

# Evidence Brief: Managing Acute Pain in Patients with Opioid Use Disorder on Medication-assisted Treatment

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## PREFACE

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- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

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## EXECUTIVE SUMMARY

### Key Findings

- We identified 8 studies on acute pain management for non-Veterans with opioid use disorder (OUD) taking methadone or buprenorphine. However, none directly evaluated the trade-offs of different ways of managing acute pain in OUD patients on MAT. Also, none were conducted in VHA settings, or evaluated naltrexone for OUD.
- These 8 studies align with current guidelines which recommend continuing methadone during acute pain episodes and state that continuing buprenorphine is a reasonable approach for most patients with mild or moderate pain. Specifically, these studies found that:
  - Continuing the use of buprenorphine and methadone for patients with OUD after surgery may reduce the need for additional opioids;
  - Patients with OUD on MAT are opioid-tolerant and need higher doses of opioid agonists for effective pain control compared to patients without OUD;
  - Ineffective management of acute pain in OUD patients taking methadone can lead to disengagement in care.
- Future research is needed to evaluate the effectiveness of adjuvant non-opioid pharmacological and non-pharmacologic acute pain management strategies for patients with OUD taking methadone and buprenorphine, as well as the benefits and harms of adjusting the dose or timing of MAT (such as increasing doses or dividing doses). Future research is also urgently needed to evaluate effective acute pain management in patients with OUD on naltrexone.

### Background

The ESP Coordinating Center (ESP CC) developed this evidence brief on acute pain management in patients with opioid use disorder (OUD) who are on medication-assisted treatment (MAT) in response to a request from VA's Health Services Research and Development Service (HSR&D). Findings from this evidence brief will be used to inform prioritization of questions for a September 2019 State-of-the-Art (SOTA) conference.

### Methods

To identify studies, we searched MEDLINE®, PsycINFO, CINAHL, and Cochrane Central Register of Controlled Trials (CENTRAL). We used prespecified criteria for study selection, data abstraction, and rating internal validity and strength of the evidence. See our PROSPERO protocol for our full methods.

Due to the national crisis of opioid-related morbidity and mortality – including deaths from overdoses – more patients are receiving medication-assisted treatment (MAT) with methadone, buprenorphine/naloxone, and naltrexone for opioid use disorder (OUD). Acute pain management in patients who have a history of OUD can be challenging due to increased pain sensitivity and the need for higher opioid doses to achieve pain relief. Clinicians may also tend to under-treat pain in patients with OUD because of concerns for drug-seeking behavior and ongoing illicit substance use. Use of MAT adds to the complexity of acute pain management in patients with OUD because of the unique pharmacologic properties of MAT medications resulting in the need for different management strategies to effectively treat acute pain. The aim of this review is to synthesize evidence on the effectiveness of acute pain management strategies for patients on MAT in terms of benefits and harms and whether benefits and harms differ for different

medications (methadone, buprenorphine, or naltrexone) or type of acute pain (such as emergency conditions vs planned surgery).

We identified 8 retrospective studies (3 studies with a control group, 1 case series, and 4 case reports) covering a range of acute pain conditions (surgical, emergency, and both) and medications (buprenorphine/naloxone alone, methadone alone, and studies that looked at both) except for naltrexone. Study size ranged from 1 in case reports to 134 in controlled studies. Most studies were conducted in hospitals/tertiary care centers or specialized pain centers and had follow-up duration ranging between 1 day to over 2 years.

Three studies with control groups provide evidence supporting the continuation of MAT in acute pain management, although detail about the timing, dosage, and rationale for administering different medications (including changes to usual MAT doses and adding opioids and non-opioid analgesics) was lacking. One study found that patients taking buprenorphine who undergo surgery and miss their buprenorphine dose the day afterwards use more patient-controlled analgesia for longer periods of time than those who do receive their dose, and similar trends were found for those taking methadone. A second study found that patients on MAT (methadone or buprenorphine/naloxone) undergoing joint replacement surgery can receive eight times the dosage of opioids at discharge, with similar outcomes on both pain and knee and hip functionality at 1 year as those without OUD. A third study found that when equivalent doses of opioids are used to manage pain in patients who are or aren't taking MAT, patients taking MAT were less satisfied with care, which manifested as higher rates of behavioral problems and increased likelihood of discharging against medical advice. The biggest limitation of these studies is that the MAT management strategies, including adjuvant analgesics, were not adequately described (*ie*, timing, dosage).

Five additional studies without control groups provide information on conditions not covered by the cohort studies – especially emergency conditions – and provide more detailed descriptions of the timing, dosage, and rationale for acute pain management strategies. However, due to imprecision and other methodological limitations such as inadequate outcome assessment, these studies do not provide a reliable evidence base to guide decision-making.

While the evidence has substantial limitations, the best-conducted studies did not suggest there is a potential benefit in *stopping* buprenorphine or methadone, and in fact several studies found that stopping MAT can cause patients to experience increased pain (measured directly as increased pain reports or indirectly as increased use of patient-controlled analgesics). Therefore, despite the limitations of the evidence, continuing MAT for most patients with OUD during an episode of acute pain seems to be a clinically sound and patient-centered approach. Future research should therefore explore the: 1) the optimal dosage and timing of continuing MAT in acute pain management based on patient characteristics and specific MAT medications used (*ie*, whether to increase or divide doses); 2) the optimal use of opioids and non-opioid pain management strategies; 3) whether certain acute pain management approaches work better for certain patients; and 4) the effect of acute pain management approaches on outcomes such as risk of relapse and overdose.

