# Low-dose Ketamine For Acute Pain Control in the Emergency Department: A Systematic Review and Meta-analysis

Nathan Balzer, MD, BScN[1], Shelley L. McLeod, PhD, MSc[2,3], Chris Walsh, MLIS, MA[4], and Keerat Grewal, MD, MSc[1,3]

## ABSTRACT

**Objective:** There has been increased interest in the use of low-dose ketamine (LDK) as an alternative analgesic for the management of acute pain in the emergency department (ED). The objective of this systematic review was to compare the analgesic effectiveness and safety profile of LDK and morphine for acute pain management in the ED.

**Methods:** Electronic searches of Medline and EMBASE were conducted and reference lists were hand-searched. Randomized controlled trials (RCTs) comparing LDK to morphine for acute pain control in the ED were included. Two reviewers independently screened abstracts, assessed quality of the studies, and extracted data. Data were pooled using random-effects models and reported as mean differences and risk ratios (RRs) with 95% confidence intervals (CIs). We used the Grading of Recommendations Assessment, Development and Evaluation approach to assess the certainty of the evidence.

**Results:** Eight RCTs were included with a total of 1,191 patients (LDK = 598, morphine = 593). There was no significant difference in reported mean pain scores between LDK and morphine within the first 60 minutes after analgesia administration and a slight difference in pain scores favoring morphine at 60 to 120 minutes. The need for rescue medication was also similar between groups (RR = 1.26, 95% CI = 0.50 to 3.16), as was the proportion of patients who experienced nausea (RR = 0.97, 95% CI = 0.63 to 1.49) and hypoxia (RR = 0.38, 95% CI = 0.10 to 1.41). All outcomes were judged to have low certainty in the evidence.

**Conclusion:** Low-dose ketamine and morphine had similar analgesic effectiveness within 60 minutes of administration with comparable safety profiles, suggesting that LDK is an effective alternative analgesic for acute pain control in the ED.

It has been estimated that acute pain accounts for more than half of all emergency department (ED) visits.[1,2] Acute pain management in the ED is an important aspect of patient care and satisfaction. Currently, the most common group of analgesics used in the ED are opioids.[3] However, there are many patients who would benefit from an alternative to opioids for safe and effective pain control in the ED. These patients include opioid-naïve adults and children, the elderly, chronic opioid users, those with a history of addiction, and those using medications for alcohol dependence or opioid misuse disorder. There

From the [1]Department of Medicine, Division of Emergency Medicine; the [2]Department of Family and Community Medicine, University of Toronto; the [3]Schwartz/Reisman Emergency Medicine Institute; and the [4]Sinai Health, Toronto, Ontario, Canada.
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continues to be an increase in ED presentations by these populations, so an equally effective and safe analgesic option would be a helpful alternative for ED physicians.[4–6]

Ketamine is a *N*-methyl-D-aspartate receptor antagonist with analgesic and anesthetic properties.[7] Historically, it was used as an anesthetic, but was replaced by newer anesthetics with more tolerable side effects. In more recent years, due to its dissociative properties that allow for preserved airway reflexes and hemodynamic stability, ketamine has been increasingly used in the ED for procedural sedation and induction for intubation.[8,9] At lower subdissociative doses (<0.5 mg/kg IV), ketamine has been shown to have analgesic properties for acute and chronic pain.[10,11] Although the use of ketamine to manage acute pain is relatively novel within the ED, it has unique features that could lend itself to improved patient outcomes, particularly for the specific populations described. An increasing number of studies have examined ketamine in comparison to opioids for pain control in the ED.[12–14] A previous systematic review and meta-analysis of three studies compared ketamine to morphine for acute pain control in the ED, but only included patients between the ages of 18 and 65 years and only examined short-term pain control as a primary outcome.[15] Other systematic reviews have compared ketamine to opioids or placebo, but none have focused specifically on low-dose ketamine (LDK) as an alternative to opioids.[16,17]

The objective of this systematic review and meta-analysis was to compare the analgesic effectiveness (pain control, need for rescue analgesia) and safety profile (proportion of patients who experienced nausea and hypoxia) of LDK and morphine for acute pain management in the ED.

## METHODS

### Data Sources and Search Strategy

In consultation with the review authors, a research librarian conducted the systematic literature searches in MEDLINE (1946 to July 2020) using both Ovid and PubMed search interfaces, EMBASE (1947 to July 2020), the Cochrane Central Register of Controlled Trials (July 2020), and electronic bibliographic databases. A comprehensive search strategy (Data Supplement S1, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.14159/full) included a combination of medical subject headings (MeSH) and free-text terms using various spelling and endings of key words.

### Eligibility Criteria and Study Selection

Randomized controlled trials (RCTs) published in the English language that compared the use of LDK administered intravenously (bolus or infusion < 30 minutes) to intravenous morphine for adult patients (≥18 years old) requiring acute pain management for any condition in the ED or prehospital setting were eligible for inclusion. We excluded the studies of pediatric populations (<18 years old), the use of ketamine outside of prehospital or ED settings (most commonly operating rooms), and ketamine for uses other than acute pain analgesia (procedural sedation, intubation, perioperative, psychiatric, chronic pain). We also excluded studies that administered LDK in conjunction with other analgesic agents. Two reviewers independently screened the search output to identify potentially eligible trials, the full texts of which were retrieved and assessed for inclusion. We also hand-searched reference lists of relevant articles and reviews as well as the regulatory website "clinicaltrials.gov" to identify any unpublished trials.

