REVIEW

Annals of Internal Medicine

Acute Pain Management in People With Opioid Use Disorder

A Systematic Review

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Background: Guidance on acute pain management among people with opioid use disorder (OUD) is limited.

Purpose: To synthesize evidence on the benefits and harms of acute pain interventions among people with OUD.

Data Sources: APA PsycArticles, APA PsycInfo, APA PsycExtra, Allied and Complementary Medicine Database, CINAHL, Cochrane Library, Google Scholar, Ovid Embase, Ovid MEDLINE, PubMed, Scopus, and the Web of Science Core Collection through 7 July 2024.

Study Selection: Studies of any design that evaluated acute pain interventions among adults with OUD and included pain or OUD outcomes.

Data Extraction: Independent dual screening, single-investigator data extraction with verification, and dual quality and strength of evidence assessment.

Data Synthesis: Seventeen trials, 20 controlled observational studies, and 78 uncontrolled observational studies met eligibility criteria. Continuing use of buprenorphine during acute pain episodes may be associated with similar or improved pain-related outcomes versus discontinuing, based on cohort studies conducted primarily in perioperative settings. Single well-conducted randomized controlled trials in emergency department (ED) or perioperative settings in adults not prescribed medications for OUD suggest oral clonidine, intramuscular haloperidol and midazolam with intravenous (IV) morphine, and intraoperative IV lidocaine may improve pain outcomes and warrant study in diverse patient populations. Few studies evaluated methadone or the effect of interventions on OUD outcomes.

Limitations: Most evidence is observational and at risk of bias due to confounding. All studies were conducted in ED or hospital settings, most before widespread use of high-potency synthetic opioids or among non-U.S. populations using opium.

Conclusion: The overall evidence for pain outcomes in people with OUD is low. The effect of pain interventions on OUD outcomes is an important evidence gap.

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The need to effectively manage acute pain among people with opioid use disorder (OUD) is a common clinical scenario with important implications in both the hospital and the ambulatory setting (1). People with OUD who have negative health care experiences during episodes of acute pain may disengage from care prematurely and may be less likely to present for future health care needs (2–4). For people with OUD in remission, experiences of poorly controlled acute pain can also be destabilizing and increase their risk for returning to nonprescribed opioid use (5). Yet, many clinicians report knowledge gaps and lack of confidence in managing acute pain for people with OUD (6–8). Factors contributing to the perceived complexity of treating acute pain among people with OUD include the use of methadone, buprenorphine, and naltrexone (medications for OUD [MOUD]), each of which has unique pharmacologic properties that affect acute pain management (9, 10). People with OUD may also have heightened pain sensitivity, opioid tolerance, and opioid-induced hyperalgesia, factors that may necessitate use of multimodal analgesia and possibly higher full-agonist opioid doses than are used among people without OUD (11, 12).

Current clinical guidance on acute pain management among people with OUD is largely informed by expert opinion (13–19). The aim of this systematic review is to synthesize available evidence on the benefits and harms of acute pain interventions for adults with OUD, including those prescribed MOUD, and to identify evidence gaps.

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METHODS

Overview

This review was conducted according to standard systematic review methods and reporting guidelines (20–22). Reporting guideline checklists are available in Supplement Table 1 (available at Annals.org). A protocol was registered a priori on Open Science Framework (https://osf.io/25hbs).

Data Sources and Searches

Using a combination of controlled vocabulary and keywords for acute pain, OUD, and MOUD, a medical librarian (A.A.G.) searched for articles published in any language through 16 March 2023 from APA PsycArticles, APA PsycInfo, APA PsycExtra, the Allied and Complementary Medicine Database, CINAHL, the Cochrane Library, Google Scholar, Ovid Embase, Ovid MEDLINE, PubMed, Scopus, and the Web of Science Core Collection. An updated search was completed on 7 July 2024. Detailed search strategies are provided in Supplement Table 2 (available at Annals.org). The search was reviewed by a second medical librarian using the Peer Review of Electronic Search Strategies (PRESS) checklist (23). Additional citations were identified using CitationChaser through 16 March 2023 and via consultation with content experts (24). CitationChaser was not used for the updated search.

Key Questions

We aimed to address 3 key questions. First, among adults with OUD, including those prescribed MOUD, what are the benefits and harms of opioid and nonopioid interventions for acute pain? Second, among adults with OUD, including those prescribed MOUD, are opioid and nonopioid interventions for acute pain associated with OUD-related outcomes, including withdrawal, return to nonprescribed opioid use (for those in remission), or treatment initiation or retention? Third, do the benefits and harms of acute pain interventions vary by use of MOUD before or during the acute pain episode?

Study Selection

Our criteria for study inclusion (Supplement Table 3, available at Annals.org) were broad given initial uncertainty about the extent of available evidence. We included studies of any design that were conducted among adults (aged ≥18 years) with OUD and acute pain in any health care setting and evaluated the effectiveness of a pharmacologic or nonpharmacologic intervention on pain- and OUD-related outcomes, although we prioritized synthesis of controlled studies, as described in greater detail later. We included studies that defined OUD according to *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria or used other specified methods to determine participant eligibility. In some cases, the study population was defined by receipt of buprenorphine rather than OUD diagnosis. We included these studies if we could infer based on buprenorphine formulation and/or dose that some of the study population had OUD. We excluded studies of adults prescribed buprenorphine for chronic pain without OUD. We included studies of intraoperative interventions only if outcomes included measures of postoperative pain severity and/or opioid use. At least 2 investigators independently screened each title and abstract for eligibility (all authors) and then reviewed potentially relevant full texts for inclusion (M.J.B., K.M., L.K., M.B.W.), consulting with a third investigator to resolve conflicts.