Researchers should ideally apply prospective study designs to evaluate these questions, although a well-described retrospective study would also provide useful information. These studies will be most useful if they have a concurrent control group (*ie*, an RCT or well-controlled cohort study)

to help establish the causality of pain management approaches on outcomes, and provide detailed information on the pain management approach taken (including timing, dose, duration of different medications) as well as the rationale for why any changes were made.

# EVIDENCE BRIEF

## INTRODUCTION

### PURPOSE

The ESP Coordinating Center (ESP CC) developed this evidence brief on acute pain management in patients with opioid use disorder (OUD) who are on medication-assisted treatment (MAT) in response to a request from VA's Health Services Research and Development Service (HSR&D). Findings from this evidence brief will be used to inform prioritization of questions for a September 2019 State-of-the-Art (SOTA) conference.

### BACKGROUND

Acute pain has been defined as sudden-onset, time-limited pain that can vary in intensity, modulating factors, and impact on functionality and quality of life.<sup>1</sup> Many cases of acute pain resolve on their own without any medical or other healthcare interventions, while others require use of pharmacological and/or nonpharmacological pain management interventions. While professional societies are reconsidering the use of opioids to manage certain acute pain conditions – such as dental procedures and ambulatory surgeries<sup>2,3</sup> – opioids remain a common treatment for many acute pain conditions.<sup>4,5</sup>

Acute pain management in patients with opioid use disorder (OUD) can be particularly challenging due to increased pain sensitivity and the need for higher opioid doses to achieve pain relief due to opioid tolerance. Clinicians may also tend to under-treat pain in patients with OUD because of concerns for drug-seeking behavior and ongoing illicit substance use.<sup>6,7</sup> Use of medication-assisted treatment (MAT) for OUD with methadone, buprenorphine/naloxone, and naltrexone adds to the complexity of acute pain management in patients with OUD because of the unique pharmacologic properties of these medications and the implications of using opioids for analgesia in addition to MAT (See Table 1).

Methadone and buprenorphine help patients manage OUD by reducing opioid cravings and preventing withdrawal, which are both potent drivers of ongoing opioid use.<sup>8</sup> Methadone is an “full opioid agonist,” meaning that it activates opioid receptors in the brain and body in the same way as other prescription opioids and illicit opioids such as heroin. Methadone is a long-acting medication that can build up quickly and unpredictably with dose adjustments, thereby increasing the risk of respiratory depression and overdose, particularly when it is used at the same time as other opioids. Patients taking methadone for OUD are monitored very closely (sometimes daily) in part due to the risks of methadone if it is used at the same time as illicit opioids. A parallel risk exists when using additional opioids for acute pain management in patients on methadone in the emergency department and hospital setting. Methadone also has multiple drug-drug interactions and a risk of heart arrhythmia that requires monitoring with electrocardiograms.

Buprenorphine is a “partial opioid agonist,” because it *partially* activates opioid receptors and thereby has a lower risk of adverse events such as respiratory depression and overdose compared to methadone and other full agonist opioids. Buprenorphine is typically co-formulated with naloxone, which helps deter misuse by blocking the effects of the opioids and causing unpleasant

opioid withdrawal if the medication is crushed and injected or snorted instead of being used under the tongue as prescribed. Buprenorphine has a strong bond with opioid receptors (*ie*, receptor affinity) when compared with other opioids. While it is an effective pain medication for many patients, there is at least a theoretical risk that use of buprenorphine will make pain control more challenging in cases of severe acute pain because higher doses of full agonist opioids may be required to displace buprenorphine from opioid receptors.<sup>9</sup> However, it is unclear how often this theoretical risk impacts clinical practice.

Naltrexone is an “opioid antagonist,” meaning that it blocks opioid receptor activity, and is available in an injectable form and oral form. Extended-release (injectable) naltrexone is the preferred MAT option for patients who would like to avoid taking any form of opioid or for whom methadone and buprenorphine are contraindicated. Naltrexone works differently than methadone and buprenorphine to treat OUD – by blocking the effects of opioids, it helps promote opioid abstinence. The challenge with acute pain management in patients taking naltrexone is that until enough time has elapsed that naltrexone is no longer active in the body, opioid pain medications will not be effective. Using higher doses of opioids may be a way to overcome the effects of naltrexone, but there is a risk of overdose once naltrexone starts wearing off.

**Table 1. Medications used to treat OUD and clinical considerations for pain management**

Medication	Opioid receptor activity	Clinical considerations for pain management
Methadone	Full activation (“full opioid agonist”)	<ul style="list-style-type: none"> <li>• Long-acting medication with unpredictable effects with dose changes</li> <li>• Risk of respiratory depression and overdose with dose adjustments and addition of other opioids</li> <li>• Multiple drug-drug interactions</li> <li>• Risk of heart arrhythmia</li> <li>• Risk of withdrawal when discontinued<sup>10</sup></li> </ul>
Buprenorphine/ naloxone	Partial activation (“partial opioid agonist”)	<ul style="list-style-type: none"> <li>• Strong bond with the opioid receptor that may reduce the effectiveness of other opioids used at the same time for acute pain</li> <li>• Risk of withdrawal when discontinued<sup>11</sup></li> </ul>
Naltrexone (extended-release injectable form or oral form)	Blocks the effects of opioids (“opioid antagonist”)	<ul style="list-style-type: none"> <li>• Blocks the effects of opioids used to treat acute pain</li> <li>• Blocking activity may be overcome with higher opioid doses, but may increase the risk of overdose when naltrexone effects wear off</li> <li>• Extended-release injectable form can last up to 30 days, complicating acute pain treatment if it occurs in this period<sup>12</sup></li> </ul>

The benefits of well-executed acute pain management in patients on MAT include effective management of pain; high functionality and quality of life after the acute pain event; satisfaction with care; and low healthcare utilization (including shorter hospital stays). Potential harms associated with inappropriate acute pain management for those with MAT include uncontrolled

pain; risk of relapse associated with uncontrolled pain and/or gaps in MAT prescribing; and risk of respiratory depression or other adverse outcomes due to addition of high doses of full opioid agonists.