### Outcome Measures

We used a standardized data collection form to extract data on patient demographics, sample size, LDK dosage/route, morphine dosage/route, mean, and standard deviation (SD) of pain scores at each reported time based on a 10-point scale, need for/type of rescue analgesia, and adverse events (nausea and hypoxia). Our primary outcome of interest was the difference in mean pain scores between LDK and morphine reported at specified time intervals after analgesic administration. Pain scores were reported based on the Numeric Pain Reporting scale, which is measured from zero (no pain) to 10 (worst pain). We categorized time intervals as a pain score reported within 15, 15 to 30, 30 to 45, 45 to 60, 60 to 90, and 90 to 120 minutes. Secondary outcomes included the need for rescue analgesics, which we defined as a change from LDK or morphine to a different medication (as opposed to redosing the same medication) and the proportion of adverse events. Adverse events that were monitored in studies varied considerably; therefore, we focused on nausea and hypoxia.

## Risk of Bias Assessment

Risk of bias for each individual trial was independently assessed by two reviewers using the Cochrane Collaboration's tool for assessing risk of bias for systematic reviews of interventions.[18] We assessed the risk of bias for each study using the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each domain was assessed as having a low, unclear, or high risk of bias. Discrepancies were resolved by discussion and consensus among the authors.

## Data Synthesis and Analysis

Direct comparisons of continuous pain scores were performed using inverse variance random-effects models to account for both within-study and between-study heterogeneity and reported as mean differences (MDs) with 95% confidence intervals (CIs) using Review Manager 5.3.4 (Nordic Cochrane Centre, Copenhagen, Denmark). A mean difference < 0 favored LDK and statistical significance was achieved if the 95% CI of the pooled point estimate excluded zero. Direct comparisons of dichotomous outcomes (need for rescue analgesia, nausea, and hypoxia) were performed using Mantel-Haenszel random-effects models and reported as risk ratios (RRs) with 95% CIs. RRs < 1 favored LDK, and statistical significance was achieved if the 95% CI of the pooled RR excluded unity. Statistical heterogeneity between studies was assessed using the $I^2$ statistic, with $I^2$ values ≥ 50% indicating substantial heterogeneity.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which provides a structured and transparent framework to assess the certainty (high, moderate, low, and very low) of the evidence.[19] We used conventional GRADE guidance and considered risk of bias, inconsistency, imprecision, indirectness, and publication bias for the body of evidence informing each outcome.

# RESULTS

The search strategy yielded 524 potentially relevant citations. After duplicate citations and studies that did not meet eligibility criteria were eliminated, 17 studies were retrieved for full article review (Figure 1). Nine studies were subsequently excluded, leaving eight studies included in the review with a total of 1,191 patients (598 patients in the LDK group and 593 patients in the morphine group). A summary of the included trials is shown in Table 1. All studies were published between 2014 and 2019.[12–14,20–24] One study was reported as an abstract.[24] Sample sizes of included studies ranged from 45 to 300 patients. The included studies used LDK doses ranging from 0.2 to 0.5 mg/kg intravenously. All studies used morphine boluses of 0.1 mg/kg intravenously. Four studies examined patients with abdominal, flank, low back, or extremity pain;[13,14,20,21] two studies examined patients with long-bone fractures;[12,22] one study examined trauma patients with musculoskeletal pain;[23] and one study examined those with a sickle cell pain crisis.[24] All studies were conducted in the ED, with no prehospital studies included. The majority of studies included in this review were found to have a low risk or unclear risk of bias for each domain (Table 2).

## Outcomes

Six studies, with a total of 757 patients (380 in the LDK group and 377 in the morphine group) reported a pain score within 15 minutes of analgesic administration (Figure 2).[12–14,20,21,23] The pooled estimate showed no significant difference in mean pain scores between LDK and morphine within 15 minutes (MD = −0.15, 95% CI = −0.68 to 0.38). Six studies reported a pain score between 15 and 30 minutes.[13,14,20–23] The pooled estimate showed no significant difference in mean pain scores between groups (MD = −0.03, 95% CI = −0.37 to 0.32). The pain scores were also similar between 30 and 45 minutes (MD = 0.40, 95% CI = −0.89 to 1.68) and between 45 and 60 minutes (MD = 0.52, 95% CI = −0.03 to 1.07). There was a small statistically significant difference in pain scores favored morphine at 60 to 90 minutes (MD = 0.12, 95% CI = 0.03 to 0.22) and 90 to 120 minutes (MD = 0.08, 95% CI = 0.05 to 0.11; Figure 3). All pain outcomes were judged to have low certainty in the evidence using GRADE criteria, downgraded for inconsistency and imprecision (Table 3).

Three studies with a total of 306 patients (153 in the LDK group and 153 in the morphine group) reported on the use of rescue medication (Figure 4).[13,20,22] The pooled estimate showed no significant difference in need for rescue medication between LDK and morphine (14.4% vs. 11.1%; RR = 1.26; 95% CI: 0.50 to 3.16, very low certainty). Seven of