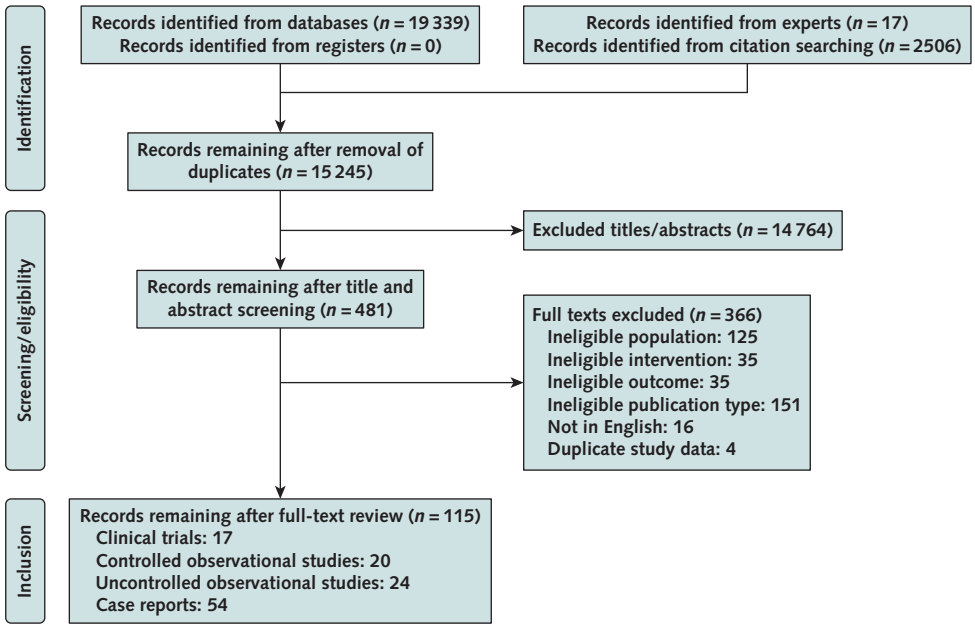
Data Extraction and Quality Assessment

One investigator (L.K., M.B.W., or K.M.) extracted study data, including setting, population characteristics, interventions, and outcomes of interest, and a second investigator (M.J.B. or M.B.W.) verified accuracy. Two investigators (M.J.B., K.M., or M.B.W.) independently assessed study risk of bias (ROB) using the Cochrane RoB-2 tool for clinical trials (25) and the ROBINS-I (Risk Of Bias In Non-randomised Studies – of Interventions) tool for controlled observational studies (26). After completing study selection, we decided not to assess study ROB for uncontrolled observational studies, case series, or reports as these study designs have inherently higher ROB. We reasoned that further detail on potential bias would be unlikely to affect our conclusions.

Data Synthesis and Analysis

We synthesized data qualitatively and organized results by study population according to use of MOUD. We did not synthesize data quantitatively because of variability in study populations (including the acute pain conditions being treated), intervention details (including specific medication doses and routes of administration), comparators, and outcome measures. We prioritized evidence from comparative studies (randomized controlled trials [RCTs] and controlled observational studies) over uncontrolled observational studies, case series, and reports and summarize these results in the main text of this manuscript. We also qualitatively synthesized data from uncontrolled observational studies, case series, and reports to evaluate harms and address gaps associated with specific study populations and/or acute pain interventions of high clinical importance if there were no data available from comparative studies; these results are included in the Supplement (available at Annals.org). When sufficient evidence was available (≥1 RCT with low ROB or ≥2 controlled observational studies evaluating similar interventions for similar populations), 3 investigators (M.J.B., K.M., M.B.W.) rated the overall strength of evidence (SOE) for a given intervention on pain- and/or OUD-related outcomes using criteria based on study limitations, directness of the population studied and outcomes measured, consistency in the direction of effects across studies, and precision of effect estimates, with consensus achieved through discussion (27).

Figure 1. Study flow diagram.



Role of the Funding Source

No funding was received specifically for this publication.

RESULTS

Our search identified 481 potentially relevant articles after title and abstract screening (**Figure 1**). Of these, 115 studies met eligibility criteria: 17 clinical trials, 20 controlled observational studies, 24 uncontrolled observational studies or case series (≥5 participants), and 54 case reports or series (<5 participants). All identified studies were conducted in hospital or emergency department (ED) settings. Because our literature search was intentionally very broad, we identified many potentially relevant studies that were ultimately excluded because they did not meet our eligibility criteria. The most common reasons for study exclusion at the full-text level were ineligible publication type and ineligible patient population (**Supplement Table 4**, available at Annals.org).

The distribution of included comparative studies by study population, intervention, and pain- or OUD-related outcomes is presented in **Table 1**. A visual representation of the distribution of study settings, pain types, and interventions across comparative studies is shown in **Figure 2**. A summary of findings is presented in **Table 2**, and detailed study characteristics and results are provided in **Supplement Tables 5 to 11** (available at Annals.org). Quality assessments of RCTs and controlled observational studies are presented in **Supplement Tables 12** and **13** (available at Annals.org).

