n=200)	ED: 1 RCT MD 0.6 (0.3 to 0.9)
Respiratory rate – 60 min	1 RCT[68] (n=200)	ED: 1 RCT MD 0.4 (-0.03 to 0.8)
Systolic blood pressure – 15 min	1 RCT[72] (n=80)	ED: 1 RCT MD 0 (-8.5 to 8.5)
Systolic blood pressure – 30 min	3 RCT[66,68,72] (n=345)	EMS: 1 RCT[66] MD 3 (-6.7 to 12.7) ED: Meta-analysis of 2 RCT[68,72] MD 1.35 (-2.02 to 4.72)
Systolic blood pressure – 60 min	2 RCT[68,72] (n=280)	ED: Meta-analysis of 2 RCT MD 4.35 (-3.51 to 12.21)
Vomiting – 30 min	1 RCT[68] (n=200)	ED: 1 RCT AR 3% vs. 13%; RD -10% (-18 to -2)
Vomiting – 60 min	1 RCT[68] (n=200)	ED: 1 RCT AR 32% vs. 38%; RD -6% (-19 to 7)
Vomiting – study period	1 RCT[72] (n=80)	ED: 1 RCT AR 12.5% vs. 10%; RD 3% (-12 to 17)

Abbreviations: AR=absolute risk; ED=emergency department; EMS=emergency medical services; MD=mean difference; RCT=randomized controlled trial; RD=risk difference

One study from the battlefield setting reported additional outcomes.[62] Schauer et al. reported values at the point of admission comparing opioid plus ketamine, morphine and fentanyl [median (IQR)]: systolic blood pressure [121 (103 to 153), 130 (106 to 144), 131 (114 to 143)], heart rate [107 (88 to 131), 93 (76 to 120), 90 (72 to 108)], respiratory rate [18 (16 to 24), 18 (16 to 22), 18 (14 to 22)] and oxygen saturation [97 (89 to 100), 99 (96 to 100), 97 (94 to 99)].

Opioids Versus Acetaminophen

Key Messages

- Opioids cause more dizziness than APAP (moderate SOE) and may cause more adverse events than APAP (low SOE).
- There is no evidence of a clinically important difference in hypotension with opioids compared with APAP (low SOE).
- Evidence was insufficient for outcomes of mild sedation and respiratory depression.
- These conclusions are based on indirect evidence from the ED and comparing IV morphine with IV APAP.

Detailed Results

We present the conclusions for the comparative harms of opioids versus APAP as initial analgesics in Table 21. This evidence base is entirely indirect from the ED setting and compares IV morphine to IV APAP.

Table 21. Conclusions and strength of evidence for the comparison of opioids versus acetaminophen, Key Question 2

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates and 95% Confidence Intervals)	Strength of Evidence (Limitations)
Any adverse event	6 RCTs[73,75,77-79,82] (n=1,484)	**Opioids may cause more adverse events than APAP.** ED: Meta-analysis of 5 RCTs[73,77-79,82] over the study period found AR 35.4% vs. 5.6%, RD 30% (-1 to 62). 1 RCT[75] 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[73,76-78,80] (n=624)	**There is no evidence of a clinically important difference in hypotension with opioids compared to APAP.** 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[73,74,77,78,80,81] (n=539)	**Opioids cause more dizziness than APAP.** ED: Meta-analysis of 6 RCTs found, AR 7.8% vs. 0.3%, RD 7% (5 to 9)	Moderate (Indirect)
Mental status changes – "mild" sedation	1 RCT[77] (n=91)	**Inconclusive.** ED**:** 1 RCT found mild sedation in 2.2% vs. 0% of patients, RD 2% (-7 to 12).	Insufficient (Unknown consistency, indirect, very imprecise)
Respiratory depression	1 RCT[78] (n=73)	**Inconclusive**. ED: No events occurred in the 1 RCT.	Insufficient (Unknown consistency, indirect)

Abbreviations: APAP=acetaminophen; AR=absolute risk; ED=emergency department; RCT=randomized controlled trial; RD=risk difference

Opioids may cause more adverse events than APAP (low SOE). This conclusion is based on meta-analysis of indirect data from the ED setting and the clinically important difference of 10 percent. Results did not rule out the possibility of a clinically important difference in favor of APAP. One RCT was not pooled with the others because it reported adverse events over an "acute" period of the study rather than the full study period but was in agreement with direction of effect from the pooled estimate.

There was 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 percent) had hypotension in the opioid group. Result from meta-analysis ruled out a clinically important difference of 5 percent in favor of either analgesic. However we considered the result imprecise because the confidence interval was shifted towards an increased risk with opioids.

Opioids cause more dizziness than APAP (moderate SOE). This conclusion is based on the meta-analysis of indirect data from the ED setting and a clinically important difference of 5 percent.

Evidence was insufficient for the outcomes of "mild" sedation and respiratory depression.

Subgroups

Location of Pain

We performed subgroup analysis by location of pain. Location (renal colic versus other/not reported) did not appear to be associated with differing effects of opioids versus APAP for the outcome of any adverse event (Appendix Figure F-79) or hypotension (Appendix Figure F-80).

Location (extremity, renal colic, other/not reported) did not appear to be associated with differing effects of opioids versus APAP for the outcome of dizziness (Appendix Figure F-81).

Type of Pain

We analyzed studies that included traumatic pain only. These results did not suggest appreciable differences in effects for the outcomes of any adverse events and dizziness (Appendix Figures F-82 and F-83).

Additional Findings

Additional findings for outcomes that are not graded with strength of evidence are in Table 22. None of the results were statistically significant.

Table 22. Findings for the comparison of opioids versus acetaminophen, Key Question 2

Outcome	Study Design and Sample Size	Findings (Setting: Effect Estimates and 95% Confidence Intervals)
Nausea	4 RCT[73,76,81,82] (n=423)	ED: Meta-analysis of 4 RCT AR 10.4% vs. 0.9%; RD 12% (-10 to 34)
Nausea and/or vomiting	2 RCT[77,78] (n=164)	ED: Meta-analysis of 2 RCT AR 2.5% vs. 4.8%; RD -2% (-8 to 3)
Vomiting	3 RCT[73,80,82] (n=368)	ED: Meta-analysis of 3 RCT AR 7.1% vs. 0.5%; RD 9% (-3 to 20)

Abbreviations: AR=absolute risk; ED=emergency department; MD=mean difference; RCT=randomized controlled trial; RD=risk difference

Opioids Versus Nitrous Oxide

Key Message

- Evidence is insufficient for the comparison of IV opioids versus inhaled nitrous oxide, for outcomes of any adverse event and dizziness. No studies reported hypotension or respiratory depression.

Detailed Results

We present the conclusions of the comparative harms of opioids versus nitrous oxide in Table 23. This evidence base included a single trial from the EMS setting comparing morphine IV with self-administered nitrous oxide/oxygen (50:50).[83] This study had a medium risk of bias as it was opEn-label and we were unable to determine consistency without another study. Thus, evidence is insufficient to make conclusions regarding this comparison. No studies reported hypotension or respiratory depression (insufficient SOE).

Table 23. Conclusions and strength of evidence for the comparison of opioids versus nitrous oxide, Key Question 2

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates and 95% Confidence Intervals)	Strength of Evidence (Limitations)
Any adverse event	1 RCT[83] (n=100)	**Inconclusive.** EMS: 1 RCT found adverse events in 20% vs. 14% of patients, RD 6% (-9 to 21)	Insufficient (Medium study limitations, unknown consistency, very imprecise)
Mental status changes - dizziness	1 RCT[83] (n=100)	**Inconclusive.** EMS: 1 RCT found dizziness in 8% vs. 4% of patients, RD 4% (-7 to 15)	Insufficient (Medium study limitations, unknown consistency, very imprecise)

Abbreviations: EMS=emergency medical services; RCT=randomized controlled trial; RD=risk difference

Additional Findings

Additional findings for outcomes that are not graded with strength of evidence are in Table 24. Subjects treated with opioids had a significantly higher heart rate compared to nitrous oxide. No other findings were significant.

Table 24. Findings for the comparison of opioids versus nitrous oxide, Key Question 2

Outcome	Study Design and Sample Size	Findings (Setting: Effect Estimates and 95% Confidence Intervals)
Diastolic blood pressure	1 RCT[83] (n=100)	ED: 1 RCT MD 1 (-1.7 to 3.7)
Heart rate	1 RCT[83] (n=100)	ED: 1 RCT MD 4 (0.29 to 7.71)
Oxygen saturation	1 RCT[83] (n=100)	ED: 1 RCT MD 0 (-0.9 to 0.9)
Respiratory rate	1 RCT[83] (n=100)	ED: 1 RCT MD 0 (-0.5 to 0.5)
Systolic blood pressure	1 RCT[83] (n=100)	ED: 1 RCT MD 0 (-5.7 to 5.7)

Abbreviations: AR=absolute risk; ED=emergency department; MD=mean difference; RCT=randomized controlled trial; RD=risk difference

Opioids Versus Nonsteroidal Anti-Inflammatory Drugs

Key Messages

- Opioids may cause more adverse events and more drowsiness than NSAIDs (low SOE), administered IV and orally.
- Evidence was insufficient for the outcomes of hypotension, dizziness and depression. No studies reported respiratory depression.
- Results from outcomes that were not graded for SOE suggest opioids lead to statistically higher risk of nausea compared with NSAIDs, administered IV and orally.

Detailed Results

We present the conclusions for the comparative harms of opioids versus NSAIDs as initial analgesics in Table 25. This evidence base was entirely indirect evidence from the ED setting. Morphine IV was compared with ketorolac IV in two studies and oral morphine was compared to oral ibuprofen in one study.

Table 25. Conclusions and strength of evidence for the comparison of opioids versus nonsteroidal anti-inflammatory drugs, Key Question 2

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates and 95% Confidence Intervals)	Strength of Evidence (Limitations)
Any adverse event	2 RCT[84,86] (n=367)	**Opioids may cause more adverse events than NSAIDs** ED: Meta-analysis of 2 RCTs found AR 24.6% vs. 7.4%, RD 21% (4 to 38)	Low (Inconsistent, indirect, imprecise)
Hypotension	1 RCT[84] (n=88)	**Inconclusive.** ED: 1 RCT found hypotension in 6.8% vs. 0% of patients. RD 7% (-3 to 18)	Insufficient (Unknown consistency, indirect, imprecise)
Mental status changes - drowsiness	2 RCT[84,86] (n=367)	**Opioids may cause more drowsiness than NSAIDs** ED: Meta-analysis of 2 RCTs found AR 3.9% vs. 0.7%, RD 3% (0 to 6%)	Low (indirect, imprecise)
Mental status changes – dizziness	1 RCT[85] (n=86)	**Inconclusive.** ED: 1 RCT found dizziness in 9.3% vs. 0% of patients, RD 9% (-2 to 22)	Insufficient (Unknown consistency, indirect, imprecise)

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates and 95% Confidence Intervals)	Strength of Evidence (Limitations)
Mental status changes – depression	1 RCT[84] (n=88)	**Inconclusive.** ED**:** 1 RCT found depression in 4.5% vs. 0% of patients, RD 4% (-5 to 15)	Insufficient (Unknown consistency, indirect, very imprecise)

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

Opioids may cause more adverse events and may cause more drowsiness than NSAIDs (low SOE). These conclusions were each based on meta-analysis of indirect data from the ED setting. The confidence intervals of these estimates did not rule out the possibility of a difference that was less than clinically important, thus the estimates are considered imprecise.

Evidence is insufficient for the outcomes of hypotension, dizziness and depression. No studies reported respiratory depression (insufficient SOE).

Additional Findings

Additional findings for outcomes that are not graded with strength of evidence are in Table 26. Opioids significantly increase the risk of nausea compared to NSAIDs.

Table 26. Findings for the comparison of opioids versus nonsteroidal anti-inflammatory drugs, Key Question 2

Outcome	Study Design and Sample Size	Findings (Setting: Effect Estimates and 95% Confidence Intervals)
Nausea	3 RCT[84-86] (n=453)	ED: Meta-analysis of 3 RCT AR 9.8% vs. 1.7%; RD 9% (3 to 15)
Vomiting	2 RCT[84,85] (n=174)	ED: Meta-analysis of 2 RCT AR 4.6% vs. 1.1%; RD 3% (-2 to 9)

Abbreviations: AR=absolute risk; ED=emergency department; MD=mean difference; RCT=randomized controlled trial; RD=risk difference

Acetaminophen Versus Nonsteroidal Anti-Inflammatory Drugs

We present results from studies that compared APAP versus NSAIDs in Table 27. This evidence base was entirely indirect evidence from the ED setting. Findings did not favor either analgesic significantly.

Table 27. Findings for the comparison of acetaminophen with nonsteroidal anti-inflammatory drugs, Key Question 2

Outcome	Study Design and Sample Size	Findings (Setting: Effect estimates and 95% Confidence Intervals)
Any adverse event	2 RCT[87,88] (n=340)	ED: Meta-analysis of 2 RCT AR 4.7% vs. 3.5%; RD 1% (-3 to 5)
Mental status changes – dizziness	1 RCT[88] (n=140)	ED: No events occurred
Nausea	1 RCT[88] (n=140)	ED: 1 RCT AR 1.4% vs. 0%; RD 1% (-5 to 8)
Vomiting	2 RCT[87,88] (n=340)	ED: Meta-analysis of 2 RCT AR 3.5% vs. 1.8%; RD 1% (-2 to 4)

Abbreviations: AR=absolute risk; ED=emergency department; MD=mean difference; RCT=randomized controlled trial; RD=risk difference

Ketamine Versus Nonsteroidal Anti-Inflammatory Drugs

We present results from a single trail that compared ketamine to NSAIDs (ketorolac) in Table 28. This evidence base is indirect, from the ED setting. Several findings suggest statistically significant differences between ketamine and ketorolac. Total adverse events and

dizziness were more frequent with ketamine versus ketorolac. Heart rate and systolic blood pressure were higher with ketamine versus ketorolac, at 15 min and 30 min, but not 60 min.

Table 28. Findings for the comparison of ketamine with nonsteroidal anti-inflammatory drugs, Key Question 2

Outcome	Study Design and Sample Size	Findings (Setting: Effect Estimates and 95% Confidence Intervals)
Any adverse event	1 RCT[90] (n=126)	ED: 1 RCT AR 62.9% vs. 14.1%; RD -49% (-62 to -33)
Heart rate – 15 min	1 RCT[90] (n=110)	ED: 1 RCT MD 5.85 (2.99 to 8.71)
Heart rate – 30 min	1 RCT[90] (n=110)	ED: 1 RCT MD 4.13 (1.35 to 6.91)
Heart rate – 60 min	1 RCT[90] (n=110)	ED: 1 RCT MD 2.59 (-0.14 to 5.32)
Mental status changes – dizziness	1 RCT[90] (n=126)	ED: 1 RCT AR 40.3% vs. 0%; RD -40% (-52 to -27)
Nausea	1 RCT[90] (n=126)	ED: 1 RCT AR 11.3% vs. 14.1%; RD 3% (-9 to 15)
Systolic blood pressure – 15 min	1 RCT[90] (n=111)	ED: 1 RCT MD 9.19 (4.98 to 13.4)
Systolic blood pressure – 30 min	1 RCT[90] (n=111)	ED: 1 RCT MD 8.38 (4.20 to 12.56)
Systolic blood pressure – 60 min	1 RCT[90] (n=111)	ED: 1 RCT MD 4.49 (0.34 to 8.64)

Abbreviations: AR=absolute risk; ED=emergency department; MD=mean difference; RCT=randomized controlled trial; RD=risk difference

Morphine Versus Fentanyl

We present results from RCTs that compared morphine versus fentanyl in Table 29 followed by a summary of findings from observational studies. Two findings from the evidence base were statistically significant. One RCT[95] from the EMS setting found fewer adverse events with morphine versus fentanyl [RD -13 percent (-23 to-2)], although meta-analysis of indirect data from the ED did not support a statistically significant difference [RD -2 percent (-21 to 18)]. Based on a single trial from the EMS setting, sedation was significantly more common with morphine versus fentanyl [RD 42 percent (20 to 60)]. Meta-analysis of 2 RCTs suggest a statistically significant increase in nausea and/or vomiting with morphine versus fentanyl [RD 6 percent (1 to 11)]. Other findings were not significantly in favor of either analgesic.

Table 29. Findings for the comparison of morphine versus fentanyl, Key Question 2

Outcome	Study Design and Sample Size	Findings (Setting: Effect Estimates and 95% Confidence Intervals)
Any adverse event	3 RCT[21,95,96] (n=391) 2 OBS[a] (n=718)[99,104]	EMS: 1 RCT[95] AR 14.9% vs. 27.5%; RD -13% (-23 to -2), 1 OBS[104] see text ED: Meta-analysis of 2 RCT[21,96] AR 6.5% vs. 9.8%; RD -2% (-21 to 18), 1 OBS[99] see text
Heart rate	3 RCT[16,92,93] (n=288)	EMS: 1 RCT[16] no events occurred, bradycardia EMS: Meta-analysis of 2 RCT[92,93] MD -0.38 (-6.49 to 5.73)
Hypotension	3 RCT[19,92,94] (n=419) 3 OBS (n=886)[99,101,104a]	EMS: Meta-analysis of 2 RCT[92,94] AR 2.5% vs. 0%; RD 2% (-3 to 7), 1 OBS see text[104] ED: 1 RCT[19] AR 0% vs. 6.3%; RD -6% (-29 to 16), 2 OBS see text[99,101]
Mental status changes – lightheadedness, loss of consciousness	1 RCT[20] (n=90)	ED: 1 RCT AR 4.7% vs. 0%; RD 5% (-4 to 16)
Mental status changes – sedation	1 RCT[93] (n=54) 1 OBS[101] (n=718)	EMS: 1 RCT 42.3% vs. 0%; RD 42% (20 to 60) 1 OBS see text

Outcome	Study Design and Sample Size	Findings (Setting: Effect Estimates and 95% Confidence Intervals)
Nausea	5 RCT[19,21,92,93,96] (n=432) 2 OBS[101,104] (n=886)	EMS: Meta-analysis of 2 RCT[92,93] AR 16.8% vs. 14.7%; RD 0% (-14 to 15), 1 OBS see text[104] ED: Meta-analysis of 3 RCT[19,21,96] AR 10.8% vs. 5.1%; RD 9% (-14 to 33), 1 OBS see text[101]
Nausea and/or vomiting	2 RCT[20,91] (n=397) 1 OBS[99] (n=NR)[a]	ED: Meta-analysis of 2 RCT AR 15.4% vs. 8.4%; RD 6% (1 to 11), 1 OBS see text
Oxygen saturation	1 RCT[93] (n=54) 2 OBS[101,104] (n=886)	EMS: MD 0 (-1.5 to 1.5), 1 OBS see text[104] ED: 1 OBS see text[101]
Respiratory depression	2 RCT[92,96] (n=274) 3 OBS[98,99,101] (n=245)[a]	EMS: 1 RCT[92] no events occurred, 1 OBS see text[98] ED: 1 RCT[96] no events occurred, 2 OBS see text[99,101]
Respiratory rate	2 RCT[92,93] (n=241) 1 OBS[104] (n=718)	EMS: Meta-analysis of 2 RCT[92,93] MD -0.60 (-1.55 to 0.35), 1 OBS see text[104]
Systolic blood pressure	1 RCT[93] (n=54)	EMS: 1 RCT MD -3 (-14.2 to 8.2)
Vomiting	6 RCT[16,92-94,96,97] (n=642)	EMS: Meta-analysis of 3 RCT[92-94] AR 2.2% vs. 1.9%; RD 0% (-1 to 2) ED: Meta-analysis of 3 RCT[16,96,97] AR 0% vs. 3.8%; RD -4% (-9 to 1)

Abbreviations: AR=absolute risk; ED=emergency department; EMS=emergency medical services; MD=mean difference; OBS=observational; RCT=randomized controlled trial; RD=risk difference

[a]Of the 31,742 subjects included in the analysis, the proportion per opioid was not reported thus the sample size from Daoust et al. is not factored into this total

Six observational studies[62,63,98,99,101,104] compared harms of morphine with fentanyl. Two studies are in the EMS setting. Fleischman et al.[104] reported frequencies of several harms comparing fentanyl with morphine, none of which reached statistically significant differences (fentanyl percent versus morphine percent, 95 percent confidence interval for difference): any adverse event 6.6 percent versus 9.9 percent, -0.8 percent to 7.3 percent), nausea or need for anti-emetics (3.8 percent versus 7.0 percent, -0.1 percent to 6.5 percent), systolic blood pressure <90 mmHg (1.1 percent versus 1.7 percent, -1.1 percent to 2.3 percent), respiratory rate <12 (0.3 percent versus 0.9 percent, -0.5 percent to 1.7 percent), oxygen saturation <92 percent and 5 percent below baseline (1.1 percent versus 0.6 percent, -1.9 percent to 0.8 percent), sedation or decreased GCS (0.8 percent versus 1.1 percent, -1.1 percent to 1.7 percent). Sharonow et al.[98] reported no patients to have respiratory depression requiring opioid antagonist or measures to secure airway; no patients had an oxygen saturation <95 percent.

Two studies are in the ED setting. Wenderoth et al.[101] reported hypotension (systolic blood pressure <90 mmHg) in 6.0 percent versus 0 percent (p=NR); respiratory rate <12 in 2.4 percent versus 0 percent, (p=NR); oxygen saturation <90 percent in 1.2 percent versus 0 percent (p=NR), but in 3 of these 8 patients that experiences an adverse event, the event was reported as present at baseline. Nausea, in those without nausea at baseline, was significantly more frequent with morphine versus fentanyl 21.4 percent versus 0 percent, p=0.088). Daoust et al.[99] reported adjusted odds ratios (AOR) and 95 percent confidence intervals for harms with fentanyl referent to morphine and found less nausea/vomiting [AOR 0.80 (0.71 to 0.91)], fewer subjects with oxygen saturation <92 percent [AOR 0.73 (0.64 to 0.83)] and more subjects with systolic blood

pressure <90 mmHg [AOR 2.50 (2.10 to 2.97)] with fentanyl. There was no significant difference in global adverse events [AOR 0.96 (0.88 to 1.04)].

Two studies are in the battlefield setting. Schauer et al.[62] reported harms at the point of hospital admission in subjects treated with morphine versus fentanyl (median, IQR): systolic blood pressure (130, 106 to 144 versus 131, 114 to 143); heart rate (93, 76 to 120 versus 90, 72 to 108); respiratory rate (18, 16 to 22 versus 18, 14 to 22); oxygen saturation (99, 96 to 100 versus 97, 94 to 99); Glasgow Coma Scale score (15, 15 to 15 versus 15, 14 to 15). Shackleford et al.[63] reported change in vital signs (mean, SD) during tactical evacuation in subjects treated with morphine versus fentanyl: systolic blood pressure [-3(13) versus 0(14), p=NR], heart rate [-3(23) versus -3(14), p=NR], respiratory rate [-1(2) versus -1(2), p=NR] and oxygen saturation [4(2) versus 1(2), p=NR].

Combination of Opioid and Ketamine Versus Ketamine

One study compared vomiting in patients treated with either morphine or fentanyl in combination with ketamine versus etamine alone, in the EMS setting.[105] There were more cases of vomiting in the fentanyl plus ketamine group (p=not reported): morphine plus ketamine 0 percent; fentanyl plus ketamine 16.7 percent; ketamine alone 0 percent.

KQ 3. In patients whose moderate-to-severe acute-onset pain level is not controlled following initial analgesic treatment, what is the comparative effectiveness of switching the analgesic regimen compared to repeating the initial treatment?

KQ 3a. How does effectiveness vary by patient characteristics?

KQ 3b. How does effectiveness vary by timing of the second treatment administration?

Additional Opioids Versus Ketamine

Key Messages

- Giving ketamine may reduce pain more and may be quicker to reduce pain to a clinically important difference compared with giving additional opioids (low SOE).
- These conclusions are based on direct evidence from the EMS setting comparing IV morphine with IV ketamine when patients inadequately respond to initial morphine IV.
- Evidence is insufficient for the outcome of pain presence.

Detailed Results

We present the conclusions for the comparative effectiveness of giving additional opioids versus giving ketamine after inadequate initial analgesics in Table 30. Two RCTs[64,65] from the EMS setting enrolled subjects who inadequately responded to morphine (5mg IV or 0.1mg/kg IV) and compared giving additional morphine with switching to ketamine IV.

Table 30. Conclusions and strength of evidence for the comparison of additional opioids versus ketamine, Key Question 3

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates and 95% Confidence Intervals)	Strength of Evidence (Limitations)
Pain severity	2 RCT[64,65] (n=162)	**Giving ketamine may reduce pain more than giving additional opioids.** 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[64] (n=135)	**Giving ketamine may be quicker to reduce pain to a clinically important difference compared to giving additional opioids.** 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

Giving ketamine may reduce pain more than giving additional opioids in patients who have inadequate pain control after initial opioids (low SOE). This conclusion is based on meta-analysis of the change in pain scores using direct evidence from the EMS setting and a clinically important difference of 2 points on a 0 to 10 scale. The confidence interval did not exclude the possibility of a clinically important difference in favor of ketamine (an increase in the MD with morphine). In addition to inconsistency in the meta-analysis result, the studies had medium risk of bias for subject outcomes because they were open-label.

Giving ketamine may be quicker to reduce pain to a clinically important difference compared to giving additional opioids. This conclusion is based on a single trial and a clinically important difference of 5 minutes. The median difference in pain score change per minute was in favor of ketamine such that within 5 minutes, there likely would be at least a 2-point difference in pain scores on a 0 to 10 scale. This study was open-label thus medium risk of bias and we were unable to judge consistency with only 1 study.

No studies reported measure of pain presence (insufficient SOE) or memory of pain.

KQ 4. In patients whose moderate-to-severe acute-onset pain level is not controlled following initial analgesic treatment, what are the comparative harms of switching to another analgesic agent?

KQ 4a. How do harms vary by patient characteristics?

KQ 4b. How do harms vary by routes of administration, dosing, and timing?

Additional Opioids Versus Ketamine

Key Message

- Evidence is insufficient for the comparison of giving additional opioids IV versus giving ketamine IV for the outcomes of any adverse event, hypotension, mental status changes and respiratory depression.

Detailed Results

We present the conclusions for the comparative harms of additional opioids versus switching to ketamine after inadequate initial analgesics in Table 31. Two RCTs[64,65] from the EMS setting enrolled subjects who inadequately responded to morphine (5mg IV or 0.1mg/kg IV) and compared giving additional morphine with switching ketamine IV. Evidence was insufficient for any adverse event, hypotension, sedation, GCS score ≤13 and respiratory depression. Trials were open-label thus for subjective outcomes risk of bias was higher. Some estimates were very imprecise where the confidence interval included the possibility of a clinically important difference in favor of either analgesic. All outcomes were based on single studies thus consistency could not be judged. No studies reported respiratory depression (insufficient SOE).

Table 31. Conclusions and strength of evidence for the comparison of additional opioids versus ketamine, Key Question 4

Outcome	Study Design and Sample Size	Conclusions (Setting: Supporting Effect Estimates and 95% Confidence Intervals)	Strength of Evidence (Limitations)
Any adverse event	1 RCT[64] (n=135)	**Inconclusive.** EMS: 1 RCT found adverse events in 13.8% vs. 38.6% of patients, RD -25% (-38 to -1)	Insufficient (Medium study limitations, unknown consistency, imprecise)
Hypotension	1 RCT[64] (n=135)	**Inconclusive.** EMS: 1 RCT found hypotension in 1.5% vs. 0% of patients, RD 2% (-40 to 9)	Insufficient (unknown consistency, very imprecise)
Mental status changes – sedation	1 RCT[65] (n=27)	**Inconclusive.** EMS: 1 RCT found no events in either arm.	Insufficient (medium study limitations, unknown consistency)
Mental status changes - GCS≤13	1 RCT[65] (n=135)	**Inconclusive.** EMS: 1 RCT found reduced GCS score in 1.5% vs. 4.3% of patients, RD -3% (-10 to 5)	Insufficient (Medium study limitations, unknown consistency, very imprecise)

Abbreviations: EMS=emergency medical services; GCS=Glasgow Coma Scale; OBS=observational; RCT=randomized controlled trial; RD=risk difference; vs=versus

Additional finding for outcomes that are not graded for strength of evidence are in Table 32. There were no significant findings.

Table 32. Findings for the comparison of additional opioid versus ketamine, Key Question 4

Outcome	Study Design and Sample Size	Findings (Setting: Effect Estimates and 95% Confidence Intervals)
Heart rate	2 RCT[64,65] (n=162)	EMS: Meta-analysis of 2 RCT MD 1.10 (-1.94 to 4.14)
Oxygen saturation	1 RCT[65] (n=27)	EMS: MD -3 (-6.2 to 0.2)
Respiratory rate	2 RCT[64,65] (n=162)	EMS: Meta-analysis of 2 RCT MD -0.16 (-1.46 to 1.14)
Systolic blood pressure	2 RCT[64,65] (n=162)	EMS: Meta-analysis of 2 RCT MD -20.22 (-45.46 to 5.02)
Nausea	2 RCT[64,65] (n=162)	EMS: Meta-analysis of 2 RCT AR 9.2% vs. 8.1%; RD -1% (-20 to 17)
Vomiting	2 RCT[64,65] (n=162)	EMS: Meta-analysis of 2 RCT AR 0% vs. 4.7%; RD -7% (-22 to 9)
Emergence delirium	1 RCT[64] (n=135)	EMS: 1 RCT AR 0% vs. 5.7%; RD -6% (-14 to 2)

Abbreviations: AR=absolute risk; EMS=emergency medical services; MD=mean difference; RCT=randomized controlled trial; RD=risk difference

Discussion

Overview

Fifty-two randomized controlled trials (RCTs) and 13 observational studies constituted the evidence base for this review. Only 14 of these studies, 8 of which compared morphine to fentanyl, were from the prehospital setting. When mapped against the analgesic comparisons and outcomes, few prehospital studies were available per comparison. Therefore, our conclusions for Key Questions (KQ) 1 and 2 are based on indirect evidence from the emergency department (ED) setting. Conclusions for KQ 3 and 4 are based on direct evidence from 2 RCTs in the prehospital setting. The focus of this report is to synthesize existing evidence. We do not make clinical recommendations and encourage the application of this evidence to future work generating evidence-based clinical guidelines.

Initial Analgesia

As initial analgesics and primarily administered intravenously (IV), opioids are no different than ketamine, acetaminophen (APAP) and nonsteroidal anti-inflammatory drugs (NSAIDs) in reducing pain. These conclusions were all with low-strength evidence, except opioids versus NSAIDS which was moderate strength. The combination of opioids and ketamine may be more effective in reducing pain, compared with opioids alone. To put these findings in context there are some key parameters concerning applicability to consider. The studies that compared the efficacy of opioids with ketamine were mostly comparing weight-based IV morphine 0.1mg/kg with IV ketamine (variable weight-based dosing). Some studies evaluated intranasal (IN) fentanyl and IN ketamine, which were prepared from the IV formulations and delivered IN via an atomizer. The IN ketamine product on the US market is not approved for pain management and is specific to management of treatment-resistant depression. The doses of ketamine varied and too few studies were available to identify associations based on subgroups of dose. When ketamine was studied in combination with opioids, a single IV dose was added to the opioid regimen. How administration of more than one 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.

We were unable to draw conclusions about the efficacy of opioids compared with nitrous oxide owning to a single study with limitations in design and inability to compare consistency of results with other studies. We did not grade outcomes for the comparisons of morphine versus fentanyl, APAP versus NSAIDs or ketamine versus NSAIDs. There were no statistically significant differences in pain scores between morphine and fentanyl. Pain decreased less with APAP versus NSAIDs at 15 minutes but the difference is smaller than what would be considered as clinically relevant. Pain decreased more with ketorolac compared with ketamine at 30 minutes but the difference as smaller than what would be considered clinically relevant. No studies, regardless of analgesic comparison, reported outcomes associated with the memory of pain (amnestic effect of the intervention).

Conclusions regarding comparative harms of initial analgesics were often inconclusive owing to insufficient data, with few studies per comparison and a lower frequency of events. Based on conclusions we were able to draw, the comparative harms of specific adverse events vary among

analgesics and in the absence of clinically important differences in pain reduction and may inform individualized treatment decisions.

The overall frequency of total adverse events in trials that compared opioids with ketamine suggests that at least 50 percent of patients treated with either opioids or ketamine will experience some type of adverse event but low-strength evidence suggests that opioids may cause fewer total adverse events than ketamine. These trials studied analgesics primarily administered through the IN route. Based on subgroup analyses, effects may be modified by age (<18 years versus 18 years and older), route and pain type, although because the same cohort of studies represented subjects <18 years old and IN routes, it is unclear what the true modifier is. Opioids may cause more respiratory depression while ketamine causes more dizziness, both based on low-strength evidence. Differences in dizziness may be associated with age or route but again, the same caveat applies as these subgroups were represented by the same studies. Results from outcomes that were not graded suggest opioids lead to statistically lower values for heart rate, respiratory rate and systolic blood pressure (SBP) compared with ketamine in 15 minutes; statistically lower SBP versus ketamine in 30 minutes; and statistically greater nausea/vomiting versus ketamine. Hemodynamic changes were mostly due to elevations with ketamine over reductions with opioids and these observations are consistent with known side effects of these drugs. We did not establish clinically important differences for these outcomes although the lower bound of the confidence interval for heart rate (-5.23 beats per minutes) and SBP (-16.22 mmHg) at 15 minutes, for SBP at 30 minutes (-11.28 mmHg), and upper bound for nausea/vomiting (risk difference 22 percent) suggest these findings may be clinically relevant changes.

In contrast to the comparison of opioids with ketamine, opioids may cause more adverse events than APAP or NSAIDs when used as initial analgesics, with low-strength evidence. Opioids cause more dizziness than APAP but there was no evidence of clinically important differences in hypotension, both based on low-strength evidence. Compared with NSAIDs, opioids were found to cause more drowsiness, based on low-strength evidence.

We were unable to conclude comparative harms of combination opioids and ketamine versus opioids alone. Results from single trials for outcomes that were not graded suggest combination therapy leads to a statistically higher oxygen saturation percentage and respiratory rate in 30 minutes and statistically fewer patients with vomiting. We did not establish clinically important differences for these outcomes although the observed differences may not be clinically relevant in the majority of patients. We did not grade outcomes for the comparisons of morphine versus fentanyl, APAP versus NSAIDs or ketamine versus NSAIDs. There were no significant differences between APAP and NSAIDs for the reported harms. Total adverse events and dizziness was more frequent with ketamine versus ketorolac. Heart rate and systolic blood pressure were higher with ketamine versus ketorolac at 15 and 30 minutes but not at 60 minutes. Some trial data suggested morphine has fewer adverse events and less sedation than fentanyl but observational data were not in agreement with these effects.

Inadequate Response to Initial Analgesia

In patients whose pain is inadequately responsive to initial morphine (KQ 3 and 4), giving ketamine IV may reduce pain more and may be quicker compared to giving more morphine IV, based on low-strength evidence. The evidence for this conclusion is directly from the prehospital setting, although conclusions were limited by the open-label nature of these trials and imprecise

effect estimates. We were unable to conclude comparative harms of this comparison owning to infrequent reporting of harms, low events leading to imprecise estimates and study limitations.

Findings in Relation to What Is Already Known

For patients experiencing moderate to severe pain due to a traumatic injury, current guidelines (based on moderate quality evidence) strongly recommend initial prehospital management with a weight-based opioid, either IV morphine or IV/IN fentanyl.[7] 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.[107] 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.

With the current opioid overdose epidemic and concerns about potential misuse of and addiction to opioids, recent interest in nonopioid alternatives has grown, specifically for ketamine. Ketamine, originally used as an anesthetic at higher doses, is used off-label for acute pain management. A position statement from The American College of Emergency Physicians (ACEP) and a joint guideline from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine and the American Society of Anesthesiologists are both in support of sub-dissociative doses of IV ketamine for acute pain management.[108,109] Our conclusions support the efficacy of ketamine, and when compared to opioids there was no evidence of a clinically important differences in reducing pain. We found that initially combining ketamine with opioids may be more effective in reducing pain compared to opioids alone and when a patient inadequately responds to IV morphine, switching to ketamine may be more effective.

The expected side effect profile of sub-dissociative doses of IV ketamine includes dysphoria, dizziness and nausea that are typically short-term and self-limiting.[108] Potential concerns regarding opioids (respiratory depression, hypoxemia, or hypotension) are not typical of sub-dissociative ketamine such that patients who are contraindicated to opioids may be candidates for ketamine.[108] Although we found opioids may cause fewer total adverse events versus ketamine, opioids may cause more respiratory depression. Respiratory depression from opioids is a potentially fatal complication of both acute and chronic pain management.[110,111]

Elevations in blood pressure and heart rate with ketamine may also be common.[112] Ketamine may cause more dizziness than opioids. We did not formulate conclusions for outcomes concerning hemodynamics or oxygenation but the observed changes are likely to be clinically important albeit consistent with the expected side effects. Experts describe emergence reactions to be uncommon at sub-dissociative ketamine doses.[108] Four studies in our review explicitly reported emergence delirium, two studies of IV ketamine 0.5mg/kg and 0.3 mg/kg and two studies of IN ketamine 1mg/kg. Collectively, 8.4 percent (12 of 143 subjects) of ketamine treated subjects were reported to experience emergence delirium.

Applicability

Population

The population of this review was limited to those with moderate to severe, acute pain. Aside from labor and delivery, etiology or location of pain did not lead to exclusion. Generally, the mean ages of studies fell within the 3rd to 4th decade of life, with few studies specific to younger and older patients. Of studies that focused on pediatric or adolescents, the mean ages were closer to 10 years old, rather than very young pediatric patients. One study was specific to elderly, enrolling subjects over the age of 65 years, thus this evidence base is not applicable to older aged patients. Whether pain was traumatic, nontraumatic or mixed varied across comparisons. The most common type of traumatic pain, in general, was pain associated with limb fractures. Major injuries such as a crushed pelvis, major burns, or patients with multiple major traumatic injuries were not represented in this evidence base. The most common type of nontraumatic pain studied was pain associated with renal colic. Baseline pain scores were no less than 7, representing more severe pain, with exception of studies comparing morphine with fentanyl where the lower bound was 5.

Contraindications

Contextual Question 1 is regarding contraindications to analgesics, which is also tied into the population related applicability of the evidence base constituting this review. The contraindications, precautions and warnings for the analgesics discussed in this report are presented in Appendix Table C-11, according to U.S. Food and Drug Administration.[112-123] All analgesics are contraindicated in the presence of an allergy. Morphine and fentanyl are contraindicated within 14 days of monoamine oxidase inhibitors (MAOI). These opioids have common warnings related to risk of respiratory and central nervous system depression and characteristics that may predispose patients to these risks. Hypotension, cardiovascular instability and adrenal insufficiency are also warnings. Guidelines on analgesia for traumatic injuries and in the prehospital setting are in general agreement and recommend refraining from opioids with a Glasgow Coma Score (GCS) less than 15, hypoxia after maximal oxygen supplementation, signs of hypoventilation, hypotension, allergy or with MAOIs.[8,107]

As a comparison to labeled contradictions, we evaluated the exclusion criteria used by trials included in this review. Studies of opioids are mostly of morphine and the common exclusion criteria are consistent with the aforementioned label and guideline contraindications. They include: a history of respiratory disorders (e.g. chronic obstructive pulmonary disease or asthma), abnormal oxygen saturation (typically <85 percent to 95 percent), abnormal respiratory rate (<8 to 12 or >20 to 30 breaths per minute), cardiovascular disorders (e.g. ischemic heart disease, heart failure, and dysrhythmias), hemodynamic instability (SBP <90 mm Hg or >160 to 180 mm Hg, heart rate <50 to 60 or >100 to 150 beats per minute), neurologic findings (e.g. decreased level of consciousness, GCS <15, cognitive impairment, altered mental status), head injury, and substance abuse (e.g. drug or opiate addiction or alcohol abuse). Unique to the use of intranasal fentanyl, subjects with nasal occlusion were excluded. As is typical in trials, patients with kidney or liver dysfunction or who were pregnant or lactating were commonly excluded.

