

# Systematic Review on Treatments for Acute Pain: Surveillance Report 1

**Literature Update Period: August 2020 through October 2021**

## Background and Purpose

This is the first update for the 2020 report *Treatments for Acute Pain: A Systematic Review* (<https://effectivehealthcare.ahrq.gov/products/treatments-acute-pain/research>),<sup>1</sup> covering the period August 2020 through October 2021. The 2020 report addressed benefits and harms of opioid, nonopioid pharmacologic, and nonpharmacologic treatments for specific types of acute pain (low back pain, neck pain, other musculoskeletal pain, neuropathic pain, postoperative pain [excluding inpatient management of pain after major surgical procedures], dental pain, pain due to kidney stones, and pain due to sickle cell disease). Given the clinical and public health importance of this topic, it is important to identify new evidence that could impact practice or policy. The purpose of this update is to identify new evidence published since the 2020 report and to determine how the new evidence impacts its findings. Subsequent updates are planned for February 2022 (based on evidence published from November 2021 to January 2022) and May 2022 (based on evidence published from February to April 2022).

## Scope

The scope and eligibility criteria established at the time of the original report<sup>1</sup> were utilized for this surveillance report; no changes were made. The report addressed the following acute pain conditions:

- Acute back pain (including back pain with radiculopathy) (Key Question [KQ] 1)
- Acute neck pain (including neck pain with radiculopathy) (KQ 2)
- Musculoskeletal pain not otherwise included in KQ 1 or KQ 2 (including fractures) (KQ 3)
- Peripheral neuropathic pain (related to herpes zoster and trigeminal neuralgia) (KQ 4)
- Postoperative pain (excluding inpatient management of pain following major surgical procedures) (KQ 5)
- Dental pain (KQ 6)
- Kidney stones (including inpatient management) (KQ 7)
- Sickle cell crisis (episodic pain) (KQ 8)

For each of these acute pain conditions, the report addressed the effectiveness and comparative effectiveness (benefits and harms) for the following comparisons:

- Opioid therapy versus nonopioid pharmacologic therapy (acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs], skeletal muscle relaxants, benzodiazepines, antidepressants, anticonvulsants, cannabis) or nonpharmacologic therapy (exercise, cognitive behavioral therapy, meditation, relaxation, music therapy, virtual reality, acupuncture, massage, manipulation/mobilization, physical modalities).



- Nonopioid pharmacologic therapy versus other nonopioid pharmacologic treatments or nonpharmacologic therapy.
- Nonpharmacologic therapy versus inactive treatments or usual care.

The report also addressed how benefits and harms varied according to demographic, clinical, and medication factors; effects of prescribing opioid therapy for acute pain conditions on short- and long-term opioid use; and factors associated with opioid prescribing for acute pain conditions. The full protocol for the original report, including detailed inclusion criteria using the PICOTS (populations, interventions, comparisons, outcomes, timing, settings) framework (<https://www.ncbi.nlm.nih.gov/books/NBK566503/table/appb.tab1/?report=objectonly>) and full KQs (<https://www.ncbi.nlm.nih.gov/books/NBK566501/#ch3.s2>), is shown in the appendixes and is also available on the Agency for Healthcare Research and Quality website (<https://effectivehealthcare.ahrq.gov/products/treatments-acute-pain/protocol>) and on the PROSPERO systematic reviews registry (CRD42020165677).

## Methods

Update searches were conducted to identify evidence published from August 2020 through October 2021. Search strategies from the original report were utilized<sup>1</sup> and we searched the same databases as in the original report (Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews). In addition, to capture articles not yet indexed in MEDLINE, we supplemented the original search strategies with an optimized (text-word only) search<sup>2</sup> in pre-MEDLINE to identify studies not yet indexed with Medical Subject Headings (MeSH). As in the original report, searches on electronic databases were for studies in English and supplemented by review of reference lists of relevant articles. Search strategies are available in [Appendix A](#). Randomized controlled trials were included for all KQs. For opioid prescribing and long-term use, accuracy and effectiveness of risk prediction instruments, and factors influencing prescribing, controlled observational studies (cohort, case-control, and before-after studies) were also included.

For this update, one investigator screened all citations identified through searches for eligibility for full-text review. (KQs and inclusion criteria are available in [Appendix B](#).) In addition, to increase efficiency of abstract review, we utilized the artificial intelligence function in Distiller SR (DistillerSR AI) in conjunction with a second investigator to assist in conducting dual review. DistillerSR AI utilizes Natural Language Processing to train itself and make inclusion predictions using manually reviewed references. For this update, DistillerSR AI was trained using 2,132 abstracts identified in the initial update search and manually reviewed by one investigator. Following training, DistillerSR AI assigned a certainty score for each citation, indicating how likely it was to qualify for inclusion (from 0.0 to 1.0 probability of inclusion). DistillerSR AI assigned a certainty score to all citations; the second investigator performed dual review on all studies assigned a DistillerSR AI certainty score of 0.40 or more. Any citation identified as potentially eligible by either reviewer underwent full-text review to determine final eligibility.

We utilized the same methods for data abstraction and quality assessment as the original report. We assessed the quality of individual controlled trials using the approach recommended in the chapter Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, developed by the Agency for Healthcare Research and Quality,<sup>3</sup> in conjunction with criteria and

methods developed by the Cochrane Back Review Group.<sup>4</sup> We excluded combination treatments except for an opioid plus NSAIDs or acetaminophen, as these combinations are commonly used in clinical practice and frequently evaluated in clinical trials. When possible, we stratified comparisons according to whether an opioid was administered alone or in combination with an NSAID or acetaminophen. We separately evaluated single dose trials and multidose trials (i.e., trials that evaluated a course of more than one dose of therapy).