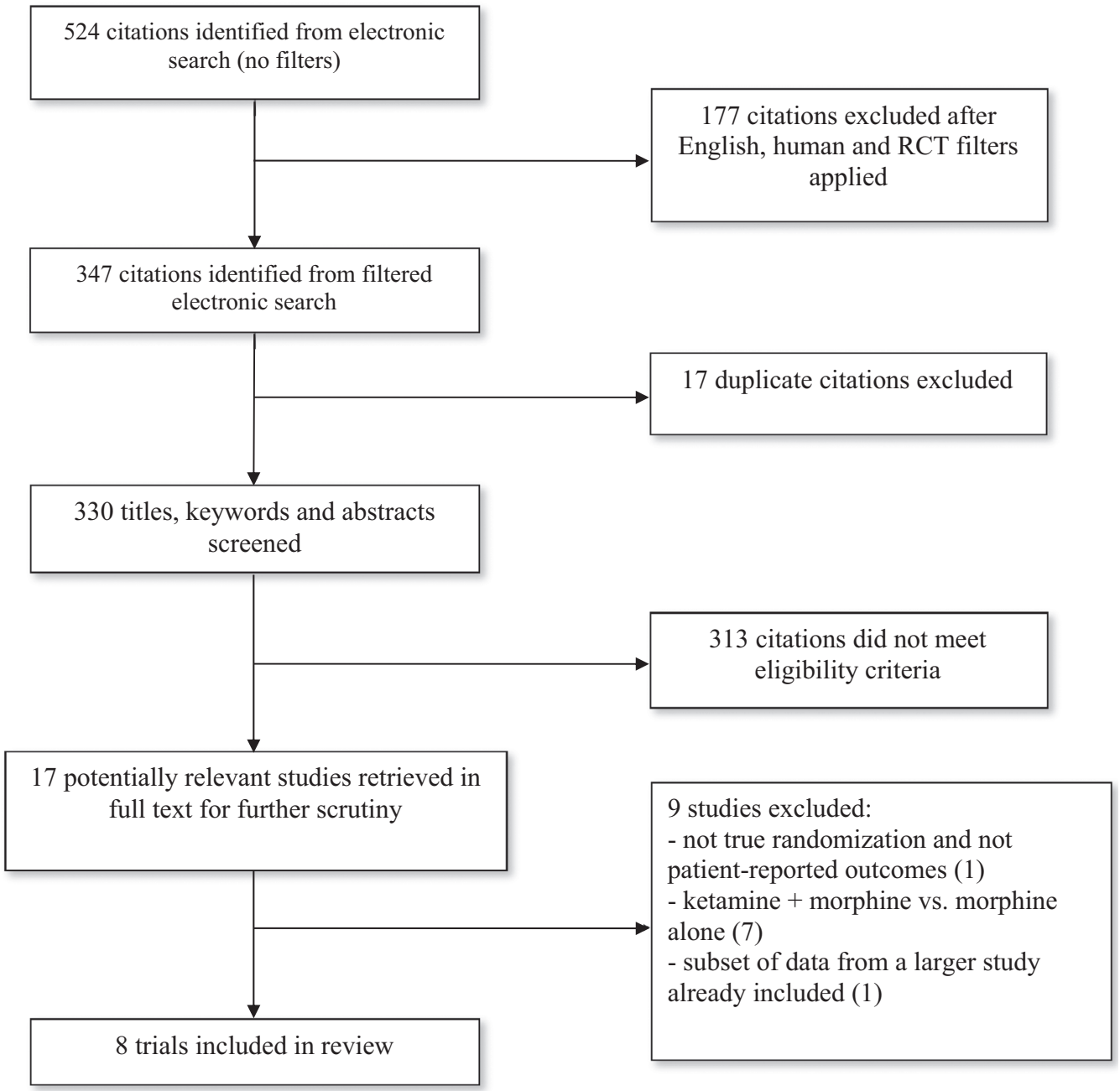



**Figure 1.** Flow diagram of included studies. RCT = randomized controlled trial.

the included studies with a total of 1,065 patients (535 in the LDK group and 530 in the morphine group) reported on nausea.[13,14,20-24] The pooled estimate showed no difference in nausea between LDK and morphine (10.7% vs. 11.1%; RR = 0.97; 95% CI: 0.63 to 1.49). Hypoxia was reported in three studies[20,21,23] with a total of 405 patients (204 in the LDK group and 201 in the morphine group). The risk of hypoxic events was not significantly different between LDK and morphine (3.9% vs. 14.4%, RR = 0.38, 95% CI = 0.10 to 1.41). The outcomes of nausea and hypoxia were judged to have low certainty in the evidence, downgraded for inconsistency and imprecision (Table 3).

## DISCUSSION

In this systematic review and meta-analysis of eight RCTs with over 1,000 patients, we found that LDK is an effective alternative to opioids for acute pain in the ED. Our findings are consistent with previous studies on this topic.[15–17,25] Specifically, there was no significant difference in reported mean pain scores between LDK and morphine within the first 60 minutes after

Table 1
Characteristics of Included Studies

| Study | Country | Intervention | Sample Size | Age (Years) | Type of Pain |
|---|---|---|---|---|---|
| Alshahrani 2019[24] | NR | LDK 0.3 mg/kg vs. Morphine 0.1 mg/kg | *N* = 278 140 LDK 138 morphine | NR | Acute sickle cell pain crisis |
| Forouzan 2019[14] | Iran | LDK 0.3 mg/kg vs. Morphine 0.1 mg/kg | *N* = 136 68 LDK 68 morphine | 18–65 | Acute renal colic patients with pain > 5/10 |
| Jahanian 2018[22] | Iran | LDK 0.5 mg/kg vs. Morphine 0.1 mg/kg | *N* = 156 78 LDK 78 morphine | 18–65 | Upper or lower extremity long-bone fractures secondary to blunt trauma, pain ≥ 7/10 |
| Mahshidfar 2017[23] | Iran | LDK 0.2 mg/kg vs. Morphine 0.1 mg/kg | *N* = 300 150 LDK 150 morphine | 18–70 | Trauma patients with MSK pain ≥ 5/10 |
| Majidinejad 2014[12] | Iran | LDK 0.5 mg/kg vs. morphine 0.1 mg/kg | *N* = 126 63 LDK 63 morphine | 18–55 | Long-bone fracture |
| Miller 2015[21] | USA | LDK 0.3 mg/kg vs. Morphine 0.1 mg/kg | *N* = 45 24 LDK 21 morphine | 18–59 | Abdominal, flank, low back, or extremity pain requiring IV opioids |
| Motov 2015[13] | USA | LDK 0.3 mg/kg vs. Morphine 0.1 mg/kg | *N* = 90 45 LDK 45 morphine | 18–55 | Acute abdominal, flank, back, or MSK pain with pain ≥ 5/10 |
| Motov 2019[20] | USA | LDK 0.3 mg/kg vs. Morphine 0.1 mg/kg | *N* = 60 30 LDK 30 morphine | ≥65 | Acute abdominal, flank, back, or MSK pain with pain ≥ 5/10 |

LDK = low-dose ketamine; MSK = musculoskeletal; NR = not reported.