Absolute and relative contraindications for ketamine in the setting of acute pain management are less agreed upon, related to the off-label use for this indication. The ACEP suggests ketamine for acute pain is contraindicated in infants less than 3 months of age and in those with stated adverse reactions or allergies to ketamine.[108] Recent consensus guidelines from the American

Society of Regional Anesthesia and Pain Medicine, American Academy of Pain Medicine, and American Society of Anesthesiologist provide differing suggestions.[109] Ketamine should be avoided in pregnancy or psychosis (Grade B, moderate certainty); severe cardiovascular disease or poorly controlled hypertension, or severe cirrhosis (Grade C, moderate certainty); and patients with moderate cirrhosis or elevated intracranial and/or intraocular pressure (Grade C, low certainty).[109] Our review of the common exclusion criteria from studies investigating ketamine are generally consistent with these contraindications and what is reported above for opioids. Because these studies were always in comparison to an opioid, ketamine specific exclusions are unclear. Studies of intranasal ketamine also excluded patients with nasal occlusion. Like trials of other analgesics, pregnant or lactating patients were also excluded in most ketamine studies.

NSAIDs, ketorolac and ibuprofen, have a variety of contraindications and warnings that center around current bleeding or the risk of serious bleeding, presence or history of peptic ulcers or gastrointestinal bleeding, renal impairment or those at risk for renal impairment and cardiovascular effects related to prostaglandin inhibition. Prehospital specific guidelines suggest NSAID be avoided in patients with an allergy, aspirin sensitive asthma, renal insufficiency, peptic ulcer disease, hypotension (due to renal toxicity) or are pregnant.[107] Studies of NSAIDs in our review excluded similar patient groups; mainly those with hemodynamic instability, liver or kidney disease, blood coagulation disorders, gastrointestinal bleeding, or peptic ulcer disease. One ibuprofen study also excluded patients with heart failure.

APAP warnings relate to concerns over liver disease or predisposition to hepatic toxicity and we found studies to commonly exclude patients with these characteristics. There appear to be few serious warnings for nitrous oxide. Suggested contraindications include patients with significant respiratory compromise or patients that cannot adequately breathe through their nose (upper respiratory tract infections, blocked sinuses, blocked nasal passages, and mouth breathers), in patients where gas expansion of body cavities could cause patient safety problems (pneumoencephalography, pneumothorax, air embolism, patients with colostomy bags or bowel obstruction, patients whom have undergone middle ear surgery, and cystic fibrosis), first trimester of pregnancy, patients undergoing treatment with bleomycin sulfate, vitamin B12 deficiency, severe emotional or psychiatric disturbances or drug related dependencies, and in patients who have received ocular surgery that included a gas bubble in the eye.[124,125]

Intervention and Comparator

Nonpharmacological management of acute pain was beyond the scope of this review and thus we cannot comment on how effectiveness and harms of these strategies compare to studied analgesics. As previously mentioned, most analgesics were delivered via the IV route, followed by IN routes for fentanyl and ketamine. Other routes were less common including nebulized IV fentanyl solution, sublingual ketorolac and oral ibuprofen. There were no studies of intraosseous delivery of analgesics which sometimes is employed in the prehospital setting. Doses for morphine and APAP were typically 0.1mg/kg and 1gm IV, once, respectively. Ketamine IV dosing varied but was generally within the range of doses (0.1 to 0.3mg/kg) considered to be sub-anesthetic.[108]

Outcomes, Timing, Setting

Pain scores were mostly reported on a 0 to 10 scale and few studies used a 100mm visual analog scale. Regardless, we were able to convert values such that all results are reported consistently in out review for a 0 to 10 scale, to enhance applicability of results. Many of the

included studies were conducted in countries outside of the United States, which may contribute to different practice patterns in the prehospital setting.

Contextual Question 2 is regarding the evidence regarding use of pain assessment tools in the prehospital setting for special populations including children, individuals with cognitive impairment, substance impaired individuals, and non-English speakers. While current guidelines recommend formal assessment of pain in prehospital patients, a paucity of data exist evaluating pain scales in this setting.[8,126] A number of pain scales have been developed and validated specifically for use in children.[127,128] These pediatric-specific pain scales are important, given the subjective nature of pain and the likelihood for observers, such as parents or other caregivers, to over or underestimate a child's pain.[129] Current guidelines[8] recommend use of the FLACC (Faces, Legs, Arms, Cry, and Consolability) or CHEOPS (Children's Hospital of Eastern Ontario Pain Scale) in patients less than 4 years old, the Wong-Baker PACES Pain Scale or the Faces Pain Scale-Revised (FPS-R) for patients 4-12 years old, and the Numeric Rating Scale (NRS) in those over 12 years old. Subsequently published evidence in pediatric emergency departments support these recommendations, showing the FLACC scale to have high interrater reliability in patients 6 months to 5 years old.[130] and that the FPS-R and Visual Analogue Scale (VAS) have strong properties in children 6-17 years old.[131] Ultimately, the choice of scale in prehospital settings should be guided by the child's age, development, clinical status, and practitioner preference. Data exist for assessing pain in both pediatric[132] and older adults with cognitive impairment,[133] although none of it is in the prehospital setting. The inability of patients, young and old alike, with cognitive impairment to self-report pain make them susceptible to under treatment leading to a worsening of their underlying condition and worsening cognitive decline. In hospitalized children with cognitive impairment, the revised FLACC scale has been most studied in acute care settings.[132] Within the emergency department, literature reports common use of the VAS combined with clinician's own intuition for assessing pain in elderly patients with cognitive impairment.[134] A combination of observational and behavioral instruments has been recommended for pain assessment in older patients with dementia, although additional validation is required.[133] No literature exists for specifically assessing pain severity in substance impaired individuals. Lastly, a number of these scales have been translated and validated for use in non-English speakers including (for example), but not limited to, Spanish,[135,136] Finnish,[137] Japanese,[138] and Korean.[139] Of note, none of these scales have been studied in the prehospital setting.

KQ 1 and 2 are answered based on indirect data from the ED.

Limitations

The major limitation of this review is the indirectness of evidence. Although our plan was to use prehospital data when possible, few studies were available for each unique comparison and outcome. Most of the literature from the prehospital setting is related to morphine versus fentanyl, which was not prioritized as a contemporary decisional dilemma for this evidence review and was not the focus of this report. With that said, we used the best available evidence to answer the KQs of this review.

The indirectness of evidence may have significant implications. The type and training of healthcare professionals administering analgesia in these two settings is different. Resources available to the medical team such as therapies, monitoring devices and diagnostic testing vary. The fact that the prehospital setting is mobile brings unique challenges not present in the ED.

Given these differences, conclusions based on ED data were downgraded for indirectness, lowering the strength of evidence.

Subgroup analysis was not possible in many cases for various reasons, but these subgroups were important to the sponsor and experts in the field that constituted the Technical Expert Panel. Patient characteristics based on mean baseline parameters were aggregated around one extreme (e.g. severe but not moderate baseline pain, adult ages). In other cases a particular route, dose or pain type dominated the evidence base for a given comparison and outcome. No subgroup analyses were possible based on medical condition, including chronic pain. A single trial was performed in subjects with opioid addiction, but again comparing morphine to fentanyl and not informing contemporary analgesic comparisons. We found no evidence to describe comparative harms to EMS personnel during analgesic administration.

Use of ED data was associated with addition challenges. Pain, and usually cardiorespiratory monitoring parameters, were measured multiple times throughout the study period. Balancing analysis of the most appropriate time points against multiple hypothesis testing was a challenge. We chose to evaluate these outcomes at 15, 30 and 60 minutes. We based this decision on the expected pharmacokinetics of the analgesics studied, and the time points which would most likely encompass the typical transport time in the US.

We were challenged with the outcomes of mental status changes and emergence delirium. Many symptoms reported as harms in a trial could be considered a mental status change. We were quite liberal in what we allowed under this outcome, but kept analyses of distinct "symptoms" separate since within a study these outcomes may not have been mutually exclusive. Emergence delirium is a concern specific to ketamine. Several signs or symptoms may be associated with this phenomenon and we were strict in collecting data explicitly reported by the authors as emergence reactions, delirium or phenomenon. We did not assume a vaguely reported symptom may have been emergence delirium.

Key Areas for Future Research

The single most important future research need is addressing the gap of evidence of comparative effectiveness and harm of analgesics specifically in the prehospital setting. This stands for both initial analgesia and best approaches for when initial analgesia fails. Ideally such studies in the prehospital setting would be prospective in nature and optimally blinded to minimize the associated bias when the primary outcomes are subjective, as is pain. We found little evidence overall for subgroups in our review and many of them were left without data regardless of the analgesic, making these areas ideal for future research. Examples of these subgroups include special populations such as pediatrics, geriatrics and patients in shock. Similarly, evaluations of specific pain assessment tools in prehospital populations are lacking (particularly those in special populations).

Importantly, we found no evidence regarding how the level of emergency medical services (EMS) personnel training may impact outcomes. This may be most important for future research related to ketamine in the prehospital setting. Recent guidance[109] for acute pain management suggests that healthcare providers that administer ketamine should hold the following qualifications: appropriately trained nurse with Advanced Cardiac Life Support training, with training in administration of moderate sedation, have knowledge of ketamine pharmacology, monitor for ketamine infusions at subanesthetic doses, and change doses based on directions from a responsible physician, who should be an anesthesiologist, intensive care physician, pain physician, or emergency medicine physician. No evidence was found for the outcomes of

diversion or the future risk of substance abuse or misuse by EMS personnel, which also present an opportunity to evaluate in future studies.

Research is needed to explore analgesic regimen characteristics. The analgesics that form the basis of this review were mostly administered IV. Some studies of ketamine and fentanyl studied IN routes, but comparatively less than IV routes, and oral routes were rarely evaluated. There are times where IV access is not ideal or possible. Thus, research of routes that will provide quick and effective analgesia, other than IV, is needed. In addition, we were unable to evaluate how dose, frequency of administration, or timing of subsequent doses may modify effects. This may be less important for doses with longstanding drugs like morphine or APAP where almost all studies used the standard 0.1mg/kg and 1g dosing, respectively. However, even for these analgesics, we found no comparative evidence regarding timing for re-dosing. For ketamine, dose effects may be more important for future research given it is a newer option for acute pain and ideal dosing and administration methods are less certain for this indication.[108]

We recognize there are setting-related characteristics that may make it challenging to conduct rigorous, prospective trials in the prehospital setting. Alternative study designs can be informative and may be more practical. The National Highway Safety and Transportation Administration funds a National Emergency Services Information System (NEMSIS) to store data from EMS encounters in the US in an effort to improve patient care.[140] Resources should be allocated to explore the feasibility of conducting rigorous observational studies that employ methods to minimize confounding and bias within this national database. Ideally, the database would include the name, dose, route and timing of administration of analgesics used during transport, transport time, hospital arrival time, re-dosing of analgesia or addition of analgesics, training of EMS personnel administering the analgesics, a pain score prior to administration of analgesia and again at the point of hospital arrival and presence of important adverse events.

Conclusion

As initial analgesia administered primarily IV, 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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Abbreviations and Acronyms

Abbreviation	Definition
AHRQ	Agency for Healthcare Research and Quality
APAP	acetaminophen
CI	confidence interval
CID	clinically important difference
CQ	Contextual Question
ED	emergency department
EMS	emergency medical services
EPC	Evidence-based Practice Center
GCS	Glasgow Coma Scale
IM	intramuscular
IN	intranasal
IQR	interquartile range
IV	intravenous
Kg	kilogram
KQ	Key Question
Mcg	microgram
MD	mean difference
Mg	milligram
NEB	nebulizer
NHTSA	National Highway Traffic Safety Administration
NR	not reported
NSAID	nonsteroidal anti-inflammatory
PO	by mouth
RCT	randomized controlled trial
RD	risk difference
SD	standard deviation
SL	sublingual
SOE	strength of evidence
SPID	summed pain intensity difference
TEP	Technical Expert Panel
UK	United Kingdom
US	United States
VS	versus

Appendixes

Table of Contents

Appendix A. Search Strategy

Search in Medline, Cochrane Central, and Embase all via OVID

1. Emergency Medical Services/
2. Emergency Medical Technicians/
3. Emergency Treatment/
4. Emergency Medicine/
5. AMBULANCES/ or AIR AMBULANCES/
6. First Aid/
7. prehospital.mp.
8. pre-hospital.mp.
9. paramedic*.mp.
10. ambulance*.mp.
11. out-of-hospital.mp.
12. out of hospital.mp.
13. ems.mp.
14. emt.mp.
15. emergency services.mp.
16. emergency medical service*.mp.
17. emergency technician*.mp.
18. emergency practitioner.mp.
19. emergency dispatch*.mp.
20. emergency despatch*.mp.
21. first responder*.mp.
22. emergency rescue*.mp.
23. emergency resus*.mp.
24. emergency triage.mp.
25. military medicine/
26. military medicine.mp
27. battlefield.mp
28. combat.mp
29. emergency department.mp
30. hospital/
31. morphine/
32. fentanyl/
33. ketamine/
34. nitrous oxide/
35. ketorolac/
36. ketorolac tromethamine/
37. ibuprofen/
38. acetaminophen/
39. morphine.mp
40. ketamine.mp
41. ketorolac.mp

42. fentanyl.mp
43. nitrous oxide*.mp
44. ibuprofen.mp
45. acetaminophen.mp
46. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 of 42 or 43 or 44 or 45
47. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
48. 46 and 47
49. epidemiologic studies/
50. exp cohort studies/
51. exp case-contol studies/
52. case control.tw.
53. (cohort adj (study or studies)).tw.
54. cohort analy$.tw.
55. (follow up adj (study or studies)).tw.
56. (observational adj (study or studies)).tw.
57. longitudinal.tw.
58. retrospective.tw.
59. cross sectional.tw.
60. cross-sectional studies/
61. or/49-60
62. randomized controlled trials as topic/
63. randomized controlled trial/
64. random allocation/
65. double blind method/
66. single blind method/
67. clinical trial/
68. clinical trial, phase i.pt.
69. clinical trial, phase ii.pt.
70. clinical trial, phase iii.pt.
71. clinical trial, phase iv.pt.
72. controlled clinical trial.pt.
73. randomized controlled trial.pt.
74. multicenter study.pt.
75. clinical trial.pt.
76. exp clinical trials as topic/
77. or/62-76
78. (clinical adj trial$).tw.
79. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
80. placebos/
81. placebo$.tw.
82. randomly allocated.tw.
83. (allocated adj2 random$).tw.
84. or/78-83
85. 77 or 84
86. case report.tw.

87. letter/
88. historical article/
89. or/86-88
90. 85 not 89
91. 61 or 90
92. 91 and 48

Appendix B. List of Excluded Studies

Not a human study n=11

1. Arora S, Wagner JG, Herbert M. Myth: parenteral ketorolac provides more effective analgesia than oral ibuprofen. CJEM. 2007 Jan;9(1):30-2. Review. PMID: 17391598.
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5. Poonai N, Bhullar G, Lin K, et al. Oral administration of morphine versus ibuprofen to manage postfracture pain in children: a randomized trial. CMAJ. 2014 Dec 9;186(18):1358-63. doi: 10.1503/cmaj.140907. PMID: 25349008.

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Appendix C. Evidence Tables

Table C-1. Study and population characteristics, randomized controlled trials

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Frey, 2019[17] United States Setting: ED Risk of bias: Low	8-17y old with acute extremity injury & VAS≥35/100 Exclusions: Significant head, chest, abdomen or spine injury, GCS<15 or inability to report a VAS score, nasal trauma or aberrant nasal anatomy, active epistaxis, drug allergy, history of psychosis, opioid administration prior to arrival, non-English speaking, in police custody, postmenarchal without a negative pregnancy test	A: Fentanyl 2 mcg/kg IN (max 100 mcg, median 1.9 mcg/kg IQR 1.7 to 1.9) (n=42) B: Ketamine 1.5 mg/kg IN (max 100 mg, median 1.5 mg/kg IQR 1.5 to 1.5) (n=44) Rescue: NR	Age A:12.2(2.3) B:11.8(2.6) Males A:74% B:59% Weight A:50.8kg(22.8) B:45.8kg(14.4) Race/ethnicity A/B: White 69%/68%, Black 24%/25%, other 7%/7% Pain etiology/location A/B: Fracture 81%/85%, dislocation 5%/9%, sprain/strain 12%/2%, other 2%/4% Pain Classification: Traumatic	Any AE Diastolic blood pressure Dissociation Heart rate Hypotension Oxygen saturation Pain severity Respiratory depression Respiratory rate Systolic blood pressure
Sotoodehnia, 2019[90] Iran Setting: ED Risk of bias: low	>18y old presenting to the ED with acute renal colic Exclusions: Sensitivity to ketamine or ketorolac, ischemic heart disease, hypertension, intracerebral vascular abnormalities, fibromyalgia, chronic pains managed with morphine, use of analgesics within 4 h before presenting to the ED, pregnancy, lactation, renal or hepatic failure, psychosis, trauma to the head or eye, and unstable vital signs	A: Ketamine 0.6mg/kg IV (n=67) B: Ketorolac 30mg IV (n=74) Rescue: Morphine 0.1 mg/kg IV for intolerable pain	Age A: 34.2(9.9) B: 37.9(10.6) Males A:71% B: 81.2% Weight NR Race/ethnicity NR Pain etiology/location: Renal colic 100% Pain classification: Non-traumatic	Any AE Heart rate Mental status changes Nausea Pain severity Systolic blood pressure

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Vahedi, 2019[91] Iran Setting: ED Risk of bias: low	≥18y old and addicted to opioids, presenting to the ED with acute pain of 6 or more on a 0 to 10 scale, from traumatic limb injury Exclusions: history of allergic reactions to fentanyl or morphine, GCS<14, NRS<5, SBP<90mmHg	A: Morphine 0.1 mg/kg IV (n=152) B: Fentanyl 1 mcg/kg IV (n=155) Rescue: If pain remained ≥3 or did not decrease by at least 50% after 60 min, ketorolac 60 mg IV was administered	Age A: 31.8(10.4) B: 31.0(10.7) Males A:92.8% B: 89% Weight NR Race/ethnicity NR Pain etiology/location: Limb injury 100% Pain classification: Traumatic	Diastolic blood pressure Heart rate Nausea Pain severity Respiratory rate Systolic blood pressure Oxygen saturation
Verki, 2019[51] Iran Setting: ED Risk of bias: low	18-55 years old with limb fracture, VAS score higher than 3 Exclusions: Consumed anti-psychotic, sedative, TCA, MAOI, SSRI drugs, opioid addicts, patients with underlying acute or chronic renal and hepatic disease, cardiac disease, upper and/or lower respiratory infection, asthma, COPD, or allergies, pregnant or breast-feeding women, fentanyl-prohibited patients, those with multiple myeloma, a history of convulsion, ketamine allergy, head injury, or avulsion fractures, and patients with unstable hemodynamic factors	A: Fentanyl 4mcg/kg nebulized (n=62) B: Ketamine 0.4mg/kg IV over 10 min (n=65) Rescue: VAS>3 after 60 min-treated with morphine 0.1 mg/kg IV	Age A: 34.5(11.97) B: 36.28(10.73) Males A:72.6% B:66.2% Weight NR Race/ethnicity NR Pain etiology/location: Limb fracture 100% Pain classification: Traumatic	Pain severity

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Abbasi, 2018[71] Iran Setting: ED Risk of bias: Low	18-65y old previously diagnosed with nephrolithiasis or urinary stone by a urologist w/VAS ≥6/10 Exclusions: Unstable vitals (SBP<90 mmHg, HR<60 or >120, RR <8 or >22, O2 saturation <92%, narcotic analgesic before admission, history of liver disease, kidney disease, chronic respiratory, CVD, known blood coagulation, chronic mental illness, use of psychiatric drugs, addiction to drugs and psychotropic substances, drug allergy, inability to understand the concept of VAS	A: Morphine 0.1 mg/kg + ketamine 0.15 mg/kg IV (n=53) B: Morphine 0.1 mg/kg + placebo IV (n=53) Rescue: Morphine IV continued until a VAS ≤3/10, 120 min or 30mg of morphine max	Age A: 51.58 (NR) B: 49.42 (NR) Males total study 67% Weight NR Race/ethnicity NR Pain etiology/location A/B: Renal colic 100% Pain Classification: Nontraumatic	Hypotension Nausea or vomiting Pain severity Respiratory depression
Al, 2018[80] Turkey Setting: ED Risk of bias: Low	16-65y old w/suspected renal colic subsequently confirmed with imaging, pain onset within 12h, VAS≥4/10 Exclusions: Hx of direct blunt trauma to the CVAT within the last week, drug allergy, SBP<90, hx prostate, renal and adrenal, and bladder malignancy or surgery on these regions within the last 6m, hx chronic pain syndrome, use of pain-killer, antidepressant, anticonvulsant, muscle relaxant, or steroid within 12h, hx of substance or alcohol dependency, pregnant, nursing mothers, PID	A: Fentanyl 2 mcg/kg IV (n=100) B: Paracetamol 10mg IV (n=100) Rescue: Study drugs, diclofenac or tramadol to those who needed them, physician discretion	Age NR Males A:67% B:67% Weight NR Race/ethnicity NR Pain etiology/location: Renal colic 100% Pain Classification: Nontraumatic	Hypotension Mental status changes Vomiting

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Burnett, 2018[28] USA Setting: ED Risk of bias: Unclear	3-17y old with medical/traumatic condition requiring IV opioid analgesics Exclusions: Trauma team activation, drug allergy, inability to provide informed consent, patient unwilling to provide assent, high suspicion of injury related to child abuse, patient/family member is non-English speaking, patient is incarcerated	A: Morphine 0.05 mg/kg IV (n=32) B: Ketamine 0.3 mg/kg IV (n=31) Rescue: Morphine given at the discretion of the treatment team	Age A:12.7(3.7) B:13.3(3.6) Males A:72% B:61% Weight NR Race/ethnicity NR Pain etiology/location NR Pain Classification: Mixed	Nausea or vomiting
Cenker, 2018[87] Turkey Setting: ED Risk of bias: Low	18-60y old presenting w/flank pain ultimately diagnosed as renal colic Exclusions: Analgesic within 6h, fever or hemodynamically unstable, peritoneal irritation signs, cardiac failure, hx of renal or hepatic failure, drug allergy, pregnancy, vision problems.	A: Ibuprofen 800mg IV (n=100) B: Paracetamol 1g IV (n=100) Rescue: Inadequate pain relief at 30min received fentanyl 1 µg/kg IV	Age total study 36(9) Males total study 64.5% Weight NR Race/ethnicity NR Pain etiology/location: Renal colic 100% Pain Classification: Nontraumatic	Any AE Pain severity Vomiting
Cozzi, 2018[88] Italy Setting: ED Risk of bias: Low	4-18y old w/moderate to severe acute abdominal pain and pain score of ≥6/10 (Wong-Baker 4-7y, NRS ≥8y) Exclusions: drug allergy, analgesic drugs in the 8h before the medical evaluation, hx nephropathy, liver disease, metabolic or neurologic disease and thrombocytopenia or bleeding disorders, abdominal pain was due to fecal stasis or severe dehydration	A: Ketorolac 0.5 mg/kg oral drops SL (max 30mg) (n=70) B: Paracetamol melt in the mouth powder 20 mg/kg melt in the mouth powder (max 1g) (n=70) Rescue: Pain score ≥6/10 at 2h, rescue analgesic of ED pediatrician's choice was given	Age A:12(9-14) B:12(9-14.3) Males A:30% B:45.7% Weight NR Race/ethnicity NR Pain etiology/location A/B: Appendicitis 7.1%/11.4%, gynecological 12.9%/14.3%, urological 4.3%/4.3%, viral infection 45.7%,41.4%, colic 22.9%/21.4%, functional 0%/2.9%, other 7.1%/4.3% Pain Classification: Mixed	Any AE Mental status changes Nausea Pain severity Presence of pain Vomiting

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Hosseininejad, 2018[68] Iran Setting: ED Risk of bias: Low	18-65y old w/kidney stones and VAS≥6/10 Exclusions: Unstable vital signs, drug allergy, pregnancy, breastfeeding, contraindications to morphine, history of opium addiction, any analgesic/narcotic within past 6h, peritoneal s/sx on abdominal exam, hx chronic CV, liver, kidney diseases, psychosis	A: Morphine 0.1 mg/kg + ketamine 0.2 mg/kg IV (n=100) B: Morphine 0.1 mg/kg IV (n=100) Rescue: Morphine 0.05 mg/kg IV	Age A:35.29(7.12) B:35.91(9.13) Males A:67% B:70% Weight A:70.3kg(7.02) B:69.86kg(8.56) Race/ethnicity NR Pain etiology/location: Renal colic 100% Pain Classification: Nontraumatic	Diastolic blood pressure Mental status changes Nausea Pain severity Respiratory rate Systolic blood pressure Vomiting
Jahanian, 2018[60] Iran Setting: ED Risk of bias: Low	18-65y old, upper or lower extremity long bone fractures caused by blunt trauma, pain score ≥7/10 Exclusions: Mental or neurological disorders, liver, kidney, stroke, asthma and other respiratory diseases, heart diseases, <45kg or >155kg, pregnant or lactating, SBP>180 or <90mmHg, HR <50 or >150, RR <10 or >30, decreased LOC, blow to the head or eyes, multiple trauma, drug allergy, drug addiction/IV use, other fractures, severe displacement, need of reduction, open fracture, compartment syndrome, analgesic before the study	A: Morphine 0.1 mg/kg IV (n=80) B: Ketamine 0.5 mg/ kg IV (n=79) Rescue: In the absence of pain relief at any time of the study, half of the previous doses of the same group was administered. If the pain score remains 9 or 10 out of 10, or more than 2 times to the administered drug, fentanyl 1 µg/kg IV was given.	Age A:36.38(9.3) B:35.87(7.3) Males A:70.5% B:71.8% Weight NR Race/ethnicity NR Pain etiology/location: Road traffic accidents 71.8%/69.3%, fall 23.1%/24.3%, assault 5.1%/6.4% Pain Classification: Traumatic	Mental status changes Nausea or vomiting Pain severity

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Mohammadshahi, 2018[72] Iran Setting: ED Risk of bias: Low	>18y old w/limb pain resulting from traumatic injuries within the last 24h, NRS≥7/10 Exclusions: open fracture, closed fracture in more than one site, fracture plus dislocation, acute traumatic pain in more than two limbs, BP< 90/60 or > 160/100, HR> 120 or <60, GCS<15, non-limb traumatic injuries, pregnancy, drug allergy, patients leaving the hospital for any reason within 3h of drug administration	A: Morphine 0.05 mg/kg IV + ketamine 1mg/kg IN using a dropper (n=40) B: Morphine 0.05 mg/kg IV + 0.02 ml/kg distilled water IN using a dropper (n=40) Rescue: After 10 min if patient requested more analgesics morphine 0.05 mg/kg IV was given	Age A:31.42(10.3) B: 31.75(8.2) Males total study 54.9% Weight NR Race/ethnicity: NR Pain etiology/location: Traumatic limb 100% Pain classification: Traumatic	Any AE Heart rate Oxygen saturation Pain severity Systolic blood pressure Vomiting
Motov, 2018[55] USA Setting: ED Risk of bias: Low	≥65y old w/ acute pain (within 7d onset), NRS≥5/10 requiring opioid analgesia, abdominal, flank, back, or musculoskeletal pain Exclusions: Altered mental status, drug allergy, weight <40 or >115kg, SBP <90 or >180, HR<50 or >150, RR<10 or >30, hx of acute head or eye injury, seizure, intracranial hypertension, severe COPD, chronic pain, renal or hepatic insufficiency, alcohol or drug abuse, psychiatric illness, or recent (4h before) opioid use	A: Morphine 0.1 mg/kg IV (mean 6.8mg(1.5)) (n=30) B: Ketamine 0.3 mg/kg IV over 15 min (mean 21.0mg(6.2)) (n=30) Rescue: Fentanyl 0.5 mcg/kg if NRS ≥5/10 and requested by patient	Age A: 77.1(8.5) B: 77.3(8.4) Males A:23.3% B:23.3% Weight NR Race/ethnicity NR Pain etiology/location A/B: Abdominal 33.3%/46.7%, cancer 16.7%/6.7%, back 3.3%/16.7%, musculoskeletal 10%/3.3%, fracture 23.3%/16.7%, flank 13.3%/10% Pain Classification: Mixed	Any AE Mental status changes Nausea Pain severity Presence of pain Respiratory depression

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Quinn, 2018[52] USA Setting: ED Risk of bias: Low	3-17y old, moderate to severe pain (NRS≥6/10 or equivalent Wong-Baker FACES Pain Scale) Exclusions: Weight>64kg, insufficient intensity to warrant opioid, facial trauma or any abnormality of the nasal anatomy, circulatory insufficiency, developmental delay, head trauma/increased intracranial pressure/altered consciousness, drug allergy, inability to provide pain scale assessment, opioid pain medication immediately before arrival to the ED	A: Fentanyl 1.5 µg/kg IN (n=11) B: Ketamine 1 mg/kg IN (n=11) Recue: Morphine 1mg/kg IV if a patient or parents requested additional pain relief	Age A:9.58(2.92) B:9.77 (2.51) Males A:73% B:91% Weight NR Race/ethnicity NR Pain etiology/location A/B: Musculoskeletal 73%/73%, abdominal 27%/27% Pain Classification: Mixed	Any AE Mental status changes Pain severity Presence of pain
Farina, 2017[54] Iran Setting: ED Risk of bias: Low	≥15y old, renal colic pain and didn't require surgical intervention Exclusions: opioid addiction, prior use of analgesics, pregnancy, drug allergy, nasal occlusion, SBP >180 or <90, respiratory distress, altered level of consciousness	A: Morphine 0.1 mg/kg IV + placebo IN (n=20) B: Ketamine 1mg/kg IN + placebo IV (n=20) Rescue: If no decrease in VAS at 30min fentanyl 1–2 mcg/kg every 5min was titrated to effect	Age A:34.75(11.71) B:39.25(10.75) Males A:85% B:40% Weight A:76.14(10.32) B:74.10(9.98) Race/ethnicity NR Pain etiology/location: Renal colic 100% Pain Classification: Nontraumatic	Any AE Emergence delirium Hypotension Mental status changes Nausea Pain severity
Le May, 2017[86] Canada Setting: ED Risk of bias: Low	6-17y old w/musculoskeletal injury to upper or lower limb, VAS>29/100 Exclusions: drug or color allergy, suspected child abuse, inability to self-report pain, chronic pain requiring daily analgesics, NSAIDs or opioid use within 3h before triage, injury to >1 limb, known hepatic or renal disease and/or dysfunction, known bleeding disorder, neurocognitive disability precluding assent and participation in the study, hx of sleep apnea or loud snoring in the past 5d	A: Morphine 0.2 mg/kg PO, max 15 mg (n=201) B: Ibuprofen 10 mg/kg PO, max 600mg (n=99) Rescue: Eligible to receive rescue analgesia at any time	Age A:11.7(2.7) B:12.2(2.6) Males A:56.4% B:58.2% Weight NR Race/ethnicity NR Pain etiology/location: Fracture 35.6%/47.3%, soft tissue 62.2%/52.74%, missing 2.1%/0% Pain Classification: Mixed	Any AE Mental status changes Nausea Pain severity Presence of pain

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Mahshidfar, 2017[56] Iran Setting: ED Risk of bias: Low	18-70y old, musculoskeletal trauma, NRS≥5/10 Exclusions: instability in vital signs, head trauma, GCS score <15, opiate users, psychiatric or cardiac problem, drug allergy, pregnancy, breast-feeding, renal or hepatic insufficiency, contraindications to interventions	A: Morphine 0.1 mg/kg IV (mean 6.8mg(1.2)) (n=155) B: Ketamine 0.2 mg/kg IV (mean 14.9mg(3.3)) (n=153) Rescue: <3/10 point decrease in pain score, morphine 3mg IV every 5 minutes	Age A:34.1(7.3) B:34.4(7.6) Males A:82% B:84% Weight A:68.4kg(12.9) B:75.1kg(14.6) Race/ethnicity NR Pain etiology/location A/B: Fracture 24%/28%, soft tissue injury 76%/72% Pain Classification: Traumatic	Hypotension Mental status changes Nausea Pain severity Respiratory depression
Masoumi, 2017[84] Iran Setting: ED Risk of bias: Low	≥18y old w/long bone fractures Exclusions: Asthma, COPD, rheumatoid fever, peptic ulcer disease, GI bleeding, drug allergy, without complete consciousness, hemodynamic instability and symptoms of respiratory distress and GIB during the pain relief injection	A: Morphine 5mg IV bolus then 2.5mg q5min X 20min if VAS≥4/10 (n=44) B: Ketorolac 10mg IV bolus then 5mg q5min X 20min if VAS≥4/10 (n=44) Rescue: NR	Age A:33.2(11.4) B:29.1(12.5) Males A:70.5% B:63.6% Weight NR Race/ethnicity NR Pain etiology/location: Long bone fracture 100% Pain Classification: Traumatic	Any AE Hypotension Mental status changes Nausea Pain severity Vomiting
Reynolds, 2017[29] USA Setting: ED Risk of bias: Low	4-17y old w/suspected fracture of any single extremity requiring analgesia, Wong-Baker FACES (4-10y) or VAS (11-17y) ≥3/10 Exclusions: GCS<15, drug allergy, pregnancy, intoxication, age-adjusted hypotension at presentation (SBP<70 +2x age if <10y, or <90 for those >10y), weight > 70kg, opioid analgesia administered prior to arrival, multiple injuries, nonverbal from developmental delay, or aberrant nasal anatomy that precluded IN medications	A: Fentanyl 1.5 mcg/kg IN (n=44) B: Ketamine 1 mg/kg IN (n=43) Rescue: 2nd dose ≥20 mins after 1st dose of ketamine 0.5 mg/kg IN or fentanyl 0.75 mcg/kg IN	Age A: 4-10y 73%, 11-17y 27% B: 4-10y 72%, 11-17y 28% Males A:64% B:61% Weight NR Race/ethnicity NR Pain etiology/location: Single extremity fracture 100% Pain Classification: Traumatic	Any AE Dissociation Hypotension Mental status changes Nausea Pain severity Presence of pain

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Sin, 2017[69] USA Setting: ED Risk of bias: Low	≥18y old w/chief complaint of acute pain (w/in 15d), moderate to severe (NRS≥3) Exclusions: RR not within 12–20, HR not within 60–110, BP<90/50 or >180/100, O2 sat <94%, altered mental status, weight >166kg, pregnancy or breastfeeding, drug allergy, opioid use within 4h, hx of schizophrenia, depression, or substance abuse, traumatic head injury with or without LOC, myocardial ischemia, headache, migraine, or increase in intracranial or intraocular pressure	A: Morphine 0.1 mg/kg IV push, max 10mg (mean 6.6mg(1.4)) + ketamine 0.3 mg/kg infused over 15 min (n=30) B: Morphine 0.1 mg/kg IV push, max 10mg (mean 5.9 mg (1.7)) + placebo infusion (n=30) Rescue: Morphine 0.1 mg/kg IV push (max 10mg) was offered at 5, 15, 30, 45, 75, 90, 105, and 120 after initial dose if the patients reported NRS≥4/10	Age A:41(16) B:48(17) Males A:40% B:40% Weight A: 81kg(22) B:85kg(24) Race/ethnicity A/B: White 10%/16.7%, African American 60%/60%, Hispanic 30%/16.7%, Asian/Pacific Islander 0%/6.7% Pain etiology/location: Abdominal 63.3%/73.3%, musculoskeletal 20%/16.6%, back 6.6%/0%, elbow fracture 0%/3.3%, abscess 0%/3.3%, hip 0%/3.3%, testicular 3.3%/0%, renal colic 6.6%/0% Pain Classification: Mixed	Dissociation Emergence delirium Nausea Pain severity Respiratory depression
Jalili, 2016[74] Iran Setting: ED Risk of bias: Low	≥18y old w/acute limb trauma and pain score >3/10 Exclusions: drug allergy or contraindication, SBP<90, pregnancy, any analgesic drug use within 6h, known pulmonary, cardiac, renal, or hepatic failure	A: Morphine 0.1 mg/kg IV (n=30) B: Paracetamol 1g IV (n=30) Rescue: Morphine IV titrated to effect at 30min if NRS>4/10	Age NR Males NR Weight NR Race/ethnicity NR Pain etiology/location: Acute limb trauma 100% Pain Classification: Traumatic	Mental status changes Pain severity

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Mollaei, 2016[81] Iran Setting: ED Risk of bias: Low	15-60y old with forearm or leg fractures, moderate to severe pain (VAS>4/10) Exclusions: GCS<15, weight<60 or >100kg, hemodynamic instability, lung problems, previous use of pain killer drugs and narcotics, addiction, previous liver or kidney disease, concussion, pregnancy, previous use of monoamine oxidase, sleeping and sedative drugs, phenobarbital and isoniazid, multiple vomiting incidents and nausea	A: Morphine 0.1 mg/kg IV over 10-15min (n=28) B: Acetaminophen 1g IV over 10-15min (n=27) Rescue: VAS>5/10 after 30min morphine will be prescribed for patient	Age A:35(11.3) B:36.0(11.1) Males A:60.7% B:63% Weight A:65.0kg(3.0) B:65.5kg(2.9) Race/ethnicity NR Pain etiology/location: Traffic accident 82.1%/81.5%, falling from height 14.3%/18.5%, direct injuries 3.6%/0% Pain Classification: Traumatic	Mental status changes Nausea Pain severity
Pathan, 2016[75] Qatar Setting: ED Risk of bias: Low	18-65y old w/renal colic and NRS≥4/10 Exclusions: drug allergy, hx of asthma, known renal or liver failure or impairment, pregnancy, pain caused by a traumatic mechanism (in the setting of injury, for example motor vehicle crash, fall, or assault), or previous use of analgesia within 6h	A: Morphine 0.1 mg/kg IV (n=548) B: Paracetamol 1g IV (n=549) Rescue: Morphine 3mg IV q5min until NRS<2/10 or participant refused further analgesia (starting 30min after initial dose)	Age A:34.4(28.6-41.5) B:34.7 (28.8-41.7) Males A:81% B:83% Weight A:72kg(65-84.6) B:74.6kg(65-84) Race/ethnicity NR Pain etiology/location: Renal colic 100% Pain Classification: Nontraumatic	Any AE Pain severity Presence of pain Time to analgesic effect
Serinken, 2016[76] Turkey Setting: ED Risk of bias: Low	21-65y old presenting w/pain radiating along sciatic nerve, VAS≥40 Exclusions: pain>1w, low back or leg trauma within 1w, sensory or motor deficit, drug allergy, unstable vital signs, fever>37.9°C, hx of malignancy, cauda equina syndrome, chronic pain syndromes, rheumatologic diseases, drug or alcohol addiction, pregnancy or lactation, analgesic, antidepressant, anticonvulsant, muscle relaxant medication, or steroid in past 6h	A: Morphine 0.1 mg/kg IV over 4-5min (n=100) B: Acetaminophen 1g IV over 4-5min (n=100) Rescue: Fentanyl 1 mcg/kg at 30min if needed	Age A:44.6(10.2) B:43.7(9.8) Males A:48% B:43% Weight NR Race/ethnicity NR Pain etiology/location: Sciatic nerve 100% Pain Classification: Nontraumatic	Hypotension Nausea Pain severity

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Shimonovich, 2016[53] Israel Setting: ED Risk of bias: High	18-70y old w/mild-moderate blunt trauma causing moderate to severe pain (VAS≥80/100) Exclusions: GCS<15, weight <50 or >110kg, HR>100, SBP <90 or >160, American Society of Anesthesiologists score other than 1 or 2, regular use of opiates, analgesia received within the prior 3h, drug allergy, a large meal ingested within the previous hour, pregnancy, deviated nasal septum or trauma to the nose, hx of psychiatric condition, head trauma, head injury complaining of LOC, dizziness, vomiting, or nausea	A: Morphine 0.1 mg/kg IV (n=24) B: Morphine 0.15 mg/kg IM (n=27) C: Ketamine 1 mg/kg IN (n=24) Rescue: NR	Age A:42.9(38.0-47.8) B:37.7(32.8-42.6) C:37.9(32.3-43.5) Males A:75% B:59.3% C:70.8% Weight NR Race/ethnicity: NR Pain etiology/location: NR Pain Classification: Traumatic	Emergence delirium Mental status changes Pain severity Presence of pain Time to analgesic effect
Weldon, 2016[92] Canada Setting: EMS, ambulance transport in urban system Risk of bias: Low	≥18y w/ischemic type chest pain not relieved by oxygen, ASA, and nitroglycerin Exclusions: SBP<100, O2 sat <95%, pregnancy, cognitive impairment, drug allergy, traumatic injury, evidence of right ventricular infarct identified by the presence of ST segment elevation	A: Morphine IV every 5min, max 4 doses (n=99) <75y and >50 kg: 5mg >75y and/or ≤50kg: 2.5mg B: Fentanyl IV every 5min, max 4 doses (n=88) <75y and >50kg: 50mcg >75y and/or <50kg: 25mcg Rescue: NR	Age A:66.1(15.8) B:64.5(16) Males A:53% B:53% Weight A:79.4kg(19.6) B:78.43kg(17.6) Race/ethnicity NR Pain etiology/location: Ischemic chest pain 100% Pain Classification: Nontraumatic	Heart rate Hypotension Nausea Respiratory depression Respiratory rate Vomiting