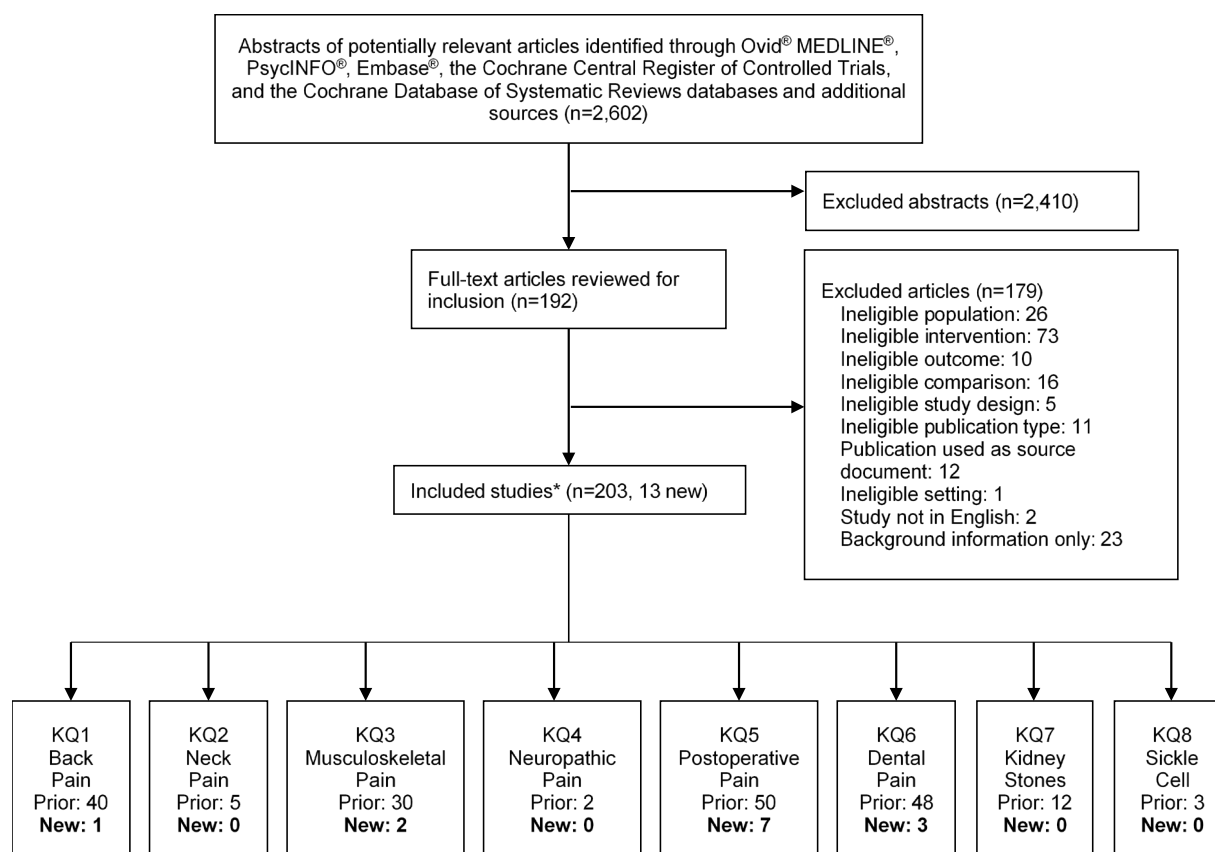
The decision to update meta-analyses from the original report was based on the number and sample sizes of new studies eligible for meta-analysis (meta-analysis performed if new evidence was large relative to the studies in the original meta-analysis); consistency in findings between the new studies and the original meta-analysis (meta-analysis performed if findings from new evidence appear inconsistent and new studies were appropriate for pooling based on similarity in populations, interventions, and comparisons, in order to determine whether new studies impact conclusions); or whether new evidence could impact the strength of evidence (meta-analysis performed if the strength of evidence based on the original meta-analysis was low or insufficient and new evidence could increase the strength of evidence due to increased precision, high quality, or other factors). The strength of evidence was based on the totality of evidence (evidence in the original report plus new evidence) and determined using the methods described in the original report. We highlighted any changes in the strength of evidence assessments.

A list of included studies identified for this update is provided in [Appendix C](#) and a list of articles excluded at full text, along with reasons for exclusion, is available in [Appendix D](#). Evidence tables providing data from included studies are available in [Appendix E](#), and quality assessments for each study are shown in [Appendix F](#).

## Results

The update search yielded 2,602 citations, and identified 13 new eligible studies (all randomized controlled trials [RCTs]) (Figure 1). One trial was conducted in patients with acute low back pain (acupuncture vs. usual care);<sup>5</sup> two trials in patients with other musculoskeletal pain (1 trial evaluated opioid vs. acetaminophen<sup>6</sup> and 1 trial evaluated topical ibuprofen vs. topical capsaicin<sup>7</sup>); seven trials in patients with postoperative pain (1 trial evaluated an opioid vs. NSAID,<sup>8</sup> 1 trial an opioid vs. acetaminophen,<sup>9</sup> 1 trial an opioid vs. mixed agent,<sup>10</sup> 3 trials cold therapy vs. usual care,<sup>11-13</sup> and 1 trial music therapy vs. no music therapy<sup>14</sup>); and three trials in patients with dental pain (2 trials evaluated an opioid vs. NSAID,<sup>15,16</sup> 2 trials evaluated an opioid vs. acetaminophen,<sup>16,17</sup> and 1 trial an NSAID vs. acetaminophen<sup>16</sup>). For acute musculoskeletal pain, the new trials evaluated comparisons for which there was no evidence in the original report; otherwise, the new evidence addressed comparisons with at least some prior evidence. No new eligible studies were identified for acute neck pain, peripheral neuropathic pain, kidney stone pain, or sickle cell pain; effects of opioid use versus non-use for specific pain conditions and likelihood of short- or long-term use; or factors associated with opioid prescribing for specific acute pain conditions. Two trials were rated good quality,<sup>6,15</sup> 10 trials were rated fair quality,<sup>5,8-14,16,17</sup> and 1 trial was rated poor quality ([Appendix F](#)).<sup>7</sup> Methodological limitations in the fair-quality trials included failure to report randomization or allocation concealment methods, open-label design, or high attrition. The poor-quality trial<sup>7</sup> had high attrition and did not conduct intention-to-treat analysis.

**Figure 1. Literature flow diagram**



Abbreviations: KQ = Key Question

\*Additional sources include prior reports, reference lists of relevant articles, systematic reviews, etc.

## Summary of Findings

- Thirteen new RCTs were identified for this update. Two of the new trials (noted below) evaluated comparisons not previously evaluated for acute musculoskeletal pain; otherwise, the trials evaluated comparisons for specific acute pain conditions with at least some prior evidence.

### KQ1: Acute Back Pain

- One new trial found no difference between traditional Chinese acupuncture versus usual care in mean pain intensity, functional status, or quality of life at 2 to 4 weeks; this was inconsistent with one trial included in the prior report that found acupuncture associated with beneficial effects on pain and function versus usual care. The original report also included trials of Chinese acupuncture versus sham acupuncture that were inconsistent with regard to effects on pain.

### KQ 2: Acute Neck Pain

- No new evidence was found.

### **KQ3: Musculoskeletal Pain Not Included in KQ1 or KQ2**

- One new trial found an opioid plus acetaminophen associated with increased likelihood of pain improvement and small decrease in pain intensity at 2 hours versus acetaminophen, although opioids were associated with increased likelihood of any adverse event and drowsiness. No study evaluated this comparison in the original report.
- One new trial evaluated topical ibuprofen versus topical capsaicin but was insufficient to assess comparative effectiveness due to poor quality. No study evaluated this comparison in the original report.

### **KQ4: Peripheral Neuropathic Pain**

- No new evidence was found.