Table 2
Risk of Bias Summary for Included Trials

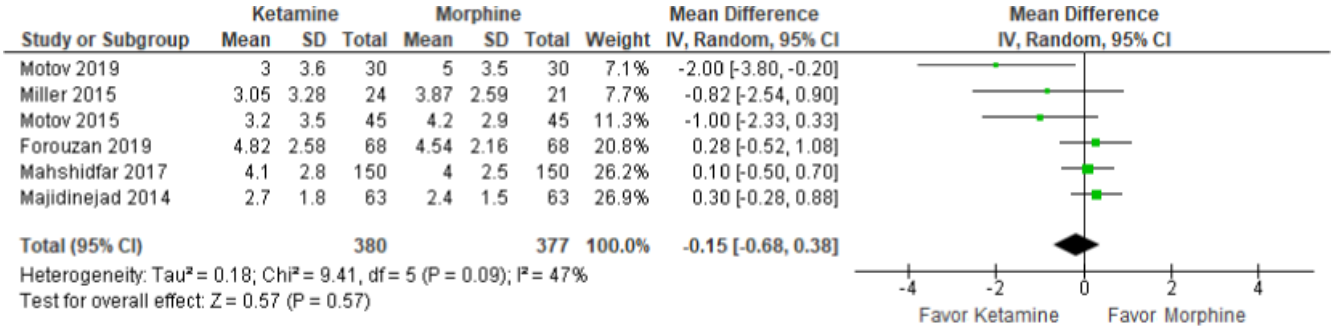
| Trial | Random Sequence Generation | Allocation Concealment | Blinding of Patients/ Personnel | Blinding of Outcome Assessment | Incomplete Outcome Data | Selective Outcome Reporting | Other Bias |
|---|---|---|---|---|---|---|---|
| Alshahrani 2019[24] | Low | Low | Low | Low | Unclear | Unclear | Low |
| Forouzan 2019[14] | Unclear | Low | Low | Low | Low | Low | Low |
| Jahanian 2018[22] | Low | Low | Low | Low | Low | Low | Low |
| Mahshidfar 2017[23] | Unclear | Unclear | Low | Unclear | Low | Low | Low |
| Majidinejad 2014[12] | Unclear | Unclear | Low | Low | Low | High* | Low |
| Miller 2015[21] | Unclear | Unclear | Unclear | Unclear | Low | Low | Low |
| Motov 2015[13] | Low | Low | Low | Low | Low | Low | Low |
| Motov 2019[20] | Low | Low | Low | Low | Low | Low | High† |

*Prespecified outcomes (respiratory complications, adverse events) detailed in the online registry were not reported.
†Trial stopped early; underpowered for primary outcome.

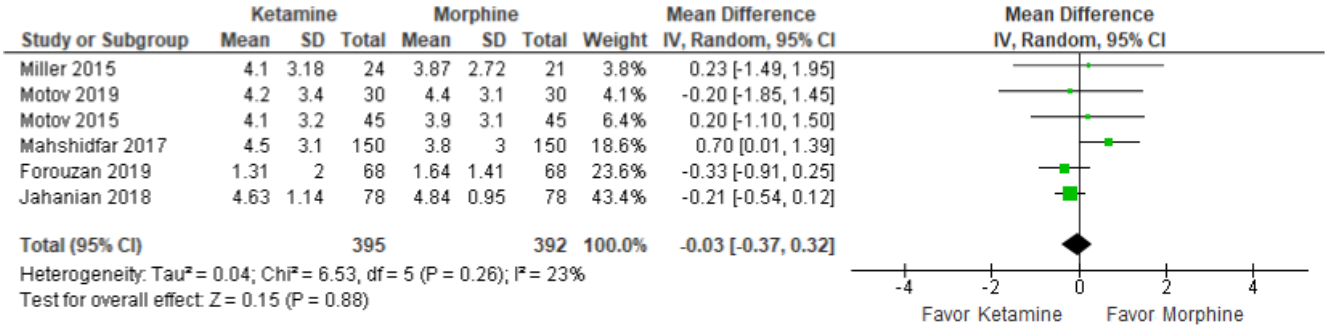
analgesia administration and a slight difference in pain scores favoring morphine at 60 to 120 minutes. The differences in pain scores after 60 minutes were quite small and may not represent a clinically important significant difference. We also found no significant difference in the proportion of patients requiring rescue analgesia with LDK compared to morphine. These findings suggest that LDK may be considered an effective alternative to opioids for controlling acute pain in the ED, particularly within the first hour after analgesia administration.

The use of LDK may be particularly helpful in situations where the treating clinician is unable to administer opioids or requires an alternative analgesic. For instance, emergency physicians may be uncomfortable using opioids for patients with chronic pain who are already on high-dose opioids due to the high doses of opioids that may be required. In this scenario, LDK may offer an alternative analgesic option. LDK also offers a unique alternative for pain management in the growing population of ED patients on naltrexone for alcohol dependence or buprenorphine for opioid