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Deaton, 2015[19] USA Setting: ED Risk of bias: Medium	18-65y old w/acute non-injury abdominal pain ≥5 Exclusions: Drug allergy, impairment in renal or hepatic function, hypothyroidism, Addison disease, prostatic hypertrophy, or urethral stricture, taking monoamine oxides inhibitors, tricyclic antidepressants, sedative hypnotics, or known cytochrome P450 3A4 inhibitors within 14d, oral or IV or IM pain medications before enrollment	A: Morphine 0.1 mg/kg IV (n=16) B: Fentanyl 2 mcg/kg NEB (n=16) Rescue: Available at any point during the study according to treating physician preference	Age A:32.38(10.76) B:30.19(10.7) Males A:50% B:38% Weight NR Race/ethnicity A/B: White 75%/56%, African American 12.5%/12.5%, Hispanic 6.25%/25%, Asian American 6.25%/6.25% Pain etiology/location: Abdomen 100% Pain Classification: Nontraumatic	Hypotension Nausea Pain severity
Graudins, 2015[30] New Zealand Setting: ED Risk of bias: Low	3-13y old w/acute limb injury with moderate to severe pain of 6 or more at triage Exclusions: serotonergic antidepressants; previous administration of parenteral or IN analgesics or opioid analgesia; opioid antagonist use; allergy to ketamine, fentanyl, or ibuprofen; aberrant nasal anatomy or acute or chronic nasal problems or nasal trauma that may have precluded adequate intranasal delivery; multiple trauma or head injury with loss of consciousness or cognitive impairment.	A: Fentanyl 1.5mcg/kg IN (n=37) B: Ketamine 1mg/kg IN (n=36) Rescue: Additional IN fentanyl or IV morphine, based on provider preference	Age A:9(6 to 11) B:7(6 to 9.5) Males A:65% B:61% Weight NR Race/ethnicity Pain etiology/location: Upper limb fracture (73%/88.9%), upper limb soft tissue injury (13.5%/8.3%), lower limb fracture (13.5%/0%), lower limb soft tissue injury (0%/2.8%) Pain classification: Traumatic	Any adverse event Emergence delirium Mental status changes Nausea Pain presence Pain severity

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Miller, 2015[58] USA Setting: ED Risk of bias: Low	18-59y old w/abdominal, flank, low back or extremity pain warranting IV opioid treatment Exclusions: O2 sat<95%, SBP<90 or >180, HR<50 or >120, RR<10 or >30, altered mental status, intoxication, fibromyalgia or other chronic pain condition requiring the use of opioids or tramadol as an outpatient, ischemic heart disease, heart failure or unstable dysrhythmias, use of an opioid or tramadol within 4h, drug allergy, required pain medication immediately, pregnant or breast-feeding, history of chronic oxygen-dependent pulmonary disease, hepatic cirrhosis, or dialysis dependent, presence of intracranial mass, a history of psychosis, weight<45kg or >115kg, presence of acute ocular or head trauma	A: Morphine 0.1 mg/kg IV over 5min (max 8mg), second dose could be given as early as 20min (n=21) B: Ketamine 0.3 mg/kg IV infusion over 5min (max 25mg), second dose could be given as early as 20min (n=24) Rescue: If the patient requested a third dose of pain medication the data collection stopped and patient was eligible for open label pain medication of the providers choosing.	Age A:29(10) B:31(12) Males A:43% B:58% Weight NR Race/ethnicity NR Pain etiology/location: Abdomen 71%/65%, back 19%/35%, extremity 10%/0% Pain Classification: Mixed	Any AE Diastolic blood pressure Dissociation Emergence delirium Heart rate Mental status changes Nausea Oxygen saturation Pain severity Respiratory depression Respiratory rate Systolic blood pressure Vomiting
Motov, 2015[57] USA Setting: ED Risk of bias: Low	18-55y old w/acute (within 7d) abdominal, flank, back or musculoskeletal pain NRS≥5/10 and required opioid analgesia Exclusions: pregnancy, breast-feeding, altered mental status, drug allergy, weight <46kg or >115kg, SBP<90 or >180, HR<50 or >150, RR<10 or >30, hx of acute head or eye injury, seizure, intracranial hypertension, chronic pain, renal or hepatic insufficiency, alcohol or drug abuse, psychiatric illness, or recent (4h) opioid use	A: Morphine 0.1 mg/kg IV push over 3 to 5min (mean 7.7mg (1.6)) (n=45) B: Ketamine 0.3 mg/kg IV push over 3 to 5min (mean 21.8mg (4.9)) (n=45) Rescue: NRS ≥5/10 and requested additional pain relief, fentanyl 1 mcg/kg was administered	Age A:36(10.5) B:35(9.5) Males A:37.8% B:33% Weight A:78kg(16.6) B:74kg(15.9) Race/ethnicity: NR Pain etiology/location A/B: Abdominal 69%/73%, flank 20%/16%, back and musculoskeletal 11%/11%, Pain Classification: Mixed	Any AE Diastolic blood pressure Heart rate Mental status changes Nausea Oxygen saturation Pain severity Presence of pain Respiratory rate Systolic blood pressure

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Beaudoin, 2014[70] USA Setting: ED Risk of bias: Low	18-65y old w/moderate to severe acute pain (NRS≥5/10) determined to require opioids by emergency physician, still study eligible if they received previous analgesics prior if NRS was still ≥5/10 Exclusions: Neurologic, respiratory, or hemodynamic compromise; drug allergy, acute psychiatric illnesses, history of stroke, renal impairment (creatinine >2mg/dL), liver failure, or history of cardiac disease (prior myocardial infarction, angina, cardiac stents, or bypass surgery); pregnant or breastfeeding	A: Morphine 0.1mg/kg IV (10mg max), after 10min ketamine 0.15mg/kg (n=20) B: Morphine 0.1mg/kg IV (10mg max), after 10min ketamine 0.3mg/kg (n=20) C: Morphine 0.1 mg/kg IV (10mg max) followed by placebo (n=20) Rescue: Morphine 0.5 to 1mg/kg every 1h PRN targeting reduction of NRS by at least 50%, encouraged to wait at least 30min before determining if rescue analgesia was needed	Age A:37.5(25.5-46.0) B: 32.5 (25.5-41.0) C:37.5(31.5-44.0) Males A:65% B:45% C:75% Weight A: 80.6kg(67.4-99.8) B:86.3kg(68.6-102.1) C:80.6kg (68.2-95.7) Race/ethnicity A/B/C: White 70%/50%/70%; Black 15%/20%/20%, Hispanic 15%/15%/0%, Asian 0%, Other 0%/15%/10% Pain etiology/location: Abdominal 25%/5%/0%; back pain/sciatica 20%/5%/5%; GI 10%/30%/10%; fracture 5%/20%/25%; genitourinary infection 10%/5%/10%; musculoskeletal 5%/10%/15%; orofacial pain/headache 5%/0%/15%; renal colic 10%/15%/5%; sickle cell disease 5%/0%/5%; skin and soft tissue infection 10%/10%/10% Pain Classification: Mixed	Respiratory depression Hypotension Mental status changes Nausea Pain severity Presence of pain Vomiting
Majidinejad, 2014[59] Iran Setting: ED Risk of bias: Unclear	18-55y old w/long bone fracture Exclusions: drug abuse, trauma to the head, symptoms and signs of increased intracranial pressure, decrease LOC, respiratory problems, hx of asthma, contraindications for ketamine (hx of cardiac problems, especially congestive heart failure, ischemic cardiac conditions, HTN, CVA) and morphine (asthma, respiratory problems, hemodynamic instability), drug allergy	A: Morphine 0.1 mg/kg IV (n=63) B: Ketamine 0.5 mg/kg IV (n=63) Rescue: Half initial dose if NRS≥3/10 after 10min	Age A: 53.6(14.3) B:35.1(13.5) Males A:81% B:71.4% Weight NR Race/ethnicity NR Pain etiology/location: Long bone fracture 100% Pain Classification: Traumatic	Emergence delirium Pain severity Presence of pain

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Masoumi, 2014[82] Iran Setting: ED Risk of bias: Low	18-55y old w/renal colic Exclusions: drug allergy, fever >38C, hemodynamic instability, evidence of peritoneal inflammation, pregnancy, proven or suspected aortic aneurysm or dissection, use of any analgesic drug up to 6h prior, heart failure, renal failure, respiratory failure, liver failure, kidney transplant and opioid addiction	A: Morphine 0.1 mg/kg IV over 5-10 min (n=55) B: Acetaminophen 1g IV over 5-10 min (n=55) Rescue: After 30 minutes, if VAS≥5/10 fentanyl 1 mcg/kg IV was administered	Age A: 34.96(8.94) B:36.07(9.7) Males A:72.2% B:79.6% Weight NR Race/ethnicity NR Pain etiology/location: Renal colic 100% Pain Classification: Nontraumatic	Any AE Nausea Pain severity Vomiting
Shervin, 2014[20] Iran Setting: ED Risk of bias: Low	15-50y old w/limb trauma in acute pain with NRS>5/10 Exclusions: opioid use or addiction, recent or hx of TCA, SSRI, MAOI, antipsychotics, and any nonspecified sedative/hypnotic, acute or chronic medical health problems w/ASA classification >2 including upper or lower respiratory tract infection, acute or chronic liver or kidney disease, reactive airway disease, unknown allergies, pregnancy, lactation	A: Morphine 0.1 mg/kg IV (n=43) B: Fentanyl 4 mcg/kg NEB (n=47) Rescue: If NRS≥5/10 after 15 min, morphine 1mg IV every 5 min until NRS<5/10	Age A:26.86(7.73) B:26.8(7.45) Males A:83.7% B:83% Weight A:72.67kg(11.88) B:75.53(13.04) Race/ethnicity NR Pain etiology/location A/B: Wound/soft tissue 34.9%/17%, fracture 41.9%/48.9%, sprain/strain 23.3%/34% Pain Classification: Traumatic	Mental status changes Nausea or vomiting Pain severity
Tran, 2014[27] Vietnam Setting: EMS transport for protracted evacuations in low resource, rural setting Risk of bias: Medium	Trauma patients in need of analgesia, at least 30 months old Exclusions: objections to pain treatment, coma, in-field anesthesia for invasive life support, deep unconsciousness upon first infield contact, prehospital evacuation time of <10min	A: Morphine 5mg (child) or 10mg (adult) IM (n=139) B: Ketamine 0.2 to 0.3 mg/kg slow intermittent IV injection (mean dose 15mg) (n=169) Rescue: NR	Age A:36.9(NR) B:35.5(NR) Males A:80% B:75% Weight NR Race/ethnicity NR Pain etiology/location: Road traffic accident casualties 61%, falls 24%, mine accidents 9% Pain Classification: Traumatic	Nausea or vomiting Pain severity Presence of pain

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Vahdati, 2014[73] Iran Setting: ED Risk of bias: Unclear	18-55y old complaining of headaches due to trauma, VAS≥40 Exclusions: GCS<15, drug allergy or contraindication, fever (>38°C), hemodynamic instability, neurological findings, pregnancy, analgesic within 6h, liver, renal, pulmonary or cardiac disease, transplanted kidney or liver	A: Morphine 0.1 mg/kg IV over 10min (n=30) B: Paracetamol 1g IV over 10min (n=30) Rescue: NR	Age A:32.9(11.1) B:37.6(12.5) Males A:80% B:60% Weight NR Race/ethnicity NR Pain etiology/location: Post-traumatic headache 100% Pain Classification: Traumatic	Any AE Hypotension Mental status changes Nausea Pain severity Vomiting
Eken, 2013[77] Turkey Setting: ED Risk of bias: Low	18-55y old w/moderate to severe acute mechanical low back pain according to 4 point VRS Exclusions: analgesic medications in the last 6h, pregnancy, peritoneal irritation signs, hemodynamic instability, renal transplantation, renal, liver, cardiac or pulmonary failure, malignancy, pain indicating sciatica, positive Straight Leg Raise Test, neurological deficit, known allergy to study drugs, probable renal or biliary colic, illiterate	A: Morphine 0.1 mg/kg IV once (n=45) B: Paracetamol 1g IV once (n=46) Rescue: Fentanyl 1mcg/kg if inadequate relief after 30min	Age total study 31.5(9.5) Males total study 60.6% Weight NR Race/ethnicity NR Pain etiology/location: Acute, mechanical low back pain 100% Pain Classification: Mixed	Any AE Hypotension Mental status changes Nausea or vomiting Pain severity
Craig, 2012[79] UK Setting: ED Risk of bias: Low	16-65y old w/ isolated limb trauma and pain score ≥7/10 Exclusions: Weight <50kg, chest pain, GCS<15, drug allergy, liver disease, or patient clinically jaundiced, major trauma, pregnancy, breast feeding, requiring an immediate limb-saving procedure, extreme distress	A: Morphine 10mg IV infusion over 15min (n=28) B: Paracetamol 1g IV infusion over 15min (n=27) Rescue: Morphine IV titrated to effect in after the initial infusion the patient's pain relief was judged to be inadequate	Age A:35(16-62) B:38(16-64) Males A:53.6% B:55.6% Weight NR Race/ethnicity NR Pain etiology/location A/B: Fracture 50%/59.2%, soft tissue 50%/40.7% Pain Classification: Traumatic	Any AE Pain severity

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Jennings, 2012[64] Australia Setting: EMS-single out-of-hospital ambulance provider Risk of bias: Low/medium	≥18y reporting traumatic pain with VNRS ≥5 after total dose of morphine 5mg IV, speaking and able to rate their pain Exclusions: Drug allergy, pregnant or lactating, current ischemic chest pain or acute pulmonary edema, SBP>180 and evidence of a head injury, history of LOC or GCS score <15, inability to obtain venous access, presumed intoxication with alcohol/illicit substances	A: Ketamine 10 or 20mg bolus, repeat 10mg every 3min until pain free or serious adverse event or arrival at the ED, mean 40.6mg (25) (n=70) B: Morphine 5mg bolus, repeat 1 to 5mg every 5min until pain free or a serious adverse event or arrival at the ED, mean 14.4mg (9.4) (n=65) Rescue: No therapies other than those randomized were allowed	Age A: 41(26-56) B:45(31-66) Males A:64% B:58% Weight NR Race/ethnicity NR Pain etiology/location A/B: Extremity fracture 37%/45%, soft tissue injury 24%/23%, fracture-other 20%/20%, dislocation 16%/11%, burn 3%/1% Pain Classification: Traumatic	Any AE Emergence delirium Heart rate Hypotension Mental status changes Nausea Pain severity Respiratory rate Systolic blood pressure Time to analgesic effect Vomiting
Serinken, 2012[78] Turkey Setting: ED Risk of bias: Low	18-55y old w/acute renal colic, moderate to severe pan on the 4-point verbal scale Exclusions: analgesics within 6h, presented with fever or were hemodynamically unstable, signs of peritoneal irritation or cardiac failure, hx of renal failure, hepatic failure or drug allergy, pregnant, vision problems, ultimately diagnosed with other renal pathology	A: Morphine 0.1 mg/kg IV (n=35) B: Paracetamol 1g IV (n=38) Rescue: Fentanyl 1mcg/kg IV if inadequate pain relief	Age A:31.3(9.0) B:29.1(8.2) Males A:65.7% B:73.7% Weight NR Race/ethnicity NR Pain etiology/location: Renal colic 100% Pain Classification: Nontraumatic	Any AE Hypotension Mental status changes Nausea or vomiting Pain severity Respiratory depression
Smith, 2012[94] USA Setting: EMS-helicopter transport Risk of bias: Medium	18-65y old transported by helicopter for evaluation of traumatic injuries, could report pain and communicate to the medical crew their pain severity on NPS Exclusions: Drug allergy, hypotensive before receiving the first dose of the study drug (SBP<100), in custody, pregnant	A: Morphine 4mg IV every 5min as needed (max 5 doses, mean 3) (n=104) B: Fentanyl 50mcg IV every 5min as needed (max 5 doses, mean 3.3) (n=100) Rescue: NR	Age A:38(NR) B:39(NR) Males A:75% B:76% Weight NR Race/ethnicity A/B: Caucasian 80.8%/81%, African American 16.4%/14%, Other 2.9%/5% Pain etiology/location A/B: Blunt 90%/85%, penetration 10%/15% Pain Classification: Traumatic	Hypotension Pain severity Presence of pain Vomiting

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Kariman, 2011[83] Iran Setting: ED Risk of bias: Low/medium	15-85y old w/isolated extremity trauma, moderate to severe pain per VAS≥4/10 Exclusions: Trauma >6h ago, associated injuries including head and trunk trauma, nonorthopedic limb injuries, GCS<15, abdominal distension, lung disease, hx of a recent dive, pneumothorax, hemothorax, received any form of prehospital analgesia	A: Fentanyl 2 mcg/kg IV, slow injection (n=50) B: Nitrous oxide:oxygen (50:50) self-administered until VAS<4/10 or 15min (n=50) Rescue: NR	Age A:35.8(19.9) B:37.0(20.2) Males A:84% B:72% Weight NR Race/ethnicity NR Pain etiology/location A/B: Fracture 30%/52%, dislocation 70%/48% Pain Classification: Traumatic	Any AE Diastolic blood pressure Heart rate Mental status changes Oxygen saturation Pain severity Respiratory rate Systolic blood pressure
Furyk, 2009[21] Australia Setting: ED Risk of bias: Medium	4-13y old w/pain (sufficient to warrant narcotic analgesia) from a clinically suspected limb fracture Exclusions: ASA grade >1, chronic medical condition (e.g. structural heart disease, hepatic or renal disease), active asthma (requiring preventers or current wheeze), concurrent upper respiratory tract infection or drug allergy	A: Morphine 0.1 mg/kg IV (n=37) B: Fentanyl 4 mcg/kg NEB (max 200 mcg) (n=35) Rescue: NR	Age A:9.4(2.5) B:8.6(2.8) Males NR Weight A:35.1kg(12.6) B:33.6kg(12.7) Race/ethnicity NR Pain etiology/location: Limb fracture 100% Pain Classification: Traumatic	Any AE Nausea Pain severity
Johansson, 2009[65] Sweden Setting: EMS Risk of bias: Low/medium	Adults w/bone fractures in acute pain (NRS>4/10) after morphine 0.1 mg/kg IV Exclusions: Inability to use the rating scale, long-term use of opioids, hx of chronic pain, hx of/or acute MI, unconsciousness	A: Morphine 0.1 mg/kg IV (n=11) B: Ketamine 0.2 mg/kg IV (n=16) Rescue: NR	Age A:70(16) B:74(14) Males A:54.5% B:43.8% Weight A:72.9kg (13.6) B:70.1kg (10.4) Race/ethnicity NR Pain etiology/location: Bone fracture 100% Pain Classification: Traumatic	Heart rate Mental status changes Nausea Oxygen saturation Pain severity Respiratory rate Systolic blood pressure Vomiting

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Borland, 2007[97] Australia Setting: ED Risk of bias: Low	7-15y old w/clinically deformed closed long-bone fractures Exclusions: Received narcotic analgesic within 4h of ED arrival, head injury resulting in impaired judgment, drug allergy, blocked or traumatized nose, preventing nasal administration; or were unable to perform pain scoring	A: Morphine 0.1 mg/kg IV once then 1.0mg every 5min until relief, max dose or patient refused (mean total 0.11 mg/kg) (n=34) B: Fentanyl 1.4 mcg/kg IN once then 15 mcg every 5min until relief, max dose or patient refused (mean total 1.7 mcg/kg) (n=33) Rescue: For inadequate pain relief after 30min, morphine IV was offered and titrated	Age A:10.7(6-15) B:11.7(7-15) Males NR Weight A:41.9kg(19-80) B:45.7(26-88) Race/ethnicity NR Pain etiology/location: Long bone fracture 100% Pain Classification: Traumatic	Pain severity Vomiting
Clark, 2007[89] Canada Setting: ED Risk of bias: Low	6-17y old presenting to ED w/pain from a musculoskeletal injury (extremities, neck, back) in preceding 48h Exclusions: contraindication to a study drug, required resuscitation, open fracture, had an IV line in place, received 1 of the study drugs in the preceding 4h (APAP) or 6h (IBU), or had a significant cognitive impairment	A: Ibuprofen 10 mg/kg (max 600mg) by mouth once (n=112) B: Acetaminophen 15mg/kg (max 650mg) by mouth once (n=112) Rescue: 60min after study drug additional pain medication was allowed, asked every 30min	Age A:11.8(2.8) B:12.0(2.9) Males A:56.9% B:66.4% Weight NR Race/ethnicity NR Pain etiology/location A/B: Soft tissue 41.3%/47.7%, fracture 58.7%/52.3% Pain Classification: Traumatic	Pain severity Presence of pain
Galinski, 2007[66] France Setting: EMS – considered “mobile intensive care units” in route to ED Risk of bias: Low	18-70y old, trauma with severe, acute pain (VAS≥60/100) Exclusions: Respiratory distress, SBP<90, GCS<15, psychiatric history; chronic respiratory, renal, or hepatic failure; drug allergy, treatment of chronic pain or treatment with opioids; incapacity to understand the VAS; pregnancy; indication for local or regional analgesia, already received an opioid analgesic	A: Morphine 0.1 mg/kg IV + ketamine 0.2mg/kg IV over 10min; then morphine 3mg every 5min until VAS≤30/100 (n=38) B: Morphine 0.1mg/kg IV + placebo over 10min, then morphine 3mg every 5min until VAS≤30/100 (n=35) Rescue: NR	Age A:35(13) B:40(14) Males A:75.8% B:71.9% Weight NR Race/ethnicity NR Pain etiology/location A/B: Suspicion of bone fracture 58%/75%; burns 6%/6%, other 36%/19% Pain Classification: Traumatic	Heart rate Mental status changes Nausea or vomiting Oxygen saturation Pain severity Presence of pain Respiratory depression Respiratory rate Systolic blood pressure

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Mahar, 2007[96] USA Setting: ED Risk of bias: Low/medium	8-18y old w/extremity deformity and/or suspected fracture with VAS>50/100 Exclusions: ASA status >2, hx of LOC, altered level of consciousness, multiple traumatic injuries, received prior medication for pain control	A: Morphine 0.1 mg/kg IV (n=40) B: Fentanyl 10-15 mcg/kg, oral transmucosal lozenge (n=47) Rescue: NR	Age A: 11.67(NR) B:11.34(NR) Males A:65% B:64% Weight A:47.6kg(NR) B:43.6kg Race/ethnicity NR Pain etiology/location A/B: Fracture 87.5%/100%, dislocation 5%/0%, soft tissue 7.5%/0% Pain Classification: Traumatic	Any AE Nausea Pain severity Respiratory depression Vomiting
Rickard, 2007[95] Australia Setting: EMS- 2 ambulance services Risk of bias: Medium	18-65y old, severe pain (VRS≥5/10 for cardiac type pain or discomfort persisting 5 minutes or more after glyceryl trinitrate or VRS≥2/10 for noncardiac pain Exclusions: Hypoxia (SpO2 </=85%); hypotension (SBP<110); HR<50 or >150, GCS<15, vomiting, drug allergy, opiate use in the past 24h, unable to provide a VRS	A: Morphine 2.5-5mg IV, then 2 more doses of 2.5-5 mg at intervals ≥5min if the VRS≥3/10 (n=122) B: Fentanyl 180mcg IN, then 2 more doses of 60mcg at intervals ≥5min if VRS≥3/10 (n=136) Rescue: At 15min, morphine 2.5-5mg IV was available if VRS≥3/10, at ≥5min intervals to a max of 20mg	Age A:41.4(13.6) B:43(13.9) Males A:70% B:56% Weight A:80.7kg(16.5) B:81.8kg (14.9) Race/ethnicity NR Pain etiology/location A/B: Fracture/dislocation 37%/33%, chest 15%/14%, back 15%/17%, abdomen 13%/18%, other 20%/17% Pain Classification: Mixed	Any AE Pain severity
Safdar, 2006[85] USA Setting: ED Risk of Bias: Low	18-55y old w/clinical diagnosis of renal colic, VAS≥5/10 or at least "moderate" pain on a 4-category verbal pain scale Exclusions: pregnancy, breastfeeding, contraindication to NSAIDs or opiates, renal dysfunction, analgesics within 6h, hx of bleeding diathesis, confirmed hx of peptic ulcer disease, current use of warfarin, hx of drug dependence or current use of methadone, peritonitis or presence of any peritoneal sign	A: Morphine 5mg IV, then 5 mg IV at 20min if incomplete relief (n=43) B: Ketorolac 15mg IV, then 15mg IV at 20min if incomplete relief (n=43) Rescue: Morphine 5mg IV for persistent pain at 40min, titrated at the discretion of the ED attending	Age A:37.3(10.0) B:39.3(9.9) Males A:67% B:67% Weight NR Race/ethnicity NR Pain etiology/location: Renal colic 100% Pain Classification: Nontraumatic	Mental status changes Nausea Pain severity Presence of pain Vomiting

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Galinski, 2005[93] France Setting: EMS – 5 prehospital "mobile intensive care units" Risk of bias: Low	18-70y with severe, acute pain defined as VAS≥60/100 Exclusions: Presence of chronic respiratory, renal, or hepatic insufficiency, known opioid allergies, treatment of chronic pain or treatment with opioids, incapacity to understand the VAS, acute hemodynamic, respiratory, or neurological compromise, pregnancy, indication for local or regional analgesia, or patients who had already received an opioid analgesic	A: Morphine 0.1 mg/kg IV followed by additional 3mg doses until VAS≤30/100 (n=26) B: Fentanyl 1 mcg/kg IV followed by additional 30mcg doses until VAS≤30/100 (n=28) Rescue: NR	Age A:40(13) B:45(13) Males A:88% B:79% Weight NR Race/ethnicity NR Pain etiology/location: Trauma 73%/50%, nontrauma 27%/50% Pain Classification: Mixed	Heart rate Mental status changes Nausea Oxygen saturation Pain severity Presence of pain Respiratory rate Systolic blood pressure Vomiting
Younge, 1999[16] Australia Setting: ED Risk of bias: Low/medium	3-10y old w/limb fracture Exclusions: patients with head injury, blocked nose or rhinorrhea, requiring immediate IV access, intellectual or visual impairment, hepatic or renal disease, with known allergy to either drug or those who had received opioid analgesia within the previous 24h	A: Morphine 0.2 mg/kg IM (n=23) B: Fentanyl 1 mcg/kg IN (n=24) Rescue: Could be given from 20min onwards	Age A:7.1(NR) B:6.6(NR) Males A:65% B:62.5% Weight NR Race/ethnicity NR Pain etiology/location: Limb fracture 100% Pain Classification: Traumatic	Heart rate Vomiting

Abbreviations: APAP=acetaminophen; ASA=American Society of Anesthesiologists; COPD=chronic obstructive pulmonary disease; CVA=cerebrovascular accident; CVAT=costovertebral angle tenderness; ED=emergency department; EMS=emergency medical services; GCS=Glasgow coma scale; h=hours; HTN=hypertension; hx=history; IBU=ibuprofen; IN=intranasal; IV=intravenous; LOC=loss of consciousness; MAOI=monoamine oxidase inhibitor; mg=milligrams; mmHg=millimeters of mercury; NR=not reported; NSAIDS= nonsteroidal anti-inflammatory drugs; PID= pelvic inflammatory disease; SBP=systolic blood pressure; SSRI= selective serotonin reuptake inhibitors; TCA= tricyclic antidepressants; VAS=visual analog scale; VNRS=verbal numeric rating scale; VRS=verbal rating scale

Table C-2. Study and population characteristics, observational studies

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Griffioen, 2019[105] United States Setting: ED Risk of bias:	Adults presenting to ED with lower extremity fractures Exclusions: NR	A: Morphine IV (n=17) B: Fentanyl IV (n=499) Rescue NR	Age total study 46(13.6) Males total study 73% Weight NR Race/ethnicity: total study Caucasian 72% Pain etiology/location: total study tibia/fibula 66% Pain classification: Traumatic	Presence of pain
Bronsky, 2018[61] United States Setting: EMS Risk of bias: Low	≥18y old with severe pain (≥7/10) Exclusions: Indications other than severe pain, received a combination of analgesics, treated solely by fire department, never visited ED, or received treatment through non-IV route	A: Fentanyl 2 mcg/kg IV q10min prn (max 2 doses, mean morphine equivalent 8.3 (2.4)) (n=79) B: Ketamine 0.3 mg/kg IV q20min prn (max 3 doses, mean morphine equivalent 8.3 (2.8)) (n=79) Rescue NR	Age A: 58.1 (19.9) B: 58.4 (21.7) Males A: 39% B: 39% Weight: NR Race/ethnicity A/B: Caucasian 91%/89%, Black 3%/6%, American Indian 0%/1%, Other 6%/4% Pain etiology/location A/B: Fall 39%/53%, MVC 11%/6%, Assault 3%/3%, Medical complication 10%/3%, Other 20%/28%, Unknown 16%/8% Pain Classification: Mixed	Diastolic blood pressure Heart rate Mental status changes Pain severity Presence of pain Respiratory depression Respiratory rate Systolic blood pressure
Zhang, 2018[106] Australia Setting: EMS Risk of bias: Medium	Patients with a traumatic injury, retrieved from a prehospital site to the ED Exclusions: Patient requiring airway intervention (intubation or laryngeal mast airway)	A: Ketamine+ morphine (n=27) B: Ketamine+fentanyl (n=6) C: Ketamine (n=4) Rescue NR	Age NR Males NR Weight NR Race/ethnicity NR Pain etiology/location: NR Pain Classification: Traumatic	Vomiting

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Oberholzer, 2017[67] Switzerland Setting: EMS Risk of bias: Low	15y old transported by EMS with moderate to severe pain (NRS>3/10) Exclusions: GCS≤12, NACA score ≥VI, patients too unstable or sedated to determine and verbalize 2 NRS scores (at scene and hospital arrival)	A: Morphine IV (mean 7.0 mg (4.6)) (n=107) OR Fentanyl IV (mean 140 mcg (109)) (n=521) B: Ketamine IV (mean 58 mg (37)) (n=137) Rescue NR	Age NR Males NR Weight NR Race/ethnicity NR Pain etiology/location: Trauma 69% Pain Classification: Mixed	Presence of pain
Scharonow, 2017[98] Germany Setting: EMS Risk of bias: Medium	Patients treated with narcotic analgesics by specially trained paramedics Exclusions NR	A: Morphine 2mg/kg IV every 3-5 min until NRS<3 or 10mg (mean 4.38 mg (2.58)) (n=23) B: Fentanyl 0.05-0.1mg IV every 3-5 min until NRS<3 or 0.3mg, (mean 150 mcg (70)) (n=53) Rescue: NR	Age total study: 51.8-66.5y Males total study: 51.8% Weight NR Race/ethnicity NR Pain etiology/location total study: Trauma 68.5%, abdomen 20.8%, ACS 11.7% Pain Classification: Mixed	Pain severity Respiratory depression
Schauer, 2017[62] Afghanistan Setting: Battlefield Risk of bias: Medium	23-28y old with battlefield injury transported directly from point-of-injury to enrolling center Exclusions: NR	A: Morphine (n=66) B: Fentanyl (n=85) C: Ketamine (n=71) Rescue: NR	Age A: 28(23-33) B: 26(21-30) C: 23(20-25) Males A: 98% B: 100% C: 100% Weight NR Race/ethnicity NR Pain etiology/location A/B/C: Blast 45%/45%/52%, penetrating 35%/47%/45%, blunt 15%/8%/4%, burn 3%/2%/0% Pain Classification: Traumatic	Heart rate Mental status changes Respiratory rate Systolic blood pressure

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Daost, 2015[99] Canada Setting: ED Risk of bias: Low	≥16y old who received an opioid in the ED Exclusions: Received ≥1 type of opioid or route of administration, patients who received opioids for palliative care, pregnancy, and patients transferred from or to another hospital	A: Morphine (n=NR)[a] B: Fentanyl (n=NR) Rescue: NR	Age total study 55.8 (20.5) Males total study 47% Weight NR Race/ethnicity NR Pain etiology/location NR Pain Classification: Mixed	Any adverse event Hypotension Respiratory depression
Schacherer, 2015[100] United States Setting: ED Risk of bias: High	3-21y old presenting to ED with expected long-bone fracture Exclusions: Prior administration of narcotics for injury, evidence of multisystem trauma, hemodynamic instability, nasal blockage, drug allergy, patients who received fentanyl IN without the use of drug pathway	A: Morphine IV (n=71) B: Fentanyl 1.5 mg/kg IN (max 100 mcg); second dose in 10 min if pain was not relieved (n=23) Rescue NR	Age A: 9 (5-12) B: 8 (6-12) Males A: 72% B: 61% Weight NR Race/ethnicity NR Pain etiology/location: Long-bone fracture 100% Pain Classification: Traumatic	Presence of pain Time to analgesic effect
Shackelford, 2015[63] Afghanistan Setting: Battlefield Risk of bias: High	Report of 238 traumatic battlefield casualties Exclusions NR	A: Morphine IV (mean 6.9 mg (2.8)); Morphine IM (mean 7.9 mg (3.2)) (n=40) B: Fentanyl IV (mean 77 mcg (38)); fentanyl IM (mean 75 mcg (35)); buccal lozenge 800 mcg (n=117) C: Ketamine IV (mean 43 mg (25)); ketamine IM (mean 58 mg (26)) (n=116) Rescue NR	Age NR Males NR Weight NR Race/ethnicity NR Pain etiology/location NR Pain Classification: Traumatic	Pain severity Heart rate Respiratory depression Respiratory rate Systolic blood pressure

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Wenderoth, 2013[101] United States Setting: ED Risk of bias: Low	Consecutive adult trauma patients with NRS≥4/10 Exclusions: Patients which did not receive one of the opioid/dose combinations as first opioid in ED, patients	A: Morphine 4mg IV (n=84) B: Fentanyl 50 mcg IV (n=84) Rescue NR	Age A: 37 (24-51) B: 38 (24-53) Males A: 67% B: 68% Weight A: 80kg (68-95) B: 81kg (66-98) Race/ethnicity A/B: White 61%/50%, Hispanic 30%/38%, other 9%/12% Pain etiology/location A/B: Blunt trauma 85.9%/83.3%, penetrating trauma 14.1%/16.7% Pain Classification: Traumatic	Hypotension Nausea Pain severity Respiratory depression Time to analgesic effect
Bendall, 2011[102] Australia Setting: EMS Risk of bias: Low	5-15y old with moderate to severe pain (VNRS-11≥5/11) Exclusions NR	A: Morphine IV 5-12y: 0.1 mg/kg q5min (max 4 doses) >12y: 2.5 to 5 mg initially followed by 2.5 mg q2min (max dose 0.5 mg/kg) (n=306) B: Fentanyl IN 1-5y: 45-60 mcg initially followed by 30 mcg q5min prn 6-12y: 60-75 mcg initially followed by 30 mcg q5min prn 13-15y: 180 mcg initially followed by 60 mcg q5min prn (n=306) Rescue NR	Age A: 13 (12-15) B: 13 (11-14) Males NR Weight NR Race/ethnicity NR Pain etiology/location A/B: Trauma 82%/75%, abdominal pain 5%/5%, back pain 1%/2%, non-specific 5%/7%, other 2%/1% Pain Classification: Mixed	Pain severity Presence of pain

Author, year Country Setting Risk of Bias	Eligibility	Intervention and Comparator	Population Characteristics	Outcomes
Garrick, 2011[103] United States Setting: EMS Risk of bias: High	≥6m old who received fentanyl during paramedic transport in moderate to severe pain (≥4/10) Exclusions: History of prior renal or hepatic insufficiency, known opioid allergies, acute hemodynamic, respiratory, or neurological compromise, head trauma, already received opioids, or protocol deviations	A: Morphine 2-5 mg IV repeat q2-5min or morphine 5-10 mg IM repeat q20min (max 15 mg) (n=66) B: Fentanyl 1 mcg/kg IV/IM repeat at half initial dose (max 3 mcg/kg); half-dose used in patients >65y (n=158) Rescue NR	Age NR Males NR Weight NR Race/ethnicity NR Pain etiology/location All: Trauma 65%, medical 31%, cardiac/congestive HF 3%, burns 1% Pain Classification: Mixed	Pain severity Mental status changes Nausea
Fleischman, 2010[104] United States Setting: EMS Risk of bias: Low	≥13y old transported from the scene of the injury and received IV morphine or fentanyl Exclusions: Interhospital transfers	A: Morphine 2-5 mg IV q5min (max 20 mg); Pediatrics 0.1 mg/kg doses (morphine equivalents/kg mean 0.10)) (n=355) B: Fentanyl 50 mcg IV initially, with 25-50 mcg q3-5min (max 200 mcg); Pediatrics 1 mcg/kg doses (morphine equivalents/kg mean 0.12)) (n=363) Rescue NR	Age A: 59 (56-61) B: 61 (59-63) Males A: 42.2% B: 36.6% Weight A: 79.5kg (77-82) B: 78.3kg (75-81) Race/ethnicity: NR Pain etiology/location A/B: Extremity and hip pain or burns 68%/67%, atraumatic abdominal or pelvic pain 8.7%/13.8%, suspected ischemic chest pain 14%/6.3%, back pain 6.4%/9.1%, other chest pain 2.5%/2.8%, head and neck pain 0.6%/0.8% Pain Classification: Mixed	Any adverse event Hypotension Mental status changes Nausea Pain severity Respiratory depression

Abbreviations: ACS=acute coronary syndrome; ED=emergency department; EMS=emergency medical services; GCS=Glasgow coma scale; IM=intramuscular; IN=intranasal; IV=intravenous; kg=kilogram; m=month; mcg=microgram; mg=milligram; min=minute; MVC=motor vehicle crash; n=number; NACA=National Advisory Committee for Aeronautics; NR=not reported; NRS=numerical rating scale; prn=as needed; q=every; VNRS-11=11-point verbal numerical rating score; y=year

[a] Total sample was 31,742 but includes all opioids and no breakdown for each opioid given

Table C-3. Relative risks, opioids versus ketamine

Outcome	Study Design and Sample Size	Setting: Effect Estimates and 95% Confidence Intervals
Key Question 1		
Pain presence – full resolution 30 min	3 RCT (n=172)	ED: Meta-analysis of 3 RCTs RR 1.03 (0.32 to 3.36)
Pain presence – full resolution 60 min	2 RCT (n=146)	ED: Meta-analysis of 2 RCTs RR 1.07 (0.58 to 1.97)
Pain presence- partial resolution - 15 min	5 RCT (n=369)	ED: Meta-analysis of 5 RCTs RR 0.97 (0.65 to 1.45)
Pain presence- partial resolution - 30 min	4 RCT (n=301)	ED: Meta-analysis of 4 RCTs RR 0.98 (0.92 to 1.06)
Pain presence- partial resolution - 60 min	3 RCT (n=208)	ED: Meta-analysis of 3 RCTs RR 1.01 (0.60 to 1.71)
Key Question 2 - graded		
Any adverse event	6 RCT (n=348)	ED: Meta-analysis of 6 RCTs RR 0.63 (0.36 to 1.08)
Hypotension	4 RCT (n=508)	ED: Meta-analysis of 4 RCTs RR 3.74 (0.40 to 34.73)
Mental status changes - dizziness	7 RCT (n=637)	ED: Meta-analysis of 7 RCTs RR 0.44 (0.22 to 0.88)
Mental status changes - drowsiness	4 RCT (n=356)	ED: Meta-analysis of 4 RCTs RR 0.79 (0.18 to 3.42)
Mental status changes - sedation	1 RCT (n=22)	ED: 1 RCT RR 0.29 (0.08 to 1.08)
Mental status changes - confusion	1 RCT (n=75)	ED: One 3-arm trial -morphine IV RR 0.25 (0.08 to 0.78), morphine IM RR 0.37 (0.15 to 0.90)
Mental status changes - difficulty concentrating	1 RCT (n=75)	ED: One 3-arm trial- morphine IV RR 0.36 (0.15 to 0.84); morphine IM RR 0.38 (0.17 to 0.83)
Mental status changes - sleepiness/tired	1 RCT (n=82)	ED: 1 RCT RR 0.94 (0.54 to 1.63)
Respiratory depression	4 RCT (n=491)	ED: Meta-analysis of 4 RCTs RR 3.88 (1.76 to 8.55)
Key Question 2- Additional Findings		
Dissociation – 15 min	1 RCT (n=86)	ED: 1 RCT RR 0.35 (0.01 to 8.33)
Dissociation – study duration	3 RCT (n=213)	ED: Meta-analysis of 3 RCT RR 0.63 (0.08 to 5.08)
Emergence delirium	4 RCT (n=284)	ED: Meta-analysis of 4 RCT RR 0.19 (0.02 to 1.76)
Nausea – 15 min	2 RCT (n=150)	ED: Meta-analysis of 2 RCT RR 0.52 (0.21 to 1.33)
Nausea – 30 min	2 RCT (n=150)	ED: Meta-analysis of 2 RCT RR 1.38 (0.59 to 3.23)
Nausea – 60 min	1 RCT (n=60)	ED: 1 RCT RR 0.33 (0.07 to 1.52)
Nausea – study period	5 RCT (n=540)	ED: Meta-analysis of 5 RCT RR 0.87 (0.54 to 1.41)
Nausea and/or vomiting	1 RCT (n=527)	EMS: 1 RCT RR 4.10 (1.93 to 8.74)
Vomiting	1 RCT (n=45)	ED: 1 RCT RR 1.14 (0.08 to 17.16)