### **KQ5: Postoperative Pain**

- One new trial found a multidose course of an opioid plus acetaminophen associated with a small increase in pain intensity versus an NSAID at day 1, with no difference at day 7. The new trial was too small to resolve the inconsistency observed in the original report for this outcome.
- One new trial found a multidose course of an opioid plus acetaminophen associated with no difference versus acetaminophen in pain intensity at day 7; the original report included three trials that each evaluated pain at different time points (none at 1 to <2 weeks) and reported inconsistent results.
- One new trial found no statistically significant differences between an opioid agonist (oxycodone) versus a mixed agent (tapentadol) in pain on mobilization or at rest at days 1 to 7, day 14, or week 8; these findings were consistent with one trial included in the original report.
- One new trial found continuous cooling for 7 days associated with moderate decrease in pain intensity versus usual care at 1 day to 1 week, with no differences at 2 or 6 weeks in pain intensity, function, or quality of life; two new trials reported somewhat inconsistent results for a cold pack for 6 to 24 hours versus usual care in pain intensity at less than 1 day to 1 day. These results are somewhat inconsistent with the original report, which found no differences between cold therapy versus sham therapy in pain intensity and other outcomes at less than 1 week, 2 to less than 4 weeks, or 4 weeks or more, but results are difficult to interpret due to potential differences in the comparators (sham or usual care).
- One new trial found music therapy associated with a small decrease versus no music therapy in pain intensity on day 1 that was not statistically significant; the difference was larger (moderate) and statistically significant on day 4 (3.18 vs. 4.40,  $p=0.006$ ). The findings at day 4 were consistent with the original report.

### **KQ6: Dental Pain**

- One new trial found similar effects of a multidose course of an opioid plus NSAID versus an NSAID on pain intensity at 6 and 24 hours in patients with postoperative dental pain; these findings were consistent with the original report. Although the new trial found the opioid was associated with increased likelihood of a positive global assessment versus the NSAID, an updated meta-analysis that included this trial was consistent with the original report in finding no difference on this outcome.

- One new trial found similar effects of a multidose course of an opioid alone versus NSAID on pain intensity and likelihood of a positive global assessment in patients with postoperative dental pain; findings were consistent with one trial included in the original report.
- Two new trials found opioid-containing regimens were associated with increased likelihood of harms versus an NSAID alone, including any adverse event, nausea, vomiting, dizziness, and drowsiness; these findings were consistent with the original report.
- One new trial found no difference in pain intensity between a multidose course of an opioid plus acetaminophen versus acetaminophen in patients with acute nonoperative dental pain at less than 1 day or 1 day to less than 1 week, and no difference in rescue analgesic use. This finding was consistent with one small trial included in the original report.
- One new trial found a single dose of an opioid plus acetaminophen associated with small to moderate decrease in pain intensity versus acetaminophen at 4 to 48 hours in patients with acute nonoperative dental pain; statistical significance was not reported, and the new trial was too small to resolve the inconsistency reported for this comparison and outcome in the original report.
- Two new trials found an opioid plus acetaminophen associated with increased likelihood of drowsiness, dizziness, nausea, and vomiting versus acetaminophen; these findings were consistent with the original report.
- One new trial found an NSAID associated with a small decrease in pain intensity at less than 1 day versus acetaminophen; these findings were consistent with the original report.

## KQ7: Kidney Stones

- No new evidence was found.

## KQ8: Sickle Cell Crisis

- No new evidence was found.

## Summary of New Evidence

Table 1 provides the conclusions from the 2020 report and the new findings from studies identified in this update report. Table 1 focuses on KQs and comparisons/outcomes with new evidence; the full strength of evidence (SOE) table is available in the full report (<https://www.ncbi.nlm.nih.gov/books/NBK566513/>).

**Table 1. Summary of conclusions and assessments informed by new evidence**

Key Question	Conclusions From 2020 Report	Findings From Update	Assessment
<b>1 (Low back pain): Traditional Chinese acupuncture vs. sham or usual care</b>	<b>Pain at 2 to &lt;4 weeks: decreased</b> (SOE: Low, based on 1 RCT) with acupuncture vs. non- penetrating sham or usual care but not needle sham	1 new RCT (n=167) found no difference between traditional Chinese acupuncture vs. usual care in pain, functional status, or quality of life at 2 to 4 weeks.	SOE downgraded to insufficient due to inconsistency

Key Question	Conclusions From 2020 Report	Findings From Update	Assessment
<b>3 (Musculoskeletal pain): Opioid plus acetaminophen vs. acetaminophen</b>	No evidence.	One new RCT (n=154) found an opioid associated with small decrease in pain but increased likelihood of adverse events and drowsiness.	New SOE (no prior evidence): Low for pain and adverse events
<b>3 (Musculoskeletal pain): Topical ibuprofen vs. capsaicin</b>	No evidence.	One new RCT (n=119) insufficient due to poor quality.	New SOE (no prior evidence): Insufficient
<b>5 (Postoperative pain): Opioid vs. NSAID, multidose</b>	<b>Pain, 1 day to &lt;1 week: Inconsistent findings</b> (SOE: insufficient, based on 4 RCTs).  <b>Rescue medication use, 1 day to &lt;1 week: RR 1.22 to 2.04</b> (SOE: moderate, based on 4 RCTs)	One new RCT (n=70) found opioid associated with a small increase in pain at day 1, with no difference at day 7.	Unchanged
<b>5 (Postoperative pain): Opioid vs. acetaminophen, multidose</b>	<b>Evidence limited and inconsistent for pain and other outcomes;</b> each RCT evaluated outcomes at a different time point (<1 day, 1 day to <1 week, and 2 to <4 weeks) (SOE: insufficient, based on 3 RCTs)	One new RCT (n=80) found no difference between an opioid vs. acetaminophen in pain at day 7.	Unchanged
<b>5 (Postoperative pain): Opioid vs. mixed agent</b>	<b>Pain: No difference</b> at <1 day (1 RCT, SOE: low), 1 day to <1 week (6 RCTs, SOE: moderate), or 1 to <2 weeks (1 RCT, SOE: low)	One new RCT (n=91) found no difference between an opioid vs. tapentadol in pain at 1 day to <1 week, 1 to <2 weeks, or ≥4 weeks.	SOE unchanged at <1 day and at 1 day to <1 week, upgraded to moderate for 1 to <2 weeks, and assessed as low for ≥4 weeks
<b>5 (Postoperative pain): Cold therapy vs. sham or no cold therapy</b>	<b>Pain, &lt;1 week: No difference</b> (SOE: low, based on 3 RCTs)  <b>Pain, function, QoL, 2 to &lt;4 weeks and ≥4 weeks: No differences</b> (SOE: low, based on 1 RCT)	One new RCT (n=100) found continuous cooling for 7 days associated with moderate decrease in pain versus usual care at 1 day to <1 week, with no differences at 1 to <2 weeks or ≥4 weeks in pain intensity, function, or QoL; two new RCTs (n=100 and 137) reported inconsistent results for a cold pack vs. usual care in pain intensity at <1 day to 1 day.	SOE unchanged for cold therapy vs. sham therapy (no new RCTs)  SOE insufficient (based on 2 new RCTs) for cold therapy vs. usual care and pain intensity at <1 day due to inconsistency; low (based on 1 new RCT) for moderate benefit at 1 day to <1 week; and low for no difference at 1 to <2 weeks and ≥4 weeks
<b>5 (Postoperative pain): Music therapy vs. no music therapy</b>	<b>Pain, &lt;1 day and 1 day to &lt;1 week: Small to moderate decrease</b> (SOE: low, based on 2 RCTs)	One new RCT (n=47) found music therapy associated with a small decrease in pain intensity on day 1 that was not statistically significant; the difference was moderate and statistically significant on day 4.	SOE at 1 day to <1 week upgraded to moderate