In cases of unplanned acute pain – such as injury or trauma – patients may be treated in the emergency department or hospital setting by providers who are meeting them for the first time. In this setting, patients may have heightened fears about pain control and stigma related to OUD, and providers may be more likely to view patients as drug-seeking or to have concerns about ongoing illicit drug use.<sup>13</sup> Elective surgeries and other planned procedures present fewer challenges related to acute pain management given that planned procedures allow clinicians time to develop individualized pain management plans and allow time for MAT dose reduction and discontinuation if needed. Another difference between elective surgeries and emergency conditions is that for planned interventions, patients are more likely to have established relationships and trust with their providers.

A possible approach to acute pain management in patients taking methadone or buprenorphine/naloxone is to continue or increase their usual dose, potentially by dividing doses throughout the day, with or without the addition of other opioids or non-opioid pain treatments. Alternatively, buprenorphine may be discontinued and other opioids can be used instead until acute pain has resolved. For patients taking naltrexone, one approach is to use non-opioid and/or non-pharmacologic acute pain management strategies or to treat with higher doses of opioids to try to overcome the opioid blocking effects of naltrexone. In cases of planned procedures or surgery in which acute pain is expected, patients are often advised to stop extended-release naltrexone in advance to allow time for the medication to wear off. Given the potential challenges of using opioids for acute pain in patients MAT, clinicians may prefer to optimize non-opioid management strategies (*eg*, non-steroidal anti-inflammatory drugs, benzodiazepines) or use non-pharmacologic options (mindfulness and relaxation techniques, acupuncture, use of heating pads and ice packs).<sup>14</sup> However, opioids may still be considered the best option in cases of severe acute pain.

Current guidelines addressing the management of acute pain in patients on MAT are primarily based on expert consensus and do not provide clear steps for clinicians to take in different acute pain scenarios. The American Society of Addiction Medicine's (ASAM) 2015 guidelines on treatment for OUD – which are based on a structured consensus method – provide some suggestions but not firm recommendations for acute pain management in patients on MAT. These guidelines state that patients on methadone maintenance may require higher doses of full agonists for acute pain control in addition to their regular daily dose of methadone.<sup>14</sup> For patients on buprenorphine, these guidelines do not conclusively recommend continuing or discontinuing buprenorphine for acute pain except in cases of severe pain, in which case these guidelines recommend stopping buprenorphine so that full agonist opioids will be more effective. For patients on naltrexone, these guidelines discuss non-opioid pain management strategies for acute unexpected pain and recommend discontinuing extended-release injectable naltrexone 30 days before elective surgery and oral naltrexone 72 hours prior to elective surgery. Educational materials produced by the Substance Abuse and Mental Health Services Administration's (SAMHSA) Providers Clinical Support System (PCSS) provide some suggestions for treatment, such as using intravenous ketamine and lidocaine,<sup>15</sup> but these are not evidence-based guidelines. The Department of Veterans Affairs (VA)/Department of Defense's (DOD) joint 2015 guidelines on management of substance use disorder do not address acute pain management for patients on

MAT,<sup>16</sup> although perioperative pain management protocols for patients on buprenorphine are being developed. Similarly, the Centers for Disease Control and Prevention (CDC) 2016 opioid guidelines encourage use of MAT for patients with OUD, but do not address acute pain management for patients on MAT.<sup>17</sup>

The most informative studies of acute pain management in patients on MAT would include patients with OUD on stable doses of methadone, buprenorphine (or buprenorphine/naloxone), or naltrexone who are undergoing elective surgery or who require emergency treatment for an acute pain condition. For patients on methadone, studies that compare the addition of opioid agonists and non-opioid treatments when baseline methadone doses are maintained would be most informative. In the case of buprenorphine, the most pressing question is whether buprenorphine should be continued or stopped for acute pain management.<sup>18</sup> An informative study would address this question by comparing patient outcomes with use of adjuvant pain treatments when buprenorphine is continued or discontinued. Studies of naltrexone would evaluate pain management strategies prior to elective surgery when naltrexone must be stopped, as well as use of non-opioid treatments for emergency acute pain conditions. Ideal studies of MAT would also evaluate the effects of acute pain management strategies on relapse risk and other adverse events such as opioid overdose.

Use of MAT is increasing in response to the national crisis of opioid-related morbidity and mortality. Although use of these medications remains disproportionately low compared to the prevalence of OUD, multiple stakeholders, including patients, clinicians, and policy-makers, are engaged in efforts to increase MAT use, and it is likely that more patients will be treated with these medications over time.<sup>19</sup> Determining best practices to manage acute pain in patients on MAT is therefore relevant to frontline clinicians in multiple settings. The aim of this review is to synthesize evidence on the effectiveness of acute pain management strategies for patients on MAT in terms of benefits and harms and whether benefits and harms differ for different MAT medications or type of acute pain (emergency condition vs planned surgery). Findings from this review will be used by VHA leadership, clinicians, and other decision-makers attending a 2019 VA State of the Art Conference (SOTA) to inform clinical decision-making around management of acute pain in MAT patients as well as to identify gaps for future research.