Abbreviations: AR=absolute risk; ED=emergency department; EMS=emergency medical services; IV=intravenous; MD=mean difference; min=minutes; RCT=randomized controlled trial; RD=risk difference

Table C-4. Relative risks, combination opioids and ketamine versus opioids

Outcome	Study Design and Sample Size	Setting: Effect Estimates and 95% Confidence Intervals
Key Question 1		
Pain presence- partial resolution	1 RCT (n=65)	EMS: 1 RCT RR 1.49 (0.9 to 2.46)
Key Question 2- graded		
Any adverse event	1 RCT (n=80)	ED: 1 RCT RR 1.29 (0.53 to 3.12)
Hypotension	1 RCT (n=106)	ED: 1 RCT RR 0.14 (0.01 to 2.7)
Mental status changes - dizziness	2 RCT (n=265)	EMS: 1 RCT RR 12.61 (0.74 to 214.93) ED: 1 RCT RR 0.93 (0.68 to 1.28)
Mental status changes - sedation	1 RCT (n=65)	EMS: 1 RCT RR 3.39 (0.76 to 15.12)
Respiratory depression	3 RCT (n=231)	EMS: 1 RCT RR 0.32 (0.01 to 7.65) ED: Meta-analysis of 2 RCTs RR 0.29 (0.05 to 1.85)
Key Question 2 – additional findings		
Nausea – 60 min	1 RCT (n=200)	ED: 1 RCT RR 0.96 (0.7 to 1.31)
Nausea – study period	1 RCT (n=60)	ED: 1 RCT RR 3.00 (0.33 to 27.23)
Nausea and/or vomiting – 30 min	1 RCT (n=65)	EMS: 1 RCT RR 1.94 (0.65 to 5.81)
Nausea and/or vomiting – study period	1 RCT (n=106)	ED: 1 RCT RR 0.57 (0.18 to 1.84)
Vomiting – 30 min	1 RCT (n=200)	ED: 1 RCT RR 0.77 (0.19 to 1.4)
Vomiting – 60 min	1 RCT (n=200)	ED: 1 RCT RR 0.84 (0.58 to 1.23)
Vomiting – study period	1 RCT (n=80)	ED: 1 RCT RR 1.25 (0.36 to 4.32)

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

Table C-5. Relative risks, opioids versus acetaminophen

Outcome	Study Design and Sample Size	Setting: Supporting Effect Estimates and 95% Confidence Intervals
Key Question 1		
Pain presence- partial resolution - 30 min	1 RCT (n=996)	ED: 1 RCT RR 1.05 (0.99 to 1.11)
Key Question 2- graded		
Any adverse event	6 RCT (n=1,484)	ED: Meta-analysis of 5 RCTs RR 3.88 (1.13 to 13.37)
Hypotension	5 RCT (n=624)	ED: Meta-analysis of 5 RCTs RR 3.86 (0.93 to 15.96)
Mental status changes - dizziness	6 RCT (n=539)	ED: Meta-analysis of 6 RCTs RR 6.51 (4.38 to 9.67)
Mental status changes – “mild” sedation	1 RCT (n=91)	ED: 1 RCT RR 3.07 (0.13 to 73.31)
Key Question 2 – additional findings		
Nausea	4 RCT (n=423)	ED: Meta-analysis of 4 RCT RR 4.93 (0.44 to 55.28)
Nausea and/or vomiting	2 RCT (n=164)	ED: Meta-analysis of 2 RCT RR 0.53 (0.10 to 2.80)
Vomiting	3 RCT (n=368)	ED: Meta-analysis of 3 RCT RR 5.36 (0.99 to 29.04)

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

Table C-6. Relative risks, opioids versus nonsteroidal anti-inflammatory drugs

Outcome	Study Design and Sample Size	Setting: Supporting Effect Estimates and 95% Confidence Intervals
Key Question 1		
Pain presence- partial resolution - 30 min	1 RCT (n=227)	ED: 1 RCT RR 1.05 (0.64 to 1.73)
Pain presence- partial resolution - 60 min	1 RCT (n=243)	ED: 1 RCT RR 0.89 (0.61 to 1.28)
Pain presence- full resolution – 30 min	1 RCT (n=86)	ED: 1 RCT RR 1.4 (0.48 to 4.07)
Key Question 2 - graded		
Any adverse event	2 RCT (n=367)	ED: Meta-analysis of 2 RCTs RR 3.64 (1.93 to 6.86)
Hypotension	1 RCT (n=88)	ED: 1 RCT RR 7 (0.37 to 131.61)
Mental status changes - drowsiness	2 RCT (n=367)	ED: Meta-analysis of 2 RCTs RR 4.90 (0.78 to 30.70)
Mental status changes – dizziness	1 RCT (n=86)	ED: 1 RCT RR 9 (0.5 to 162.16)
Mental status changes – depression	1 RCT (n=88)	ED: 1 RCT RR 5 (0.25 to 101.21)
Key Question 2 – additional findings		
Nausea	3 RCT (n=453)	ED: Meta-analysis of 3 RCT RR 5.94 (1.92 to 18.42)
Vomiting	2 RCT (n=174)	ED: Meta-analysis of 2 RCT RR 2.84 (0.44 to 18.20)

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

Table C-7. Relative risks, acetaminophen versus nonsteroidal anti-inflammatory drugs

Outcome	Study Design and Sample Size	Setting: Effect estimates and 95% Confidence Intervals
Key Question 1		
Pain presence – partial resolution 30 min	1 RCT (n=92)	ED: 1 RCT RR 1.05 (0.64 to 1.72)
Pain presence – partial resolution 60 min	2 RCT (n=340)	ED: Meta-analysis of 2 RCT RR 0.87 (0.56 to 1.34)
Key Question 2		
Any adverse event	2 RCT (n=340)	ED: Meta-analysis of 2 RCT RR 1.33 (0.47 to 3.77)
Nausea	1 RCT (n=140)	ED: 1 RCT RR 3 (0.12 to 72.4)
Vomiting	2 RCT (n=340)	ED: Meta-analysis of 2 RCT RR 1.98 (0.49 to 7.96)

Abbreviations: AR=absolute risk; MD=mean difference; RCT=randomized controlled trial; RD=risk difference

Table C-8. Relative risks, ketamine versus nonsteroidal anti-inflammatory drugs

Outcome	Study Design and Sample Size	Setting: Effect estimates and 95% Confidence Intervals
Key Question 2		
Any adverse event	1 RCT (n=126)	ED: 1 RCT RR 4.47 (2.37 to 8.44)
Mental status changes – dizziness	1 RCT (n=126)	ED: 1 RCT RR 52.63 (3.27 to 845.96)
Nausea	1 RCT (n=126	ED: 1 RCT RR 0.80 (0.32 to 2.02)

Abbreviations: AR=absolute risk; MD=mean difference; RCT=randomized controlled trial; RD=risk difference

Table C-9. Relative risks, morphine versus fentanyl

Outcome	Study Design and Sample Size	Findings Setting: Effect estimates and 95% Confidence Intervals
Key Question 1		
Pain presence – partial resolution 15 min	1 RCT (n=54)	EMS: 1 RCT RR 0.78 (0.37 to 1.64)
Pain presence – partial resolution 30 min	2 RCT (n=163)	EMS: Meta-analysis of 2 RCT RR 0.94 (0.76 to 1.16)
Key Question 2		
Any adverse event	3 RCT (n=391)	EMS: 1 RCT RR 0.54 (0.32 to 0.93)
Hypotension	3 RCT (n=419)	EMS: Meta-analysis of 2 RCT RR 4.44 (0.42 to 47.12) ED: 1 RCT RR 0.33 (0.01 to 7.6)
Mental status changes – lightheadedness, loss of consciousness	1 RCT (n=90)	ED: 1 RCT RR 5.46 (0.27 to 110.58)
Mental status changes – sedation	1 RCT (n=54)	EMS: 1 RCT RR 24.74 (1.53 to 399.35)
Nausea	5 RCT (n=432)	EMS: Meta-analysis of 2 RCT RR 1.03 (0.41 to 2.60) ED: Meta-analysis of 3 RCT RR 1.97 (0.41 to 9.39)
Nausea and/or vomiting	2 RCT (n=397)	ED: Meta-analysis of 2 RCT RR 1.75 (1.01 to 3.03)
Vomiting	6 RCT (n=642)	EMS: Meta-analysis of 3 RCT RR 1.22 (0.36 to 4.09) ED: Meta-analysis of 3 RCT RR 0.29 (0.05 to 1.76)

Abbreviations: AR=absolute risk; ED=emergency department; EMS=emergency medical services; MD=mean difference; RCT=randomized controlled trial; RD=risk difference

Table C-10. Relative risk, additional opioids versus ketamine, Key Question 4

Outcome	Study Design and Sample Size	Setting: Supporting Effect Estimates and 95% Confidence Intervals
Key Question 4 – graded		
Any adverse event	1 RCT (n=135)	EMS: 1 RCT RR 0.36 (0.18 to 0.7)
Hypotension	1 RCT (n=135)	EMS: 1 RCT RR 3.23 (0.13 to 77.87)
Mental status changes - GCS≤13	1 RCT (n=135)	EMS: 1 RCT RR 0.36 (0.04 to 3.36)
Key Question 4 – additional findings		
Nausea	2 RCT (n=162)	EMS: Meta-analysis of 2 RCT RR 1.06 (0.19 to 5.83)
Vomiting	2 RCT (n=162)	EMS: Meta-analysis of 2 RCT RR 0.24 (0.02 to 2.24)
Emergence delirium	1 RCT (n=135)	EMS: 1 RCT RR 0.12 (0.01 to 2.18)

Abbreviations: EMS=emergency medical services; GCS=Glasgow Coma Scale; OBS=observational; RCT=randomized controlled trial; RD=risk difference; vs=versus

Table C-11. Contraindications to analgesics, per package insert[112-125]

Analgesic	Contraindications	Warning/Precautions
Morphine PO, IV, IM	-Known hypersensitivity -Significant respiratory depression -Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment -Concurrent use of MAOIs or use within the past 14 days -Known or suspected GI obstruction, including paralytic ileus	-Life-threatening respiratory depression in patients with chronic pulmonary disease or in the elderly, cachectic or debilitated patients -Adrenal insufficiency -Risks of use in patients with increased intracranial pressure, brain tumors, head injury, impaired consciousness -Severe hypotension -IV/IM only: cardiovascular instability
Fentanyl IV, IM	-Hypersensitivity	-Risk of skeletal muscle rigidity and skeletal muscle movement -Severe cardiovascular depression -Serotonin syndrome -Adrenal insufficiency -Risks of use in patients with increased intracranial pressure, brain tumors, head injury, impaired consciousness
Fentanyl -IN	-Opioid non-tolerant patients -Management of acute or postoperative pain including headache/migraine or dental pain -Intolerance or hypersensitivity	-Clinically significant respiratory and CNS depression can occur -Do not convert patients from other fentanyl products on a mcg per mcg basis, or substitute -Can be fatal to a child, ensure proper storage and disposal -Use with other CNS depressants and potent CYP450 3A4 inhibitors may increase depressant effects -Titrate cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression and in patients susceptible to intracranial effects of CO retention
Fentanyl - transmucosal lozenge	-Opioid non-tolerant patients. -Significant respiratory depression -Management of acute or postoperative pain including headache/migraines and dental pain -Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment -Known or suspected gastrointestinal obstruction, including paralytic ileus -Known hypersensitivity	-Life-threatening respiratory depression in patients with chronic pulmonary disease or in elderly, cachectic, or debilitated patients -Serotonin syndrome -Adrenal insufficiency -Severe hypotension -Risks of use in patients with increased intracranial pressure, brain tumors, head injury, or impaired consciousness
Ketamine – IV	-In those whom a significant elevation of blood pressure would constitute serious hazard -Hypersensitivity	-HTN or cardiac decompensation -Postoperative operative confusion states may occur during recovery period -Respiratory depression
Ketamine - IN	-Not FDA approved for pain, no label	-Not FDA approved for pain, no label
APAP- IV, PO	-Known hypersensitivity -Severe hepatic impairment or severe active liver disease	-Caution in patients with active hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment -Administration in doses higher than recommended may result in hepatic injury, including the risk of liver failure and death

Analgesic	Contraindications	Warning/Precautions
Ketorolac – IV, PO	-Known hypersensitivity -Active PUD, recent GI bleeding, perforation, history of PUD or GIB -Patients who have experienced asthma, urticarial, or allergic type reactions after taking aspirin or other NSAIDs -Prophylactic analgesic before any major surgery -CABG -Advanced renal impairment or in patients at risk of renal failure due to volume depletion -Labor and delivery -Suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis, and those at high risk for bleeding -In patients currently receiving aspirin, NSAIDs, probenecid or pentoxifylline IV only: Neuraxial (epidural or intrathecal) administration	-Do not exceed use for 5 days (combined duration for all routes) -Not indicated for use in pediatric patients -Most serious risks include ulceration, bleeding, perforation, hemorrhage, renal effects, impaired renal function, anaphylactic reactions, cardiovascular effects, and skin reactions
Ibuprofen – IV, PO	-Known hypersensitivity -CABG -History of asthma, urticarial, or allergic type reactions after taking aspirin or other NSAIDs	-Hypertension -Heart failure and edema -Renal toxicity -Anaphylactic reactions -Serious skin reactions -Premature closure of fetal ductus arteriosus -Hematologic toxicity -IV only: Hepatotoxicity, exacerbation of asthma related to aspirin sensitivity, hematologic toxicity
Nitrous oxide[a]	-Known hypersensitivity -Patients having undergone vitreoretinal surgery and presence of intraocular gas bubble -Should not be administered without oxygen	-May be addictive -Avoid use in pneumothorax, pneumocephalus, middle ear surgery, bowel obstruction -Prolonged use may produce neurologic dysfunction -Do not use in patients who have had intravitreal gas bubbles unless completely reabsorbed

Abbreviations: APA=acetaminophen; CABG=coronary artery bypass graft; CNS=central nervous system; CO=carbon dioxide; CYP=cytochrome P; FDA=Food and Drug Administration; GI=gastrointestinal; IM=intramuscular; IN=intranasal; IV=intravenous; MAOI=monoamine-oxidase inhibitors; NSAIDs=nonsteroidal anti-inflammatory drugs; PO=by mouth; PUD=peptic ulcer disease

[a]:FDA label unavailable, source as referenced

Appendix D. Risk of Bias Assessment

Table D-1. Risk of bias assessment

Study, Year	Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of Outcome assessors	Incomplete outcome data	Selective outcome reporting	Risk of bias
Sotoodehnia, 2019[90]	Unclear	Unclear	Low	Low	Low	Low	Low
Vahedi, 2019[91]	Unclear	Unclear	Low	Unclear	Low	Low	Low
Verki, 2019[51]	Unclear	Unclear	Low	Unclear	Low	Low	Low
Frey, 2019[17]	Low	Low	Low	Unclear	Low	Low	Low
Abbasi, 2018[71]	Unclear	Unclear	Low	Low	Low	Low	Low
Al, 2018[80]	Low	Low	Low	Unclear	Low	Low	Low
Burnett, 2018[a28]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Cenker, 2018[87]	Unclear	Low	Low	Low	Low	Low	Low
Cozzi, 2018[88]	Low	Low	Low	Unclear	Low	Low	Low
Hosseininejad, 2018[68]	Low	Low	Low	Low	Low	Low	Low
Jahanian, 2018[60]	Low	Low	Low	Low	Low	Low	Low
Mohammadshahi, 2018[72]	Low	Low	Low	Unclear	Low	Low	Low
Motov, 2018[55]	Low	Unclear	Low	Low	Low	Low	Low
Quinn, 2018[52]	Low	Unclear	Low	Low	Low	Low	Low
Farina, 2017[54]	Unclear[b]	Unclear[b]	Low	Low	Low	Low	Low
Le May, 2017[86]	Low	Low	Low	Unclear	Low	Low	Low
Mahshidfar, 2017[56]	Unclear	Unclear	Low	Unclear	Low	Low	Low
Masoumi, 2017[84]	High[c]	High[c]	Low	Low	Low	Low	Medium
Reynolds, 2017[29]	Low	Low	Low	Low	Low	Low	Low
Sin, 2017[69]	Low	Low	Low	Low	Low	Low	Low
Jalili, 2016[74]	Low	Low	Low	Low	Unclear	Low	Low
Mollaei, 2016[81]	Low	Unclear	Low	Low	Unclear	Low	Low
Pathan, 2016[75]	Low	Low	Low	Low	Low	Low	Low
Serinken, 2016[76]	Low	Low	Low	Low	Low	Low	Low
Shimonovich, 2016[53]	High	High	High	High	High	Low	High[d]
Weldon, 2016[92]	Low	Low	Low	Unclear	Low	Low	Low
Deaton, 2015[19]	Low	Low	Low	Low	High[e]	Low	Medium
Graudins, 2015[30]	Low	Unclear	Low	Unclear	Low	Low	Low
Miller, 2015[58]	Unclear	Low	Low	Low	Low	Low	Low
Motov, 2015[57]	Low	Unclear	Low	Low	Low	Low	Low
Beaudoin, 2014[70]	Low	Low	Low	Low	Low	Low	Low
Majidinejad, 2014[59]	Unclear	Unclear	Low	Unclear	Unclear	Low	Unclear
Masoumi, 2014[82]	Low	Low	Low	Unclear	Low	Low	Low
Shervin, 2014[20]	Low	Low	Low	Low	Low	Present[f]	Low
Tran, 2014[27]	High	Low	High	High	Low	Present[g]	Medium[h]

Study, Year	Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of Outcome assessors	Incomplete outcome data	Selective outcome reporting	Risk of bias
Vahdati, 2014[73]	Low	Unclear	Low	Unclear	Unclear	Low	Unclear
Eken, 2013[77]	Low	Low	Low	Low	Low	Low	Low
Craig, 2012[79]	Unclear	Low	Low	Unclear	Low	Low	Low
Jennings, 2012[64]	Low	Low	High	Unclear	Low	Low	Low/Medium[i]
Serinken, 2012[78]	Unclear	Low	Low	Unclear	Low	Low	Low
Smith, 2012[94]	High[j]	High[j]	Low	Low	Low	Low	Medium
Kariman, 2011[83]	Low	Low	High	High	Low	Low	Low/Medium[k]
Furyk, 2009[21]	Low	Low	High	Unclear	Low	Present[l]	Medium[m]
Johansson, 2009[65]	Unclear	Unclear	High	High	Low	Low	Low/Medium[n]
Borland, 2007[97]	Unclear	Low	Low	Unclear	Low	Low	Low
Clark, 2007[89]	Low	Low	Low	Unclear	Low	Low	Low
Galinksi, 2007[66]	Low	Low	Low	Low	Low	Low	Low
Mahar, 2007[96]	Low	Low	High	Unclear	Low	Low	Low/Medium[o]
Rickard, 2007[95]	Low	Low	High	High	Low	Low	Medium
Safdar, 2006[85]	Unclear	Low	Low	Low	Low	Present[p]	Low
Galinski, 2005[93]	Low	Low	Low	Low	Low	Low	Low
Younge, 1999[16]	Unclear	Low	High	High	Unclear	Low	Low/Medium[q]

[a] Only source of information is the registration in www.clinicaltrials.gov

[b] Although randomization procedures were not reported thus rated unclear, authors report an imbalance in baseline pain scores thus used and adjusted analysis for this outcome. Other characteristics were stated to be balanced.

[C] Despite non-random and lack of allocation concealment (used every other patient), baseline characteristics were similar at the start of the trial.

[d] Used a personal ID number for randomization which was not concealed, the trial was open-label, high differential attrition between ketamine (30%) and both morphine arms (IV 8%, IM 10%) that could be related to the study outcomes

[e] Attrition at 20% without methods to handle dropouts, didn't use ITT.

[f] Methods indicate that vitals and oxygenation were collected but the results are not reported

[g] Methods indicate that blood pressure and heart rate were collected but the results are not reported.

[h] Non-random assignment (clustered randomization using every other month) but baseline characteristics are balanced at the start of the trial. Not blinded and all subjective outcomes.

[i] Low for HR, BP, RR, vomiting, hypotension. Medium for pain, time to analgesic effect, mental status changes, nausea, emergence delirium, any adverse event.

[j] Despite non-random drug assignment (even and odd calendar day methods) the baseline characteristics were similar at the start of the trial.

[k] Low for BP, HR, RR, respiratory depression. Medium for pain, any AE, emergence delirium

[l] Methods indicate that heart rate, respiratory rate, GCS and oxygen saturation were collected but the results are not reported.

[m] Patient were aware of drug assignment, no placebos were used. Only subjective outcomes thus all medium

[n] Low for vomiting, blood pressure, heart rate, respiratory rate, oxygen saturation. Medium for pain, nausea and mental status changes

[o] Low for vomiting, blood pressure, heart rate, respiratory rate, oxygen saturation. Medium for pain, nausea and mental status changes

[p] Methods indicate that blood pressure, heart rate, respiratory rate and oxygen saturation were collected but the results are not reported

[q] Low for bradycardia and vomiting, medium for pain

Table D-2. Risk of bias assessment- cohort

Study, Year	Representative-ness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-up long enough	Adequacy of follow-up of cohorts	Risk of Bias
Griffioen, 2019[105]	*Somewhat representative	*Drawn from same community	*Secure record	*Yes	Uncontrolled	*Secure records	*Yes	No statement	Medium
Bronsky, 2018[61]	*Truly representative	*Drawn from same community	*Secure record	*Yes	**Controls for multiple factors	*Secure records	Unknown	*Complete follow-up	Low
Oberholzer, 2017[67]	*Truly representative	*Drawn from same community	*Secure record	*Yes	**Controls for multiple factors	*Secure records	*Yes	*Complete follow-up	Low
Scharonow, 2017[98]	*Truly representative	*Drawn from same community	*Secure record	*Yes	Uncontrolled	*Secure records	Unknown	*Complete follow-up	Medium
Schauer, 2017[62]	Selected group of users	*Drawn from same community	*Secure record	*Yes	*Controlled for single factor	*Secure records	Unknown	No statement	Medium
Daoust, 2015[99]	*Somewhat representative	*Drawn from same community	*Secure record	*Yes	**Controls for multiple factors	*Secure records	*Yes	*Subjects lost unlikely to introduce bias	Low
Shacherer, 2015[100]	*Somewhat representative	*Drawn from a different source	*Secure record	*Yes	Uncontrolled	*Secure records	*Yes	Not quantified, no explanation	High
Shackelford, 2015[63]	Selected group of users	*Drawn from same community	*Secure record	*Yes	Uncontrolled	*Secure records	Unknown	Inadequate follow-up rate	High
Wenderoth, 2013[101]	*Somewhat representative	*Drawn from same community	*Secure record	*Yes	**Controls for multiple factors	*Secure records	*Yes	Inadequate follow-up rate	Low
Bendall, 2011[102]	*Truly representative	*Drawn from same community	*Secure record	*Yes	**Controls for multiple factors	*Secure records	*Yes	Inadequate follow-up rate	Low
Fleischman, 2010[104]	*Truly representative	Drawn from a different source	*Secure record	*Yes	**Controls for multiple factors	*Secure records	*Yes	*Subjects lost unlikely to introduce bias	Low

Study, Year	Representative-ness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-up long enough	Adequacy of follow-up of cohorts	Risk of Bias
Garrick, 2011[103]	*Truly representative	Drawn from a different source	*Secure record	*Yes	Uncontrolled	*Secure records	Unknown	Inadequate follow-up rate	High

Table D-3. Risk of bias assessment- case control

Study, Year	Case definition	Representative-ness of the cases	Selection of controls	Comparability of cases and controls	Ascertainment of exposure	Same ascertainment for cases and controls	Non-response rate	Risk of Bias
Zhang, 2018[106]	*Independent validation	*Consecutive	*Community controls	Uncontrolled	*Secure records	*Yes	NA	Medium

Abbreviations: NA=not applicable.

Appendix E. Strength of Evidence Assessments

Table E-1. Strength of evidence ratings for the comparison of opioids vs. ketamine, Key Questions 1 and 2

Outcome	Conclusions statement, rationale[a]	Study Design and Sample Size	Study Limitations[b]	Consistency[c]	Directness[d]	Precision[e]	Publication Bias[f]	Strength of Evidence
Pain severity – 15 min	**There is no evidence of a clinically important difference between opioids and ketamine in the change of pain scores in 15 min.** **ED**: Meta-analysis of 12 RCTs found MD 0.35 (-0.36 to 1.06) at 15 min	12 RCTs (n=1128)	Low	Inconsistent	Indirect	Precise	Unsuspected	Low
Pain severity – 30 min	**There is no evidence of a clinically important difference between opioids and ketamine in the change of pain scores in 30 min.** **ED:** Meta-analysis of 12 RCTs found MD 0.26 (-0.23 to 0.75) at 30 min	12 RCTs (n=1153)	Low	Inconsistent	Indirect	Precise	Unsuspected	Low

Outcome	Conclusions statement, rationale[a]	Study Design and Sample Size	Study Limitations[b]	Consistency[c]	Directness[d]	Precision[e]	Publication Bias[f]	Strength of Evidence
Pain severity – 60 min	**There is no evidence of a clinically important difference between opioids and ketamine in the change of pain scores in 60 min.** **EMS**: 1 RCT found MD -0.4 (-0.8 to 0.09) over the prehospital period. 1 OBS study found the decrease in pain score to be greater with ketamine vs. morphine over the prehospital period [-5.5(3.1) vs. -2.5 (2.4), p<0.001] **ED:** Meta-analysis of 11 RCTs found MD -0.36 (-0.94 to 0.23) at 60 min	12 RCTs (n=1409) 1 OBS (n=158)	Low	Inconsistent	Indirect	Precise	Unsuspected	Low
Presence of pain – full resolution 15 min	**Inconclusive.** **ED:** 1 RCT AR 16.7% vs. 50% RD -33% (-53 to -9) Single study with other domain limitations.	1 RCT (n=60)	Low	Unknown	Indirect	Precise	Unsuspected	Insufficient
Presence of pain – full resolution 30 min	**Inconclusive.** **ED**: Meta-analysis of 3 RCTs found AR 26.7% vs. 27.9% RD -1% (-39 to 38) CI includes appreciable harms and benefit beyond CID in either direction.	3 RCT (n=172)	Low	Consistent	Indirect	Very imprecise	Unsuspected	Insufficient

Outcome	Conclusions statement, rationale[a]	Study Design and Sample Size	Study Limitations[b]	Consistency[c]	Directness[d]	Precision[e]	Publication Bias[f]	Strength of Evidence
Presence of pain – full resolution 60 min	**Inconclusive**. **ED**: Meta-analysis of 2 RCTs found AR 23.3% vs. 21.9% RD 1% (-13 to 14) CI includes appreciable harms and benefit beyond CID in either direction.	2 RCT (n=146)	Low	Consistent	Indirect	Very imprecise	Unsuspected	Insufficient
Presence of pain – partial resolution 15 min	**Inconclusive.** **ED**: Meta-analysis of 5 RCTs found AR 76.1% vs. 77.3% RD 2% (-25 to 28) CI includes appreciable harms and benefit beyond CID in either direction.	5 RCT (n=369)	Low	Inconsistent	Indirect	Very imprecise	Unsuspected	Insufficient
Presence of pain – partial resolution 30 min	**Inconclusive.** **ED**: Meta-analysis of 4 RCTs found AR 74.5% vs. 75.7% RD -1% (-6 to 4) CI includes appreciable harms and benefit beyond CID in either direction.	4 RCT (n=301)	Low	Consistent	Indirect	Imprecise	Unsuspected	Insufficient

Outcome	Conclusions statement, rationale[a]	Study Design and Sample Size	Study Limitations[b]	Consistency[c]	Directness[d]	Precision[e]	Publication Bias[f]	Strength of Evidence
Presence of pain – partial resolution 60 min	**Inconclusive.** **EMS:** 1 OBS study found more patients to have at least 50% improvement in pain scores with ketamine over the prehospital period. **ED**: Meta-analysis of 3 RCTs found AR 76.9% vs. 74.0% RD 1% (-38 to 39) CI includes appreciable harms and benefit beyond CID in either direction.	3 RCT (n=208) 1 OBS (n=158)	Low	Inconsistent	Indirect	Very imprecise	Unsuspected	Insufficient
Time to analgesic effect – onset	**Inconclusive**. **ED**: 1 RCT found time to onset (min) IN ketamine 14.3 (9.8-18.8) IV morphine 8.9 (6.6-11.2) IM morphine 26.0 (20.3-31.7) IN ketamine v IV morphine p=0.3 IN ketamine v IM morphine p=0.003 Single trial with high risk of bias and other domains with limitation.	1 RCT (n=48)	High	Inconsistent	Indirect	Imprecise	Unsuspected	Insufficient

Outcome	Conclusions statement, rationale[a]	Study Design and Sample Size	Study Limitations[b]	Consistency[c]	Directness[d]	Precision[e]	Publication Bias[f]	Strength of Evidence
Time to analgesic effect – max effect	**Inconclusive.** **ED**: 1 RCT found time to max effect (min) IN ketamine 40.4 (33.9 -46.9) IV morphine 33.4 (26.2-40.6) IM morphine 46.7 (41.1-52.3) IN ketamine v IV morphine p=0.386 IN ketamine v IM morphine p=0.441 Single trial with high risk of bias and other domains with limitation	1 RCT (n=48)	High	Inconsistent	Indirect	Imprecise	Unsuspected	Insufficient
Any adverse event	**Opioids may cause fewer total adverse events than ketamine.** **EMS:** No data **ED**: Meta-analysis of 6 RCTs over the study period AR 50.0% vs. 82.4% RD -30% (-56 to -4) Two RCTs reported AEs at 15 min (pooled: RD -39% (-53 to -24) and at 30 min (pooled: RD -19% (-53 to 15) are generally in support of the conclusion.	8 RCTs (n=398)	Low	Inconsistent	Indirect	Imprecise	Unsuspected	Low

Outcome	Conclusions statement, rationale[a]	Study Design and Sample Size	Study Limitations[b]	Consistency[c]	Directness[d]	Precision[e]	Publication Bias[f]	Strength of Evidence
Hypotension	**Inconclusive.** **EMS**: No data **ED**: Meta-analysis of 4 RCTs over the study period AR 3.6% vs. 0% RD 8% (-20 to 37) CI includes appreciable harms and benefit beyond CID in either direction.	4 RCTs (n=508)	Low	Inconsistent	Indirect	Very imprecise	Unsuspected	Insufficient
Mental status Changes-dizziness	**Opioids cause less dizziness than ketamine.** **EMS**: No data **ED**: Meta-analysis of 7 RCTs over the study period AR 25.4% vs. 43.5% RD -29% (-52 to -6) Two RCTs reported dizziness at 15 min (pooled: RD -25% (-40 to -10) and at 30 min (pooled: RD -20% (-63 to 23) are generally in support of the conclusion. 1 RCT also reported dizziness at 60 min (RD -13% (-34 to 9).	9 RCTs (n=723)	Low	Inconsistent	Indirect	Precise	Unsuspected	Low

Outcome	Conclusions statement, rationale[a]	Study Design and Sample Size	Study Limitations[b]	Consistency[c]	Directness[d]	Precision[e]	Publication Bias[f]	Strength of Evidence
Mental status changes-drowsiness	**Inconclusive.** **EMS**: No data **ED**: Meta-analysis of 4 RCTs of the study period AR 8.5% vs. 11.2% RD -2% (-19 to 15) CI includes appreciable harms and benefit beyond CID in either direction.	4 RCTs (n=356)	Low	Consistent	Indirect	Very imprecise	Unsuspected	Insufficient
Mental status change – GCS	**Inconclusive.** **EMS:** 1 OBS study found small decrease in GCS score in both groups and no difference in the change from baseline between arms [mean (SD) -0.1 (0.8) vs. 0.03 (0.4), p=0.16] Single study with unknown consistency and other domain limitations.	1 OBS (n=158)	Low	Unknown	Direct	Imprecise	Unsuspected	Insufficient
Mental status changes-sedation	**Inconclusive.** **EMS:** No data **ED**: 1 RCT found sedation over the study period in 18.2% vs. 63.6% of patients, RD -45% (-70 to -5). A second trial found sedation scores to be similar between groups.	2 RCT (n=95)	Low	Inconsistent	Indirect	Imprecise	Unsuspected	Insufficient

Outcome	Conclusions statement, rationale[a]	Study Design and Sample Size	Study Limitations[b]	Consistency[c]	Directness[d]	Precision[e]	Publication Bias[f]	Strength of Evidence
Mental status changes-confusion	**Inconclusive.** **EMS:** No data **ED:** 1 RCT with 3 arms (2 opioid, 1 ketamine) found confusion over the study period in 33.3% vs. 50% of patients. RD -38% (-58 to -11) RD -31% (-53 to -5) Single study with high risk of bias, unknown consistency and other domain limitations.	1 RCT (n=75)	High	Unknown	Indirect	Precise	Unsuspected	Insufficient
Mental status changes-difficulty concentrating	**Inconclusive.** **EMS:** No data **ED:** 1 RCT with 3 arms (2 opioid, 1 ketamine) found difficulty concentrating over the study period in 21.6% vs. 58.3% of patients. RD -38% (-58 to -10) RD -36% (-57 to -9) Single study with high risk of bias, unknown consistency and other domain limitations.	1 RCT (n=75)	High	Unknown	Indirect	Precise	Unsuspected	Insufficient

Outcome	Conclusions statement, rationale[a]	Study Design and Sample Size	Study Limitations[b]	Consistency[c]	Directness[d]	Precision[e]	Publication Bias[f]	Strength of Evidence
Mental status changes-sleepiness/tired	**Inconclusive.** **EMS:** No data **ED:** 1 RCT found sleepiness/tired to occur in 36.6% vs. 46.3%, RD -2% (-22 to 18) CI includes appreciable harms and benefit beyond CID in either direction.	1 RCT (n=82)	Low	Unknown	Indirect	Very Imprecise	Unsuspected	Insufficient
Mental status changes - RAAS	**Inconclusive.** **EMS:** No data **ED:** 1 RCT evaluated RAAS scores at various times throughout the trial and found no significant differences between groups. Median scores were 0 in both arms at all evaluated times. Single study with unknown consistency and other domain limitations.	1 RCT (n=36)	Low	Unknown	Indirect	Imprecise	Unsuspected	Insufficient

Outcome	Conclusions statement, rationale[a]	Study Design and Sample Size	Study Limitations[b]	Consistency[c]	Directness[d]	Precision[e]	Publication Bias[f]	Strength of Evidence
Respiratory depression	**Opioids may cause more respiratory depression than ketamine.** **EMS**: 1 observational study (n=158) 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 over the study period AR 11.5% vs 2.4% RD 4% (-2 to 11)	4 RCTs (n=491) 1 OBS (n=158)	Low	Inconsistent	Indirect	Imprecise	Unsuspected	Low

Abbreviations: AR=absolute risk; CID=clinically important difference; ED=emergency department; EMS=emergency medical services; NA=not applicable; OBS=observational; RCT=randomized controlled trial; RD=risk difference

[a]: Rationale is provided for inconclusive statements (with insufficient strength of evidence).

[b]: Study limitations were downgraded when the majority of the evidence base came from medium or high risk of bias studies.

[c]: Consistency was judged using the I2 statistic when meta-analysis was conducted, with values over 50% considered to be inconsistent. When data were not pooled, we inspected study level results for overall agreement in the direction and magnitude of effects. When evidence was available from trials and observational studies, we considered agreement of direction and magnitude of effect from these sources.

[d]: Directness was downgraded when the majority of evidence for the given comparison/outcome came from emergency department studies rather than prehospital studies.

[e]: Precision was judged using the effect estimate and clinically important difference set for the outcome. Estimates were considered imprecise if the confidence interval crossed the clinically important difference. Estimates were considered very imprecise when the confidence interval spanned the clinically important difference in both directions, thus uninformative.

[f]: Publication bias was judged using p-value <0.05 (when data was meta-analyzed), suggesting presence of publication bias.

Table E-2. Strength of evidence ratings for the comparison of additional opioid vs. switching to ketamine, Key Questions 3 and 4

Outcome	Conclusions statement, rationale	Study Design and Sample Size	Study Limitations[a]	Consistency[b]	Directness[c]	Precision[d]	Publication Bias[e]	Strength of Evidence
Pain severity	**Adding ketamine may reduce pain more than giving additional opioids.** **EMS**: Meta-analysis of 2 RCTs found MD 1.99 (0.95 to 3.03) over the prehospital period.	2 RCT (n=162)	Medium	Consistent	Direct	Imprecise	Unsuspected	Low
Presence of pain	**Inconclusive.** No data	None	NA	NA	NA	NA	NA	Insufficient
Time to analgesic effect	**Adding ketamine may be quicker to reduce pain to a clinically important difference compared to giving additional opioids.** **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.	1 RCT (n=135)	Medium	Unknown	Direct	Precise	Unsuspected	Low
Any adverse event	**Inconclusive.** **EMS**: 1 RCT found total AEs in 13.8% vs. 38.6% of patients. RD -25% (-38 to -1) Single study with unknown consistency and additional domain limitations.	1 RCT (n=135)	Medium	Unknown	Direct	Imprecise	Unsuspected	Insufficient

Outcome	Conclusions statement, rationale	Study Design and Sample Size	Study Limitations[a]	Consistency[b]	Directness[c]	Precision[d]	Publication Bias[e]	Strength of Evidence
Hypotension	**Inconclusive.** **EMS**: 1 RCT found hypotension in 1.5% vs. 0% of patients. RD 2% (-40 to 9) Single study with unknown consistency and additional domain limitations. CI crosses appreciable differences in either direction.	1 RCT (n=135)	Low	Unknown	Direct	Very Imprecise	Unsuspected	Insufficient
Mental status Changes – sedation	**Inconclusive.** **EMS**: 1 RCT found no events in either arm. Single study with unknown consistency and additional domain limitations.	1 RCT (n=27)	Medium	Unknown	Direct	Precise	Unsuspected	Insufficient
Mental status changes – GCS score ≤13	**Inconclusive.** **EMS**: 1 RCT found reduced GCS score in 1.5% vs. 4.3% of patients. RD -3% (-10 to 5) Single study with unknown consistency and additional domain limitations. CI crosses appreciable differences in either direction.	1 RCT (n=135)	Medium	Unknown	Direct	Very imprecise	Unsuspected	Insufficient
Respiratory depression	**Inconclusive.** No data.	None	NA	NA	NA	NA	NA	Insufficient

Abbreviations: NA=not applicable; OBS=observational; RCT=randomized controlled trial

[a]: Rationale is provided for inconclusive statements (with insufficient strength of evidence).

[b]: Study limitations were downgraded when the majority of the evidence base came from medium or high risk of bias studies.

[c]: Consistency was judged using the I2 statistic when meta-analysis was conducted, with values over 50% considered to be inconsistent. When data were not pooled, we inspected study level results for overall agreement in the direction and magnitude of effects. When evidence was available from trials and observational studies, we considered agreement of direction and magnitude of effect from these sources.