Key Question	Conclusions From 2020 Report	Findings From Update	Assessment
<b>6 (Dental pain): Opioid plus acetaminophen or NSAID vs. NSAID, multidose</b>	<b>Pain, 1 day to &lt;1 week: No difference</b> (SOE: low, based on 3 RCTs)  <b>Global improvement: No difference</b> (SOE: low, based on 2 RCTs)	One new RCT (n=620) found similar effects of a multidose course of an opioid plus NSAID vs. an NSAID on pain intensity at 6 and 24 hours and increased likelihood of a positive global assessment.	Unchanged (an updated meta-analysis for likelihood of positive global assessment again found no difference)
<b>6 (Dental pain): Opioid vs. NSAID, multidose</b>	<b>Pain, &lt;1 day and 1 day to &lt;1 week: no difference</b> (SOE: insufficient, based on 1 RCT)	One new RCT (n=412) found similar effects of a multidose course of an opioid alone vs. NSAID on pain intensity and likelihood of a positive global assessment in patients with postoperative dental pain.	SOE upgraded to low
<b>6 (Dental pain): Opioid (with or without acetaminophen or NSAID) vs. NSAID</b>	<b>Opioid increased risk of: Any adverse event:</b> RR 1.72 (95% CI 1.29 to 2.28) <b>Nausea:</b> RR 2.72 (95% CI 1.84 to 4.01) <b>Dizziness:</b> RR 2.97 (95% CI 1.59 to 5.54) <b>Drowsiness:</b> RR 1.76 (95% CI 1.00 to 3.10) (SOE: moderate, based on 9 to 12 RCTs)	Two new RCTs (n=825 and 60) found opioids associated with increased risk of any adverse events, nausea, dizziness, and drowsiness.	Unchanged
<b>6 (Dental pain): Opioid plus acetaminophen vs. acetaminophen, multidose course</b>	<b>Pain, &lt;1 day:</b> One very small (n=20) RCT found opioid associated with large improvement (SOE: insufficient)	One new RCT (n=39) found no differences in pain or rescue analgesic use among patients with nonoperative dental pain.	Unchanged (remained insufficient due to imprecision and inconsistency)
<b>6 (Dental pain): Opioid plus acetaminophen vs. acetaminophen, single dose</b>	<b>Pain, &lt;1 day: Inconsistent effect</b> (SOE: moderate, based on 11 RCTs)  <b>Rescue or repeat medication use, &lt;1 day: RR 0.81 (95% CI 0.56 to 0.97)</b> (SOE: moderate, based on 7 RCTs)	One new RCT (n=60) found an opioid associated with moderate to large decrease in pain intensity versus the NSAID at <1 day and 1 day to <1 week, although statistical significance was not reported.	Unchanged
<b>6 (Dental pain): Opioid plus acetaminophen vs. acetaminophen</b>	<b>Opioids increased risk of: Any adverse event:</b> RR 1.43 (95% CI 0.87 to 2.37) <b>Nausea:</b> RR 1.55 (95% CI 0.75 to 3.18) <b>Drowsiness:</b> RR 2.03 (95% CI 0.70 to 5.93) <b>Dizziness:</b> RR 2.49 (95% CI 0.66 to 9.49) (SOE: low, based on 4 to 8 RCTs)	Two new RCTs (n=39 and 60) found opioids associated with increased risk of any adverse events (2 RCTs, 26.6% vs. 0% and 35% vs. 16%), dizziness (1 RCT, 15% vs. 5%), nausea (1 RCT, 40% vs. 11%), and vomiting (1 RCT, 10% vs. 0%).	Unchanged



Key Question	Conclusions From 2020 Report	Findings From Update	Assessment
<b>6 (Dental pain): NSAID vs. acetaminophen</b>	<b>Pain intensity, rescue or repeat medication use: Moderate to large decrease</b> <b>Rescue or repeat medication use: decrease</b> (RR 0.64, 95% CI 0.58 to 0.71) (SOE: moderate, based on 11 to 15 RCTs)	One new RCT (n=60) found an NSAID associated with small decrease in pain at <1 day (p-value not reported).	Unchanged

Abbreviations: CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug; QoL = quality of life; RCT = randomized controlled trial; RR = relative risk; SOE = strength of evidence

## Evidence Details

### Key Question 1: Acute Back Pain

#### Acupuncture Versus Usual Care

The original report included one trial that found traditional Chinese acupuncture associated with decreased likelihood of persistent low back pain versus usual care (46.9% vs. 72.1%, relative risk [RR] 0.65, 95% confidence interval [CI] 0.48 to 0.88) and increased likelihood of functional improvement (74% vs. 44%, RR 1.66, 95% CI 1.23 to 2.24) at 2 to 4 weeks, but there were no differences between acupuncture and usual care on these outcomes at 3 months (SOE: low). The original report also included two trials that compared acupuncture versus different types of sham acupuncture (penetrating or non-penetrating), with somewhat inconsistent results for pain and function (SOE: low).

One new fair-quality trial (n=167) was inconsistent with the prior trial, as it found no differences between traditional Chinese acupuncture versus usual care in mean pain intensity, functional status, or quality of life at 2 to 4 weeks (at 4 weeks, mean pain intensity 1.8 vs. 1.7, mean Roland Morris Disability Questionnaire score 3 vs. 4; no difference in EQ-5D-3L [data not provided]<sup>5</sup>). Estimates for changes in opioid medication use were imprecise, and rates of adverse events were similar between groups. As in the original report, the new trial reported no serious adverse events.

### Key Question 2: Acute Neck Pain

We did not identify any new trials evaluating interventions for acute neck pain.

### Key Question 3: Musculoskeletal Pain Not in KQ1 or KQ2

#### Opioid Plus Acetaminophen Versus Acetaminophen

The original report included no trials of an opioid versus acetaminophen for acute musculoskeletal pain. One new good-quality trial (n=154) compared a single dose of oxycodone 10 mg/acetaminophen 650 mg versus acetaminophen 650 mg in patients with musculoskeletal pain (upper extremities, lower extremities, neck or back, or thorax) who experienced insufficient pain relief after a single dose of ibuprofen 600 mg.<sup>6</sup> It found the opioid associated with decreased likelihood of pain improvement less than 1.3 points (the predefined threshold for a minimum clinically important difference) on a 0 to 10 scale (14% vs. 32%, RR 0.44, 95% CI 0.23 to 0.83) and small decrease in pain intensity at 2 hours (4.4 vs. 5.2, difference -0.8, 95% CI -1.7 to 0.0).