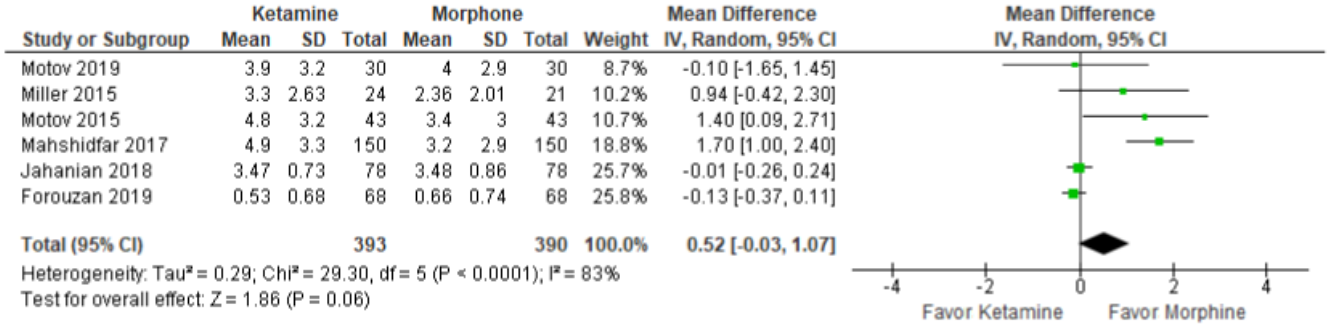
**Pain score within 15 minutes:**




**Pain score at 15-30 minutes:**




**Pain score at 30-45 minutes:**




**Pain score at 45-60 minutes:**

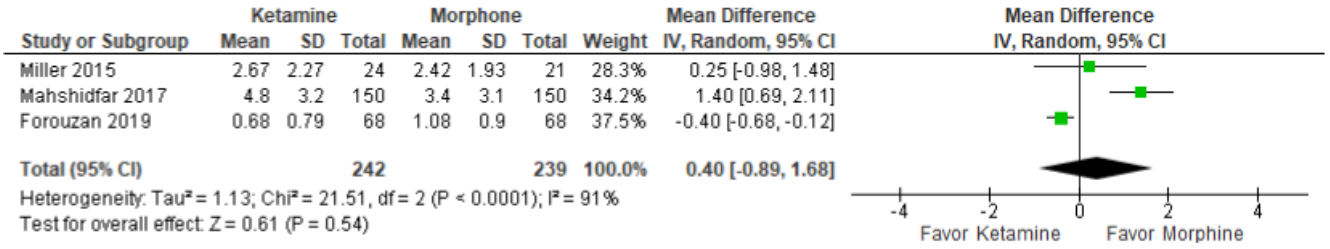



**Figure 2.** Mean pain score differences within 60 minutes between LDK and morphine. LKD = low-dose ketamine.

use disorder. In the setting of alcohol dependence, naltrexone acts as a competitive opioid antagonist that decreases pleasure associated with alcohol.[26] However, naltrexone may make opioids less effective and cause intense withdrawal symptoms once stopped.[26] Buprenorphine, for opioid use disorder, is a partial mu-opioid receptor agonist and kappa-opioid antagonist that decreases the efficacy and safety of opioids for acute pain in the ED.[27,28] With the increasing number of patients prescribed these medications, it is

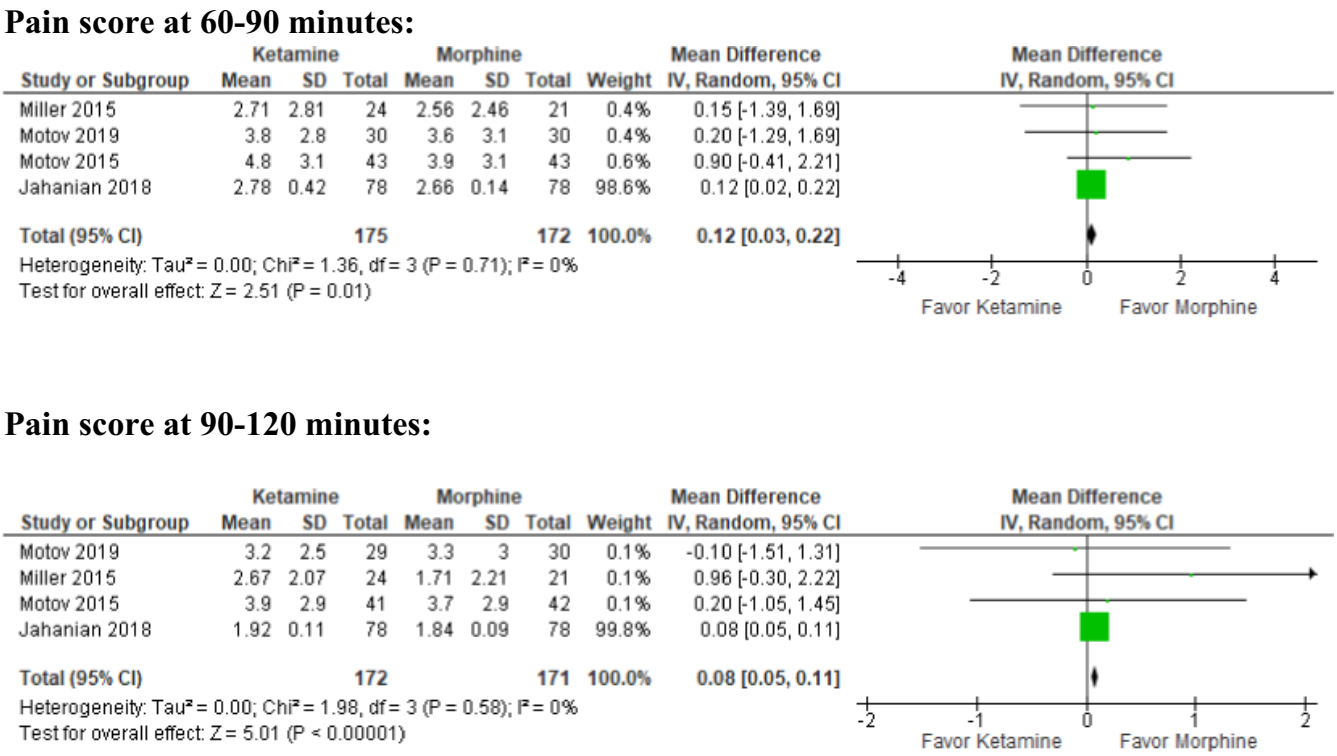



**Figure 3.** Mean pain score differences from 60-120 minutes between LDK and morphine. LKD = low-dose ketamine.

imperative that ED physicians find safe and effective alternatives to opioids for pain control, and ketamine may represent such an alternative. However, before ketamine can be widely used for these patients, further studies of these patient populations are needed.