## SCOPE

This rapid evidence review addresses the following key questions and eligibility criteria:

### Key Questions

Key Question 1: What are the benefits and harms of strategies to manage acute pain in adults with OUD on MAT?

Key Question 2: Do these benefits and harms vary by patient characteristics, such as MAT medication or type of acute pain (emergency condition vs planned surgery)?

### Eligibility Criteria

This review includes studies that meet the following criteria:

- **Population:** Adults (excluding pregnant women) with OUD on MAT (methadone, buprenorphine [with or without naloxone], or naltrexone) with acute pain, defined as sudden onset, time-limited pain
- **Intervention:** Any pain management approach (*eg*, discontinuation or dose change in medication used for MAT, substitution with another opioid, addition of another opioid, or non-opioid or non-pharmacological therapies)
- **Comparator:** Any (*ie*, studies that compare different pain management approaches, or describe effects of a single pain management approach)
- **Outcomes:** Pain severity, pain-related function, quality of life, patient satisfaction, healthcare utilization, opioid withdrawal symptoms, substance use relapse, opioid overdose, suicidal ideation and suicidal self-directed violence, and other adverse events
- **Timing:** Any
- **Setting:** Any (including primary care, emergency department, dental, perioperative, and palliative care settings)
- **Study design:** Any, but may prioritize to accommodate timeline using a best-evidence approach

## METHODS

### SEARCHES AND STUDY SELECTION

To identify articles relevant to the key questions, our research librarian searched MEDLINE, PsycINFO, CINAHL, and Cochrane Central Register of Controlled Trials (CENTRAL) using terms for *opioid use disorder*, *medication-assisted treatment*, and *acute pain* (see Supplemental Materials for complete search strategies) from database inception to April 2019. Additional citations were identified from hand-searching reference lists and consultation with content experts. We limited the search to published and indexed articles involving human subjects available in the English language. Study selection was based on the eligibility criteria described above. Titles and abstracts were reviewed by 1 investigator. Full-text articles were reviewed by 1 investigator and checked by another. All disagreements were resolved by consensus.

### QUALITY ASSESSMENT AND DATA EXTRACTION

We used predefined criteria to rate the internal validity of all included cohort studies as well as the quality of reporting for case series and case reports. For cohort studies, we used criteria from Cochrane's ROBINS-I tool<sup>20</sup> which evaluates the potential for bias from participant selection, classification of interventions, departure from intended interventions, measurement of outcomes, confounding, and missing/unreported data. Overall bias ratings range from low, unclear, to high risk of bias. For case series and case reports, we adapted criteria from ROBINS-I as well as the CARE Checklist<sup>21</sup> and focused on the quality of reporting, rather than the potential for bias. Overall quality of reporting ratings range from not reported, partly reported, mostly reported, to well-reported. We abstracted data from all studies, including study characteristics, populations, comparators, intervention, and results. All data abstraction and internal validity/quality of reporting ratings were first completed by 1 reviewer and then checked by another. All disagreements were resolved by consensus.

### STRENGTH OF EVIDENCE ASSESSMENT

We graded the strength of the evidence based on the AHRQ Methods Guide for Comparative Effectiveness Reviews.<sup>22</sup> This approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias. Strength of evidence is graded for each key outcome measure and ratings range from high to insufficient, reflecting our confidence that the evidence reflects the true effect.

### SYNTHESIS OF DATA

Due to limited data and heterogeneity, we synthesized the evidence qualitatively.

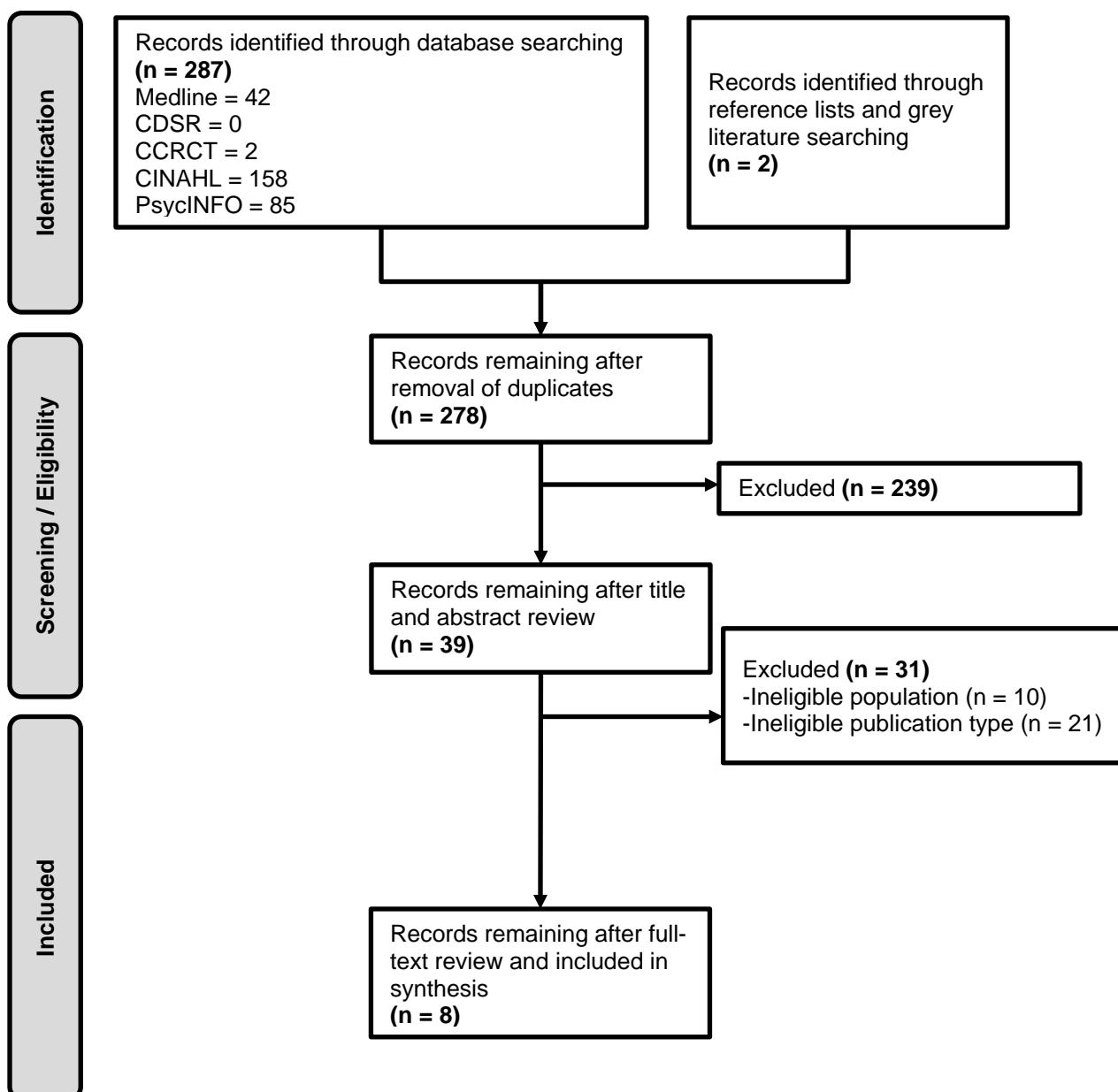
The complete description of our full methods can be found on the PROSPERO international prospective register of systematic reviews (<http://www.crd.york.ac.uk/PROSPERO/>; registration number CRD42019132924).