There was no difference in the proportion of patients who reported that their medication controlled pain (78% vs. 69%, RR 1.13, 95% CI 0.93 to 1.37). Opioids were associated with increased likelihood of any adverse event (34% vs. 9%, RR 3.62, 95% CI 1.67 to 7.82) and drowsiness (22% vs. 8.1%, RR 2.76, 95% CI 1.15 to 6.61).

### **Topical Ibuprofen Versus Topical Capsaicin**

The original report included no trials of topical ibuprofen versus topical capsaicin. One new trial (n=119) compared topical ibuprofen 5% versus topical capsaicin 0.5% three times daily for 3 days in patients with musculoskeletal pain due to blunt upper extremity trauma with no fracture or dislocation.<sup>7</sup> It was rated poor quality due to high attrition and no intention-to-treat analysis. There was no difference between topical ibuprofen versus topical capsaicin in pain intensity at 2 hours, though there was a small, non-statistically significant difference favoring topical capsaicin at 24 hours (3.23 vs. 2.69 on a 0 to 10 scale, p=0.06) and a moderate, statistically significant difference for topical capsaicin at 72 hours (2.68 vs. 1.53 at 72 hours, p=0.0004). Topical ibuprofen was also associated with decreased likelihood of pain reduction more than 50 percent at 72 hours (60% vs. 84.7%, RR 0.71, 95% CI 0.56 to 0.89). Topical ibuprofen was associated with decreased likelihood of any adverse event, although the estimate was imprecise (10.0% vs. 18.6%, RR 0.54, 95% CI 0.21 to 1.36); there was no difference in the likelihood of transient skin reactions.

### **Key Question 4: Peripheral Neuropathic Pain**

We did not identify any new trials evaluating interventions for peripheral neuropathic pain.

### **Key Question 5: Postoperative Pain**

#### **Opioid Versus NSAID**

The original report found no difference between a single dose of an opioid versus NSAID in pain or rescue medication use at less than 1 day, based on two trials (SOE: low). A multidose course of opioids was associated with increased likelihood of repeat or rescue medication use at 1 day to less than 1 week versus NSAIDs (4 trials, RRs ranged from 1.22 to 2.04), and effects on pain intensity were inconsistent (SOE: moderate for repeat or rescue medication use, insufficient for pain intensity). At 1 week, one trial found an opioid plus NSAID associated with increased rescue medication use and higher, but small and statistically non-significant, increase in pain intensity versus ibuprofen (SOE: low for rescue medication use, insufficient for pain intensity).

One new trial (n=70) compared a multidose course of hydrocodone 5 mg/acetaminophen 325 mg versus ibuprofen 400 mg every 4 to 6 hours as needed in patients who underwent rhinoplasty.<sup>8</sup> Opioids were associated with a small increase in pain intensity at day 1 (2.46 vs. 1.84 on a 0 to 10 scale, p=0.01), with no difference at day 7 (3.14 vs. 3.29, p=0.17). Rescue medication use was not reported. No adverse events were reported in the NSAID arm; other harms were not reported.

#### **Opioid Versus Acetaminophen**

The original report included one trial that found no difference in pain intensity between a single dose of an opioid versus acetaminophen at less than 1 day and no difference in need for re-medication, based on one trial (SOE: low). Evidence on the effects of a multidose course of an opioid versus acetaminophen on pain intensity and other outcomes was limited and inconsistent;

each trial evaluated a different time point (<1 day, 1 day to <1 week, or 2 to <4 weeks) (SOE: insufficient). Opioids were associated with increased risk of withdrawal due to severe nausea and vomiting versus acetaminophen in one trial and increased risk of withdrawal due to any adverse event in two trials (SOE: low).

One new trial (n=80) compared a multidose course of oxycodone 5 mg/acetaminophen 325 mg 1-2 tabs versus acetaminophen 650 mg every 6 hours as needed in patients who underwent hip arthroscopy.<sup>9</sup> There were no differences between the opioid versus acetaminophen in pain intensity at 1, 4, and 7 days; the proportion of patients who reported satisfaction with pain relief was very similar between groups (90% vs. 88%). No adverse events were reported.

## **Opioid Versus Mixed Agent**

The original report included one trial that found no difference between an opioid agonist versus mixed agent in pain at less than 1 day (1 trial), 1 day to less than 1 week (6 trials), or 1 to less than 2 weeks (1 trial) (SOE: low to moderate).

One new trial (n=91) compared the opioid agonist oxycodone (10 mg controlled release) versus the mixed agent tapentadol (50 mg extended release) twice daily in patients who underwent total knee arthroplasty.<sup>10</sup> There were no statistically significant differences between oxycodone versus tapentadol in pain on mobilization or at rest at days 1 to 7, day 14, or week 8. Oxycodone was associated with a lower likelihood of withdrawal due to adverse events, but the estimate was imprecise (4% vs. 17%, RR 0.26, 95% CI 0.57 to 1.14).

## **Cold Therapy Versus Sham or No Cold Therapy**

The original report found no difference between cold therapy versus sham therapy in pain intensity at 1 day to <1 week, based on three fair-quality trials (SOE: low). There was also no difference between cold therapy versus sham therapy in pain intensity, function, or quality of life at 2 to less than 4 weeks or 4 weeks or more, based on one good quality trial, although cold therapy was associated with decreased pain medication use in the first 4 days (SOE: low). Seven poor-quality trials identified for the original report did not contribute to the SOE assessments. In the fair- and good-quality trials, the cold therapy intervention varied from an ice pack for 20 minutes twice daily to continuous application using a circulating device for 7 days; in the trials, patients had undergone anterior cruciate ligament reconstruction or total knee arthroplasty.

Three new fair-quality trials (n=100, 100, and 137) evaluated cold therapy versus usual care for postoperative pain; no new trial compared cold therapy versus sham therapy. Cold therapy consisted of continuous application via a cooling brace with pre-specified temperatures controlled by computer (1 trial<sup>12</sup>) or 6 to 24 hours of a cold pack (2 trials<sup>11,13</sup>). The surgical procedure was total knee arthroplasty in one trial,<sup>12</sup> cesarean section in one trial,<sup>13</sup> and laparoscopic hysterectomy in one trial.<sup>11</sup>

One new (n=100) trial compared cold therapy (cooling brace at specified temperatures from day of surgery to postoperative day 7 three times daily) versus usual care following total knee arthroplasty.<sup>12</sup> At 7 days, cold therapy was associated with moderate decrease in pain intensity at rest (1.8 vs. 2.8 on a 0 to 10 scale,  $p<0.05$ ) and while loading (2.9 vs. 4.0,  $p<0.05$ ); there were no statistically significant differences at 2 or 6 weeks on these outcomes. There were no differences in function or quality of life based on the Knee Injury and Osteoarthritis Outcome Score at 2 or 6 weeks. Cold therapy was associated with reduced use of oxycodone 5 mg at day 1 (18% vs. 52%) and day 6 (11% vs. 41%), with a smaller and non-statistically significant difference at day 7 (11% vs. 24%). No serious adverse events or withdrawal due to adverse events were reported.