Opioids have several well-known side effects such as hypotension, apnea, nausea, and vomiting.[29] While we were unable to report on hypotension and vomiting, our review found no significant difference in nausea or hypoxia between patients who received LDK versus morphine. Although the difference in hypoxia was not significantly different between groups, there was a smaller absolute number of hypoxic events among patients who received LDK compared to morphine (3.9% vs. 14.4%). There are several scenarios in the ED where specific side effects associated with opioids would want to be avoided. For instance, in hypotensive or critically ill patients, opioids may lead to further hypotension and worse outcomes. In patients with underlying lung disease or decreased level of consciousness, opioids may increase the risk of apnea and associated hypoxia. Patients with renal impairment present another population that could benefit from LDK as opposed to opioids. Dose reductions in opioids are typically recommended in patients with renal disease due to an increased risk for opioid adverse effects, whereas such reductions are not necessarily recommended with ketamine.[30] As such, LDK may offer an alternative to opioids in these populations.

In 2017, the American College of Emergency Physicians released a policy statement on optimizing the treatment of acute pain in the ED.[31] It was suggested that treatment of acute pain should begin with nonopioid agents. Furthermore, LDK was suggested as an analgesic option to be used alone or as a part of a multimodal approach to acute pain relief in the ED. The results of our systematic review, which is the largest systematic review to date on this topic, suggests that LDK may be a safe and effective analgesic option to opioids. While the side effect profile ketamine is more favorable compared to opioids, there are well-recognized adverse events associated with ketamine, such as laryngospasm, hypertension, tachycardia, and emergence reactions. Two studies in this review commented on emergence reactions: one study[12] reported 9.5% of patients who received LDK experienced an emergence reaction whereas the other study[21] reported no emergence reactions in either group. The study by Motov and colleagues[20] reported a higher number of pooled adverse events unique to LDK (dizziness, feeling of unreality, etc.) in patients in the LDK group. As

Table 3
Summary of Findings and GRADE Assessment for the Comparison of LDK and Morphine for Acute Pain Management in the ED

| | | Certainty Assessment | | | | | No. of Patients | | Effect | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Outcome | No. of Studies | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other | LDK | Morphine | RR (95% CI) | Absolute (95% CI) | Certainty |
| Δ within 15 min | 6 | Not serious | Serious* | Not serious | Serious† | None | 380 | 377 | — | MD 0.15 lower (0.68 lower to 0.38 higher) | ⊕⊕◯◯ Low |
| Δ at 15–30 min | 6 | Not serious | Serious* | Not serious | Serious† | None | 395 | 392 | — | MD 0.03 lower (0.37 lower to 0.32 higher) | ⊕⊕◯◯ Low |
| Δ at 30–45 min | 3 | Not serious | Serious* | Not serious | Serious† | None | 242 | 239 | — | MD 0.40 higher (0.89 lower to 1.68 higher) | ⊕⊕◯◯ Low |
| Δ at 45–60 min | 6 | Not serious | Serious* | Not serious | Serious† | none | 393 | 390 | — | MD 0.52 higher (0.03 lower to 1.07 higher) | ⊕⊕◯◯ Low |
| Δ at 60–90 min | 4 | Not serious | Serious* | Not serious | Serious‡ | None | 175 | 172 | — | MD 0.12 higher (0.03 higher to 0.22 higher) | ⊕⊕◯◯ Low |
| Δ at 90–120 min | 4 | Not serious | Serious* | Not serious | Serious‡ | None | 172 | 171 | — | MD 0.08 higher (0.05 higher to 0.11 higher) | ⊕⊕◯◯ Low |
| Need for rescue medication | 3 | Not serious | Serious* | Not serious | Very serious† | None | 22/153 (14.4%) | 17/153 (11.1%) | 1.26 (0.50 to 3.16) | 29 more per 1,000 (from 56 fewer to 240 more) | ⊕◯◯◯ Very low |
| Nausea | 7 | Not serious | Serious* | Not serious | Serious† | None | 57/535 (10.7%) | 59/530 (11.1%) | 0.97 (0.63 to 1.49) | 3 fewer per 1,000 (from 41 fewer to 55 more) | ⊕⊕◯◯ Low |
| Hypoxia | 3 | Not serious | Serious* | Not serious | Serious† | None | 8/204 (3.9%) | 29/201 (14.4%) | 0.38 (0.10 to 1.41) | 89 fewer per 1,000 (from 130 fewer to 59 more) | ⊕⊕◯◯ Low |

Δ = difference in pain scores between groups; LDK = low-dose ketamine; MD = mean difference; RR = relative risk.
*Results inconsistent across trials.
†The 95% CI includes both a reduction and an increase in pain scores.
‡Clinically unimportant difference.