[d]: Directness was downgraded when the majority of evidence for the given comparison/outcome came from emergency department studies rather than prehospital studies.

[e]: Precision was judged using the effect estimate and clinically important difference set for the outcome. Estimates were considered imprecise if the confidence interval crossed the clinically important difference. Estimates were considered very imprecise when the confidence interval spanned the clinically important difference in both directions, thus uninformative.
[f]: Publication bias was judged using p-value <0.05 (when data was meta-analyzed), suggesting presence of publication bias.

Table E-3. Strength of evidence ratings for the comparison of opioids plus ketamine vs. opioids

Outcome	Conclusions statement, rationale	Study Design and Sample Size	Study Limitations[a]	Consistency[b]	Directness[c]	Precision[d]	Publication Bias[e]	Strength of Evidence
Pain severity – 15 min	**Combining an opioid and ketamine may reduce pain more than an opioid alone at 15 min.** **EMS:** 1 RCT found mean difference in the change of pain scores to be MD -1.3 (-2.6 to 0.02) at 15 min. **ED:** Meta-analysis of 3 RCT found MD -1.04 (-2.55 to 0.47).	4 RCT (n=336)	Low	Inconsistent	Indirect	Imprecise	Unsuspected	Low
Pain severity – 30 min	**Combining an opioid and ketamine may reduce pain more than an opioid alone at 30 min.** **EMS**: 1 RCT 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 found MD -0.59 (-2.24 to 1.06).	5 RCT (n=545)	Low	Inconsistent	Indirect	Imprecise	Unsuspected	Low
Pain severity – 60 min	**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.** **ED:** Meta-analysis of 3 RCT found MD -0.07 (-1.14 to 1.00).	3 RCT (n=241)	Low	Inconsistent	Indirect	Precise	Unsuspected	Low

Outcome	Conclusions statement, rationale	Study Design and Sample Size	Study Limitations[a]	Consistency[b]	Directness[c]	Precision[d]	Publication Bias[e]	Strength of Evidence
Presence of pain – partial resolution	**Inconclusive.** **EMS**: 1 RCT found partial response in 60.6% vs. 40.6% of patients, RD 20% (-4 to 41). 1 OBS study found the proportion of sufficient response was 69% vs. 70.9%. Trial alone was insufficient to conclude, disagreement between sources of evidence.	1 RCT (n=65) 1 OBS (n=606)	Low	Inconsistent	Direct	Imprecise	Unsuspected	Insufficient
Time to analgesic effect	**Inconclusive.** No data	None	NA	NA	NA	NA	NA	Insufficient
Any adverse event	**Inconclusive.** **ED**: 1 RCT found total AEs to occur in 22.5% vs. 17.5% of patients. RD 5% (-13 to 22) Single study with additional domain limitations, CI crosses appreciable differences in either direction.	1 RCT (n=80)	Low	Unknown	Indirect	Very imprecise	Unsuspected	Insufficient
Hypotension	**Inconclusive.** **EMS**: No data **ED**: 1 RCT found hypotension to occur in 0% vs. 3% of patients. RD -6% (-16 to 3) Single study with additional domain limitations.	1 RCT (n=106)	Low	Unknown	Indirect	Imprecise	Unsuspected	Insufficient

Outcome	Conclusions statement, rationale	Study Design and Sample Size	Study Limitations[a]	Consistency[b]	Directness[c]	Precision[d]	Publication Bias[e]	Strength of Evidence
Mental status Changes-dizziness	**Inconclusive.** **EMS**: 1 RCT found dizziness in 18.2% vs. 0% of patients 30 min after the dose. RD 18% (3 to 34). **ED**: 1 RCT found dizziness in 22% vs. 11% at 20 mins [RD 11% (1 to 21)] and 42% vs. 45% at 40 min [RD -3% (-16 to 11). CI crosses appreciable differences in either direction.	2 RCTs (n=265)	Low	Inconsistent	Indirect	Very imprecise	Unsuspected	Insufficient
Mental status changes-sedation	**Inconclusive.** **EMS**: 1 RCT found sedation in 21.2% vs. 6.3% of patients 30 min after the dose. RD 15% (-2 to 32) Single study with other domain limitations.	1 RCT (n=65)	Low	Unknown	Direct	Imprecise	Unsuspected	Insufficient
Respiratory depression	**Inconclusive.** **EMS**: 1 RCT found respiratory depression to occur in 0% vs. 3.1% of patients. RD -3% (-16 to 9) **ED**: Meta-analysis of 2 RCTs found AR 1.2% vs. 6.0% RD -3% (-10 to 4) Both sources of evidence are uninformative, CI crosses appreciable differences in either direction, other domain limitations.	3 RCTs (n=231)	Low	Consistent	Indirect	Very imprecise	Unsuspected	Insufficient

Abbreviations: NA=not applicable; OBS=observational; RCT=randomized controlled trial

[a]: Rationale is provided for inconclusive statements (with insufficient strength of evidence).

[b]: Study limitations were downgraded when the majority of the evidence base came from medium or high risk of bias studies.

[c]: Consistency was judged using the I2 statistic when meta-analysis was conducted, with values over 50% considered to be inconsistent. When data were not pooled, we inspected study level results for overall agreement in the direction and magnitude of effects. When evidence was available from trials and observational studies, we considered agreement of direction and magnitude of effect from these sources.
[d]: Directness was downgraded when the majority of evidence for the given comparison/outcome came from emergency department studies rather than prehospital studies.
[e]: Precision was judged using the effect estimate and clinically important difference set for the outcome. Estimates were considered imprecise if the confidence interval crossed the clinically important difference. Estimates were considered very imprecise when the confidence interval spanned the clinically important difference in both directions, thus uninformative.
[f]: Publication bias was judged using p-value <0.05 (when data was meta-analyzed), suggesting presence of publication bias.

Table E-4. Strength of evidence ratings for the comparison of opioids vs. nitrous oxide

Outcome	Conclusions statement, rationale	Study Design and Sample Size	Study Limitations[a]	Consistency[b]	Directness[c]	Precision[d]	Publication Bias[e]	Strength of Evidence
Pain severity – 15 min	**Inconclusive.** **EMS**: 1 RCT found MD 0.8 (0.0 to 1.6) Single study with additional domain limitations.	1 RCT (n=100)	Medium	Unknown	Direct	Precise	Unsuspected	Insufficient
Pain severity – 60 min	**Inconclusive.** **EMS**: 1 RCT found MD 0.1 (-0.6 to 0.8) Single study with additional domain limitations.	1 RCT (n=100)	Medium	Unknown	Direct	Precise	Unsuspected	Insufficient
Presence of pain	**Inconclusive**. No data	None	NA	NA	NA	NA	NA	Insufficient
Time to analgesic effect	**Inconclusive**. No data	None	NA	NA	NA	NA	NA	Insufficient
Any adverse event	**Inconclusive.** **EMS**: 1 RCT found total AEs to occur in 20% vs. 14% of patients. RD 6% (-9 to 21) Single study with additional domain limitations, CI crosses appreciable differences in either direction.	1 RCT (n=100)	Medium	Unknown	Direct	Very imprecise	Unsuspected	Insufficient
Hypotension	**Inconclusive**. No data	None	NA	NA	NA	NA	NA	Insufficient

Outcome	Conclusions statement, rationale	Study Design and Sample Size	Study Limitations[a]	Consistency[b]	Directness[c]	Precision[d]	Publication Bias[e]	Strength of Evidence
Mental status Changes-dizziness	**Inconclusive.** **EMS**: 1 RCT found dizziness in 8% vs. 4% of patients. RD 4% (-7 to 15) Single study with additional domain limitations, CI crosses appreciable differences in either direction.	1 RCT (n=100)	Medium	Unknown	Direct	Very imprecise	Unsuspected	Insufficient
Respiratory depression	**Inconclusive**. No data	None	NA	NA	NA	NA	NA	Insufficient

Abbreviations: NA=not applicable; OBS=observational; RCT=randomized controlled trial

[a]: Rationale is provided for inconclusive statements (with insufficient strength of evidence).

[b]: Study limitations were downgraded when the majority of the evidence base came from medium or high risk of bias studies.

[c]: Consistency was judged using the I2 statistic when meta-analysis was conducted, with values over 50% considered to be inconsistent. When data were not pooled, we inspected study level results for overall agreement in the direction and magnitude of effects. When evidence was available from trials and observational studies, we considered agreement of direction and magnitude of effect from these sources.

[d]: Directness was downgraded when the majority of evidence for the given comparison/outcome came from emergency department studies rather than prehospital studies.

[e]: Precision was judged using the effect estimate and clinically important difference set for the outcome. Estimates were considered imprecise if the confidence interval crossed the clinically important difference. Estimates were considered very imprecise when the confidence interval spanned the clinically important difference in both directions, thus uninformative.

[f]: Publication bias was judged using p-value <0.05 (when data was meta-analyzed), suggesting presence of publication bias.

Table E-5. Strength of evidence ratings for the comparison of opioids vs. acetaminophen

Outcome	Conclusions statement, rationale	Study Design and Sample Size	Study Limitations[a]	Consistency[b]	Directness[c]	Precision[d]	Publication Bias[e]	Strength of Evidence
Pain severity – 15 min	**There is no evidence of a clinically important difference between opioids and IV APAP in the change of pain scores in 15 min.** **ED**: Meta-analysis of 7 RCTs found MD 0.19 (-1.05 to 1.42).	7 RCT (n=647)	Low	Inconsistent	Indirect	Precise	Unsuspected	Low
Pain severity – 30 min	**There is no evidence of a clinically important difference between opioids and IV APAP in the change of pain scores in 30 min.** **ED**: Meta-analysis of 9 RCTs found MD 0.23 (-0.93 to 1.38).	9 RCT (n=1795)	Low	Inconsistent	Indirect	Precise	Unsuspected	Low
Pain severity – 60 min	**There is no evidence of a clinically important difference between opioids and IV APAP in the change of pain scores in 60 min.** **ED**: Meta-analysis of 3 RCT found MD 0.13 (-0.72 to 0.97).	3 RCT (n=1260)	Low	Inconsistent	Indirect	Precise	Unsuspected	Low
Presence of pain – partial response 30 min	**Inconclusive.** **ED**: 1 RCT found a partial response in pain score in 81.8% vs. 78.1% of patients, RD 4% (-1 to 8) Single study with additional domain limitations.	1 RCT (n=996)	Low	Unknown	Indirect	Imprecise	Unsuspected	Insufficient

Outcome	Conclusions statement, rationale	Study Design and Sample Size	Study Limitations[a]	Consistency[b]	Directness[c]	Precision[d]	Publication Bias[e]	Strength of Evidence
Time to analgesic effect	**There is no evidence of a clinically important difference in the time to analgesia with opioids compared with IV APAP** **ED**: Median time to NRS<2 was 60 min in both arms, IQR 30 to 90 min.	1 RCT (n=1097)	Low	Unknown	Indirect	Precise	Unsuspected	Low
Any adverse event	**Opioids may cause more adverse events than IV APAP.** **ED**: Meta-analysis of 5 RCTs over the study period found AR 35.4% vs. 5.6% RD 30% (-1 to 62). 1 RCT reporting total AEs "during acute" management found 1.3% vs. 3.5%, RD -2% (-4 to 0.00)	6 RCTs (n=1,484)	Low	Inconsistent	Indirect	Imprecise	Unsuspected	Low
Hypotension	**There is no evidence of a clinically important difference in hypotension with opioids compared to IV APAP.** **ED**: Meta-analysis of 5 RCTs found AR 2.6% vs. 0% RD 2% (0.00 to 4%)	5 RCTs (n=624)	Low	Consistent	Indirect	Imprecise	Unsuspected	Low
Mental status Changes-dizziness	**Opioids cause more dizziness than IV APAP.** **ED**: Meta-analysis of 6 RCTs found AR 7.8% vs. 0.3% RD 7% (5 to 9)	6 RCTs (n=539)	Low	Consistent	Indirect	Precise	Unsuspected	Moderate

Outcome	Conclusions statement, rationale	Study Design and Sample Size	Study Limitations[a]	Consistency[b]	Directness[c]	Precision[d]	Publication Bias[e]	Strength of Evidence
Mental status change – "mild" sedation	**Inconclusive.** **ED:** 1 RCT found mild sedation in 2.2% vs. 0% of patients. RD 2% (-7 to 12). Single study with additional domain limitations, CI crosses appreciable differences in either direction.	1 RCT (n=91)	Low	Unknown	Indirect	Very imprecise	Unsuspected	Insufficient
Respiratory depression	**Inconclusive**. **ED**: 1 RCT found no cases of respiratory depression to occur. Single study with additional domain limitations.	1 RCT (n=73)	Low	Unknown	Indirect	Precise	Unsuspected	Insufficient

Abbreviations: NA=not applicable; OBS=observational; RCT=randomized controlled trial

[a]: Rationale is provided for inconclusive statements (with insufficient strength of evidence).

[b]: Study limitations were downgraded when the majority of the evidence base came from medium or high risk of bias studies.

[c]: Consistency was judged using the I2 statistic when meta-analysis was conducted, with values over 50% considered to be inconsistent. When data were not pooled, we inspected study level results for overall agreement in the direction and magnitude of effects. When evidence was available from trials and observational studies, we considered agreement of direction and magnitude of effect from these sources.

[d]: Directness was downgraded when the majority of evidence for the given comparison/outcome came from emergency department studies rather than prehospital studies.

[e]: Precision was judged using the effect estimate and clinically important difference set for the outcome. Estimates were considered imprecise if the confidence interval crossed the clinically important difference. Estimates were considered very imprecise when the confidence interval spanned the clinically important difference in both directions, thus uninformative.

[f]: Publication bias was judged using p-value <0.05 (when data was meta-analyzed), suggesting presence of publication bias.

Table E-6. Strength of evidence ratings for the comparison of opioids vs. nonsteroidal anti-inflammatory drugs

Outcome	Conclusions statement, rationale	Study Design and Sample Size	Study Limitations[a]	Consistency[b]	Directness[c]	Precision[d]	Publication Bias[e]	Strength of Evidence
Pain severity – 15 min	**Inconclusive.** **ED**: 1 RCT found MD 0.2 (-0.4 to 0.8) Single study with additional domain limitations.	1 RCT (n=88)	Medium	Unknown	Indirect	Precise	Unsuspected	Insufficient
Pain severity – 30 min	**There is no evidence of a clinically important difference between opioids and NSAIDs in the change of pain scores in 30 min.** **ED**: Meta-analysis of 3 RCT found MD 0.01 (-0.29 to 0.32)	3 RCT (n=453)	Low	Consistent	Indirect	Precise	Unsuspected	Moderate
Pain severity – 60 min	**There is no evidence of a clinically important difference between opioids and NSAIDs in the change of pain scores in 60 min.** **ED**: Meta-analysis of 3 RCT found MD 0.21 (-0.10 to 0.51)	3 RCT (n=453)	Low	Consistent	Indirect	Precise	Unsuspected	Moderate
Presence of pain – partial response 30 min	**Inconclusive.** **ED**: 1 RCT found partial response in 20.7% vs. 19.8%, RD 1% (-10 to 10) Single study with additional domain limitations, CI crosses appreciable differences in either direction.	1 RCT (n=227)	Low	Unknown	Indirect	Very imprecise	Unsuspected	Insufficient

Outcome	Conclusions statement, rationale	Study Design and Sample Size	Study Limitations[a]	Consistency[b]	Directness[c]	Precision[d]	Publication Bias[e]	Strength of Evidence
Presence of pain – partial response 60 min	**Inconclusive.** **ED**: 1 RCT found partial response in 29.3% vs. 33.0%, RD -4% (-16 to 7) Single study with additional domain limitations, CI crosses appreciable differences in either direction.	1 RCT (n=243)	Low	Unknown	Indirect	Very imprecise	Unsuspected	Insufficient
Presence of pain – full resolution 30 min	**Inconclusive.** **ED:** 1 RCT found 16.3% vs. 11.6%, RD 5% (-11 to 20) Single study with additional domain limitations, CI crosses appreciable differences in either direction.	1 RCT (n=86)	Low	Unknown	Indirect	Very imprecise	Unsuspected	Insufficient
Time to analgesic effect	**Inconclusive.** No data	None	NA	NA	NA	NA	NA	Insufficient
Any adverse event	**Opioids may cause more adverse events than NSAIDs** **ED**: Meta-analysis of 2 RCTs found AR 24.6% vs. 7.4%, RD 21% (4 to 38)	2 RCTs (n=367)	Low	Inconsistent	Indirect	Imprecise	Unsuspected	Low
Hypotension	**Inconclusive.** **ED**: 1 RCT found hypotension in 6.8% vs. 0% of patients. RD 7% (-3 to 18) Single study with additional domain limitations.	1 RCT (n=88)	Low	Unknown	Indirect	Imprecise	Unsuspected	Insufficient

Outcome	Conclusions statement, rationale	Study Design and Sample Size	Study Limitations[a]	Consistency[b]	Directness[c]	Precision[d]	Publication Bias[e]	Strength of Evidence
Mental status Changes-drowsiness	**Opioids may cause more drowsiness than NSAIDs** **ED**: Meta-analysis of 2 RCTs found AR 3.9% vs. 0.7%, RD 3% (0 to 6%)	2 RCTs (n=367)	Low	Consistent	Indirect	Imprecise	Unsuspected	Low
Mental status changes – Dizziness	**Inconclusive.** **ED:** 1 RCT found dizziness in 9.3% vs. 0% of patients, RD 9% (-2 to 22) Single study with additional domain limitations.	1 RCT (n=86)	Low	Unknown	Indirect	Imprecise	Unsuspected	Insufficient
Mental status changes-depression	**Inconclusive.** **ED:** 1 RCT found depression in 4.5% vs. 0% of patients, RD 4% (-5 to 15) Single study with additional domain limitations, CI crosses appreciable differences in either direction.	1 RCT (n=88)	Low	Unknown	Indirect	Very imprecise	Unsuspected	Insufficient
Respiratory depression	**Inconclusive.** No data	None	NA	NA	NA	NA	NA	Insufficient

Abbreviations: NA=not applicable; OBS=observational; RCT=randomized controlled trial

[a]: Rationale is provided for inconclusive statements (with insufficient strength of evidence).

[b]: Study limitations were downgraded when the majority of the evidence base came from medium or high risk of bias studies.

[c]: Consistency was judged using the I2 statistic when meta-analysis was conducted, with values over 50% considered to be inconsistent. When data were not pooled, we inspected study level results for overall agreement in the direction and magnitude of effects. When evidence was available from trials and observational studies, we considered agreement of direction and magnitude of effect from these sources.

[d]: Directness was downgraded when the majority of evidence for the given comparison/outcome came from emergency department studies rather than prehospital studies.

[e]: Precision was judged using the effect estimate and clinically important difference set for the outcome. Estimates were considered imprecise if the confidence interval crossed the clinically important difference. Estimates were considered very imprecise when the confidence interval spanned the clinically important difference in both directions, thus uninformative.

[f]: Publication bias was judged using p-value <0.05 (when data was meta-analyzed), suggesting presence of publication bias.

Appendix F. Forest Plots

Figure F-1. Risk difference presence of pain – full resolution at 30 minutes, opioids versus ketamine

	Opioid		Ketamine				
Source	**Events**	**Total**	**Events**	**Total**	**RD [95%-CI]**	**Favors Ketamine**	**Favors Opioid**	**Weight**
Motov, 2015	11	45	12	45	-0.02 [-0.20; 0.16]			43.6%
Motov, 2018	4	30	7	30	-0.10 [-0.29; 0.09]			40.6%
Quinn, 2018	8	11	5	11	0.27 [-0.12; 0.67]			15.9%
Random effects model	**23**	**86**	**24**	**86**	**-0.01 [-0.39; 0.38]**			**100.0%**

Heterogeneity: I^2 = 29%, τ^2 = 0.0099, p = 0.25

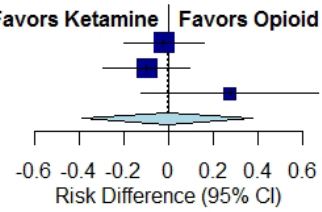

Figure F-2. Risk difference presence of pain – full resolution at 60 minutes, opioids versus ketamine

	Opioid		Ketamine				
Source	**Events**	**Total**	**Events**	**Total**	**RD [95%-CI]**	**Favors Ketamine**	**Favors Opioid**	**Weight**
Motov, 2015	12	43	9	43	0.07 [-0.11; 0.25]			55.4%
Motov, 2018	5	30	7	30	-0.07 [-0.27; 0.14]			44.6%
Random effects model	**17**	**73**	**16**	**73**	**0.01 [-0.13; 0.14]**			**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.32

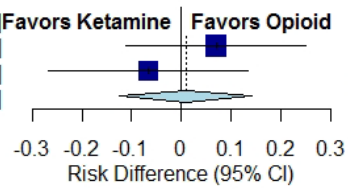

Figure F-3. Risk difference presence of pain – partial resolution at 15 minutes, opioids versus ketamine

	Opioid		Ketamine				
Source	**Events**	**Total**	**Events**	**Total**	**RD [95%-CI]**	**Favors Opioid**	**Favors Ketamine**	**Weight**
Majidinejad, 2014	61	63	59	63	0.03 [-0.04; 0.11]			26.1%
Graudins, 2015	25	35	26	36	-0.01 [-0.22; 0.20]			20.3%
Motov, 2015	31	45	34	45	-0.07 [-0.25; 0.12]			21.5%
Motov, 2018	16	30	22	30	-0.20 [-0.44; 0.04]			18.8%
Quinn, 2018	7	11	2	11	0.45 [0.09; 0.82]			13.3%
Random effects model	**140**	**184**	**143**	**185**	**0.02 [-0.25; 0.28]**			**100.0%**

Heterogeneity: I^2 = 59%, τ^2 = 0.0331, p = 0.05

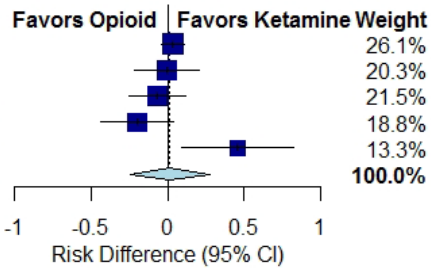

Figure F-4. Risk difference presence of pain – partial resolution at 30 minutes, opioids versus ketamine

	Opioid		Ketamine				
Source	**Events**	**Total**	**Events**	**Total**	**RD [95%-CI]**	**Favors Opioid**	**Favors Ketamine**	**Weight**
Graudins, 2015	27	34	28	34	-0.03 [-0.22; 0.16]			26.7%
Motov, 2015	31	45	33	45	-0.04 [-0.23; 0.14]			26.6%
Reynolds, 2017	35	44	30	39	0.03 [-0.15; 0.20]			29.4%
Motov, 2018	21	30	21	30	0.00 [-0.23; 0.23]			17.3%
Random effects model	**114**	**153**	**112**	**148**	**-0.01 [-0.06; 0.04]**			**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.95

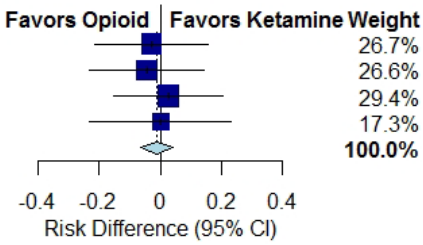

Figure F-5. Risk difference presence of pain – partial resolution at 60 minutes, opioids versus ketamine

	Opioid		Ketamine				
Source	**Events**	**Total**	**Events**	**Total**	**RD [95%-CI]**	**Favors Opioid**	**Favors Ketamine**	**Weight**
Graudins, 2015	25	31	28	31	-0.10 [-0.27; 0.08]			36.1%
Motov, 2015	33	43	25	43	0.19 [-0.01; 0.38]			33.2%
Motov, 2018	22	30	24	30	-0.07 [-0.28; 0.15]			30.7%
Random effects model	**80**	**104**	**77**	**104**	**0.01 [-0.38; 0.39]**			**100.0%**

Heterogeneity: I^2 = 61%, τ^2 = 0.0146, p = 0.08

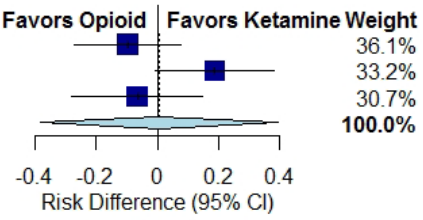

Figure F-6. Mean difference change in pain at 15 minutes – subgroup age <18 years old, ≥18 years old, opioids versus ketamine

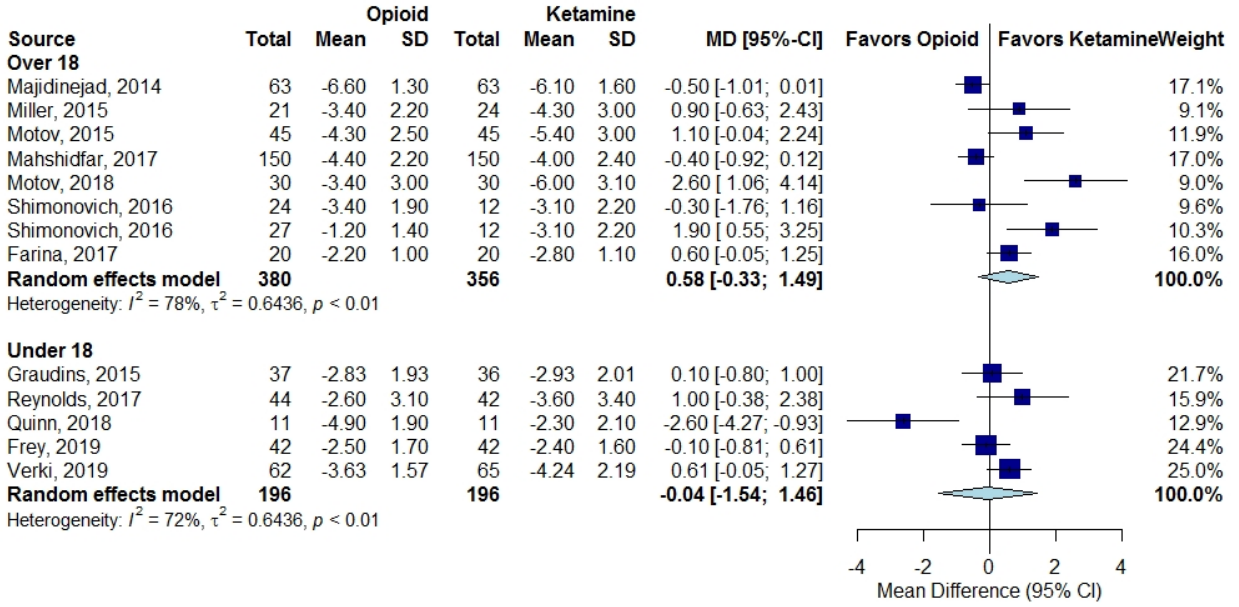

Figure F-7. Mean difference change in pain at 30 minutes – subgroup age <18 years old, ≥18 years old, opioids versus ketamine

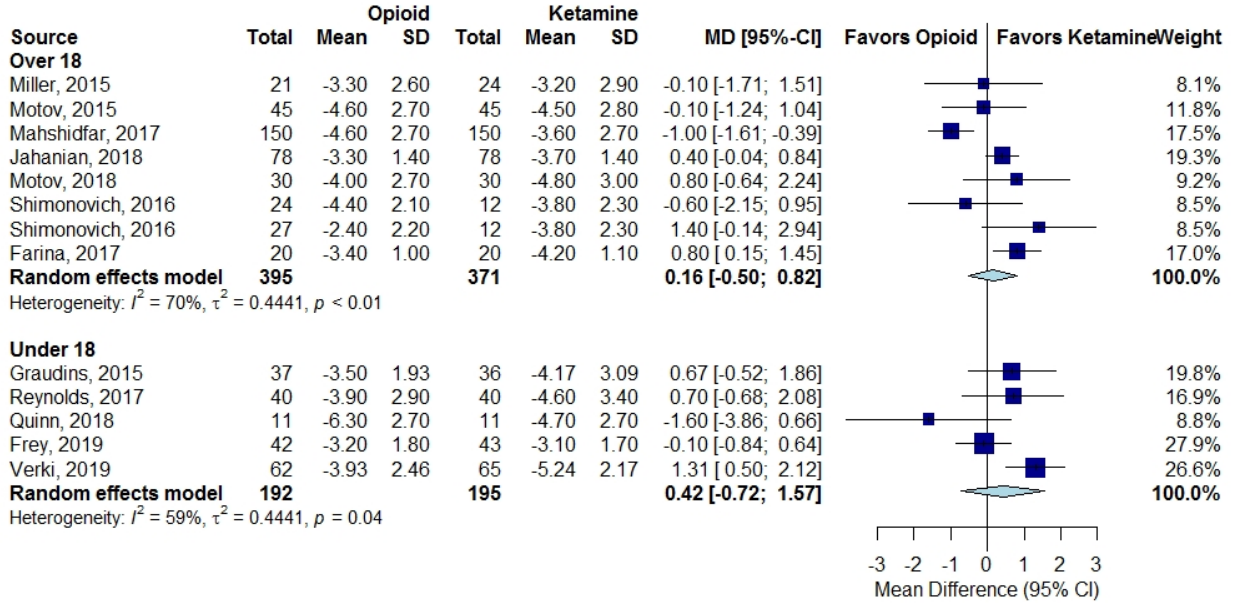

Figure F-8. Mean difference change in pain at 60 minutes – subgroup age <18 years old, ≥18 years old, opioids versus ketamine

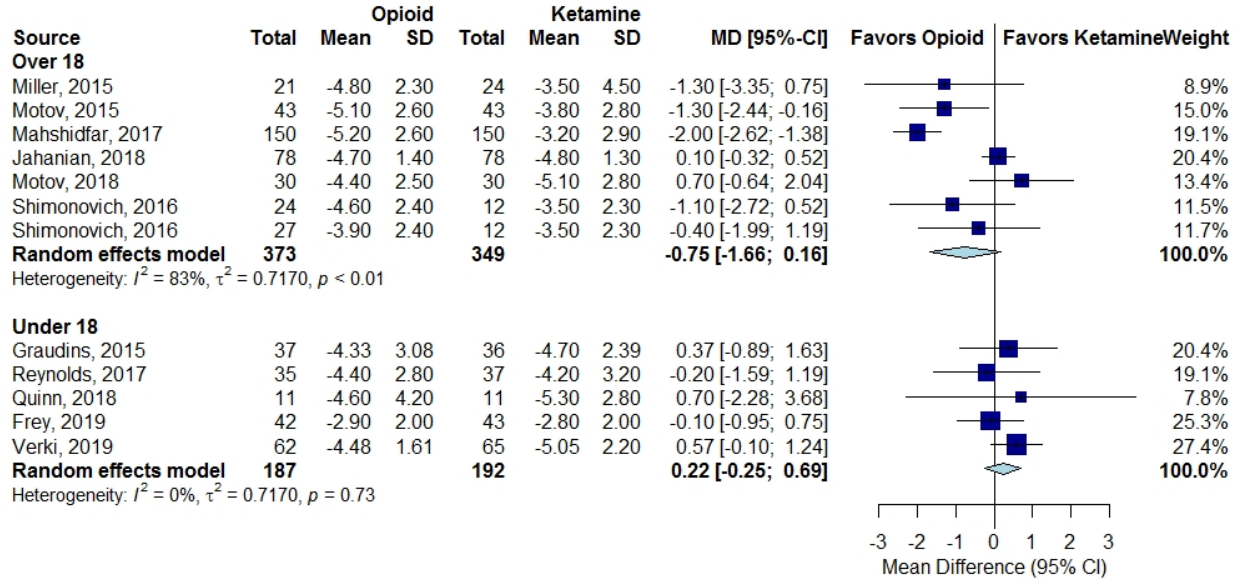

Figure F-9. Mean difference change in pain at 15 minutes – subgroup traumatic pain, opioids versus ketamine

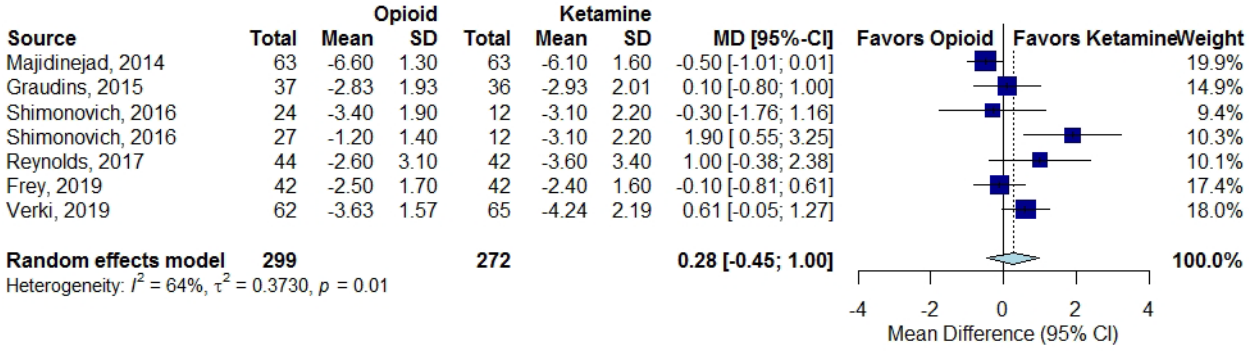

Figure F-10. Mean difference change in pain at 30 minutes – subgroup traumatic pain, opioids versus ketamine

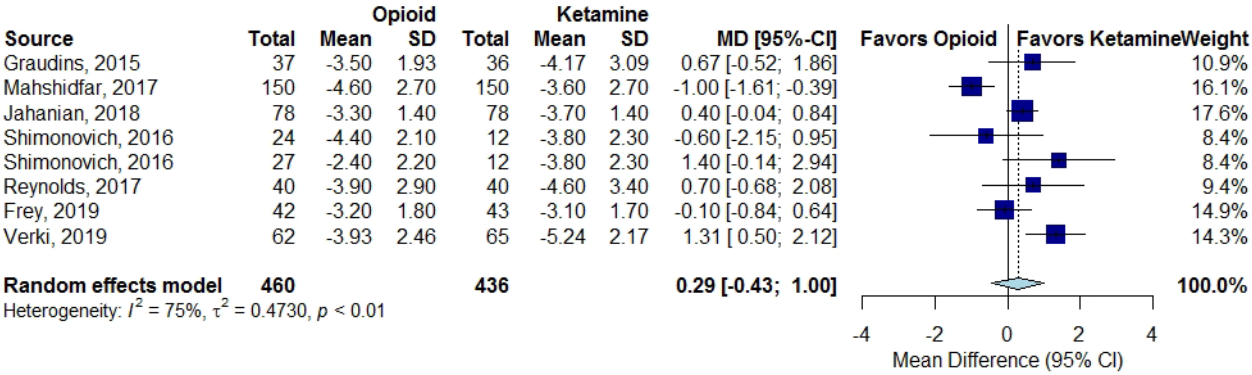

Figure F-11. Mean difference change in pain at 60 minutes – subgroup traumatic pain, opioids versus ketamine

	Opioid			Ketamine				
Source	**Total**	**Mean**	**SD**	**Total**	**Mean**	**SD**	**MD [95%-CI]**	**Weight**
Graudins, 2015	37	-4.33	3.08	36	-4.70	2.39	0.37 [-0.89; 1.63]	10.7%
Mahshidfar, 2017	150	-5.20	2.60	150	-3.20	2.90	-2.00 [-2.62; -1.38]	15.9%
Jahanian, 2018	78	-4.70	1.40	78	-4.80	1.30	0.10 [-0.32; 0.52]	17.4%
Shimonovich, 2016	24	-4.60	2.40	12	-3.50	2.30	-1.10 [-2.72; 0.52]	8.3%
Shimonovich, 2016	27	-3.90	2.40	12	-3.50	2.30	-0.40 [-1.99; 1.19]	8.5%
Reynolds, 2017	35	-4.40	2.80	37	-4.20	3.20	-0.20 [-1.59; 1.19]	9.8%
Frey, 2019	42	-2.90	2.00	43	-2.80	2.00	-0.10 [-0.95; 0.75]	14.0%
Verki, 2019	62	-4.48	1.61	65	-5.05	2.20	0.57 [-0.10; 1.24]	15.5%
Random effects model	**455**			**433**			**-0.33 [-1.09; 0.42]**	**100.0%**

Heterogeneity: I^2 = 83%, τ^2 = 0.5391, p < 0.01

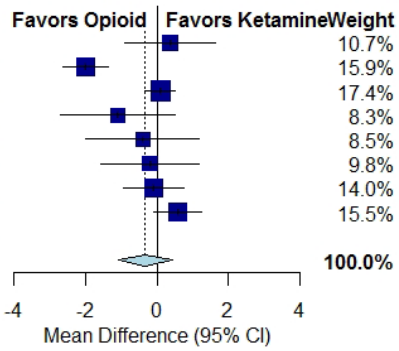

Figure F-12. Mean difference change in pain at 15 minutes – subgroup location of pain, opioids versus ketamine

	Opioid			Ketamine				
Source	**Total**	**Mean**	**SD**	**Total**	**Mean**	**SD**	**MD [95%-CI]**	**Weight**
Extremity								
Majidinejad, 2014	63	-6.60	1.30	63	-6.10	1.60	-0.50 [-1.01; 0.01]	18.9%
Graudins, 2015	37	-2.83	1.93	36	-2.93	2.01	0.10 [-0.80; 1.00]	15.6%
Mahshidfar, 2017	150	-4.40	2.20	150	-4.00	2.40	-0.40 [-0.92; 0.12]	18.8%
Reynolds, 2017	44	-2.60	3.10	42	-3.60	3.40	1.00 [-0.38; 2.38]	11.6%
Frey, 2019	42	-2.50	1.70	42	-2.40	1.60	-0.10 [-0.81; 0.61]	17.3%
Verki, 2019	62	-3.63	1.57	65	-4.24	2.19	0.61 [-0.05; 1.27]	17.7%
Random effects model	**398**			**398**			**0.05 [-0.54; 0.63]**	**100.0%**

Heterogeneity: I^2 = 53%, τ^2 = 0.5306, p = 0.06

Mixed-NR								
Miller, 2015	21	-3.40	2.20	24	-4.30	3.00	0.90 [-0.63; 2.43]	15.8%
Motov, 2015	45	-4.30	2.50	45	-5.40	3.00	1.10 [-0.04; 2.24]	20.2%
Motov, 2018	30	-3.40	3.00	30	-6.00	3.10	2.60 [1.06; 4.14]	15.6%
Shimonovich, 2016	24	-3.40	1.90	12	-3.10	2.20	-0.30 [-1.76; 1.16]	16.5%
Shimonovich, 2016	27	-1.20	1.40	12	-3.10	2.20	1.90 [0.55; 3.25]	17.7%
Quinn, 2018	11	-4.90	1.90	11	-2.30	2.10	-2.60 [-4.27; -0.93]	14.3%
Random effects model	**158**			**134**			**0.69 [-1.15; 2.53]**	**100.0%**

Heterogeneity: I^2 = 81%, τ^2 = 0.5306, p < 0.01

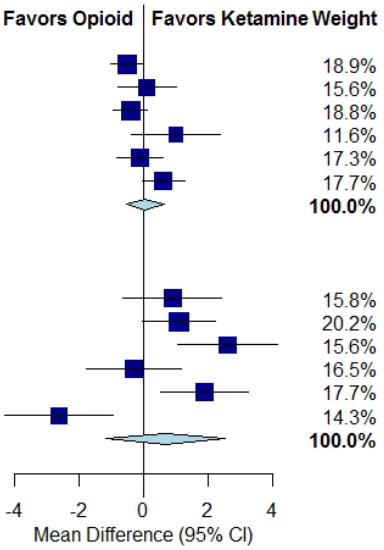

Figure F-13. Mean difference change in pain at 30 minutes – subgroup location of pain, opioids versus ketamine