The other two new trials of cold packs versus usual care reported somewhat inconsistent results,<sup>11,13</sup> and results are difficult to interpret due to differences in the interventions, timing of follow-up, and populations; in addition, the use of a usual care comparator (rather than sham therapy) makes it difficult to compare results against the trials in the original report. In one trial (n=137), there was no difference between a cold pack versus usual care following laparoscopic hysterectomy on the Brief Pain Inventory pain severity (median 3.0 vs. 3.3 on a 0 to 10 scale, p=0.80) or pain interference (median 2.1 vs. 2.8, p=0.36) at 4 hours.<sup>11</sup> The other trial (n=100), which evaluated patients following cesarean section, found a cold pack associated with large decrease in pain intensity versus usual care at 6 to 24 hours (differences ranged from 2.2 to 3.7 points on a 0 to 10 scale) and decreased likelihood of pain 4 or more on a 0 to 10 scale at 24 hours (6% vs. 38%, p<0.001<sup>13</sup>). One of the trials<sup>11</sup> reported a similar rate of any adverse event (11.6% vs. 13.2%), and the other trial<sup>13</sup> reported no postoperative complications of adverse events from cold compression.

## **Music Therapy Versus No Music Therapy**

The original report found music therapy was associated with moderate decrease in pain intensity versus no music therapy at less than 1 day (1 trial, hernia repair) and small to moderate decrease in pain intensity at 1 day to less than 1 week (1 trial, knee arthroplasty) (SOE: low).

One new, fair-quality trial (n=47) compared music therapy versus no therapy following knee or hip arthroplasty.<sup>14</sup> Music therapy was administered 30 minutes three times daily postoperatively in the hospital and for 2 days post-discharge. Music therapy was associated with a small decrease in pain intensity on day 1 that was not statistically significant (5.05 vs. 5.67 on a 0 to 10 scale, p=0.21); however, the difference was larger (moderate) and statistically significant on day 4 (3.18 vs. 4.40, p=0.006). There was no difference between groups in opioid use. Harms were not reported.

## **Key Question 6: Dental Pain**

### **Opioid Versus NSAID**

The original report found a single dose of an opioid plus acetaminophen or NSAID associated with small to moderate increase in pain intensity versus an NSAID at less than 1 day (12 trials), increased likelihood of rescue or repeat medication use (9 trials, RR 1.35, 95% CI 1.23 to 1.48), and decreased likelihood of global improvement (5 trials, RR 0.64, 95% CI 0.53 to 0.76) (SOE: low for pain intensity and global improvement, moderate for rescue or repeat medication use). There was no difference between a multidose course of therapy with an opioid plus acetaminophen or an NSAID versus an NSAID alone in pain intensity at 1 day to less than 1 week (3 trials) or likelihood of global improvement (2 trials, RR 1.15, 95% CI 0.52 to 2.57) (SOE: low). There was insufficient evidence to determine effects of a single dose of an opioid alone versus NSAID on pain intensity, due to inconsistent results from six trials; only one trial evaluated a multidose course of an opioid alone versus NSAID (SOE: insufficient). Opioids were associated with increased likelihood of any adverse event (11 trials, pooled RR 1.72, 95% CI 1.29 to 2.28), nausea (12 trials, pooled RR 2.72, 95% CI 1.84 to 4.01), dizziness (10 trials, pooled RR 2.97, 95% CI 1.59 to 5.54), and drowsiness (9 trials, pooled RR 1.76, 95% CI 1.00 to 3.10) versus an NSAID alone (SOE: moderate). Most trials in the original report evaluated patients with acute postoperative dental pain (most commonly, third molar extraction). In the original report, meta-analysis was not performed for mean pain intensity because results at

specific time points were estimated in most trials from figures, and standard deviations were not reported; sums of pain intensity differences were not pooled because methods of calculation varied (pain scales utilized and number and timing of assessments).

Two new trials evaluated opioids versus NSAIDs for acute dental pain.<sup>15,16</sup> The trials differed in terms of opioid dosing (single dose or multidose) and type of dental pain (postoperative versus non-surgical). Both trials evaluated an opioid in combination with an NSAID or acetaminophen; one<sup>15</sup> of the trials also evaluated an opioid alone.

One new, good-quality trial (n=825) compared a multidose (3 doses) course of therapy of three different opioid regimens (tramadol 25 mg/diclofenac 25mg, tramadol 50 mg/diclofenac 50 mg, or tramadol 50 mg) versus an NSAID (diclofenac) in persons undergoing third molar extraction.<sup>15</sup> It found both combination regimens associated with larger reduction in pain intensity versus tramadol or diclofenac alone at 4 hours (mean improvement from baseline 5.2 to 5.6 vs. 4.5 on a 0 to 10 scale), but effects of the two regimens were similar at 6 hours (mean improvement ranged from 4.8 to 5.3 points) and 24 hours (mean improvement ranged from 5.7 to 6.0 points). The combination regimens were also associated with larger sum of pain intensity differences from 0 to 24 hours versus diclofenac (91.99 and 107.15 vs. 72.08,  $p<0.0001$ ). The combination regimens were associated with increased likelihood of global assessment “very good” or “excellent” versus diclofenac alone (at 24 hours, 86.6% and 90.9% vs. 71.4%); as in the original report, an updated meta-analysis found no difference between a multidose course of an opioid plus NSAID or acetaminophen versus NSAID alone in likelihood of global improvement (3 trials, RR 1.17, 95% CI 0.81 to 1.70,  $I^2=84\%$ ). The trial did not report likelihood of rescue or repeat medication use. Effects of tramadol alone versus diclofenac on pain intensity were similar to each other at 4, 6, and 24 hours; there were also no differences in sum of pain intensity differences or likelihood of “good” or “excellent” global assessment (68.8% vs. 71.4%).

A smaller new fair-quality trial (n=60) compared a single dose of an opioid plus acetaminophen (tramadol 37.5 mg/acetaminophen 325 mg) versus an NSAID (ketorolac, 10 mg) in patients with non-surgical (irreversible pulpitis) acute dental pain.<sup>16</sup> The opioid was associated with small to moderate decrease in pain intensity versus the NSAID at 4 to 48 hours (mean differences ranged from 0.6 to 1.9 points), although statistical significance was not reported. The trial did not report likelihood of rescue or repeat medication use or likelihood of global improvement.