Not all included studies clearly reported the number of participants with OUD or the method of OUD diagnosis. Of the 37 comparative studies, 4 did not report the number of participants with OUD, although all were prescribed buprenorphine or methadone (30, 32, 38, 42). Among the remaining 33 comparative studies, all participants had OUD in 27 studies and 36% to 80% had OUD in 6 studies. Most comparative studies ($n = 22$ [59%]) included participants experiencing postoperative pain only (rather than other types of acute pain), and all were conducted in the hospital or ED: 22 in perioperative settings, 6 in obstetric (labor and delivery or post–cesarean section) settings, 5 in the ED, 1 in a nonoperative hospital setting, and 3 in multiple hospital-based settings. Pain outcomes were assessed in 15 comparative studies of participants prescribed buprenorphine, 2 studies of participants prescribed methadone, 2 studies of participants prescribed buprenorphine or methadone, and 16 studies of participants not prescribed MOUD. Outcomes related to OUD were assessed in 4 comparative studies of participants prescribed buprenorphine and 3 studies of participants not prescribed MOUD (**Table 1**). No comparative studies of participants prescribed methadone assessed OUD outcomes. Furthermore, no comparative studies assessed pain or OUD outcomes in people prescribed naltrexone for OUD.

Pain Outcomes Among People Prescribed Buprenorphine

Twelve retrospective cohort studies conducted in the United States among a total of 1529 participants evaluated a pain-related outcome (pain severity or

opioid analgesic use) with buprenorphine continuation compared with discontinuation during an acute pain episode (28–39). Among these, 9 cohorts included adults treated for postoperative pain (28–31, 34–38), 1 for post–cesarean section pain (39), 1 for trauma-related pain (32), and 1 for a mix of surgical and nonsurgical acute pain (33). The proportion of participants with OUD was 100% in 5 studies, ranged from 36% to 80% in 4 studies, and was not reported in 3 studies. Median baseline sublingual (SL) buprenorphine doses ranged from 8 to 16 mg. Buprenorphine doses above 16 mg/d occupy 80% or more of μ-opioid receptors, which has been postulated to complicate acute pain treatment, but none of the identified studies included participants prescribed buprenorphine doses above this threshold (65). Among 10 controlled cohort studies that evaluated pain severity (assessed most frequently via the numerical rating scale), 6 found that postoperative pain scores were lower among those who continued SL buprenorphine at most or all time points compared with those who discontinued it (longest follow-up was 72 hours) (29, 31, 32, 34, 35, 37), whereas 4 found no difference (28, 30, 33, 36). Among 12 cohorts comparing use of opioid analgesics as an outcome, 7 found that patients who continued SL buprenorphine received lower full-agonist opioid doses (including 1 cohort with 60-day follow-up) (29, 31–33, 37–39) and 5 found no difference (28, 30, 34–36). No studies reported harms attributed to SL buprenorphine continuation, such as severe pain or premature hospital discharge due to pain.

Although studies varied in terms of whether buprenorphine continuation was associated with improved pain control or no difference compared with discontinuation, no studies found that buprenorphine continuation was associated with worsened (or more difficult) pain control, as has been postulated due to buprenorphine's partial opioid agonist properties (66). Nonetheless, our overall confidence is low that continuing rather than discontinuing buprenorphine among adults with OUD already prescribed it is associated with lower or similar pain severity due to methodological limitations of the studies, particularly ROB due to confounding in cohort studies (detailed SOE assessments are presented in **Supplement Table 14** [available at Annals.org]).

Three controlled retrospective cohort studies evaluated other pharmacologic interventions for acute pain among adults with OUD prescribed buprenorphine. These studies assessed use of neuraxial clonidine, neuraxial fentanyl, and gabapentin among pregnant persons treated for peripartum pain in the United States (42, 49, 52). Evidence for these interventions, which is limited to single small cohorts, is insufficient to assess their effectiveness.