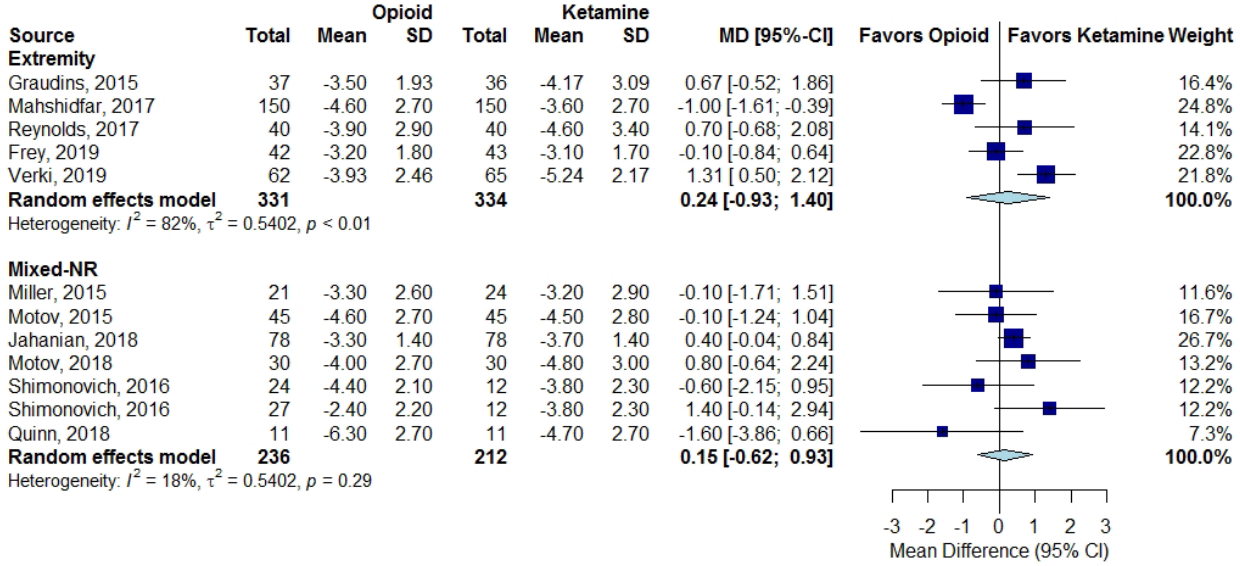

Figure F-14. Mean difference change in pain at 60 minutes – subgroup location of pain, opioids versus ketamine

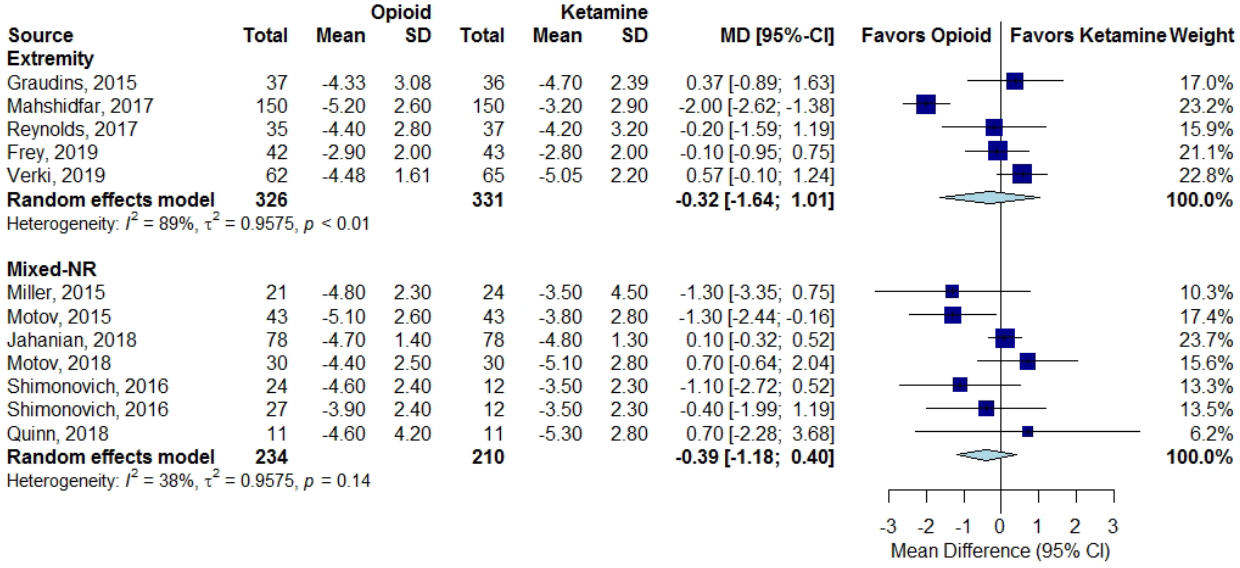

Figure F-15. Mean difference change in pain at 15 minutes – subgroup route of administration, opioids versus ketamine

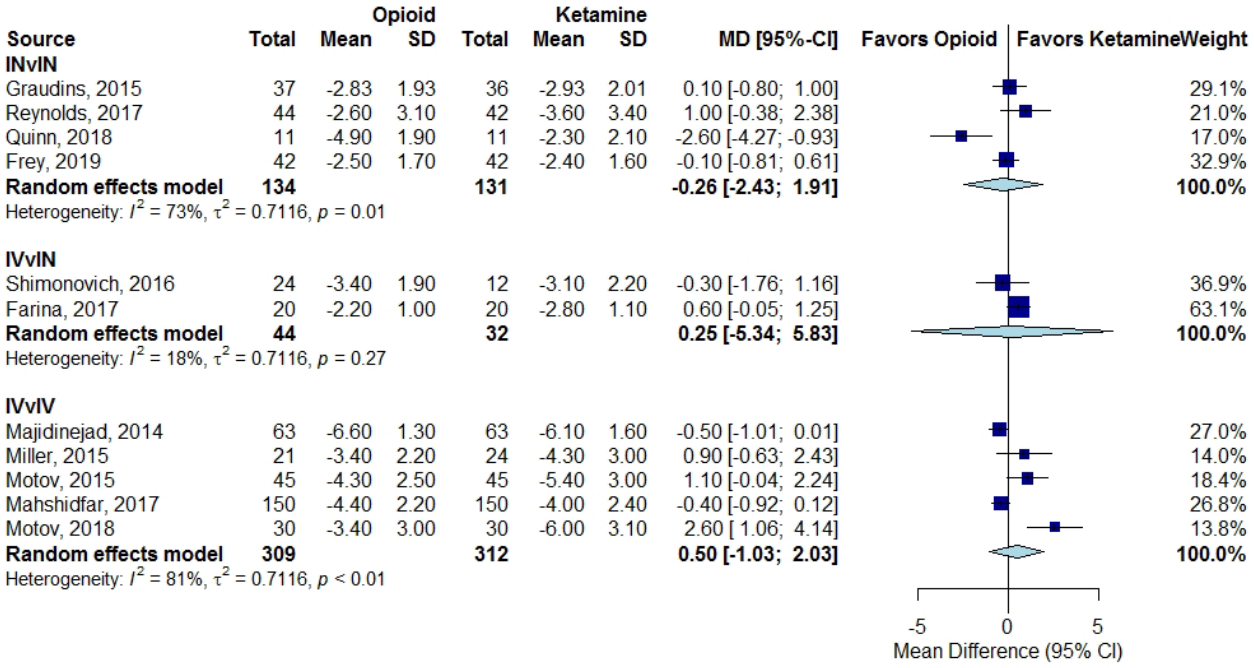

Figure F-16. Mean difference change in pain at 30 minutes – subgroup route of administration, opioids versus ketamine

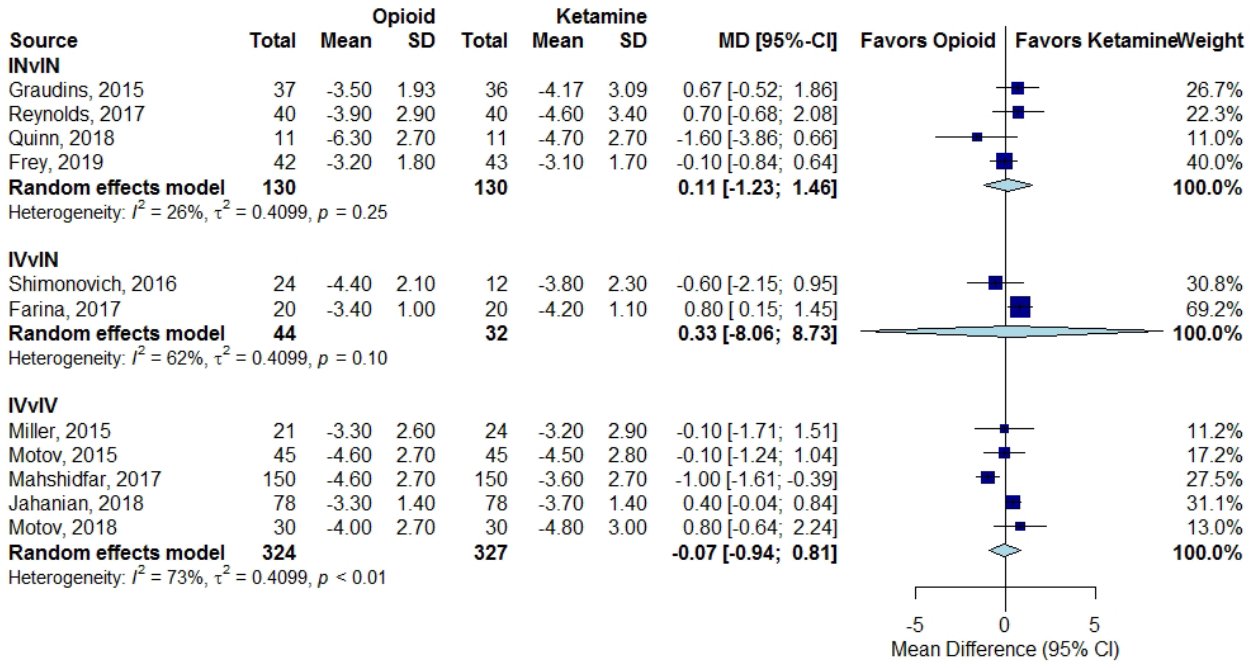

Figure F-17. Mean difference change in pain at 60 minutes – subgroup route of administration, opioids versus ketamine

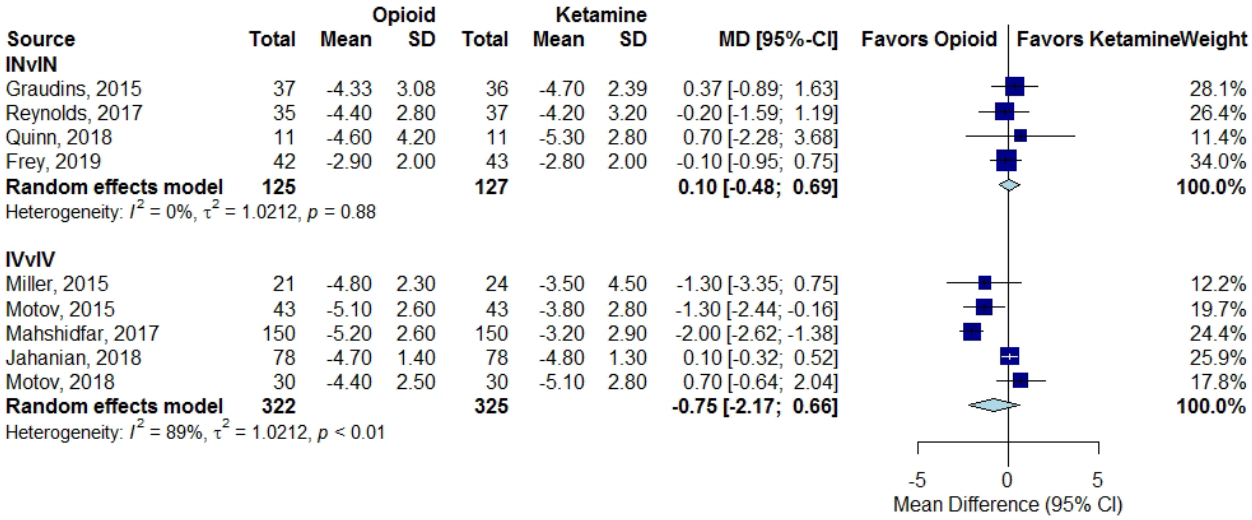

Figure F-18. Mean difference change in pain at 15 minutes – subgroup frequency of administration, opioids versus ketamine

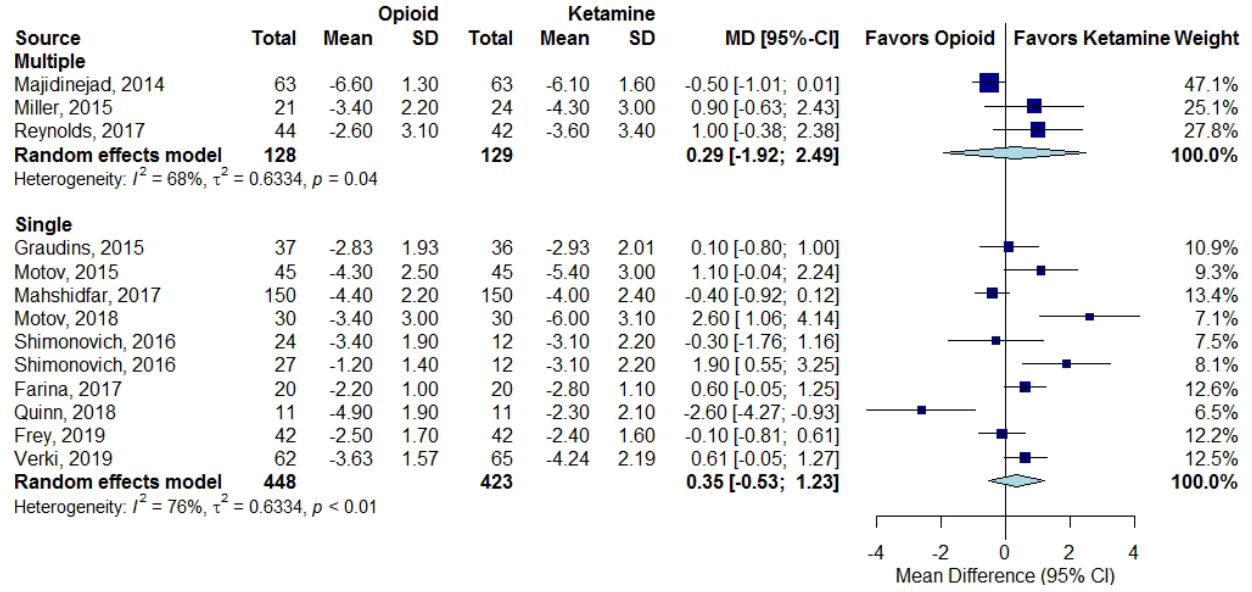

Figure F-19. Mean difference change in pain at 30 minutes – subgroup frequency of administration, opioids versus ketamine

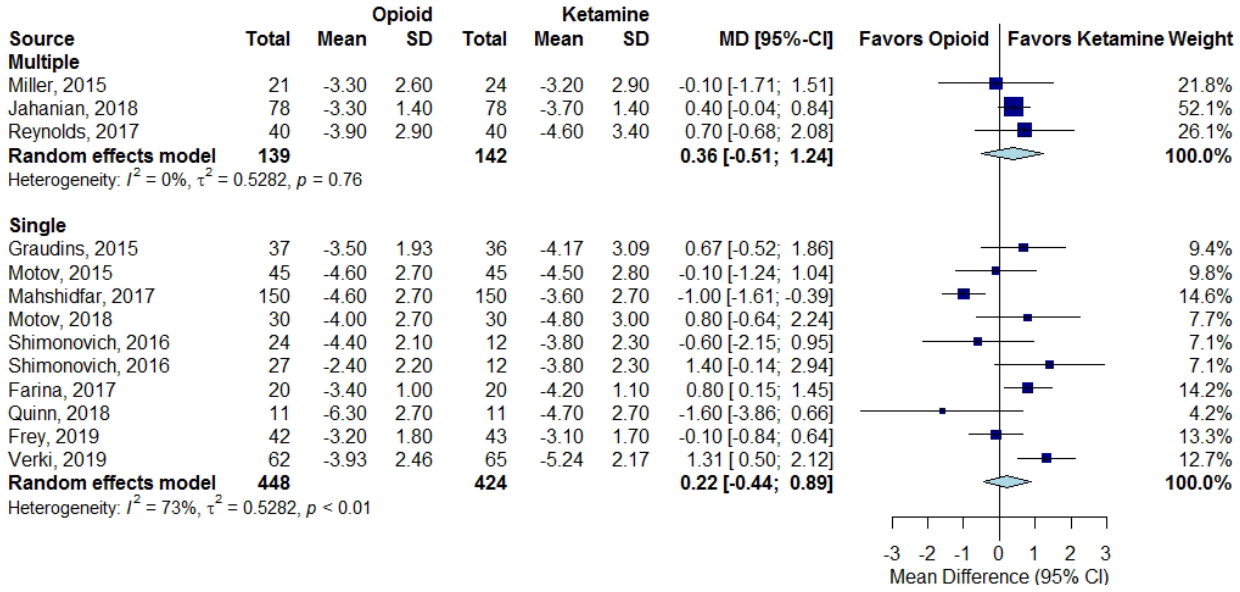

Figure F-20. Mean difference change in pain at 60 minutes – subgroup frequency of administration, opioids versus ketamine

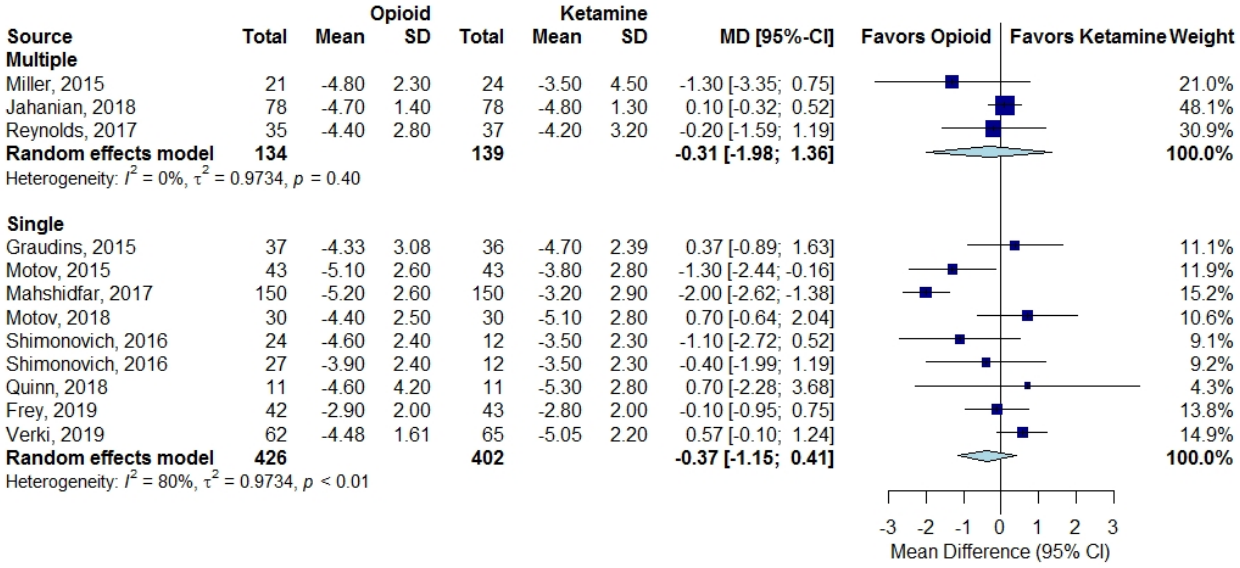

Figure F-21. Mean difference change in pain at 15 minutes – subgroup traumatic pain, opioids versus intravenous acetaminophen

Source	MD	95%-CI
Craig, 2012	0.20	[-0.70; 1.10]
Vahdati, 2014	1.80	[1.00; 2.60]
Jalili, 2016	1.30	[0.40; 2.20]
Random effects model	**1.12**	**[0.19; 2.04]**

Heterogeneity: I^2 = 71%, τ^2 = 0.4757, p = 0.03

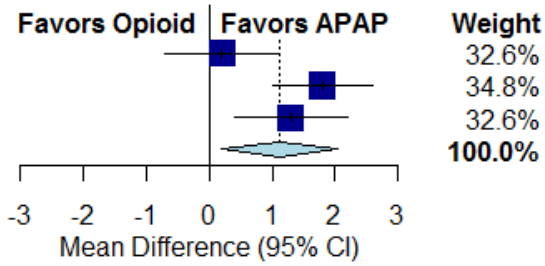

Figure F-22. Mean difference change in pain at 30 minutes – subgroup traumatic pain, opioids versus acetaminophen

Source	MD	95%-CI
Craig, 2012	-0.30	[-1.5; 0.9]
Vahdati, 2014	2.30	[1.4; 3.2]
Jalili, 2016	1.70	[0.8; 2.6]
Mollaei, 2016	-0.70	[-1.3; -0.1]
Random effects model	**0.75**	**[-0.7; 2.2]**

Heterogeneity: I^2 = 92%, τ^2 = 1.9732, p < 0.01

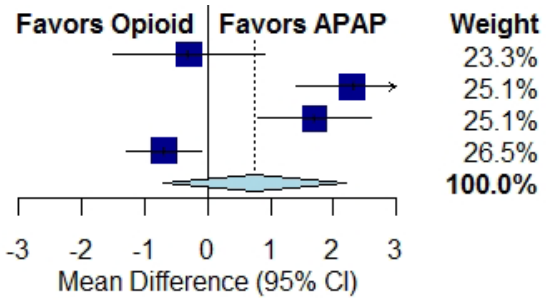

Figure F-23. Mean difference change in pain at 30 minutes – pain severity, acetaminophen versus nonsteroidal anti-inflammatory drugs

		APAP			NSAID			
Source	Total	Mean	SD	Total	Mean	SD	MD [95%-CI]	Weight
Clark, 2007	103	-0.70	2.3000	103	-1.20	1.8000	0.50 [-0.06; 1.06]	33.4%
Cenker, 2018	99	-3.40	2.3000	97	-5.20	2.0000	1.80 [1.20; 2.40]	33.1%
Cozzi, 2018	70	-2.34	1.3100	70	-1.94	1.9800	-0.40 [-0.96; 0.16]	33.5%
Random effects model	**272**			**270**			**0.63 [-0.62; 1.88]**	**100.0%**

Heterogeneity: I^2 = 93%, τ^2 = 1.1349, p < 0.01

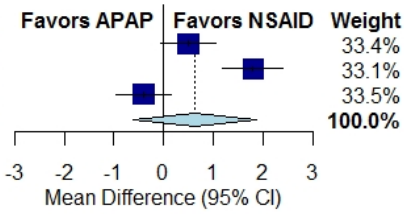

Figure F-24. Mean difference change in pain at 60 minutes – pain severity, acetaminophen versus nonsteroidal anti-inflammatory drugs

		APAP			NSAID			
Source	Total	Mean	SD	Total	Mean	SD	MD [95%-CI]	Weight
Clark, 2007	100	-1.20	2.0000	100	-2.40	2.3000	1.20 [0.60; 1.80]	52.9%
Cozzi, 2018	70	-3.67	2.7300	70	-3.44	2.6900	-0.23 [-1.13; 0.67]	47.1%
Random effects model	**170**			**170**			**0.53 [-0.87; 1.92]**	**100.0%**

Heterogeneity: I^2 = 85%, τ^2 = 0.8711, p < 0.01

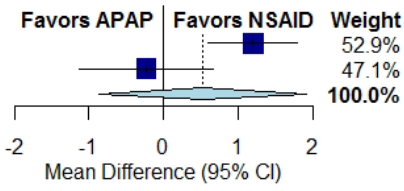

Figure F-25. Risk difference presence of pain – partial resolution at 60 minutes, acetaminophen versus nonsteroidal anti-inflammatory drugs

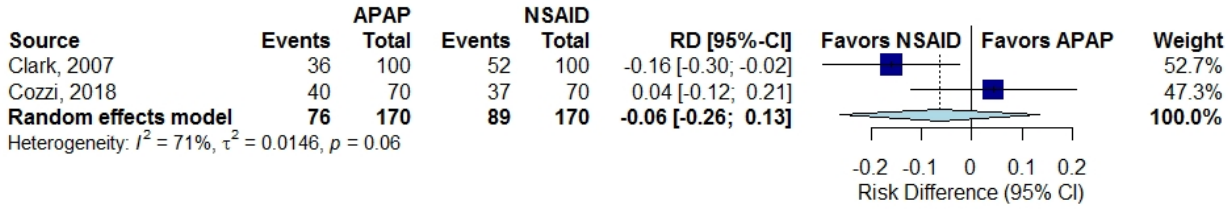

Figure F-26. Mean difference change in pain at 15 minutes – pain severity, morphine versus fentanyl

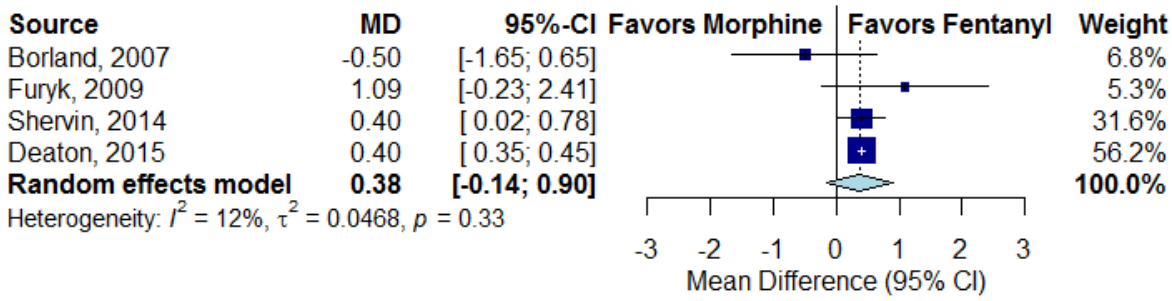

Figure F-27. Mean difference change in pain at 30 minutes – pain severity, morphine versus fentanyl – emergency medical services

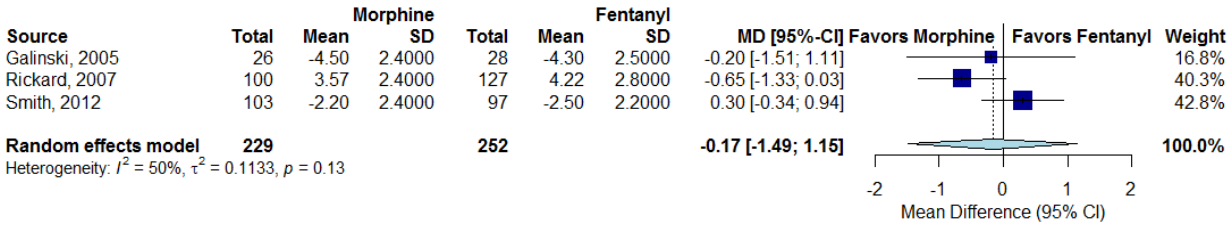

Figure F-28. Mean difference change in pain at 30 minutes – pain severity, morphine versus fentanyl – emergency department

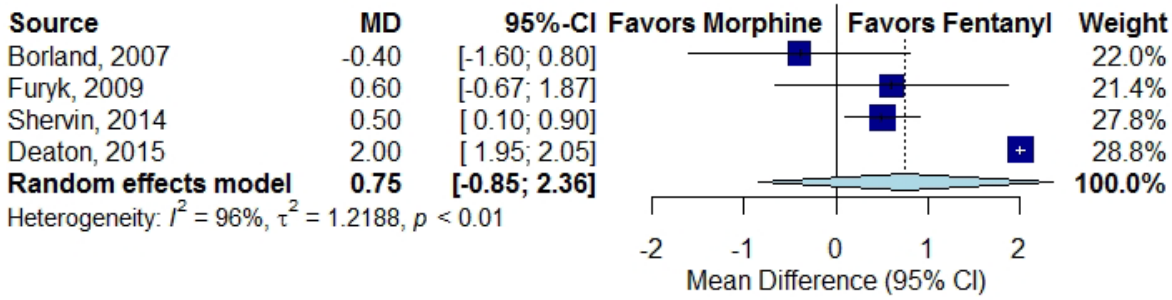

Figure F-29. Mean difference change in pain at 60 minutes – pain severity, morphine versus fentanyl

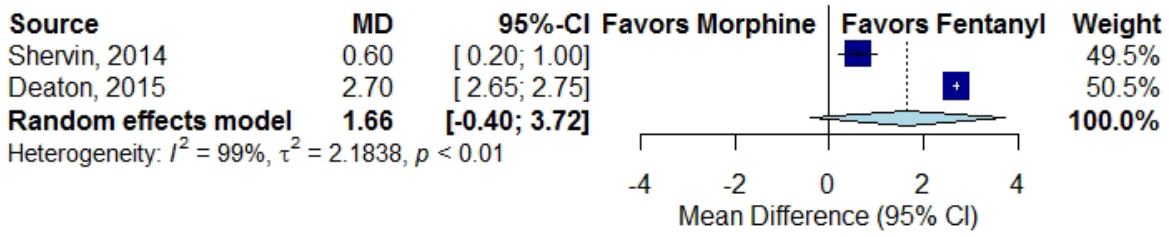

Figure F-30. Risk difference presence of pain – partial resolution at 30 minutes, morphine versus fentanyl – emergency medical services

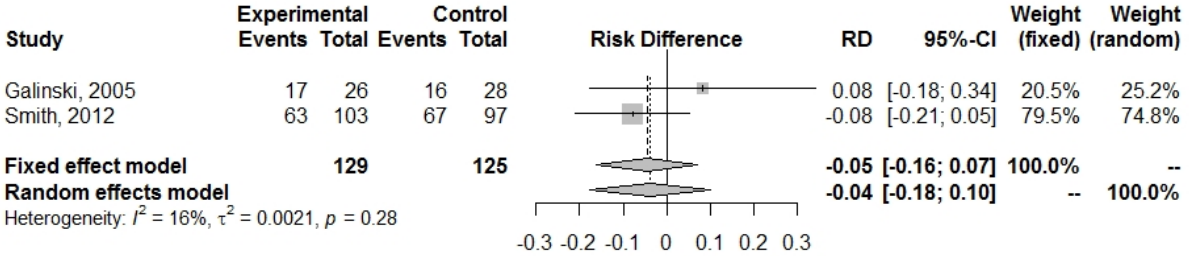

Figure F-31. Risk difference any adverse event, opioids versus ketamine

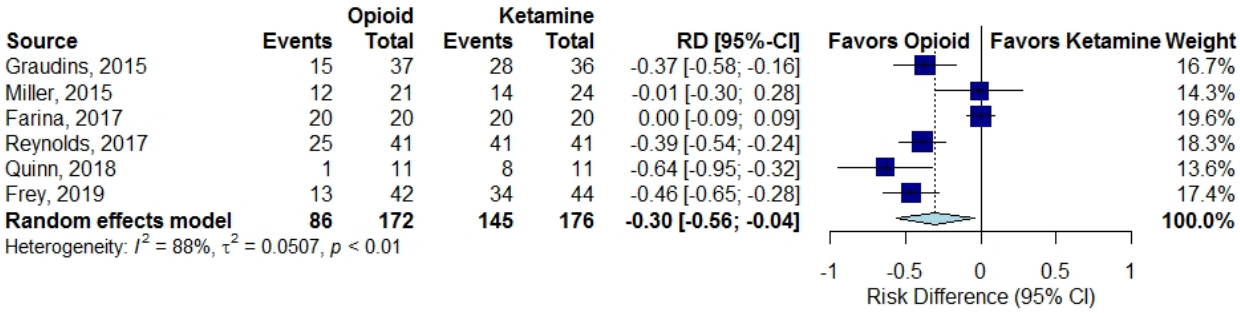

Figure F-32. Risk difference any adverse event at 15 minutes, opioids versus ketamine

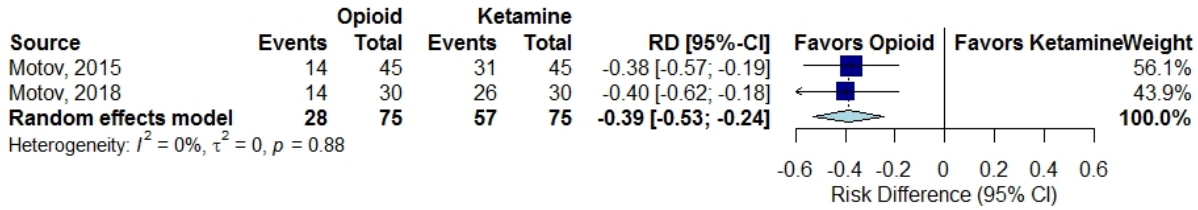

Figure F-33. Risk difference any adverse event at 30 minutes, opioids versus ketamine

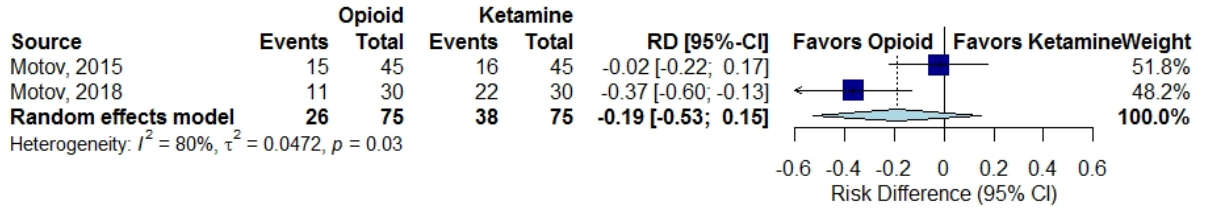

Figure F-34. Risk difference hypotension, opioids versus ketamine

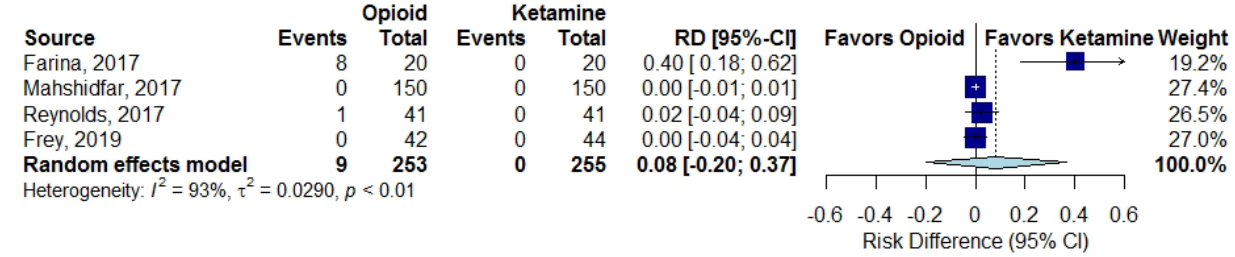

Figure F-35. Risk difference mental status changes dizziness, opioids versus ketamine

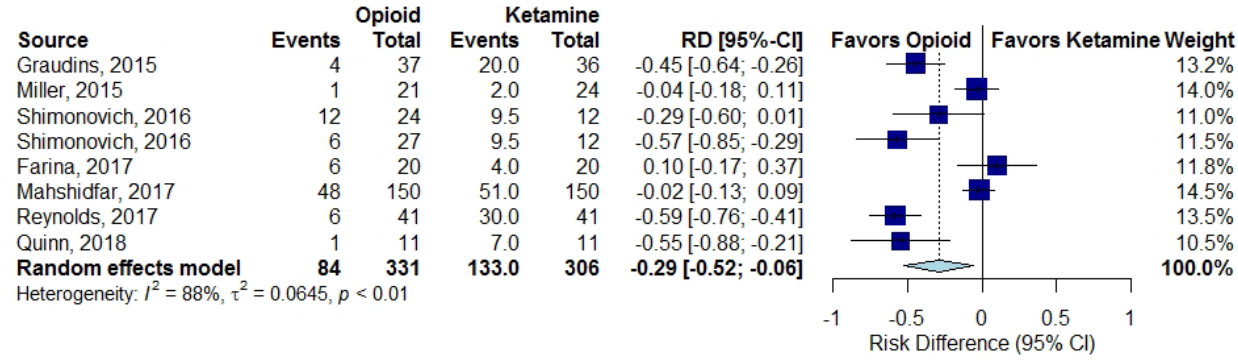

Figure F-36. Risk difference mental status changes dizziness at 15 minutes, opioids versus ketamine

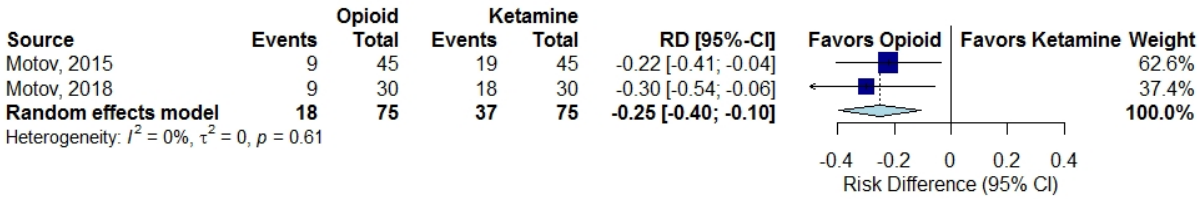

Figure F-37. Risk difference risk mental status changes dizziness 30 minutes, opioids versus ketamine

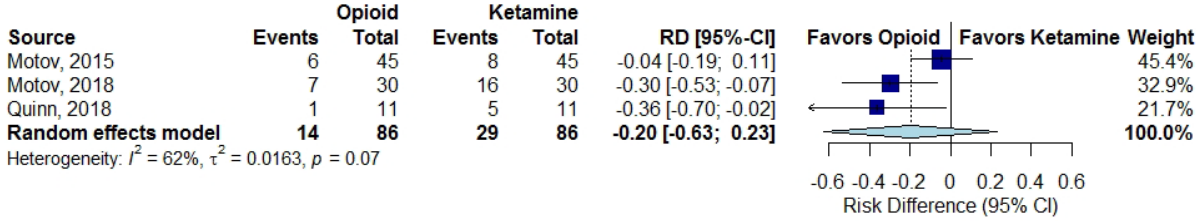

Figure F-38. Risk difference mental status changes drowsiness, opioids versus ketamine

Source	Opioid Events	Opioid Total	Ketamine Events	Ketamine Total	RD [95%-CI]	Weight
Graudins, 2015	5	37	11	36	-0.17 [-0.36; 0.02]	17.7%
Miller, 2015	2	21	0	24	0.10 [-0.05; 0.24]	23.1%
Reynolds, 2017	3	41	6	41	-0.07 [-0.21; 0.06]	24.4%
Jahanian, 2018	5	78	3	78	0.03 [-0.04; 0.09]	34.8%
Random effects model	**15**	**177**	**20**	**179**	**-0.02 [-0.19; 0.15]**	**100.0%**

Heterogeneity: I^2 = 54%, τ^2 = 0.0069, p = 0.09

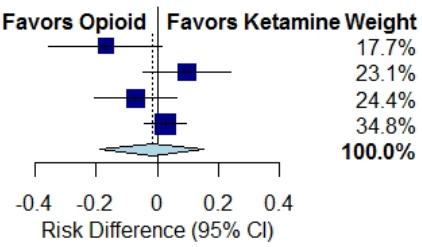

Figure F-39. Risk difference respiratory depression, opioids versus ketamine

Source	Opioid Events	Opioid Total	Ketamine Events	Ketamine Total	RD [95%-CI]	Weight
Miller, 2015	1	21	0	24	0.05 [-0.07; 0.17]	16.7%
Mahshidfar, 2017	27	150	6	150	0.14 [0.07; 0.21]	25.7%
Motov, 2018	0	30	0	30	0.00 [-0.06; 0.06]	27.0%
Frey, 2019	0	42	0	44	0.00 [-0.04; 0.04]	30.6%
Random effects model	**28**	**243**	**6**	**248**	**0.04 [-0.02; 0.11]**	**100.0%**

Heterogeneity: I^2 = 89%, τ^2 = 0.0033, p < 0.01

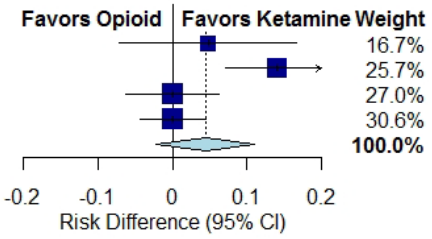

Figure F-40. Risk difference dizziness – subgroup age <18 years old, ≥18 years old, opioids versus ketamine