As in the prior report, the new trials found opioids (with or without an NSAID) were associated with increased likelihood of adverse events versus an NSAID alone, including any adverse event (30.2% to 51.0% vs. 23.2%), nausea (7.3% to 25.2% vs. 3.4%), vomiting (5.9% to 21.4% vs. 1.4%), dizziness (5.4% to 14.1% vs. 2.9%), and drowsiness (26.6% vs. 0%).

## **Opioid Versus Acetaminophen**

The original report found inconsistent effects of an opioid plus acetaminophen versus acetaminophen alone on pain intensity at less than 1 day (11 trials), but an opioid plus acetaminophen was associated with larger sum of pain intensity differences at less than 1 day (10 trials) and decreased likelihood of rescue or repeat medication use (7 trials, pooled RR 0.81, 95% CI 0.67 to 0.97) (SOE: moderate for sum of pain intensity differences and rescue or repeat medication use). Most trials in the original report evaluated patients with postoperative dental pain (most commonly, third molar extraction).

Two new fair-quality trials (n=60 and n=39) compared an opioid plus acetaminophen versus acetaminophen alone for acute nonoperative dental pain.<sup>16,17</sup> One trial<sup>16</sup> evaluated a single dose and the other trial<sup>17</sup> evaluated a multidose course of therapy.

The first trial (n=60) compared a single dose of an opioid plus acetaminophen (tramadol 37.5 mg/acetaminophen 325 mg) versus acetaminophen (500 mg) in patients with nonoperative dental pain (irreversible pulpitis).<sup>16</sup> The opioid was associated with moderate to large decrease in pain intensity versus acetaminophen at 4 to 48 hours (mean differences ranged from 1.3 to 2.7 points on a 0 to 10 scale), although statistical significance was not reported. The other trial (n=39) found no differences in pain intensity between a 3-day course of codeine 30 mg/acetaminophen 1,000 mg every 6 hours versus acetaminophen alone in patients with an acute apical abscess (median 5.2 vs. 4.5 at 6 hours, p=0.33, 2.5 vs. 2.4 at 24 hours, p=0.61, 0.5 vs. 0 at 3 days, p=0.25).<sup>17</sup> There was no difference in the likelihood of rescue analgesic use in the first 48 hours (25% vs. 26%). Neither trial reported the sum of pain intensity differences.

As in the original report, the new trials found opioids were associated with increased likelihood of drowsiness versus acetaminophen (26.6% vs. 0% and 35% vs. 16%), dizziness (15% vs. 5%), nausea (40% vs. 11%), and vomiting (10% vs. 0%).

## **NSAID Versus Acetaminophen**

The original report found a single dose of NSAIDs associated with moderate to large decrease in pain intensity versus acetaminophen at less than 1 day (14 trials) and decreased likelihood of rescue or repeat medication use (11 trials, pooled RR 0.64, 95% CI 0.58 to 0.71) (SOE: moderate). It also found that NSAIDs might be associated with slightly decreased risk of any adverse event versus acetaminophen (12 trials, pooled RR 0.85, 95% CI 0.72 to 1.00) (SOE: low). The trials in the original report all evaluated patients with acute postoperative dental pain (third molar extraction in all trials except for one); no trial evaluated a multiday course of therapy.

One new trial (n=60) that described opioid versus NSAID or acetaminophen comparisons also compared a single dose of NSAID (ketorolac 10 mg) versus acetaminophen 500 mg for acute nonoperative (apical abscess) dental pain.<sup>16</sup> The NSAID was associated with a small decrease in pain intensity at 4 hours (3.0 vs. 3.9) and 6 hours (4.9 vs. 5.6), although statistical significance was not reported. There were no adverse events (drowsiness or gastritis) with either the NSAID or acetaminophen.

## **Key Question 7: Kidney Stones (Including Inpatient Management)**

We did not identify any new trials evaluating interventions for kidney stone pain.

## **Key Question 8: Sickle Cell Crisis (Episodic Pain)**

We did not identify any new trials evaluating interventions for pain associated with acute sickle cell crises.

## **Conclusions**

The original report evaluated opioid therapy, nonopioid pharmacologic therapies, and nonpharmacologic therapies for selected acute pain conditions. It found that opioid therapy was associated with decreased or similar effectiveness for pain versus an NSAID for surgical dental pain, kidney stone pain, and low back pain. Opioids and NSAIDs were more effective than acetaminophen for surgical dental pain, but opioids were less effective than acetaminophen for

kidney stone pain. Opioids were associated with increased risk of short-term adverse events versus NSAIDs or acetaminophen, including any adverse event, nausea, dizziness, and somnolence. Serious adverse events were uncommon for all interventions, but studies were not designed to assess risk of overdose, opioid use disorder, or long-term harms. Being prescribed an opioid for acute low back pain or postoperative pain was associated with increased likelihood of use of opioids at long-term followup versus not being prescribed, based on observational studies, although potential confounding could have impacted findings. Evidence on nonpharmacologic therapies was limited, but heat therapy, spinal manipulation, massage, acupuncture, acupressure, a cervical collar, and exercise were effective for specific acute pain conditions. Evidence was limited on the comparative effectiveness of therapies for sickle cell pain, acute neuropathic pain, neck pain, and management of postoperative pain following discharge; effects of therapies for acute pain on non-pain outcomes; effects of therapies on long-term outcomes, including long-term opioid use; and how benefits and harms of therapies vary in subgroups.

New evidence on therapies for acute pain identified for this update was generally consistent with the findings of the original report, with main findings unchanged. For musculoskeletal pain, new evidence enabled an assessment of opioids versus acetaminophen (no evidence in the original report) and suggested that opioids may be associated with a small decrease in pain but increased likelihood of adverse events versus acetaminophen. For postoperative pain, new evidence strengthened findings for no differences between opioids versus mixed agents and beneficial effects of music therapy. Although new evidence was available on acupuncture for low back pain and cold therapy for postoperative pain, findings were difficult to interpret due to differences from the original report with regard to the comparators evaluated (sham or usual care) and interventions. Although new trials of pharmacologic therapy for dental pain (opioids, NSAIDs, or acetaminophen) were generally consistent with the original report, two of the three trials evaluated nonoperative dental pain, which complicates interpretation because the trials in the original report focused on acute postoperative dental pain. More evidence is needed to determine whether effects of pharmacologic therapy differs for acute post-surgical and nonoperative dental pain. New trials were restricted to postoperative pain, dental pain, musculoskeletal pain, and low back pain; therefore, previously identified gaps for sickle cell pain, acute neuropathic pain, and neck pain remain. No new studies were identified on the association between opioid use versus non-use for specific acute pain conditions and short- or long-term opioid use or factors associated with opioid use for specific acute pain conditions.

The next surveillance report is scheduled for February 2022.