# RESULTS

## LITERATURE FLOW

The literature flow diagram (Figure 1) summarizes the results of our search and study selection (See Supplementary Materials Appendix A for the full list of excluded studies). Our search identified 278 unique, potentially relevant articles. Of these we included 8 articles<sup>23-30</sup> that addressed our key questions. All 8 addressed Key Question 1, and none addressed Key Question 2.

**Figure 1. Literature flowchart**



## KEY QUESTION 1: What are the benefits and harms of strategies to manage acute pain in adults with OUD on MAT?

We identified 8 retrospective studies (3 studies with a control group and 5 without): 2 studies examined patients with OUD taking buprenorphine/naloxone,<sup>24,26</sup> 4 examined those taking methadone,<sup>25,27-29</sup> and 2 examined a mixed group of MAT medications.<sup>23,30</sup> No studies examined the use of naltrexone. Four studies examined those with emergency conditions,<sup>24,26-28</sup> 3 examined those undergoing planned surgery,<sup>23,29,30</sup> and 1 examined a mixed group of emergency and surgical patients.<sup>25</sup> Study size ranged from 1 to 134 participants, were conducted in hospitals/tertiary care centers or specialized pain centers, and follow-up ranged between 1 day to over 2 years. Detailed descriptions of these studies appear in Appendix C and key findings appear below. For studies of buprenorphine, we first report whether the study evaluated buprenorphine alone or in co-formulation with naloxone, then subsequently refer to both medications as “buprenorphine,” as it is our assumption that these drugs were taken as prescribed and thus acted like buprenorphine alone.

### Studies with control groups

The best available evidence comes from the 3 studies with control groups, although these had considerable limitations. Table 2 provides an overview of these studies, including study characteristics, patients examined, acute pain management strategies, results, and limitations. One study<sup>30</sup> compared 2 groups of surgical patients (orthopedic, abdominal, orofacial, thoracic, and other) on MAT – those taking methadone and those taking buprenorphine – 24 hours after surgery. The study found similar pain management strategies (high doses of morphine-equivalent opioids in the intraoperative period) and outcomes (use of patient-controlled analgesia [PCA], pain severity, and adverse events like nausea, vomiting, and sedation) between groups. However, only half of patients taking buprenorphine and three-quarters of patients taking methadone received their MAT dose the day after surgery. Those taking buprenorphine who missed their dose used more PCA for longer periods of time than those that didn’t, and similar trends were found in patients taking methadone. Study authors did not know why some patients missed their dose. A second study<sup>23</sup> compared patients with OUD taking MAT (methadone or buprenorphine/naloxone) versus non-OUD patients receiving hip or knee joint replacements. Patients taking MAT received 8 times the dose of opioids at discharge as patients not taking MAT. This difference reflected a decrease in opioid dosage from baseline for patients taking MAT and an increase in dosage from baseline for patients not taking MAT. Both groups had similar pain, functionality, and quality of life outcomes at 6 weeks and 1 year. It was unclear whether MAT was continued or discontinued in these patients, as study authors only reported overall doses of morphine-equivalent doses. It was also unclear whether these high opioid doses were titrated down over time. A third study<sup>25</sup> compared patients with OUD taking methadone with acute pain from surgery or injury (type of surgery or injury not reported) to patients not on methadone (presumably without OUD but the study does not specify) and found that when similar doses of opioids were used to manage pain, patients taking methadone had similar number of pain reports but higher rates of behavioral problems and were more likely to discharge against medical advice. Due to limitations in how data on patients’ pain was collected, study authors could not determine why patients were discharging against medical advice. They hypothesized it may have been because either these patients were using illicit opioids in addition to MAT before hospitalization and were driven by opioid cravings, or because their pain was not being effectively managed. The study did not report any follow-up information on these patients, for example, whether they continued OUD treatment in outpatient settings.