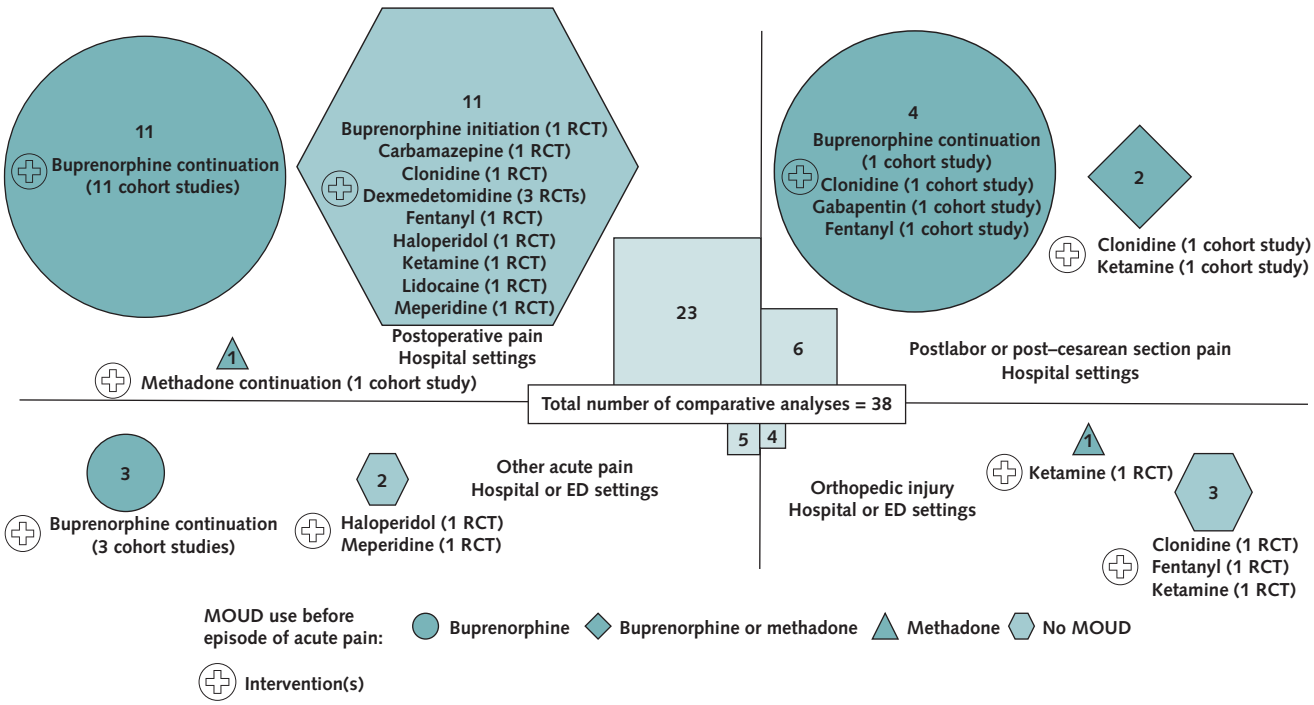
Finally, we did not identify any comparative studies evaluating the effect of adjusting the dose and/or

Table 1. Distribution of Included Comparative Studies by Study Population, Acute Pain Intervention, and Pain or OUD Outcomes

Acute Pain Intervention	MOUD				
	Buprenorphine	**Methadone**	**Buprenorphine or Methadone**	**Naltrexone**	**Not Prescribed**
Included outcomes for pain severity and/or opioid analgesic use					
Buprenorphine continuation	12 cohort studies (28–39)*†‡§‖	NA	NA	NA	NA
Buprenorphine initiation	NA	No studies	No studies	No studies	1 RCT (40)†¶
Carbamazepine	No studies	No studies	No studies	No studies	1 RCT (41)†
Clonidine	1 cohort study (42)‖	No studies	1 cohort study (43)‖	No studies	2 RCTs (44, 45)†**
Dexmedetomidine	No studies	No studies	No studies	No studies	3 RCTs (46–48)†¶
Fentanyl	1 cohort study (49)††	No studies	No studies	No studies	2 RCTs (50, 51)†¶**
Gabapentin	1 cohort study (52)‖	No studies	No studies	No studies	No studies
Haloperidol	No studies	No studies	No studies	No studies	2 RCTs (53, 54)†‡‡
Ketamine	No studies	1 RCT (55)**	1 cohort study (56)‖	No studies	2 RCTs (57, 58)†**
Lidocaine	No studies	No studies	No studies	No studies	1 RCT (59)†
Meperidine	No studies	No studies	No studies	No studies	2 RCTs (60, 61)†§¶
Methadone continuation	NA	1 cohort study (28)†	NA	NA	NA
Included outcomes related to OUD					
Buprenorphine continuation	4 cohort studies (29, 62–64)†§	NA	NA	NA	NA
Buprenorphine initiation	NA	No studies	No studies	No studies	1 RCT (40)†¶
Meperidine	No studies	No studies	No studies	No studies	2 RCTs (60, 61)†§¶

MOUD = medication for opioid use disorder; NA = not applicable; OUD = opioid use disorder; RCT = randomized controlled trial.
* Median buprenorphine dose range: 8 to 16 mg.
† Postoperative pain.
‡ Trauma-related pain.
§ Multiple pain conditions (surgical and nonsurgical acute pain).
‖ Post–cesarean section pain.
¶ The comparator in 5 studies (40, 46, 51, 60, 61) was intravenous morphine.
** Orthopedic injury or fracture.
†† Postlabor pain.
‡‡ Acute nonsurgical pain.

Figure 2. Number of comparative studies by type of acute pain, use of MOUD, and interventions.



ED = emergency department; MOUD = medication for opioid use disorder; RCT = randomized controlled trial.

frequency of buprenorphine on pain outcomes among adults prescribed SL buprenorphine or any comparative studies conducted among adults prescribed long-acting injectable buprenorphine. A qualitative data synthesis from relevant uncontrolled studies is shown in Supplement Table 8.

OUD Outcomes Among People Prescribed Buprenorphine

Four retrospective cohort studies of buprenorphine continuation conducted among participants with diagnosed OUD (100% of sample analyzed) included OUD outcomes (n = 340) (Supplement Table 7) (29, 62–64), but only 2 stratified results by buprenorphine continuation or discontinuation (29, 62). In these 2 cohorts, OUD outcomes (opioid cravings, return to nonprescribed opioid use, and treatment retention) were similar regardless of whether buprenorphine was continued or discontinued. However, each outcome was evaluated in only 1 cohort, and this evidence is therefore insufficient to assess the effects of buprenorphine continuation on OUD outcomes.