Source	Opioid Events	Opioid Total	Ketamine Events	Ketamine Total	RD [95%-CI]	Weight
Over 18						
Miller, 2015	1	21	2.0	24	-0.04 [-0.18; 0.11]	22.3%
Shimonovich, 2016	12	24	9.5	12	-0.29 [-0.60; 0.01]	17.5%
Shimonovich, 2016	6	27	9.5	12	-0.57 [-0.85; -0.29]	18.4%
Farina, 2017	6	20	4.0	20	0.10 [-0.17; 0.37]	18.7%
Mahshidfar, 2017	48	150	51.0	150	-0.02 [-0.13; 0.09]	23.1%
Random effects model	**73**	**242**	**76.0**	**218**	**-0.15 [-0.47; 0.17]**	**100.0%**
Heterogeneity: I^2 = 77%, τ^2 = 0.0541, p < 0.01						
Under 18						
Graudins, 2015	4	37	20.0	36	-0.45 [-0.64; -0.26]	35.5%
Reynolds, 2017	6	41	30.0	41	-0.59 [-0.76; -0.41]	36.3%
Quinn, 2018	1	11	7.0	11	-0.55 [-0.88; -0.21]	28.2%
Random effects model	**11**	**89**	**57.0**	**88**	**-0.53 [-0.72; -0.33]**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.57						

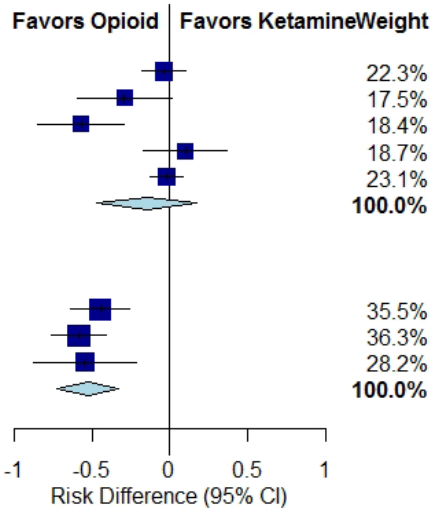

Figure F-41. Risk difference hypotension – subgroup age <18 years old, ≥18 years old, opioids versus ketamine

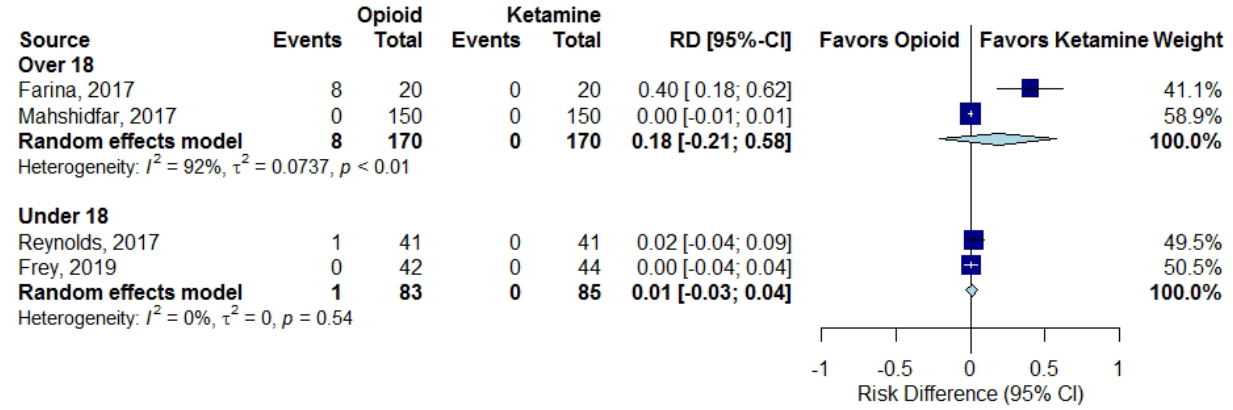

Figure F-42. Risk difference dizziness – subgroup traumatic pain, opioids versus ketamine

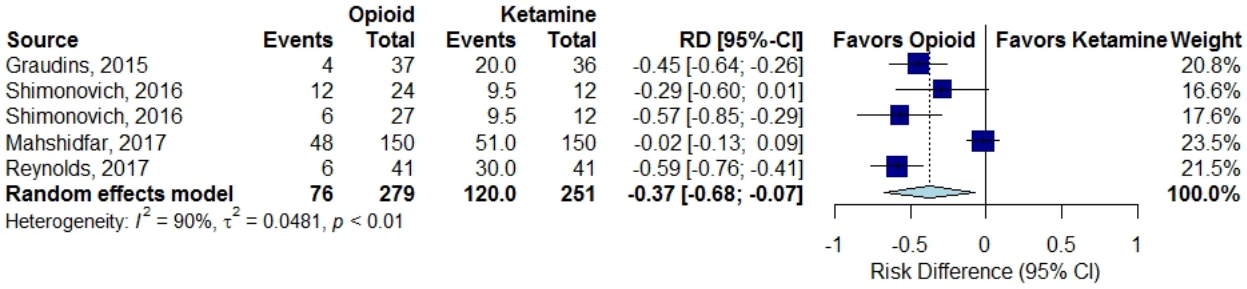

Figure F-43. Risk difference drowsiness – subgroup traumatic pain, opioids versus ketamine

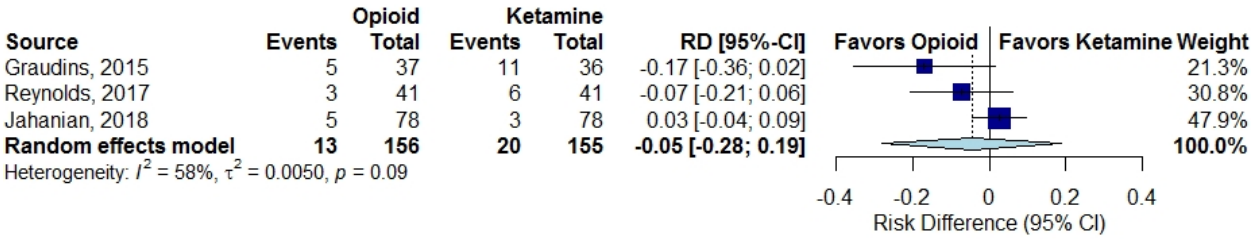

Figure F-44. Risk difference hypotension – subgroup traumatic pain, opioids versus ketamine

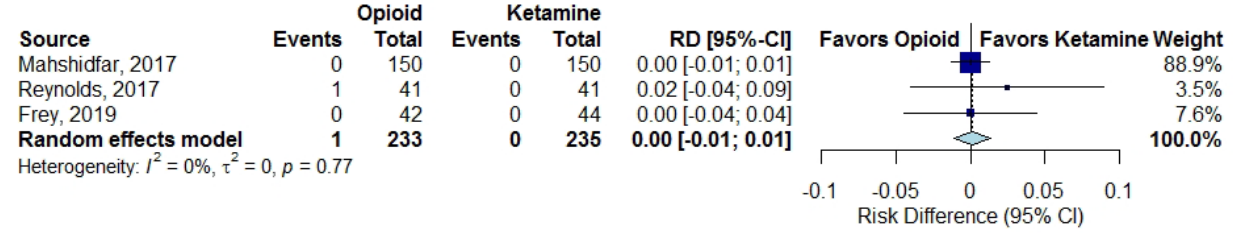

Figure F-45. Risk difference respiratory depression – subgroup traumatic pain, opioids versus ketamine

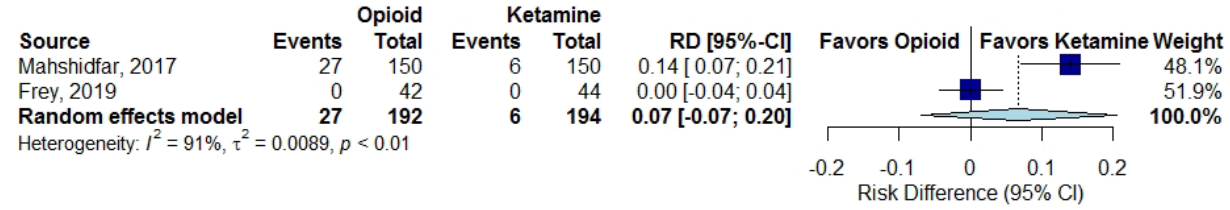

Figure F-46. Risk difference any adverse event – subgroup traumatic pain, opioids versus ketamine

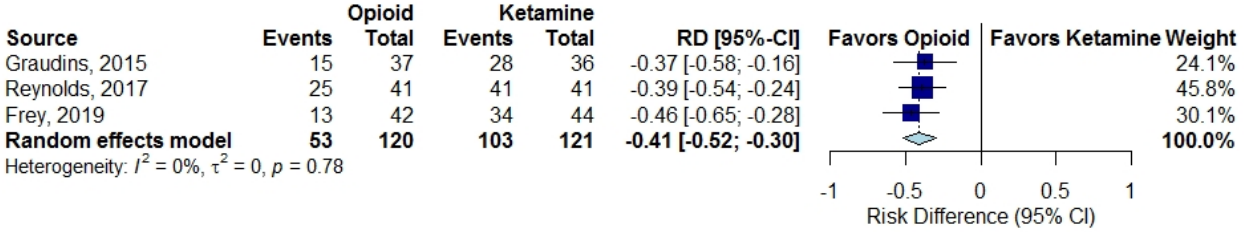

Figure F-47. Risk difference any adverse event – subgroup location of pain, opioids versus ketamine

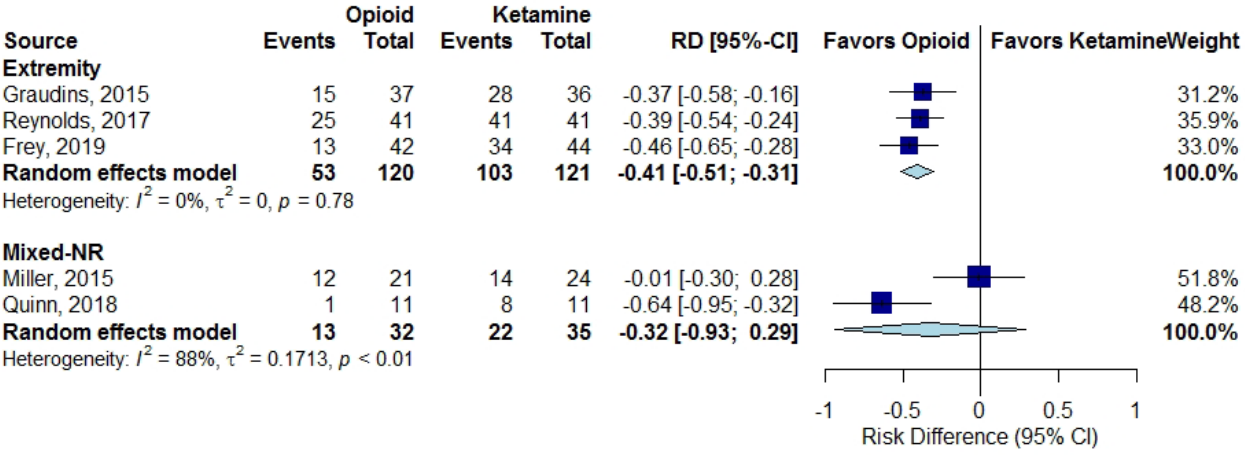

Figure F-48. Risk difference dizziness – subgroup location of pain, opioids versus ketamine

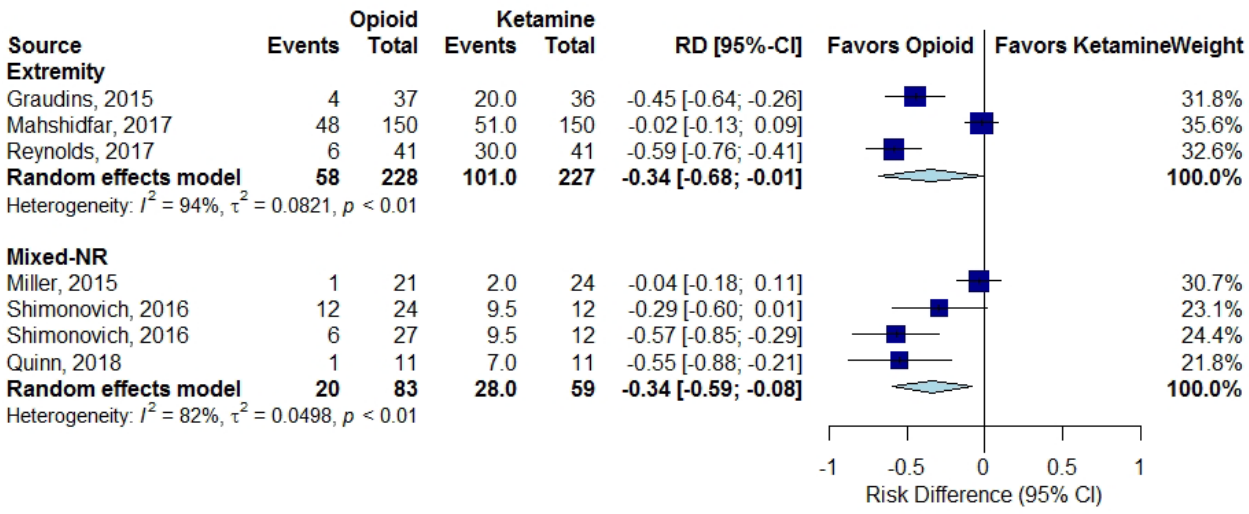

Figure F-49. Risk difference respiratory depression – subgroup location of pain, opioids versus ketamine

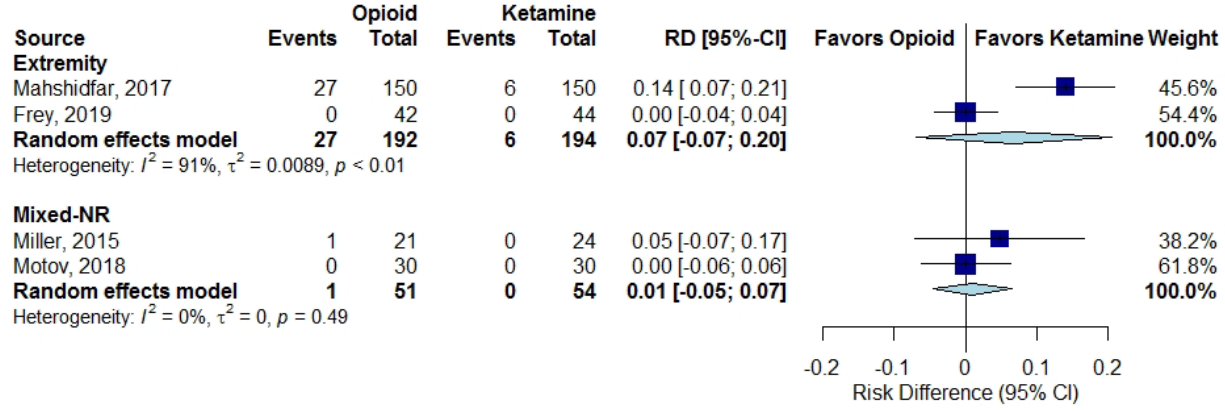

Figure F-50. Risk difference dizziness – subgroup route of administration, opioids versus ketamine

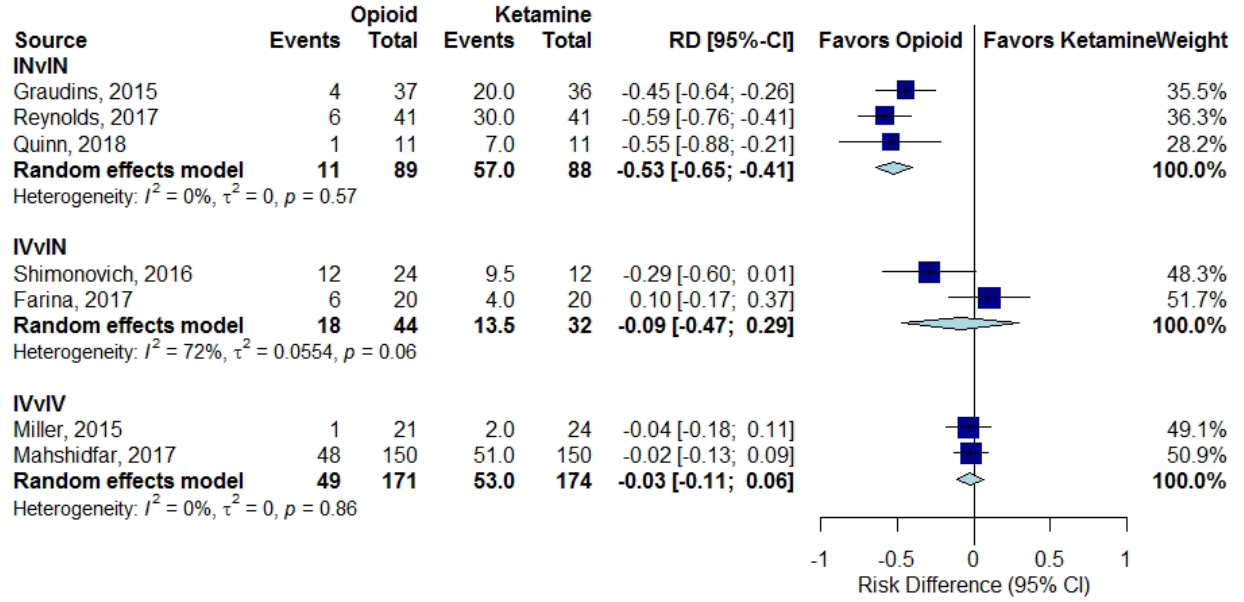

Figure F-51. Risk difference dizziness – subgroup frequency of administration, opioids versus ketamine

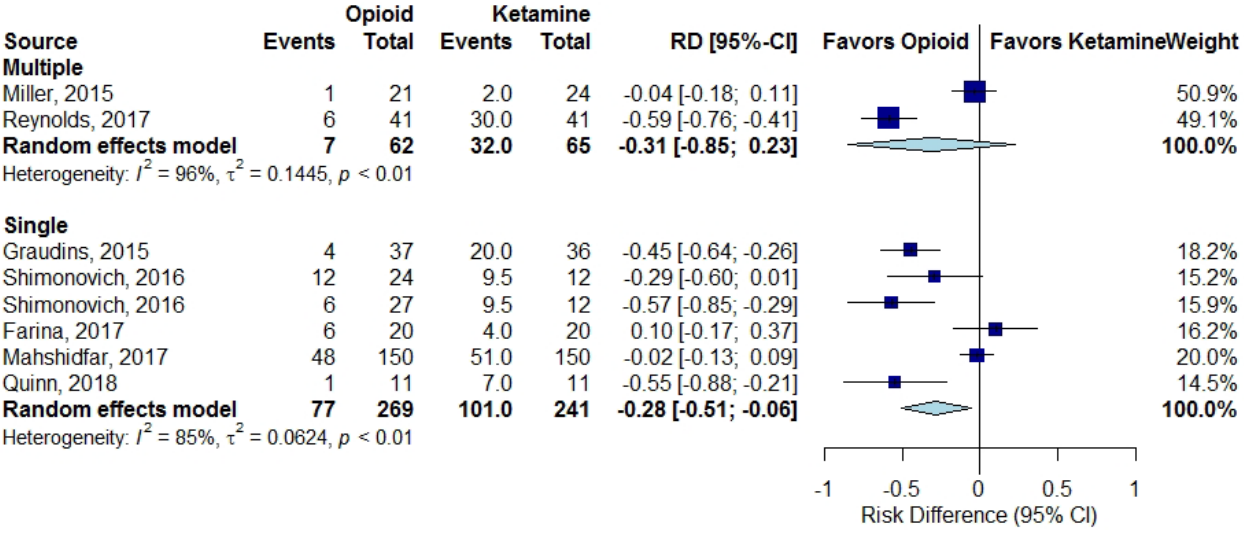

Figure F-52. Risk difference any adverse event – subgroup frequency of administration, opioids versus ketamine

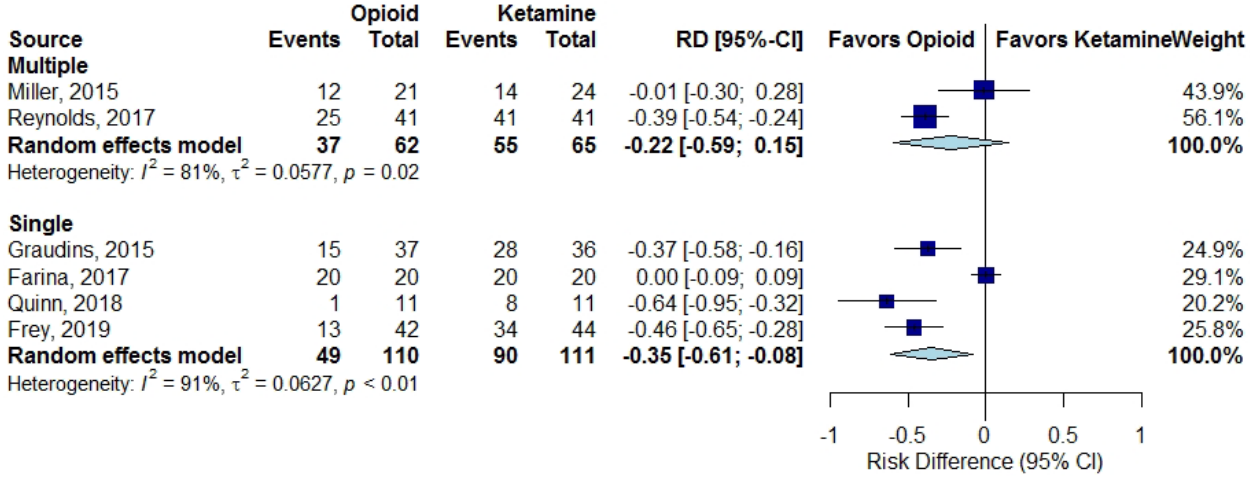

Figure F-53. Mean difference change in diastolic blood pressure at 15 minutes – additional findings, opioids versus ketamine

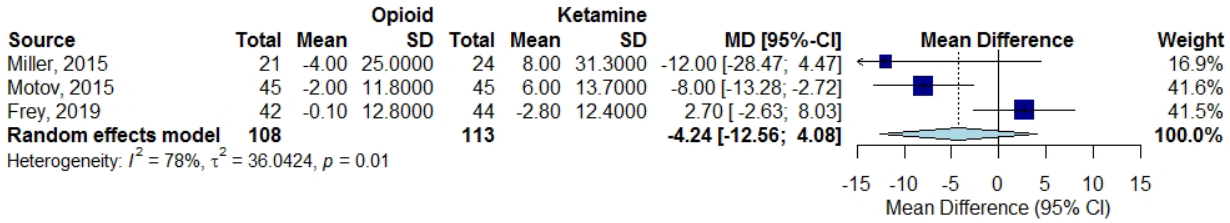

Figure F-54. Mean difference change in diastolic blood pressure at 30 minutes – additional findings, opioids versus ketamine

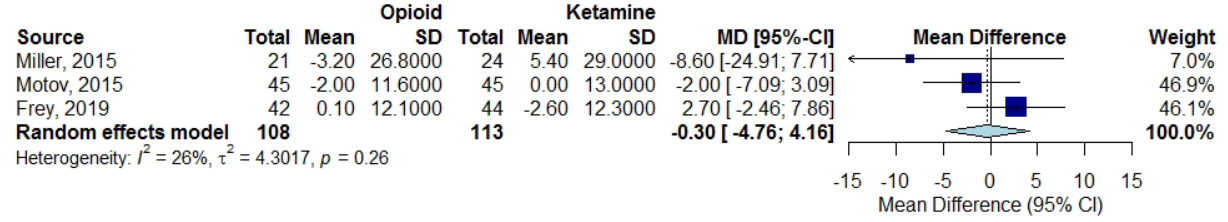

Figure F-55. Mean difference change in diastolic blood pressure at 60 minutes – additional findings, opioids versus ketamine

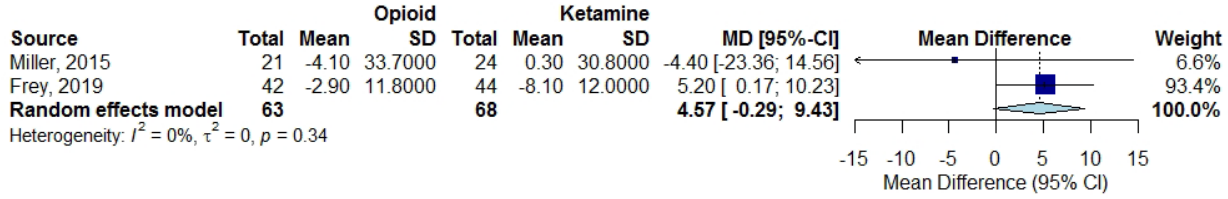

Figure F-56. Risk difference dissociation – additional findings, opioids versus ketamine

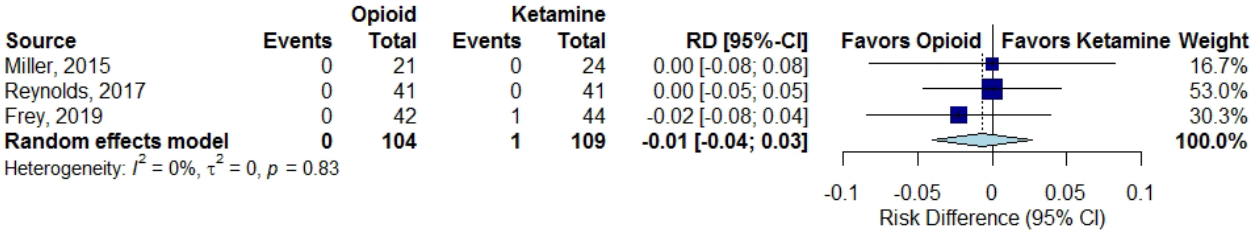

Figure F-57. Risk difference emergence delirium – additional findings, opioids versus ketamine

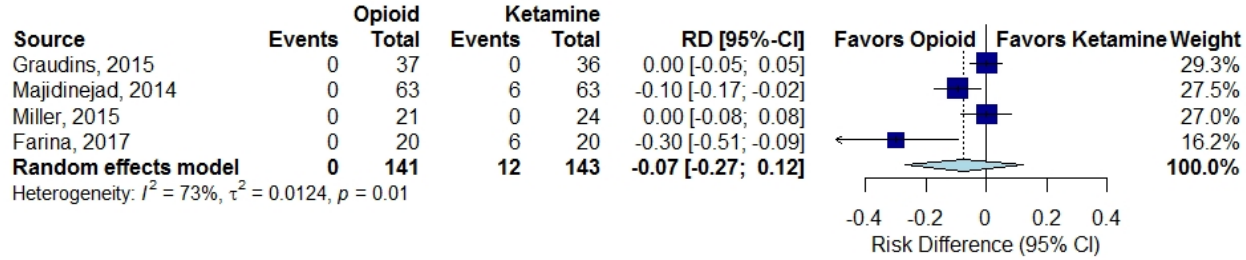

Figure F-58. Mean difference change in heart rate at 15 minutes – additional findings, opioids versus ketamine

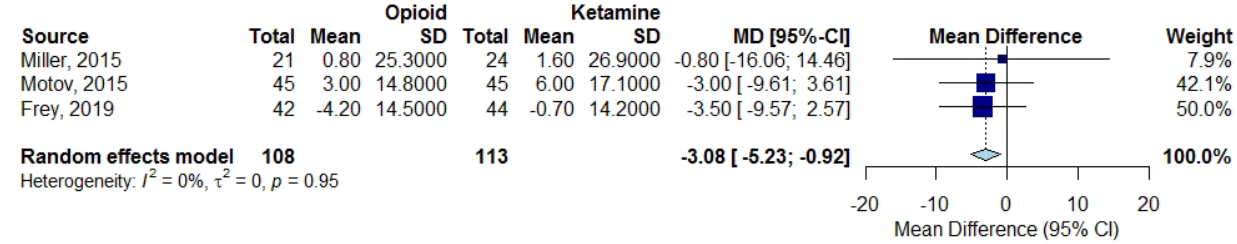

Figure F-59. Mean difference change in heart rate at 30 minutes – additional findings, opioids versus ketamine

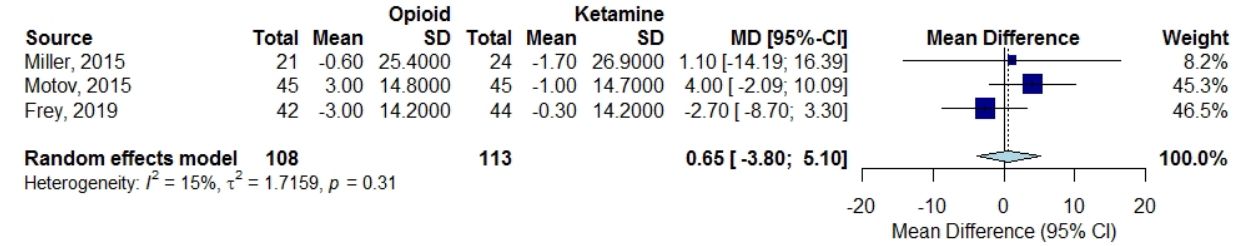

Figure F-60. Mean difference change in heart rate at 60 minutes – additional findings, opioids versus ketamine

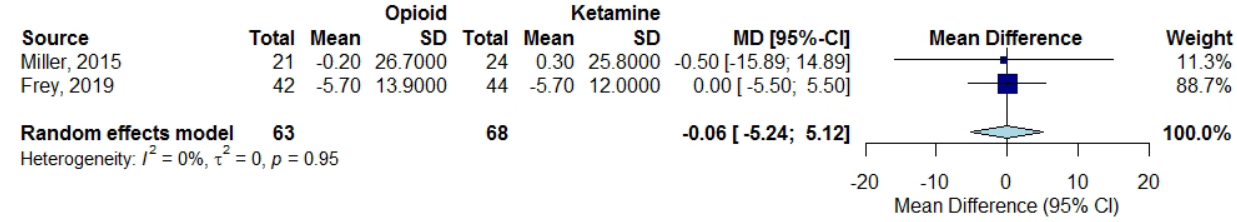

Figure F-61. Risk difference nausea at 15 minutes – additional findings, opioids versus ketamine

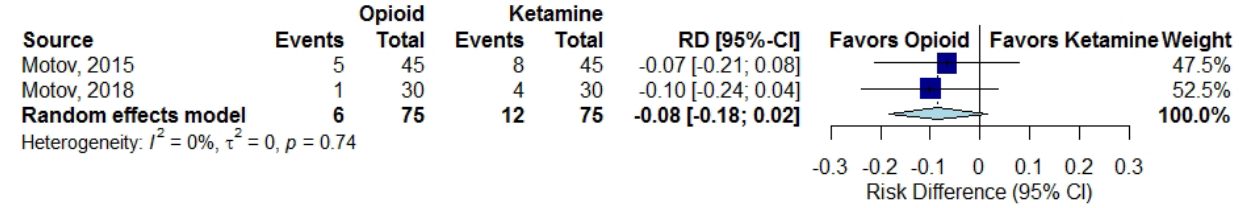

Figure F-62. Risk difference nausea at 30 minutes – additional findings, opioids versus ketamine

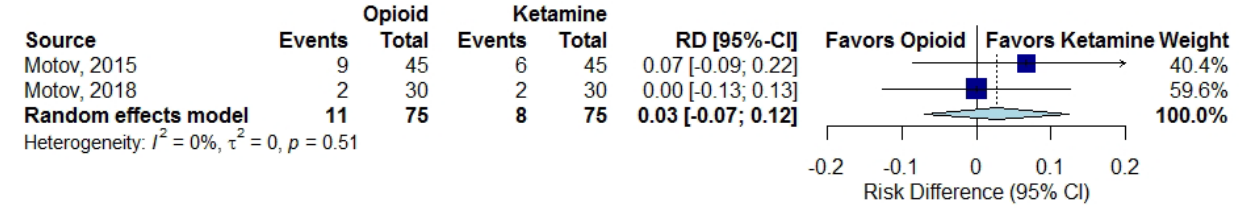

Figure F-63. Risk difference nausea – additional findings, opioids versus ketamine

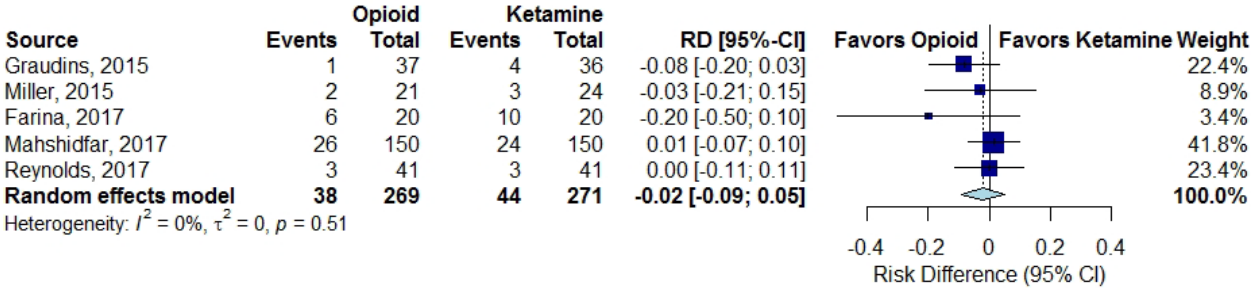

Figure F-64. Mean difference change in oxygen saturation at 15 minutes – additional findings, opioids versus ketamine

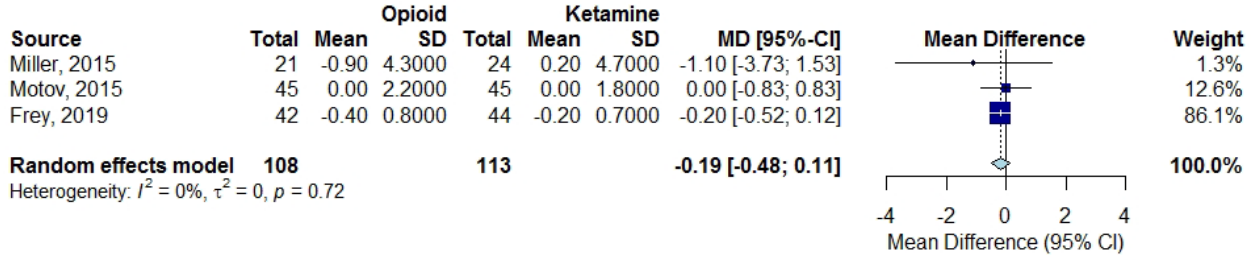

Figure F-65. Mean difference change in oxygen saturation at 30 minutes – additional findings, opioids versus ketamine

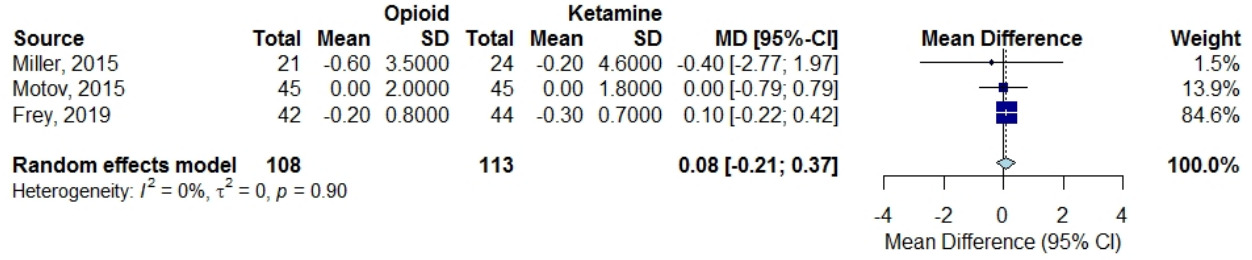

Figure F-66. Mean difference change in oxygen saturation at 60 minutes – additional findings, opioids versus ketamine

		Opioid			Ketamine				
Source	**Total**	**Mean**	**SD**	**Total**	**Mean**	**SD**	**MD [95%-CI]**	**Mean Difference**	**Weight**
Miller, 2015	21	-1.20	5.0000	24	-0.10	4.3000	-1.10 [-3.84; 1.64]		1.5%
Frey, 2019	42	-0.30	0.8000	44	-0.50	0.8000	0.20 [-0.14; 0.54]		98.5%
Random effects model	**63**			**68**			**0.18 [-0.16; 0.52]**		**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.36

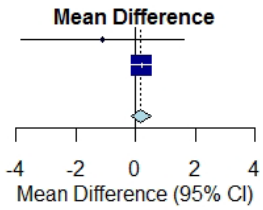

Figure F-67. Mean difference change in respiratory rate at 15 minutes – additional findings, opioids versus ketamine

		Opioid			Ketamine				
Source	**Total**	**Mean**	**SD**	**Total**	**Mean**	**SD**	**MD [95%-CI]**	**Mean Difference**	**Weight**
Miller, 2015	21	-1.30	6.1000	24	0.30	7.8000	-1.60 [-5.67; 2.47]		15.4%
Motov, 2015	45	-1.00	4.3000	45	1.00	5.2000	-2.00 [-3.97; -0.03]		65.5%
Frey, 2019	42	-0.70	6.7000	44	1.00	10.3000	-1.70 [-5.36; 1.96]		19.1%
Random effects model	**108**			**113**			**-1.88 [-2.39; -1.38]**		**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.98

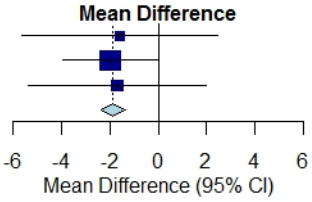

Figure F-68. Mean difference change in respiratory rate at 30 minutes – additional findings, opioids versus ketamine

		Opioid			Ketamine				
Source	**Total**	**Mean**	**SD**	**Total**	**Mean**	**SD**	**MD [95%-CI]**	**Mean Difference**	**Weight**
Miller, 2015	21	-0.70	5.6000	24	0.00	6.4000	-0.70 [-4.21; 2.81]		27.5%
Motov, 2015	45	0.00	4.2000	45	0.00	5.4000	0.00 [-2.00; 2.00]		41.5%
Frey, 2019	42	-3.10	6.7000	44	1.20	7.9000	-4.30 [-7.39; -1.21]		31.0%
Random effects model	**108**			**113**			**-1.52 [-4.13; 1.08]**		**100.0%**

Heterogeneity: I^2 = 62%, τ^2 = 3.2232, p = 0.07

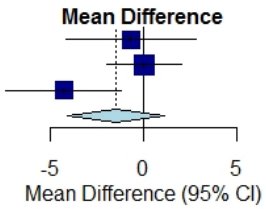

Figure F-69. Mean difference change in respiratory rate at 60 minutes – additional findings, opioids versus ketamine

		Opioid			Ketamine				
Source	**Total**	**Mean**	**SD**	**Total**	**Mean**	**SD**	**MD [95%-CI]**	**Mean Difference**	**Weight**
Miller, 2015	21	-1.60	5.7000	24	-0.90	5.7000	-0.70 [-4.04; 2.64]		44.8%
Frey, 2019	42	-3.30	6.7000	44	-0.30	7.5000	-3.00 [-6.00; 0.00]		55.2%
Random effects model	**63**			**68**			**-1.97 [-4.21; 0.27]**		**100.0%**

Heterogeneity: I^2 = 1%, τ^2 = 0.0209, p = 0.32

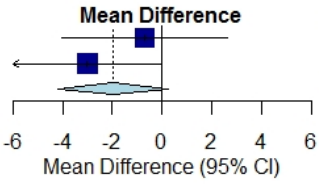

Figure F-70. Mean difference change in systolic blood pressure at 15 minutes – additional findings, opioids versus ketamine

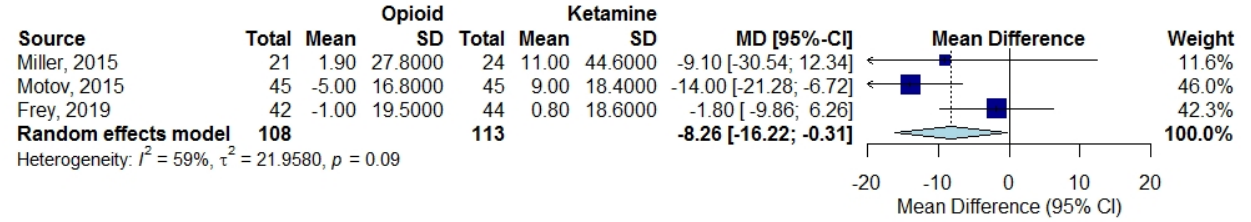

Figure F-71. Mean difference change in systolic blood pressure at 30 minutes – additional findings, opioids versus ketamine