Overall, findings from these studies align with ASAM 2015 guidelines<sup>14</sup> on treatment for OUD which state that patients on MAT are opioid-tolerant and need higher doses of opioid agonists for effective pain control. Findings of these studies also suggest that continuing the use of methadone and buprenorphine in patients on MAT after surgery may reduce total doses of opioids. However, our confidence in these findings is low due to several limitations, including that pain management strategies, including use of MAT and adjuvant analgesics, were not adequately described (*ie*, timing, dosage), inadequate methods were used to assess pain severity outcomes, and few studies reported patient-important outcomes other than pain severity.

**Table 2. Findings from studies with control groups**

<b>Author, year</b>	<b>Study design Study size Duration Comparison</b>	<b>Population</b>	<b>Acute pain management strategies</b>	<b>Key findings</b>	<b>Major limitations</b>
MacIntyre, 2013 <sup>30</sup>	Retrospective cohort  N=51  24 hours after surgery  Methadone vs buprenorphine groups as well as those who did and did not miss their MAT dose after surgery	Surgical patients (33% orthopedic, 27% abdominal, 16% orofacial, 13% thoracic, and 10% other) on MAT (57% methadone; 43% buprenorphine) who required IV PCA.	<ul style="list-style-type: none"> <li><b>MAT use:</b> 64% of buprenorphine group received MAT (mean 13.7 mg) and 79% of methadone group received MAT (mean 78.9 mg) the day of surgery. Only 50% of buprenorphine and 76% of methadone group received MAT the day after surgery.</li> <li><b>Use of opioids:</b> Similar, high doses of morphine equivalent doses given in the postoperative period (mean 200 mg/day for buprenorphine group vs 221 mg/day for methadone group). &lt;1/4 of patients received tramadol</li> <li><b>Use of adjuvant analgesics:</b> Patients received regular paracetamol &amp; varying doses of non-steroidal anti-inflammatory drug or continuous ketamine infusion. 1/4 of patients received ketamine, 1/8 received clonidine, and 1 patient received remifentanil.</li> </ul>	<ul style="list-style-type: none"> <li>Methadone and buprenorphine groups, and those that did and did not receive their MAT dose the day after surgery, were similar in terms of pain, functionality, and adverse events (nausea, vomiting, sedation) the day after surgery.</li> <li>Buprenorphine patients who were not given their usual MAT dose the day after surgery used significantly more PCA for longer periods of time, and similar trends were seen in PCA amount in methadone patients.</li> </ul>	<ul style="list-style-type: none"> <li>Differences between groups at baseline in terms of substance use (alcohol, cannabis and benzodiazepines) that were not controlled for.</li> <li>Some patients had MAT discontinued and it is unclear why.</li> </ul>
Hansen, 2016 <sup>23</sup>	Retrospective cohort  N=51  27.2 months  MAT vs non-MAT groups	17 knee or hip replacement surgical patients on MAT (methadone or buprenorphine/naloxone) were matched to 34 controls not on MAT	<ul style="list-style-type: none"> <li><b>MAT use:</b> MAT group was taking methadone or buprenorphine/haloxone at baseline (median 870 mg/day), but not clear whether MAT was continued, discontinued, etc during surgery</li> <li><b>Use of opioids:</b> MAT group received 8 times the morphine-equivalent dose of oral opioids at discharge compared to non-OUD group (mean 793 mg/day vs 109 mg/day). This is a decrease from baseline for the MAT group and an increase from baseline for the non-OUD group.</li> </ul>	<ul style="list-style-type: none"> <li>Similar pain, functionality, and quality of life at 6 weeks and 1 year, except the MAT group had worse knee range of motion at 1 year.</li> </ul>	<ul style="list-style-type: none"> <li>Unclear if MAT was continued for all, some, or no patients.</li> <li>No information on which opioids were prescribed at discharge.</li> <li>Different MAT medications grouped together</li> </ul>

			<ul style="list-style-type: none"> <li><u>Use of adjuvant analgesics:</u> Similar pain management approaches in both groups including regional block and preoperative anesthesia adjunct medications.</li> </ul>		and no subgroup analysis
Hines, 2008 <sup>25</sup>	Retrospective cohort  N=134  7 days	67 with acute or surgical condition taking methadone were matched to 67 controls not taking methadone	<ul style="list-style-type: none"> <li><u>MAT use:</u> Patients taking methadone received an average of 82.4 mg methadone at admission; a total of 12% of patients had methadone increased. 16% experienced withdrawal symptoms (of which 18% had methadone dose increased).</li> <li><u>Use of opioids:</u> Median morphine-equivalent dose of opioids similar in methadone and non-methadone groups (5.07 vs 6.67 mg/day respectively).</li> <li><u>Use of adjuvant analgesics:</u> Some patients in both methadone and non-methadone groups received a non-opioid analgesic (42% vs 40% respectively) and very few received non-drug pain relief (8% vs 5%). Methadone group received a higher median dosage of benzodiazepines than non-methadone group (5 vs 2.67 mg/day respectively).</li> </ul>	<ul style="list-style-type: none"> <li>Patients taking methadone had the same number of pain reports per day as controls.</li> <li>Patients taking methadone spent a higher median number of days in the hospital, although this difference was not significant when obstetric cases were excluded.</li> <li>Methadone patients were more likely to have behavioral problems, to discharge themselves against medical advice, and to transfer to another hospital. Methadone patients also had longer hospital stays overall compared to non-methadone patients.</li> </ul>	<ul style="list-style-type: none"> <li>Pain assessments based on how often the word "pain" appears in a patient's ward notes.</li> <li>Unclear why some patients had methadone dose increased.</li> <li>Authors do not report the source of acute pain or types of surgery.</li> </ul>