Pain Outcomes Among People Prescribed Methadone

One retrospective controlled cohort study from Australia with high ROB (n = 29) provided insufficient evidence on pain outcomes among participants who continued or discontinued their usual methadone dose. This study found that mean pain scores and cumulative morphine doses were similar between those who continued their usual methadone dose perioperatively and those who discontinued it (28). However, more people in this study who discontinued methadone were treated with nonsteroidal anti-inflammatory drugs (36% in the continued group vs. 71% in the discontinued group) and/or intravenous (IV) ketamine (55% in the continued group vs. 71% in the discontinued group), and the study did not control for the effects of these co-interventions.

We did not identify any comparative studies evaluating the effect of adjusting the dose and/or frequency of methadone on pain outcomes among adults prescribed methadone for OUD. A qualitative data synthesis from relevant uncontrolled studies is shown in Supplement Table 8.

One high-ROB RCT of 100 male participants prescribed methadone in Iran provided insufficient evidence on the effectiveness of a single dose of IV ketamine or IV fentanyl to treat acute pain due to limb fracture (55). In this trial, mean visual analogue scale scores were lower among the group receiving ketamine at 15 minutes but did not differ at 30 or 60 minutes. Complications (nausea or vomiting, hypotension, and reduced oxygen saturation) were more frequent in the fentanyl group. However, participants were excluded if their pain was not controlled with the study drugs, and the number of participants excluded for this reason was not clearly reported.

Collectively, evidence on acute pain interventions among adults with OUD prescribed methadone is limited to single comparative studies and is insufficient to assess their effectiveness.

Table 2. Summary of Findings From Comparative Studies, by Study Population and Acute Pain Intervention

Intervention and Comparator	Included Studies	Study ROB	Total Participants, *n*	Acute Pain Conditions; Country; Population	Pain and OUD Outcomes and Adverse Events	Overall Findings and SOE*
Adults with OUD prescribed buprenorphine						
Buprenorphine continuation vs. discontinuation	15 cohort studies† (28–39, 62–64)	Unclear (8 studies) High (6 studies)	1744	Postoperative pain (10 studies)‡ (28–31, 34–38, 64) Post–cesarean section pain (1 study) (39); United States; 100% with OUD Trauma (1 study) (32); United States; proportion with OUD NR Multiple (3 studies): United States; 100% with OUD (33) United States; 100% with OUD (62) United States; 79% with OUD (63)	Pain severity: lower (6 studies) (29, 31, 32, 34, 35, 37) or no difference (4 studies) (28, 30, 33, 36) Opioid analgesic use: lower (7 studies) (29, 31–33, 37–39) or no difference (5 studies) (28, 30, 34–36) Postoperative opioid cravings: no difference (1 study) (62) Return to nonprescribed opioid use after discharge: no difference (1 study) (62) OUD treatment retention: no difference (1 study) (29) No AEs reported with buprenorphine continuation	Continuing buprenorphine during an acute pain episode may be associated with similar or improved pain-related outcomes compared with discontinuing buprenorphine (low SOE) The effects of continuing buprenorphine on OUD-related outcomes (opioid cravings, return to use, and treatment retention) are unclear (insufficient evidence to assess overall SOE for each individual outcome)
Neuraxial clonidine vs. usual care	1 cohort study (42)	Low	196	Post–cesarean section pain; United States; proportion with OUD NR; 100% using buprenorphine	Lower pain severity at 0–24 h No difference in opioid analgesic use AEs not evaluated§	Benefits and harms are unclear (SOE not assessed)
Neuraxial fentanyl vs. usual care	1 cohort study (49)	Unclear	19	Postlabor pain; United States; 100% with OUD	No difference in opioid analgesic use AEs not evaluated	Benefits and harms are unclear (SOE not assessed)
Oral gabapentin vs. usual care	1 cohort study (52)	High	214	Post–cesarean section pain; United States; 100% with OUD	No difference in pain severity or opioid analgesic use AEs not evaluated	Benefits and harms are unclear (SOE not assessed)
Adults with OUD prescribed methadone						
Methadone continuation vs. discontinuation	1 cohort study (28)	High	29	Postoperative pain; Australia; 100% with OUD	No difference in pain severity or opioid analgesic use No difference in postoperative nausea/vomiting	Benefits and harms are unclear (SOE not assessed)
IV ketamine vs. IV fentanyl	1 RCT (55)	High	100	Limb fracture; Iran; 100% with OUD	Lower pain severity at 15 min with ketamine compared with IV fentanyl, but no difference at 30 or 60 min No difference in AEs	Benefits and harms are unclear (SOE not assessed)
Adults with OUD prescribed buprenorphine or methadone						
Regional or combined spinal-epidural anesthesia with or without IT clonidine	1 cohort study (43)	High	160	Post–cesarean section pain; United States; 100% with OUD	Lower pain severity on POD 0 No other differences in pain severity on PODs 0–3 No differences in opioid analgesic use	Benefits and harms are unclear (SOE not assessed)