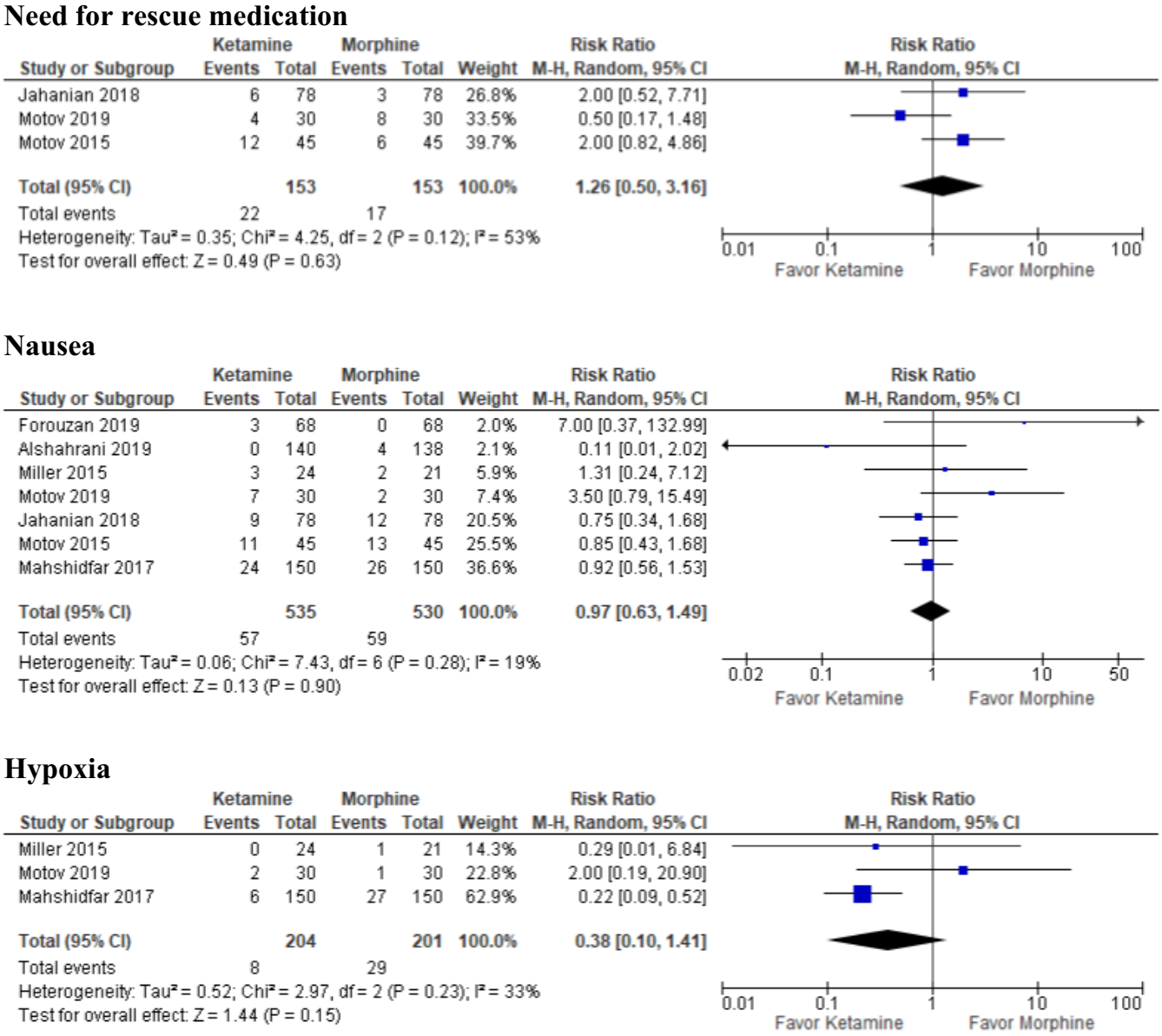



**Figure 4.** Direct comparison of the need for rescue medication and safety profile between LDK and morphine for acute pain management in the ED. LKD = low-dose ketamine.

such, it is important to consider these events and monitor for them when choosing an analgesic for each patient.

## LIMITATIONS

As with all systematic reviews and meta-analyses, the results from this study are limited by the quality of trials that were included. One of the included trials was an abstract that was unlikely to be peer reviewed to the same level of scrutiny as the full-text journal articles. Furthermore, this abstract was limited with respect to the amount of information that could be included, resulting in high or unclear risks of bias in study methodology, varying or unclear definitions of outcomes, and how they were measured. We could not include data for studies that only reported a change in pain scores without raw pain scores. Although four study authors were contacted for further information, only two replied providing additional data for review. Although the search strategy used to identify potentially relevant studies was comprehensive, only English-language articles were included in this review. It is possible that some studies may have been missed if they were published in other languages. The doses of LDK that were used across the studies varied from 0.2 to 0.5 mg/kg. As such, differences in LDK dose may have impacted study results. We were also not able to comment on the duration of the LDK infusion. Only four studies specified over how long

the LDK was given. Previous research has supported LDK given as a short infusion over 15 minutes is associated with significantly lower rates of sedation and psychogenic effects with no difference in analgesic quality.[32] For pain outcomes, there were six time intervals that were assessed—there may be a correlation between these results over time. The reporting of adverse events varied widely between studies. Therefore, we only reported on nausea and hypoxia. However, there are other significant adverse events associated with opioids and ketamine that warrant further study. For instance, we could not examine emergence reaction or perceptual disturbances that have been commonly associated with ketamine. Finally, it is important to note that all outcomes assessed were judged to have low certainty in the evidence, which were downgraded for inconsistency and imprecision in the studies.

## CONCLUSION

In conclusion, this systematic review and meta-analysis of eight randomized controlled trials with over 1,000 patients found that low-dose ketamine is an effective alternative to opioids for acute pain in the ED. We found no significant difference in reported mean pain scores between low-dose ketamine and morphine within the first 60 minutes after analgesia administration and a slight difference in pain scores favoring morphine at 60 to 120 minutes. We also found no significant difference in the proportion of patients requiring rescue analgesia with low-dose ketamine compared to morphine. These findings suggest that low-dose ketamine may be considered an effective alternative to opioids for controlling acute pain in the ED.