Abbreviations: IV=intravenous; MAT = medication-assisted treatment; PCA = patient-controlled analgesia

## **Studies without control groups**

Additional evidence from 5 studies<sup>24,26-29,31</sup> that lacked control groups (1 case series and 4 case reports) provide information on conditions not covered by the cohort studies – especially emergency conditions – and provide more detailed descriptions of the timing, dosage, and sequence of acute pain management strategies. Table 3 provides an overview of these studies, including study characteristics, population, acute pain management strategies and key findings, and major limitations. Overall, these studies suggest that management of acute pain in emergency conditions may require some trial and error, as most studies attempted multiple strategies before achieving pain relief. These findings also support current clinical guidance that methadone should be continued in patients acute pain,<sup>27</sup> and that higher doses of opioids may be required in patients taking MAT to achieve pain relief<sup>26</sup> and provide one example of a case in which buprenorphine needed to be discontinued before adequate pain control was achieved.<sup>24</sup> However, because these studies examined small numbers of patients, rarely used measurement tools to assess outcomes, and are by design at high risk of both selection and reporting bias, they do not provide a strong foundation on which to guide clinical decision-making.

**Table 3. Findings from studies without control groups**

<b>Author, year</b>	<b>Study design Study size Duration</b>	<b>Population</b>	<b>Acute pain management strategies &amp; key findings</b>	<b>Major limitations</b>
Kornfeld, 2010 <sup>29</sup>	Case series N=5 2-9 days	Patients taking sublingual buprenorphine for chronic musculoskeletal pain for >1 year before major surgery	Pain management with opioids, bupivacaine, and/or ketamine in the intra-operative and postoperative period led to generally good pain control.	<ul style="list-style-type: none"> <li>- Risk of selection &amp; reporting bias.</li> <li>- Only a portion of patients in study had OUD and it is unclear which ones they were.</li> </ul>
Harrington, 2010 <sup>24</sup>	Case study N=1 6 days	30-year-old man with multi-system injuries from a motorcycle accident on buprenorphine	Initial treatment with full-agonist opiates could not be down-titrated without increasing pain. Buprenorphine was eventually removed, which helped to stabilize pain, improved mental status, and reduced agitation.	<ul style="list-style-type: none"> <li>- Risk of selection &amp; reporting bias</li> </ul>
Sartain, 2002 <sup>27</sup>	Case study N=1 34 days	25-year-old man on methadone treatment then slow-release morphine prior to a major trauma	Administration of PCA morphine, naproxen, MS contin, and ketamine did not help in alleviating initial pain or subsequent pain from surgeries. Morphine and ketamine were stopped and methadone was added, which resulted in pain relief.	<ul style="list-style-type: none"> <li>- Risk of selection &amp; reporting bias</li> </ul>
McCormick, 2013 <sup>26</sup>	Case study N=1 2 months	50-year-old man with acute thigh pain due to McArdle's Disease taking buprenorphine/ naloxone	Treatment with buprenorphine/naloxone required higher than expected doses of hydrocodone for pain relief.	<ul style="list-style-type: none"> <li>- Risk of selection &amp; reporting bias</li> <li>- Not clear if/when buprenorphine was discontinued or how pain was managed during the resultant fasciotomies to relieve compartment pressure.</li> </ul>
Tucker, 1990 <sup>28</sup>	Case study N=1 7 days	52-year-old man in a methadone maintenance program with abdominal pain who eventually underwent surgery on his appendix	Patient received morphine, then switched to acetaminophen with codeine and methadone until his discharge at 7 days.	<ul style="list-style-type: none"> <li>- Risk of selection &amp; reporting bias</li> <li>- Pain not reported</li> </ul>

Abbreviations: MAT = Medication-assisted treatment; OUD= opioid use disorder; PCA = patient-controlled analgesia

**KEY QUESTION 2: Do these benefits and harms vary by patient characteristics, such as MAT medication or type of acute pain (emergency condition vs planned surgery)?**

It is not possible to determine whether benefits and harms of acute pain management strategies vary by patient characteristics or type of acute pain due to the insufficiency in descriptions of the acute pain management strategies, including adjuvant analgesics. For example, in 3 studies<sup>23,25,26</sup> that included patients undergoing surgery who were taking methadone, detail was lacking on whether methadone was continued, whether the dosage stayed the same, increased, or decreased, and why those decisions were made. Without that information, it is impossible to know whether there were any differences in outcomes based on different management approaches.

## SUMMARY AND DISCUSSION

To our knowledge, this is the first evidence review focusing on acute pain management in patients with OUD on MAT. Because of the unique pharmacologic properties of methadone, buprenorphine/naloxone, and naltrexone, acute pain management in patients on MAT can be highly nuanced and dependent on the MAT medication used. Given the high prevalence of opioid misuse (11.4 million people or 4.2% of the population 12 and older reported misusing opioids in the past year<sup>32</sup>) and increasing use of MAT to manage patients with OUD, there is an urgent need for evidence-based strategies for managing acute pain in these patients.