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Table 2–Continued

Intervention and Comparator	Included Studies	Study ROB	Total Participants, *n*	Acute Pain Conditions; Country; Population	Pain and OUD Outcomes and Adverse Events	Overall Findings and SOE*
IV ketamine vs. usual care	1 cohort study (56)	High	26	Post–cesarean section pain; United States; 100% with OUD	Lower pain severity and opioid analgesic use on POD 0 No difference in pain severity on POD 1	Benefits and harms are unclear (SOE not assessed)
Adults with OUD not prescribed MOUD						
SL buprenorphine vs. IV morphine	1 RCT (40)	High	68	Postoperative pain; Iran; 100% with OUD	Lower pain severity at 6 and 24 h, but no difference at 1 h Higher COWS in SL buprenorphine group at 1 h, but lower COWS at 6 and 24 h compared with IV morphine AEs not evaluated	Benefits and harms are unclear (SOE not assessed)
Oral carbamazepine vs. usual care	1 RCT (41)	Some concerns	90	Postoperative pain; Iran; 67% with OUD vs. 33% without OUD	Lower pain severity at 1 and 12 h AEs not evaluated	Benefits and harms are unclear (SOE not assessed)
IV morphine, midazolam, and antiemetics with or without IV clonidine vs. IV morphine alone	1 RCT (44)	Some concerns	90	Postoperative pain; Iran; 100% with OUD	Lower pain severity and opioid analgesic use at 48 h No difference in nausea/vomiting between groups	Benefits and harms are unclear (SOE not assessed)
Oral clonidine vs. placebo	1 RCT (45)	Low	70	Orthopedic fracture; Iran; 100% with OUD	Lower pain severity at 1 h, but no difference at 30 min or time of disposition (3–6 h) Lower opioid analgesic use Systolic blood pressure lower in clonidine group at 30 and 60 min, but not considered clinically significant AEs not evaluated	Oral clonidine may decrease pain severity (up to 1 h) and opioid analgesic use compared with placebo for acute pain due to orthopedic fracture (low SOE)
IV dexmedetomidine vs. IV morphine, added to IV fentanyl and IV midazolam	1 RCT (46)	Some concerns	60	Post-cataract surgery pain; Iran; 100% with OUD	Higher pain severity and use of opioid analgesia in IV dexmedetomidine group AEs higher in morphine group	Benefits and harms are unclear (SOE not assessed)
Spinal analgesia with IV dexmedetomidine vs. placebo added to IV bupivacaine and IV midazolam	1 RCT (47)	Some concerns	57	Postoperative pain; Iran; 100% with OUD	Lower opioid analgesia use at 24 h AEs not evaluated	Benefits and harms are unclear (SOE not assessed)
Spinal analgesia with IV dexmedetomidine and IV bupivacaine vs. IV fentanyl and IV bupivacaine vs. IV bupivacaine alone	1 RCT (48)	Some concerns	84	Postoperative pain; Iran; 100% with OUD	Lower pain severity scores at postoperative hours 1, 3, and 6 and lower opioid analgesia use at postoperative hour 24 in dexmedetomidine group Postoperative nausea/vomiting lower in dexmedetomidine group	Benefits and harms are unclear (SOE not assessed)

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Table 2–Continued

Intervention and Comparator	Included Studies	Study ROB	Total Participants, *n*	Acute Pain Conditions; Country; Population	Pain and OUD Outcomes and Adverse Events	Overall Findings and SOE*
Spinal analgesia with IV fentanyl and IV bupivacaine vs. IV midazolam and IV bupivacaine vs. IV bupivacaine alone	1 RCT (50)	High	90	Postoperative pain; Iran; 100% with OUD	Lower opioid analgesia use in fentanyl group compared with bupivacaine group, but higher use compared with midazolam group AEs not evaluated	Benefits and harms are unclear (SOE not assessed)
IV fentanyl vs. IV morphine	1 RCT (51)	Some concerns	307	Traumatic limb injury; Iran; 100% with OUD	Lower pain severity scores at 30 min in fentanyl group, but no difference at 15 or 60 min No difference in AEs	Benefits and harms are unclear (SOE not assessed)
IM haloperidol and IM midazolam, and IV morphine vs. IM placebo added to IV morphine once	1 RCT (53)	Low	87	Limb or abdominal pain (nonsurgical); Iran; 100% with OUD	Lower pain severity at 1, 3, and 6 h and lower opioid analgesic use in haloperidol/midazolam group No AEs reported in either group	IM haloperidol, IM midazolam, and IV morphine in combination may decrease pain severity (up to 6 h) and opioid analgesic use compared with IV morphine alone for acute nonsurgical limb and abdominal pain (low SOE)
IV haloperidol and IV morphine vs. placebo and IV morphine	1 RCT (54)	High	101	Postoperative pain; Iran; 100% with OUD	Lower pain severity scores and opioid analgesic use at 2 h No AEs attributed to haloperidol	Benefits and harms are unclear (SOE not assessed)
IV ketamine and IV morphine vs. placebo/IV morphine	2 RCTs (57, 58)	Low (1 study) Some concerns (1 study)	278	Postoperative pain (1 study) (57); Iran; 100% with OUD Limb fracture (1 study) (58); Iran; 100% with OUD	Pain severity: lower (1 study) or no difference (1 study) Opioid analgesic use: higher (1 study) AEs: higher, particularly hallucinations and loss of consciousness (1 study)	The benefits and harms of IV ketamine and IV morphine in combination to treat acute pain compared with IV morphine alone are unclear (insufficient due to inconsistency in the direction of effects)
IV ketamine vs. IV lidocaine vs. placebo administered after general anesthesia induction	1 RCT (59)	Low	180	Postoperative pain; Iran; 100% with OUD	Lower pain severity and opioid analgesic use in lidocaine group compared with ketamine or placebo No difference in AEs	IV lidocaine administered during general anesthesia may decrease postoperative pain severity and opioid analgesic use compared with IV ketamine or placebo (low SOE)
IV meperidine vs. IV morphine	2 RCTs (60, 61)	Some concerns (1 study) High (1 study)	202	Postoperative pain (1 study) (61); Egypt; 100% with OUD Multiple (1 study) (60); Iran; 100% with OUD	Pain severity: higher in meperidine group up to 48 h (2 studies) Opioid withdrawal: higher COWS in meperidine group up to 60 min (2 studies) AEs: higher in meperidine group (1 study)	IV meperidine may be less effective than IV morphine for treatment of acute pain and opioid withdrawal symptoms (low SOE)