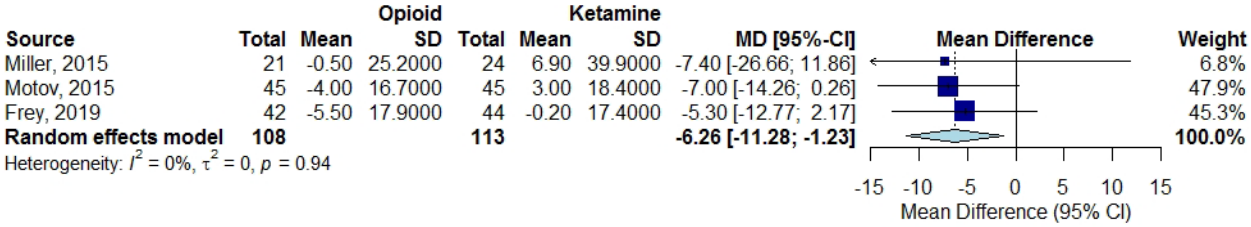

Figure F-72. Mean difference change in systolic blood pressure at 60 minutes – additional findings, opioids versus ketamine

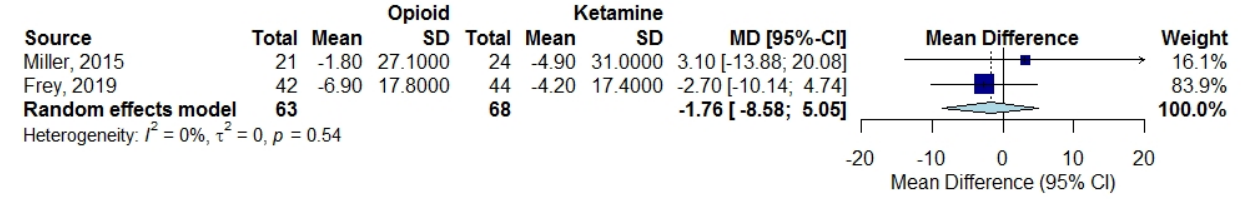

Figure F-73. Risk difference respiratory depression, combination opioids and ketamine versus opioids

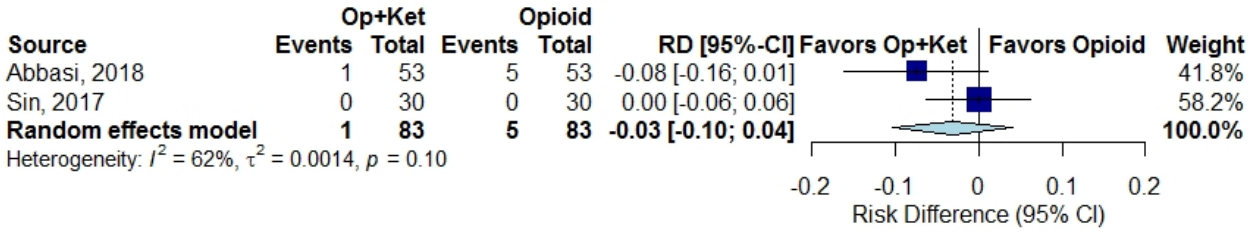

Figure F-74. Mean difference change in systolic blood pressure at 30 minutes – additional findings, combination opioids and ketamine versus opioids

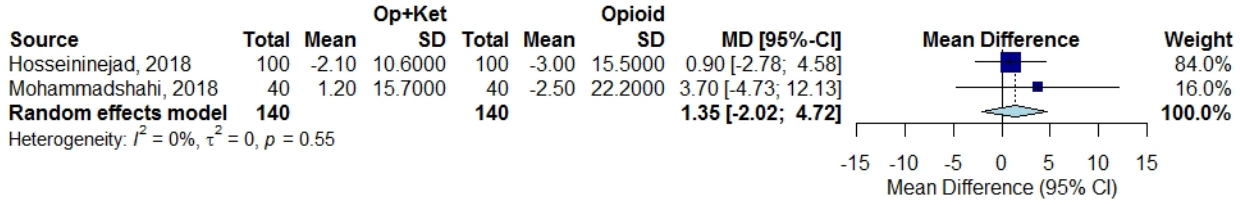

Figure F-75. Mean difference change in systolic blood pressure at 60 minutes – additional findings, combination opioids and ketamine versus opioids

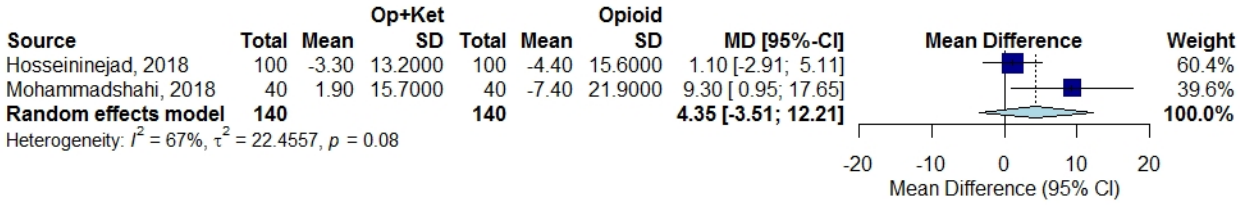

Figure F-76. Risk difference any adverse event, opioids versus acetaminophen

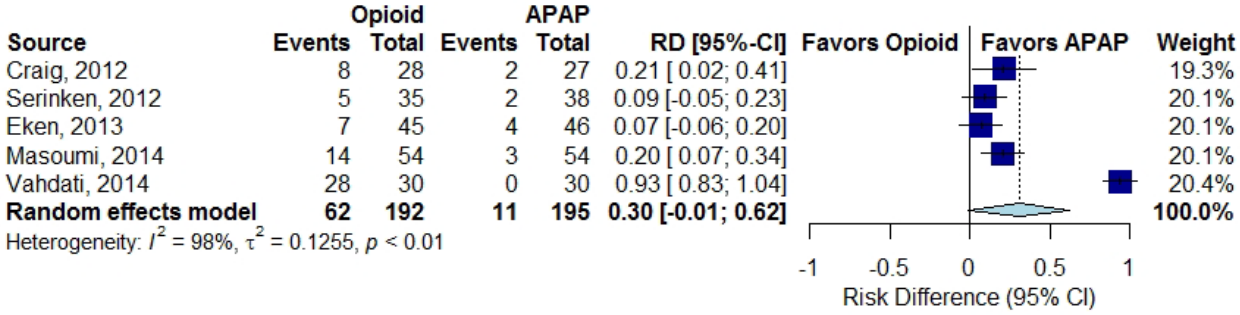

Figure F-77. Risk difference hypotension, opioids versus acetaminophen

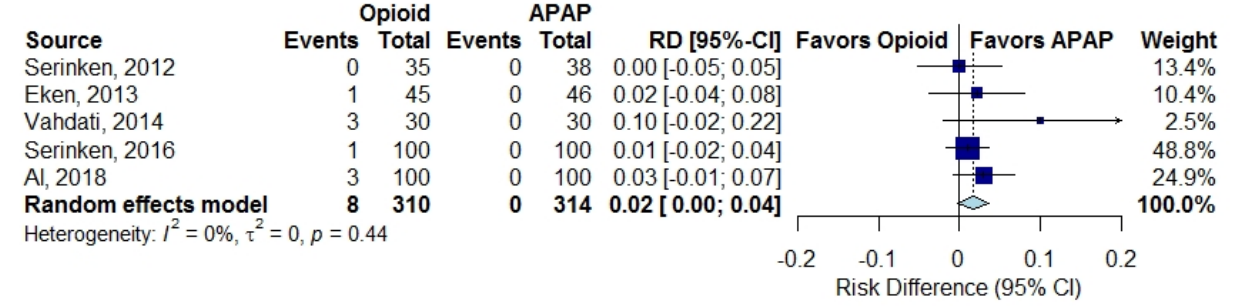

Figure F-78. Risk difference mental status changes dizziness, opioids versus acetaminophen

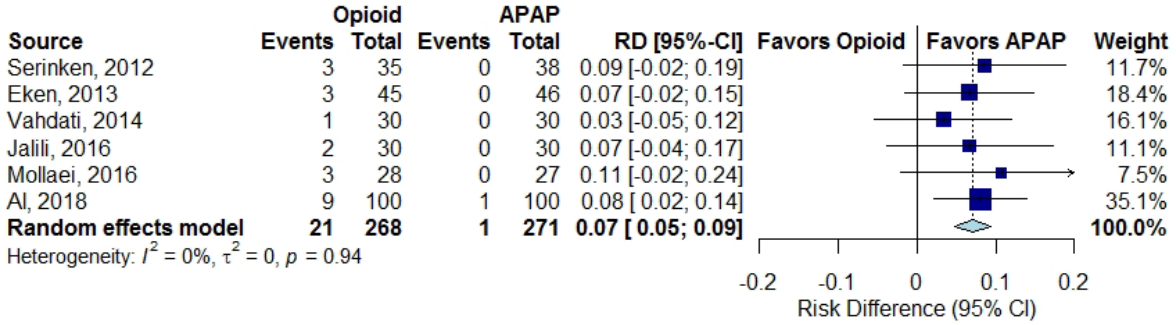

Figure F-79. Risk difference any adverse event – subgroup location of pain, opioids versus acetaminophen

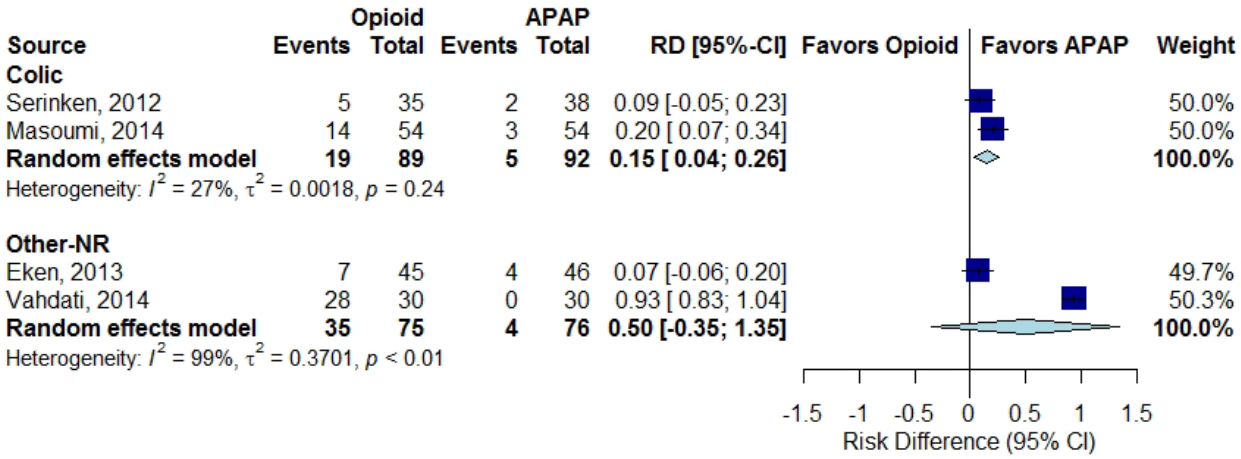

Figure F-80. Risk difference hypotension – subgroup location of pain, opioids versus acetaminophen

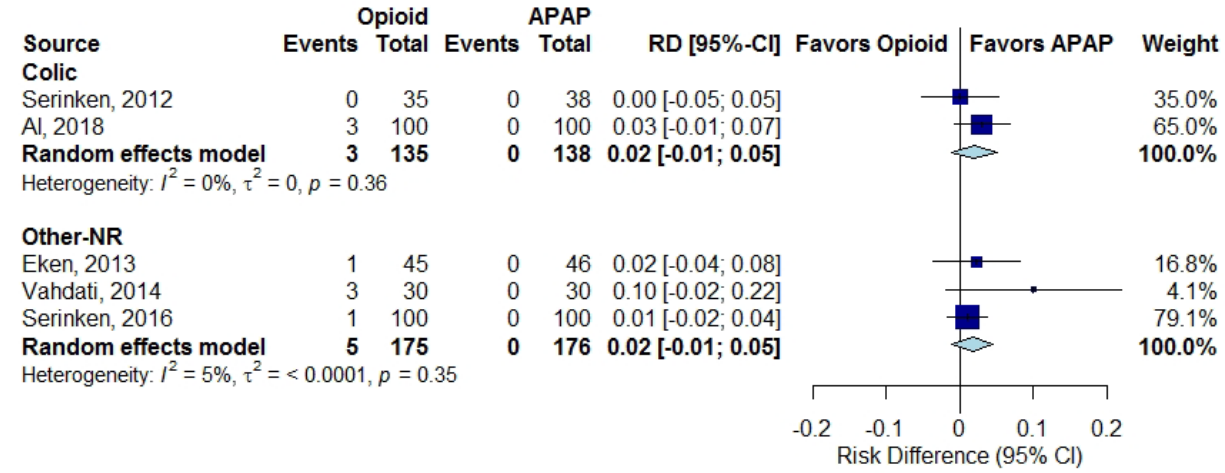

Figure F-81. Risk difference dizziness – subgroup location of pain, opioids versus acetaminophen

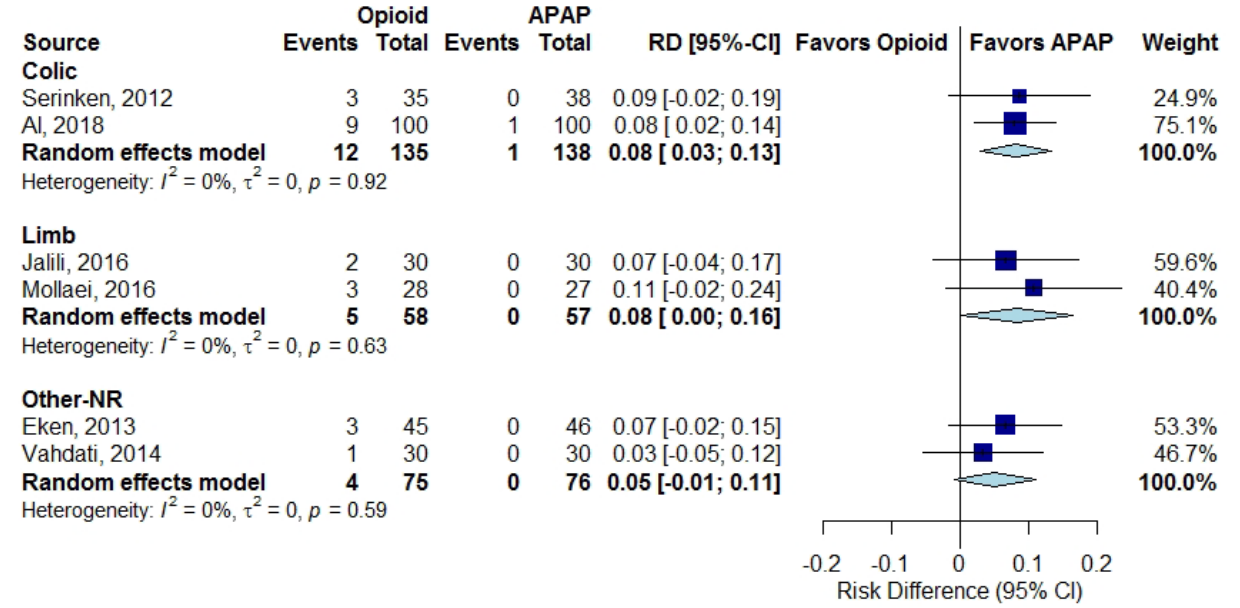

Figure F-82. Risk difference any adverse event – subgroup traumatic pain, opioids versus acetaminophen

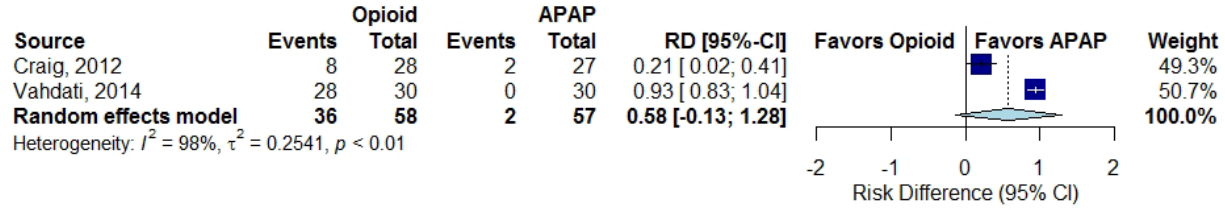

Figure F-83. Risk difference dizziness – subgroup traumatic pain, opioids versus acetaminophen

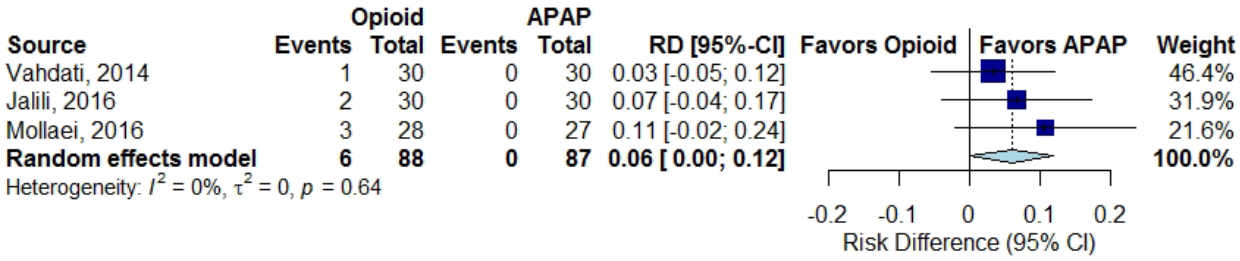

Figure F-84. Risk difference nausea – additional findings, opioids versus acetaminophen

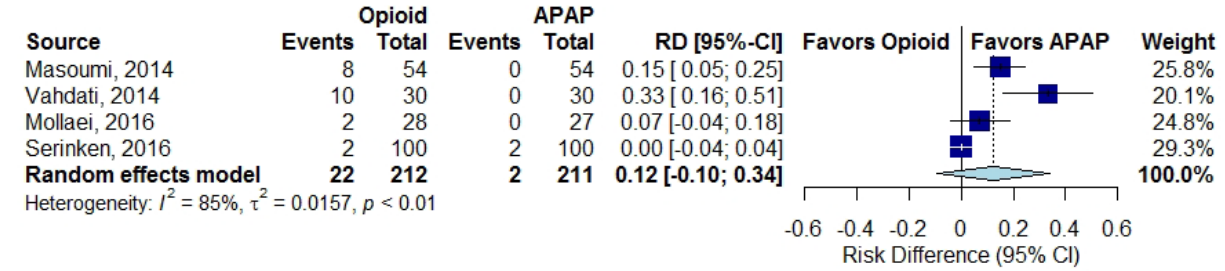

Figure F-85. Risk difference nausea and/or vomiting – additional findings, opioids versus acetaminophen

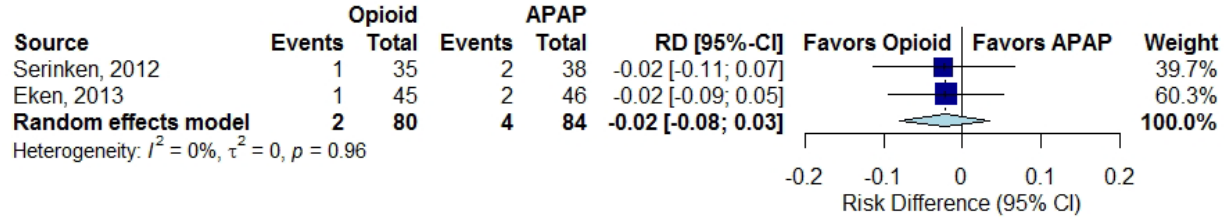

Figure F-86. Risk difference vomiting – additional findings, opioids versus acetaminophen

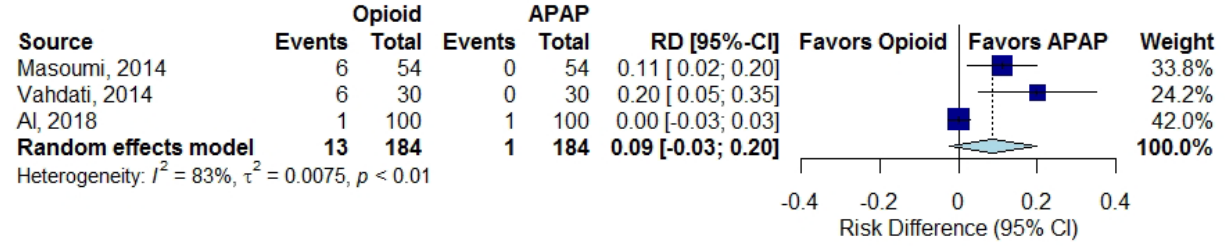

Figure F-87. Risk difference any adverse event, opioids versus nonsteroidal anti-inflammatory drugs

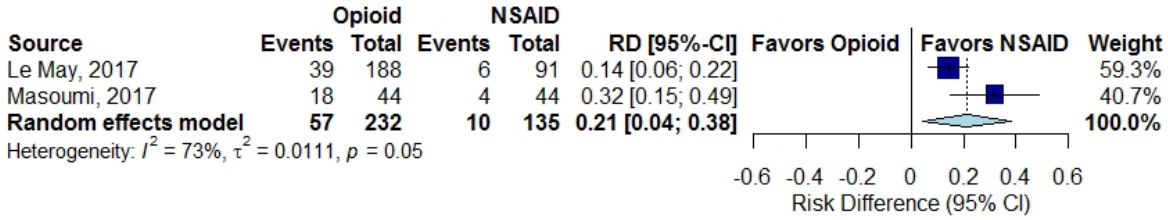

Figure F-88. Risk difference mental status changes drowsiness, opioids versus nonsteroidal anti-inflammatory drugs

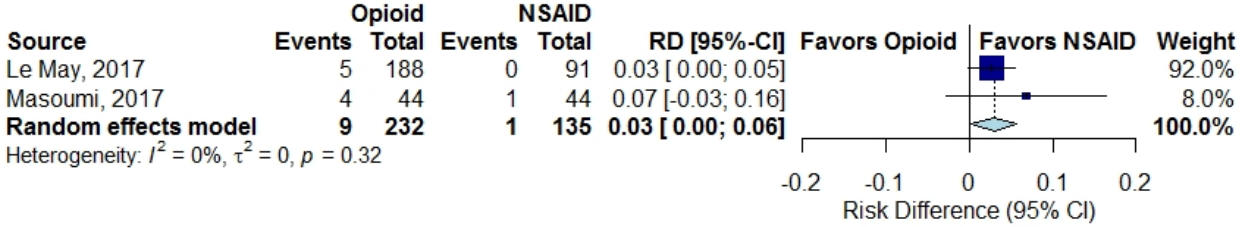

Figure F-89. Risk difference nausea – additional findings, opioids versus nonsteroidal anti-inflammatory drugs

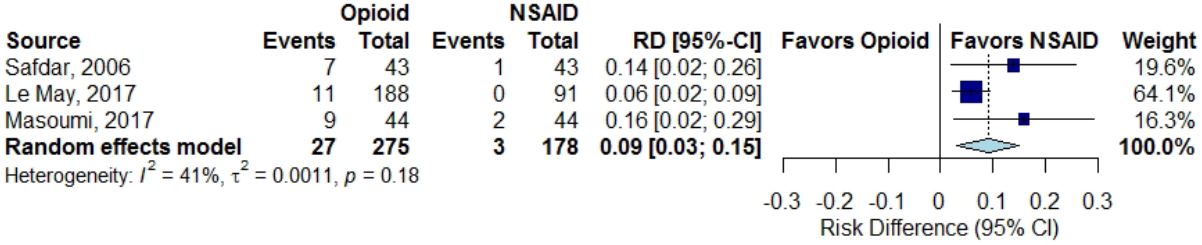

Figure F-90. Risk difference vomiting – additional findings, opioids versus nonsteroidal anti-inflammatory drugs

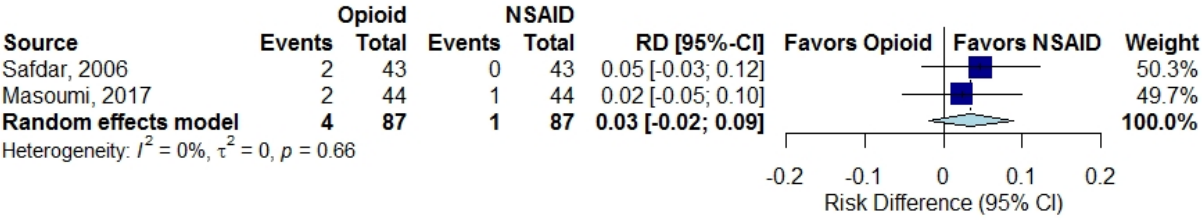

Figure F-91. Risk difference any adverse event, acetaminophen versus nonsteroidal anti-inflammatory drugs

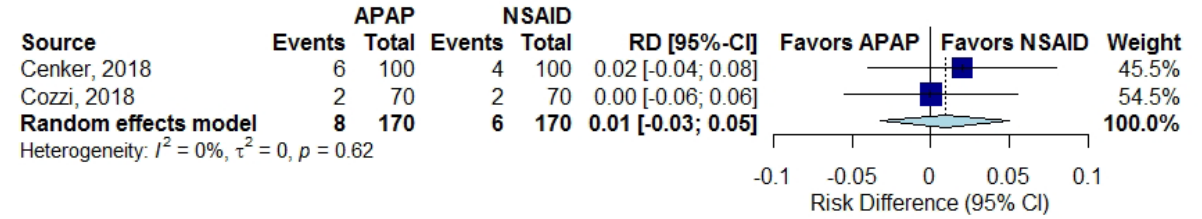

Figure F-92. Risk difference vomiting, acetaminophen versus nonsteroidal anti-inflammatory drugs

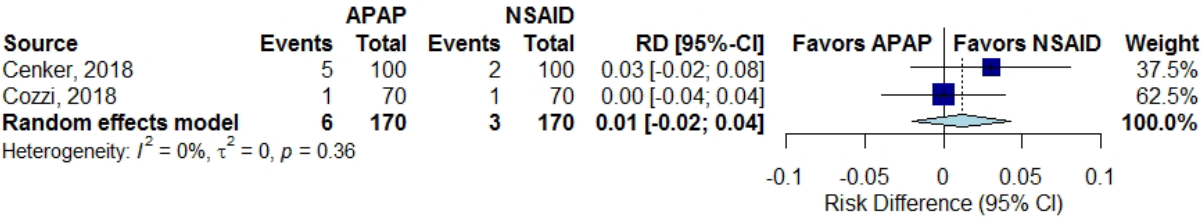

Figure F-93. Risk difference any adverse event, morphine versus fentanyl

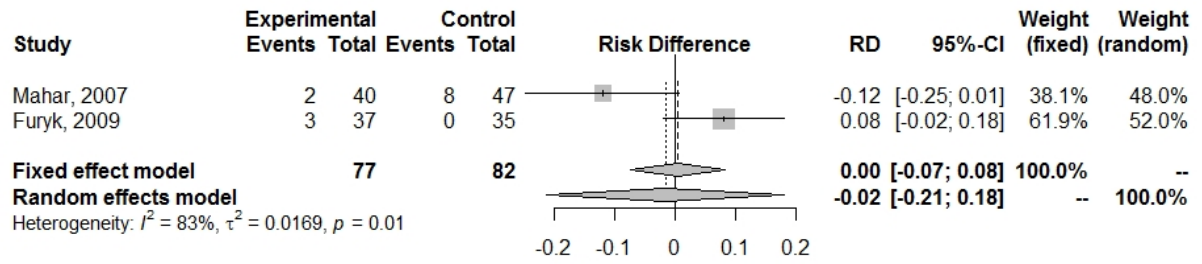

Figure F-94. Mean difference change in heart rate, morphine versus fentanyl

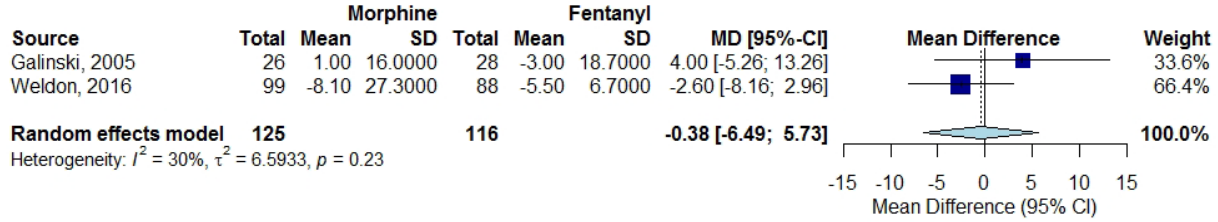

Figure F-95. Risk difference hypotension, morphine versus fentanyl

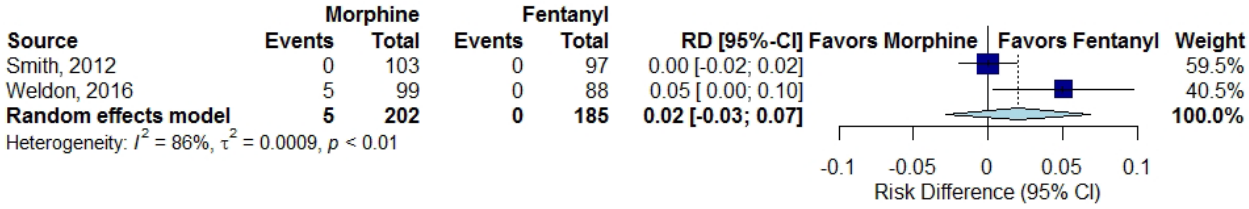

Figure F-96. Risk difference nausea, morphine versus fentanyl – emergency medical services

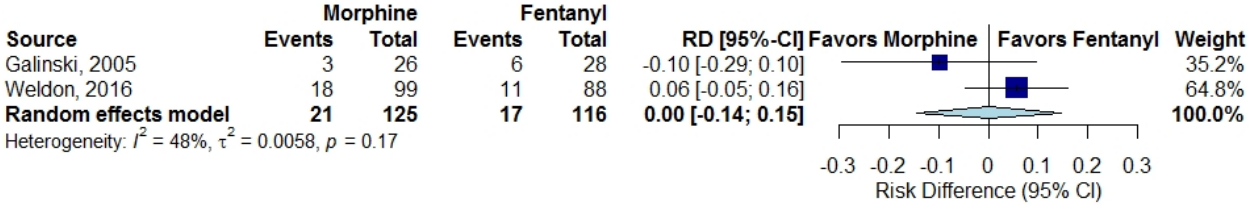

Figure F-97. Risk difference nausea, morphine versus fentanyl – emergency department

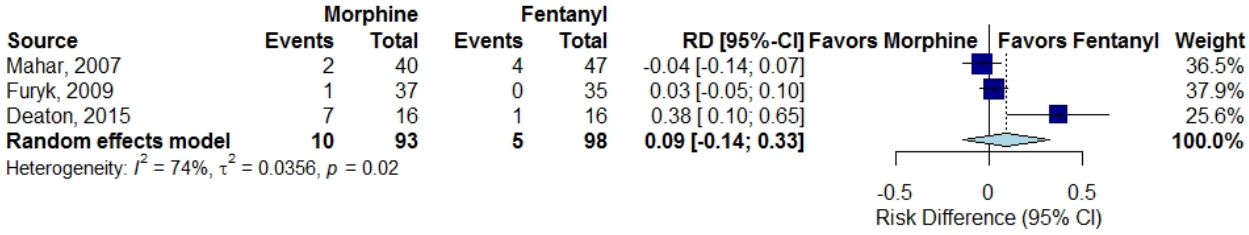

Figure F-98. Risk difference nausea and/or vomiting, morphine versus fentanyl

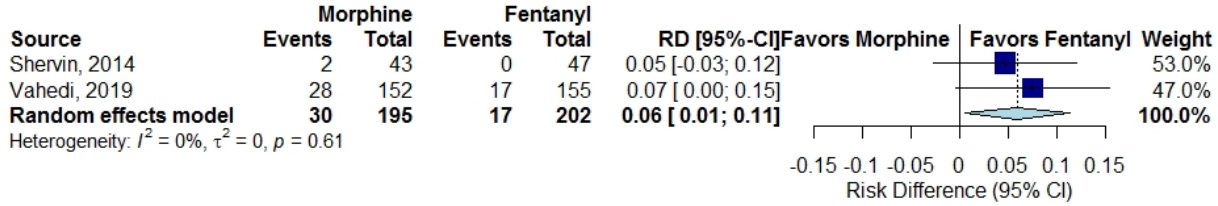

Figure F-99. Mean difference change in respiratory rate, morphine versus fentanyl – emergency medical services

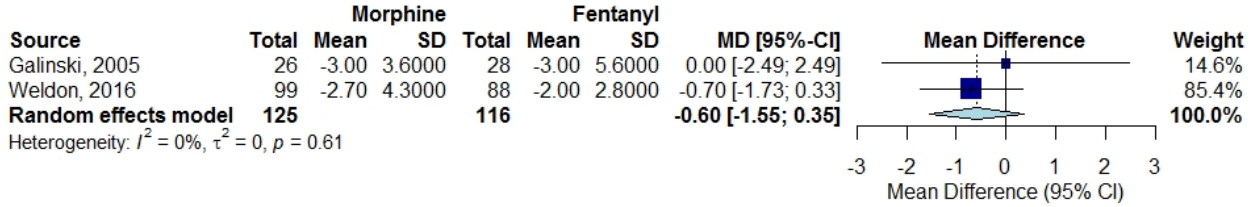

Figure F-100. Risk difference vomiting, morphine versus fentanyl – emergency medical services

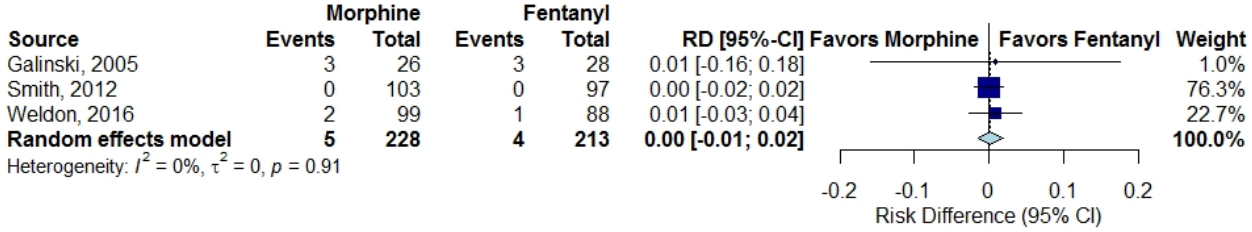

Figure F-101. Risk difference vomiting, morphine versus fentanyl – emergency department

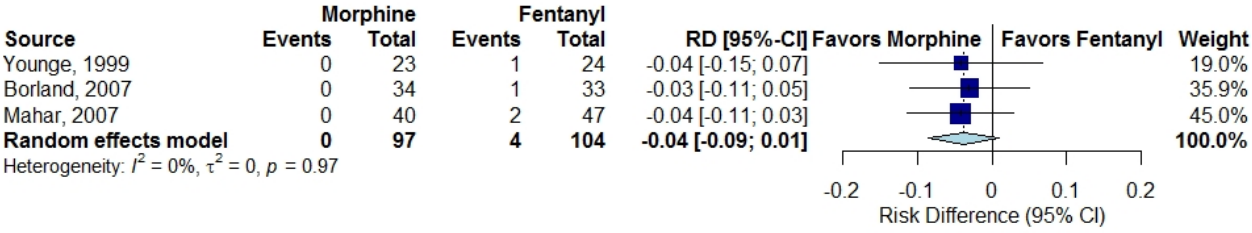

Figure F-102. Mean difference change in pain, additional opioids versus ketamine – emergency medical services

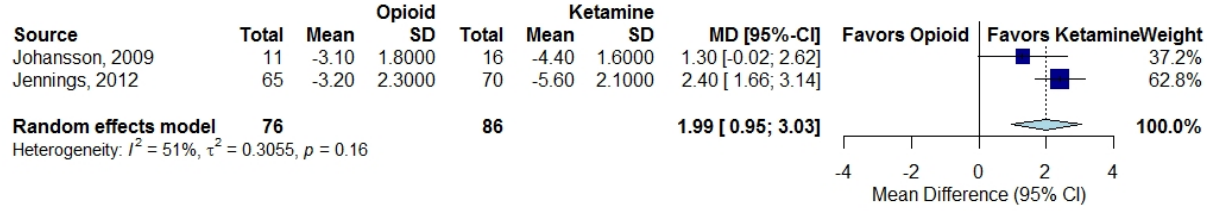

Figure F-103. Mean difference change in heart rate, additional opioids versus ketamine – emergency medical services

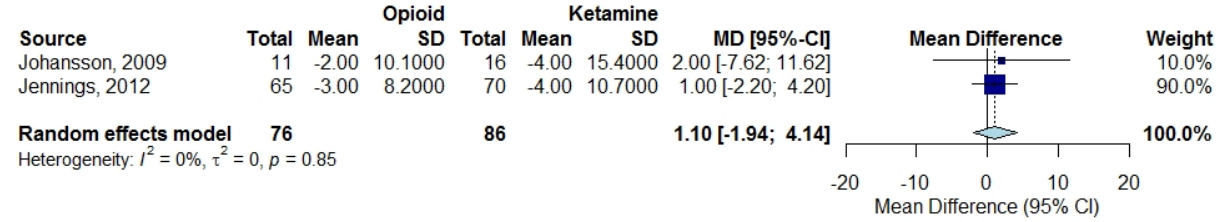

Figure F-104. Mean difference change in respiratory rate, additional opioids versus ketamine – emergency medical services

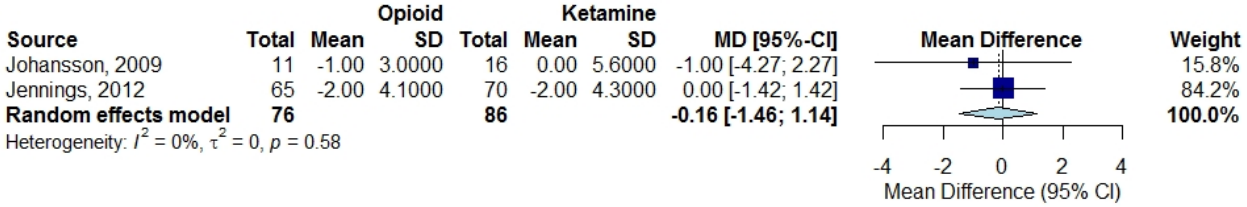

Figure F-105. Mean difference change in systolic blood pressure, additional opioids versus ketamine – emergency medical services

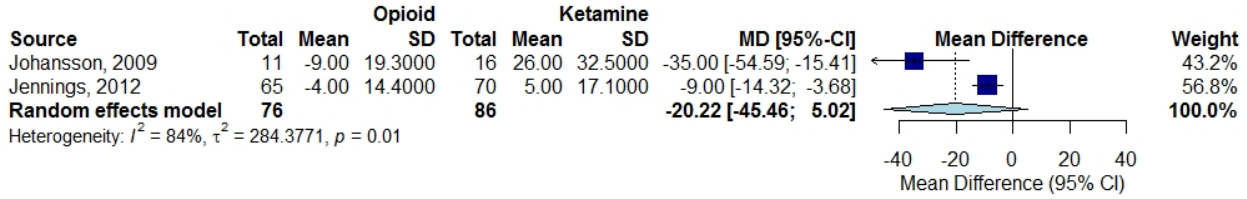

Figure F-106. Risk difference nausea, additional opioids versus ketamine – emergency medical services

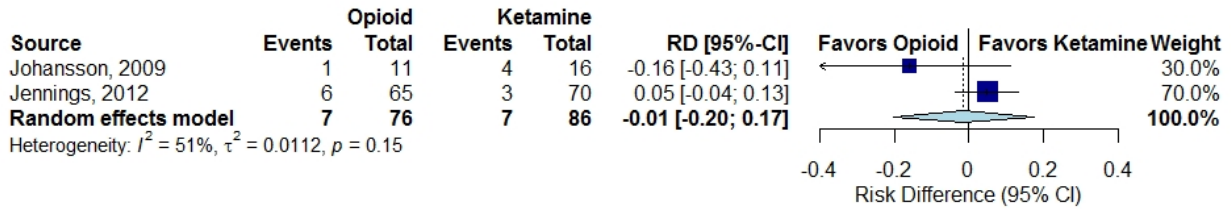

Figure F-107. Risk difference vomiting, additional opioids versus ketamine – emergency medical services