Unfortunately, we identified limited evidence to address our questions, and our overall confidence in the effect of any specific strategy on the management of acute pain is low. Three retrospective studies support recent guidelines based on a structured consensus method<sup>14</sup> that continuing the use of MAT for patients undergoing major surgery may reduce overall opioid doses, that patients on MAT are opioid-tolerant and need higher doses of opioid agonists for effective pain control, and that discontinuing MAT can lead to patient disengagement from care. The best-conducted studies did not identify a benefit of discontinuing methadone or buprenorphine, with several studies suggesting that discontinuation or missed doses can result in patients experiencing more pain (measured directly as increased pain reports or indirectly as increased patient use of patient-controlled analgesia). Only one case study found that buprenorphine needed to be discontinued to achieve adequate pain control with full agonist opioids.<sup>24</sup> Therefore, our findings align with current guidelines which recommend continuing methadone during acute pain episodes and state that continuing buprenorphine is a reasonable approach for most patients with mild or moderate pain. Although guidelines state that discontinuing buprenorphine may be necessary in cases of severe pain, we did not identify studies supporting that statement except for one case study. Future research is needed to evaluate the effectiveness of adjuvant non-opioid and non-pharmacologic acute pain management strategies for patients with OUD taking methadone and buprenorphine, as well as the benefits and harms of adjusting the dose or timing of MAT (such as increasing doses or dividing doses). Future research is also urgently needed to evaluate effective acute pain management in patients with OUD on naltrexone.

## LIMITATIONS

### Primary study limitations

Primary studies in this review had several limitations that make it difficult to interpret and apply findings. First, there are no prospectively designed studies, which means that evidence is limited to information that researchers collected and aggregated from data sources not originally designed to address these questions. This practice is problematic because it means 1) researchers could introduce bias by selecting certain populations or outcomes that best support their hypothesis and 2) the data available (such as information collected from medical records) is not always the best suited to address the research question. This is most notable in patients' assessments in pain – some studies assessed pain through a scale, but others just noted how often a patient mentioned the word pain or gave a physicians' overall impression of a patient's pain, which does not sufficiently address the question of whether a patients' pain is being effectively managed. Second, there were considerable methodological limitations of the retrospectively designed studies that make it difficult to determine the *causality* connecting pain management

approaches to outcomes. For example, 2 studies with control groups<sup>23,25</sup> lacked detailed information on whether MAT was continued, whether the dosage stayed the same, increased, or decreased, and why those decisions were made. Without that information, it is difficult to know whether continuing MAT is a safe and effective approach towards managing pain in these patients. Furthermore, the fact that patient groups were different at baseline in all the retrospective cohort studies makes it difficult to determine whether findings are due to the *intervention*, or due to *confounders* such as patients physical and mental health status. This is especially problematic when the 2 groups being compared were so different (*ie*, patients on MAT vs not on MAT) that you would not expect to manage pain the same way, making it difficult to interpret data on the effects of different pain management strategies for each.

### Rapid review limitations

In addition to primary study limitations, there were limitations in our rapid review methodology. First, our search required that a study include the term “acute pain,” which may have missed studies in which it is assumed that the patient is in acute pain but is not described that way, such as studies that look at long-term outcomes for MAT patients that include a subset of patients that underwent surgery. However, we likely identified most of the studies that explicitly sought to examine strategies for management of acute pain in MAT patients. Second, our use of first-reviewer inclusion and data abstraction with second-reviewer checking may have resulted in missing eligible studies or study data. However, given that our results align with a recent guidelines, we likely identified most of the important data on this topic.

## GAPS AND FUTURE RESEARCH

There are several important gaps in the available literature that should be addressed by future research:

1. **Well-described studies (such as randomized controlled trials or cohort studies) examining specific acute pain management strategies:** We did not identify any studies that adequately described a specific pain management strategy and its effects on patient outcomes. Prospective studies are the best designed to allow for the deliberate recording of intervention elements that are important to clinicians deciding which treatment approach to take (such as the specific medication including MAT medications, other opioids, and non-opioid medications; dosage; timing and justification). Prospective studies would also allow for the randomization of patients into different interventions (*eg*, a structured pain management approach vs clinical judgement; or continuing buprenorphine with opioids as needed vs continuing buprenorphine with non-opioid analgesics as needed). Randomizing patients into different groups would provide the most rigorous, defensible answers to what pain management approaches are safe and effective; however, even a well-described, well-controlled cohort study that adjusts for differences in patient groups at baseline would be a useful step forward.
2. **Management of patients taking naltrexone:** We did not identify any evidence on the management of patients taking naltrexone, an opioid antagonist. Acute pain is especially challenging to manage in these patients as naltrexone blocks the effects of opioids. Research on management of acute pain in these patients is urgently needed.

3. **Measurement of patient outcomes:** Of the best available evidence, only 1 study<sup>23</sup> used validated tools to measure quality of life or functionality. All other studies provided limited information on how outcomes were measured, with many commenting that outcomes were retrospectively collected from medical records. We identified no studies that rigorously evaluated patient satisfaction, healthcare utilization (other than length of hospitalization), opioid withdrawal symptoms, substance use relapse, opioid overdose, or suicide ideation or suicidal self-directed violence. Furthermore, with few exceptions, studies ended when patients were discharged, so it is impossible to determine what the long-term effects of pain management strategies were on patients' health, especially the impact of administering opioids on patients' likelihood of relapse or overdose.

## CONCLUSIONS

This review confirmed a lack of rigorous evidence on the management of acute pain in patients taking methadone, buprenorphine, or naltrexone. Although it has important limitations , the best available evidence suggests that continuing methadone or buprenorphine during an acute pain episode is a clinically sound approach for most patients taking these medications for OUD. More research is urgently needed that evaluates patient outcomes following well-characterized acute pain management interventions including MAT dose and schedule adjustments and use of non-opioid pain management strategies.

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In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting 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.

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### **Operational Partners**

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend Technical Expert Panel (TEP) participants; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

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### **Peer Reviewers**

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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