AE = adverse event; COWS = clinical opiate withdrawal scale; IM = intramuscular; IT = intrathecal; IV = intravenous; MOUD = medication for opioid use disorder; NR = not reported; OUD = opioid use disorder; POD = postoperative day; RCT = randomized controlled trial; ROB = risk of bias; SL = sublingual; SOE = strength of evidence.

* SOE assessed if sufficient evidence available (≥1 RCT with low ROB or ≥2 cohorts with similar populations and interventions).

† Cannot rule out overlapping populations in 2 cohort studies (34, 35).

‡ Postoperative pain (11 studies): Australia, 100% with OUD (28); United States, proportion with OUD NR (30); United States, 100% with OUD (29); United States, 100% with OUD (64); United States, 39% with OUD (31); United States, 100% with OUD (33); United States, 76% with OUD (34); United States, 80% with OUD (35); United States, 36% with OUD (36); United States, 100% with OUD (37); United States, proportion with OUD NR (38).

§ In a case series of 14 pregnant persons prescribed buprenorphine who received epidural clonidine during labor, 4 (29%) experienced hypotension requiring intervention.

OUD Outcomes Among People Prescribed Methadone

We did not identify any studies of acute pain interventions among adults prescribed methadone that evaluated OUD-related outcomes.

Pain and OUD Outcomes Among People Prescribed Buprenorphine or Methadone

Two retrospective controlled cohort studies with high ROB compared interventions to treat post-cesarean section pain among adults with OUD who were prescribed buprenorphine or methadone (in a combined study cohort) (43, 56). These studies each evaluated a single intervention (regional or combined spinal-epidural anesthesia with and without intrathecal clonidine, and IV ketamine vs. usual care, respectively) and had methodological concerns due to potential selection bias and/or confounding, providing insufficient evidence to assess their effectiveness.

Pain and OUD Outcomes Among People Prescribed Naltrexone

We did not identify any comparative studies of acute pain interventions among adults prescribed naltrexone that evaluated pain or OUD outcomes. A qualitative data synthesis from relevant uncontrolled studies is shown in Supplement Table 8.

Pain and OUD Outcomes Among People Not Prescribed MOUD

Sixteen RCTs conducted among adults with OUD who were not prescribed MOUD evaluated a total of 14 unique acute pain interventions (Table 2) (40, 41, 44–48, 50, 51, 53, 54, 57–61). Aside from 1 RCT conducted in Egypt (61), these RCTs were all done in Iran among predominantly male participants who were using opium. Ten RCTs included adults treated for postoperative pain (40, 41, 44, 47, 48, 50, 54, 57, 59, 61), 1 included adults treated for pain after cataract surgery (46), 3 included adults treated for traumatic limb injury or orthopedic fracture (45, 51, 58), and 2 included adults with different types of surgical and nonsurgical acute pain (53, 60). Two interventions (SL buprenorphine compared with IV morphine and receipt of oral carbamazepine before surgery) were evaluated in a single RCT (40, 41). Interventions featuring ketamine, clonidine, dexmedetomidine, haloperidol, meperidine, morphine, and fentanyl were each evaluated in at least 2 RCTs, but the specifics of the intervention, co-interventions, and comparators varied among trials (46–48, 50, 51, 53, 54, 57–61).

Based on findings from a single RCT with low ROB conducted among 70 Iranian adults with OUD presenting to the ED for acute pain due to orthopedic fracture, oral clonidine, 0.2 mg, may decrease pain severity (up to 1 hour) and opioid analgesic use compared with placebo (low SOE) (45). Based on a single RCT with low ROB conducted among 87 Iranian adults with OUD presenting to the ED with acute traumatic or nontraumatic limb or abdominal pain, the combination of intramuscular (IM) haloperidol, IM midazolam, and IV morphine may decrease pain severity (up to 6 hours) and opioid analgesic use compared with IV morphine alone (low SOE) (53). For postoperative pain, IV lidocaine administered during general anesthesia may decrease postoperative pain severity and opioid analgesic use compared with IV ketamine or placebo, based on a single RCT with low ROB conducted among 180 Iranian adults with OUD (low SOE) (59). Based on 2 RCTs (with moderate or high ROB) with a total of 202 participants from Egypt and Iran, IV meperidine may be less effective than IV morphine in the treatment of acute pain and opioid withdrawal symptoms (low SOE) (60, 61). Evidence for other interventions either had insufficient strength or was presented in a single RCT with moderate to high ROB and was therefore not assessed.

Benefits and Harms of Acute Pain Interventions in Patients Prescribed Different Types of MOUD

We did not identify any studies that directly compared the benefits and harms of specific acute pain interventions between patients with OUD prescribed different types of MOUD in order to address our third key question. A qualitative data synthesis and results from relevant uncontrolled studies are shown in Supplement Tables 8 and 9.