## REFERENCES


1. Cordell WH, Keene KK, Giles BK, Jones JB, Jones JH, Brizendine EJ. The high prevalence of pain in emergency medical care. Am J Emerg Med 2002;20:165–9.
2. Todd KH, Ducharme J, Choiniere M, et al. Pain in the emergency department: results of the pain and emergency medicine initiative (PEMI) multicenter study. J Pain 2007;8:460–6.
3. Todd KH. A review of current and emerging approaches to pain management in the emergency department. Pain Ther 2017;6:198–202.
4. Hawk K, D'Onofrio G. Emergency department screening and interventions for substance use disorders. Addict Sci Clin Pract 2018;13:18.
5. Brown AM, DeFrances C, Crane E, Cai R, Naeger S. Identification of substance-involved emergency department visits using data from the national hospital care survey. Natl Health Stat Report 2018;114:1–15.
6. Ukkonen M, Jämsen E, Zeitlin R, Pauniaho SL. Emergency department visits in older patients: a population-based survey. BMC Emerg Med 2019;19:20.
7. National Center for Biotechnology Information. PubChem Compound Summary for CID 3821, Ketamine. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/Ketamine. Accessed Aug 15, 2020.
8. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med 2011;57:449–61.
9. Beatty L, MacQuarrie K. Airway Management Pharmacology. G Kovacs, JA Law, Airway Management in Emergencies. Halifax, NS: Airway Interventions and Mangement in Emergencies, 2020. https://aimeairway.ca/book#/19. Accessed Aug 15, 2020.
10. Kurdi MS, Theerth KA, Deva RS. Ketamine: current applications in anesthesia, pain, and critical care. Anesth Essays Res 2014;8:283–90.
11. American College of Emergency Physicians (ACEP). Sub-dissociative Ketamine for Analgesia: Policy Resource and Education Paper (PREP). 2019. Available at: https://www.acep.org/globalassets/new-pdfs/preps/sub-dissociative-dose-ketamine-for-analgesia--prep.pdf Accessed Aug 15, 2020.
12. Majidinejad S, Esmailian M, Emadi M. Comparison of intravenous ketamine with morphine in pain relief of long bones fractures: a double blind randomized clinical trial. Emerg (Tehran) 2014;2:77–80.
13. Motov S, Rockoff B, Cohen V, et al. Intravenous subdissociative-dose ketamine versus morphine for analgesia in the emergency department: a randomized controlled trial. Ann Emerg Med 2015;66:222–29.e1.
14. Forouzan A, Masoumi K, Motamed H, Esfahani SR, Delirrooyfard A. Comparison of the analgesic effect of intravenous ketamine versus intravenous morphine in reducing pain of renal colic patients: double-blind clinical trial study. Rev Recent Clin Trials 2019;14:1–6.
15. Karlow N, Schlaepfer CH, Stoll CR, et al. A systematic review and meta-analysis of ketamine as an alternative to opioids for acute pain in the emergency department. Acad Emerg Med 2018;25:1086–97.
16. Lee EN, Lee JH. The effects of low-dose ketamine on acute pain in an emergency setting: a systematic review and meta-analysis. PLoS One 2016;11:e0165461.

17. Sin B, Ternas T, Motov SM. The use of subdissociative-dose ketamine for acute pain in the emergency department. Acad Emerg Med 2015;22:251–7.
18. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA.Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JP, Thomas J, Chandler J, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available at: https://training.cochrane.org/handbook/current/chapter-08 Accessed Aug 15, 2020.
19. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383–94.
20. Motov S, Mann S, Drapkin J, et al. Intravenous subdissociative-dose ketamine versus morphine for acute geriatric pain in the emergency department: a randomized controlled trial. Am J Emerg Med 2019;37:220–7.
21. Miller JP, Schauer SG, Ganem VJ, Bebarta VS. Low-dose ketamine vs morphine for acute pain in the ED: a randomized controlled trial. Am J Emerg Med 2015;33:402–8.
22. Jahanian F, Hosseininejad SM, Amini Ahidashti H, et al. Efficacy and safety of morphine and low dose ketamine for pain control of patients with long bone fractures: a randomized, double-blind, clinical trial. Bull Emerg Trauma 2018;6:31–6.
23. Mahshidfar B, Mofidi M, Fattahi M, et al. Acute pain management in emergency department, low dose ketamine versus morphine, A randomized clinical trial. Anesth Pain Med 2017;7:e60561.
24. Alshahrani MS, Alsulaibikh AH, ElTahan SZ, et al. Ketamine use for acute painful crisis of sickle cell disease: a randomize controlled trial. Ann Emerg Med 2019;74:S89–90.
25. Ghate G, Clark E, Vaillancourt C. Systematic review of the use of low-dose ketamine for analgesia in the emergency department. CJEM 2018;20:36–45.
26. Center for Substance Abuse Treatment. Incorporating Alcohol Pharmacotherapies into Medical Practice. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2009. (Treatment Improvement Protocol (TIP) Series, No. 49.) Chapter 4-Oral Naltrexone. Available at: https://www.ncbi.nlm.nih.gov/books/NBK64042/. Accessed Aug 15, 2020.
27. Kumar R, Viswanath O, Saadabadi A. Buprenorphine. [Updated 2020 May 27] In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020. Available at: https://www.ncbi.nlm.nih.gov/books/NBK459126/. Accessed Aug 15, 2020.
28. Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction – A Treatment Improvement Protocol (TIP 40). Rockville, MD: Substance Abuse and Mental Health Services Administration, 2012. Available at: https://www.ncbi.nlm.nih.gov/books/NBK64245/pdf/Bookshelf_NBK64245.pdf. Accessed Aug 15, 2020.
29. Rogers E, Mehta S, Shengelia R, Reid MC.Four strategies for managing opioid-induced side effects in older adults. Clin Geriatr 2013;21:http://www.consultant360.com/articles/four-strategies-managing-opioid-induced-side-effects-older-adults. Accessed Aug 15, 2020.
30. Davison SN. Clinical pharmacology considerations in pain management in patients with advanced kidney failure. Clin J Am Soc Nephrol 2019;14:917–31.
31. American College of Emergency Physicians (ACEP). Policy Statement - Optimizing the Treatment of Acute Pain in the Emergency Department. Dallas, TX: ACEP, 2017. Available at: https://www.acep.org/globalassets/new-pdfs/policy-statements/optimizing-the-treatment-of-acute-pain-in-the-ed.pdf. Accessed Aug 15, 2020.
32. Motov S, Mai M, Pushkar I, et al. A prospective randomized, double-dummy trial comparing IV push low dose ketamine to short infusion of low dose ketamine for treatment of pain in the ED. Am J Emerg Med 2017;35:1095–100.

## Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.14159/full

**Data Supplement S1.** Search strategy.