DISCUSSION

From an extensive search of the literature on the benefits and harms of acute pain interventions for adults with OUD, this systematic review divided the available evidence into 2 distinct populations—people with OUD prescribed MOUD (primarily buprenorphine), and those not prescribed MOUD—across perioperative, obstetric (labor and delivery or post-cesarean section), ED, and/or nonoperative hospital settings. From 10 controlled cohort studies, we found that continuing (vs. discontinuing) buprenorphine in patients already prescribed it during episodes of acute pain may be associated with lower or similar pain severity. These studies were conducted in the United States primarily among adults with postoperative pain but also included participants with other acute pain conditions, such as trauma or multiple pain conditions.

We speculate that findings of similar or improved pain outcomes with buprenorphine continuation may be due to the analgesic properties of buprenorphine as well as its role in preventing pain related to opioid withdrawal and that this finding is relevant to all inpatient and outpatient clinical scenarios in which pain and opioid withdrawal are possible. However, despite consistent results across studies in terms of the direction of effect, our overall confidence about pain outcomes with buprenorphine continuation is low due to methodological limitations of the studies, primarily ROB due to confounding among cohort studies. Within

a given study, clinical decisions to continue or discontinue buprenorphine were most often made at the discretion of the treating clinical team. People with OUD who were advised to continue buprenorphine could have important clinical differences compared with those who discontinued buprenorphine. For example, people who continued buprenorphine might have been predisposed to experience lower pain severity and/or favor use of nonopioid adjunctive medications, and cohorts were not designed to identify or control for these factors. Although evidence currently suggests that the best practice is to continue buprenorphine during acute pain episodes for most people, RCTs or prospective cohort studies could be designed to minimize confounding and improve our understanding of which patient populations are likely to benefit most. In addition, most studies were conducted before the current era of high-potency synthetic opioid use (for example, fentanyl) and the resulting trend toward prescription of higher SL buprenorphine doses (for example, ≥24 mg). Whether findings on buprenorphine continuation apply to people prescribed higher doses is unclear and should be studied further.

We found very little evidence for acute pain management among people prescribed methadone. This research gap is problematic because more than 400 000 people in the United States receive methadone for the treatment of OUD, and many are likely to experience acute pain (67, 68). However, we note that, as for buprenorphine, contemporary best practice is to continue methadone during acute pain episodes for most people, and we did not identify any studies reporting harms attributed to this approach.

For people with OUD not prescribed MOUD, numerous acute pain interventions have been evaluated in RCTs conducted almost exclusively in Iran among mostly male participants using opium in hospital settings. Some interventions evaluated in single well-conducted RCTs, such as oral clonidine, IM haloperidol and midazolam with concurrent IV morphine, and intraoperative IV lidocaine, resulted in improved pain outcomes (all low SOE), but whether the results are applicable to people in the United States with OUD using high-potency synthetic opioids is unclear. Results of these RCTs provide a rationale for further study in more diverse patient populations, including among adults prescribed MOUD.

In addition to finding very little evidence regarding people with OUD prescribed methadone, this review highlights other important gaps in the available evidence. Perhaps most critically, despite episodes of acute pain representing a period of heightened return to opioid use, most studies of acute pain interventions have not included OUD outcomes or extended study periods long enough to determine the overall trajectories of participants. We recommend that future studies of acute pain interventions among people with OUD include outcomes related to opioid withdrawal and cravings, return to nonprescribed opioid use, and treatment retention. The rate of premature ED or hospital discharge is another outcome that would inform efforts to improve acute care delivery. Second, important evidence gaps exist regarding acute pain management strategies among people prescribed long-acting injectable buprenorphine and naltrexone, which are currently only described in case reports or series. Finally, comparative studies were conducted exclusively in hospital or ED settings rather than in primary care or other outpatient settings. Although findings related to MOUD management (such as buprenorphine continuation) likely apply to all settings, findings for other acute pain interventions (such as ketamine) are probably specific to the setting in which they were studied. The lack of evidence for outpatient practice settings is an important research gap.

In addition, the evidence base described in this review has limitations. First, much of the evidence is observational and has potential bias due to confounding, as discussed earlier. Second, studies of people prescribed buprenorphine did not always report the medication indication (OUD or chronic pain). However, the effectiveness of medications on pain control likely overlaps due to similar pain sensitivity and opioid tolerance among patients receiving buprenorphine for chronic pain and populations with OUD. Similarly, although many of the non-U.S. studies included participants using opium and some used methods for participant eligibility other than DSM criteria for OUD, the results remain relevant because all participants had physical dependence on opioids.

In conclusion, available evidence supports the contemporary best practice of continuing buprenorphine during episodes of acute pain for people with OUD already prescribed this medication. Several unique interventions have been evaluated in non-U.S. hospital or ED settings among people with OUD. Some interventions (oral clonidine, IM haloperidol and midazolam with concurrent IV morphine, and intraoperative IV lidocaine) have shown benefits in single well-conducted RCTs and warrant further study in more diverse patient populations and settings, including among people with OUD in the United States using high-potency synthetic opioids and among adults prescribed MOUD. Important evidence gaps exist, including for acute pain management among people prescribed methadone, long-acting injectable buprenorphine, or naltrexone. Most critically, the effects of acute pain management interventions on OUD outcomes have not been well characterized and merit urgent study in light of the ongoing crisis of opioid-related overdoses and other harms.

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