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# Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: research associate Christina Bougatsos, M.P.H., and student research assistant Keeley Black, B.S., both from Oregon Health & Science University; and Task Order Officer Suchitra Iyer, Ph.D., at the Agency for Healthcare Research and Quality.

# Disclaimers

This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 75Q80120D00005). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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AHRQ appreciates appropriate acknowledgment and citation of its work. Suggested language for acknowledgment: This work is the first update report of a living systematic review, Treatments for Acute Pain: A Systematic Review, by the Evidence-based Practice Center Program at the Agency for Healthcare Research and Quality (AHRQ).

**Suggested citation:** Chou R, Griffin JC, Blazina I, Schwarz E, Atchison C, Mauer K. Systematic Review on Treatments for Acute Pain: Surveillance Report 1. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 75Q80120D00005.) AHRQ Publication No. 22-EHC009. Rockville, MD: Agency for Healthcare Research and Quality; February 2022.

DOI: <https://doi.org/10.23970/AHRQEPSCSURVEILLANCE1ACUTEPAIN>. Posted final reports are located on the Effective Health Care Program [search page](#).

# Afterword

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see <https://effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis>.

This and future quarterly progress reports will provide up-to-date information about the evidence base to inform health plans, providers, purchasers, government programs, and the healthcare system as a whole on the state of the science. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website ([www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov). They will be considered in the next update of the report.

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## Appendix A. Literature Search Strategies

Ovid MEDLINE(R), All 1946 to November 5, 2021

1. Pain/
2. Acute Pain/
3. Pain Management/
4. (acute adj3 pain).ti,ab,kf.
5. exp back pain/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp Facial Pain/ or exp Nephrolithiasis/ or exp Anemia, Sickle Cell/ or Pain, Postoperative/
6. (back or spine or spinal or radicular or neck or musculoskeletal or fracture\* or neuropathic or neuralgia or neuropathy or sciatica or "dental pain" or "ondotogenic pain" or "kidney stone\*" or urolithiasis or nephrolithiasis or "sickle cell" or "postoperative pain").ti,ab,kf.
7. treatment outcome/
8. exp Therapeutics/
9. (dh or dt or pc or rh or th).fs.
10. (treatment or therap\* or intervention\*).ti,ab,kf.
11. (or/1-4) and (5 or 6) and (or/7-10)
12. exp cohort studies/
13. cohort\$.tw.
14. controlled clinical trial.pt.
15. epidemiologic methods/
16. limit 15 to yr=1966-1989
17. exp case-control studies/
18. (case\$ and control\$).tw.
19. or/12-14,16-18
20. randomized controlled trial.pt.
21. (random\* or placebo\* or control\* or trial or blind\*).ti,ab.
22. (animals not humans).sh.
23. (comment or editorial or meta-analysis or practice-guideline or review or letter).pt.
24. (20 or 21) not (22 or 23)
25. review.pt.
26. (medline or medlars or embase or pubmed or cochrane).tw,sh.
27. (scisearch or psychinfo or psycinfo).tw,sh.
28. (psychlit or psyclit).tw,sh.
29. cinahl.tw,sh.
30. ((hand adj2 search\$) or (manual\$ adj2 search\$)).tw,sh.
31. (electronic database\$ or bibliographic database\$ or computeri?ed database\$ or online database\$).tw,sh.
32. (pooling or pooled or mantel haenszel).tw,sh.
33. (peto or dersimonian or der simonian or fixed effect).tw,sh.
34. or/26-33
35. 25 and 34

36. meta-analysis.pt.
37. meta-analysis.sh.
38. (meta-analys\$ or meta analys\$ or metaanalys\$).tw,sh.
39. (systematic\$ adj5 review\$).tw,sh.
40. (systematic\$ adj5 overview\$).tw,sh.
41. (quantitativ\$ adj5 review\$).tw,sh.
42. (quantitativ\$ adj5 overview\$).tw,sh.
43. (quantitativ\$ adj5 synthesis\$).tw,sh.
44. (methodologic\$ adj5 review\$).tw,sh.
45. (methodologic\$ adj5 overview\$).tw,sh.
46. (integrative research review\$ or research integration).tw.
47. or/36-46
48. 35 or 47
49. 19 or 24 or 48
50. 11 and 49
51. or/7-10
52. or/1-4
53. 51 and 52
54. (ultrasound or TENS or cold or cryotherapy).tw.
55. 53 and 54
56. ankle.tw.
57. 55 and 56
58. 57 not 50
59. limit 58 to english language
60. 49 and 59
61. musculoskeletal.tw.
62. 55 and 61
63. limit 62 to english language
64. 50 or 63
65. 60 or 64
66. (animal\* or mouse or mice or rat\* or dog\* or canine or cow\* or bovine or horse\* or mare\* or pig\* or porcine or rabbit\* or llama\* or sheep or ewe\*).ti.
67. 65 not 66
68. (202008\$ or 202009\$ or 20201\$ or "2020 08 \$" or "2020 09 \$" or "2020 1\$" or "2020 aug \$" or "2020 sep \$" or "2020 oct \$" or "2020 nov \$" or "2020 dec \$").dp.
69. 67 and 68
70. limit 67 to yr="2021 -Current"
71. 69 or 70

**Ovid MEDLINE(R), All 1946 to November 5, 2021**

Key Question: Post operation pain supplemental search

1. treatment outcome/

2. exp Therapeutics/
3. (dh or dt or pc or rh or th).fs.
4. (treatment or therap\* or intervention\*).ti,ab,kf.
5. Pain, Postoperative/
6. "postoperative pain".ti,ab,kf.
7. 5 or 6
8. or/1-4
9. 7 and 8
10. (opioid\* or hydrocodone or oxycodone or hydromorphone or fentanyl or buprenorphine or naltrexone or naloxone or tramadol or tapentadol).tw.
11. (acetaminophen or "nonsteroidal anti-inflammatory" or NSAID\* or "skeletal muscle relaxant\*" or SMR\* or benzodiazepine\* or antidepressant\* or anticonvulsant\* or cannabis or cannabinoid\*).tw.
12. (exercise or "cognitive behavioral therapy" or CBT or meditation or relaxation or music or "virtual reality" or acupuncture or acupressure or electroacupuncture or massage or manipulation or mobilization or mobilisation or "physical modalit\*" or "transcutaneous electrical nerve stimulation" or TENS or ultrasound or brace\* or traction or heat or cold or cryo\*).tw.
13. or/10-12
14. 9 and 13
15. and (random\* or control\* or placebo or sham or trial).ti,ab,kf.
16. randomized controlled trial.pt.
17. (random\* or placebo\* or control\* or trial or blind\*).ti,ab.
18. (animals not humans).sh.
19. (comment or editorial or meta-analysis or practice-guideline or review or letter).pt.
20. (16 or 17) not (18 or 19)
21. 14 and 20
22. 15 or 21
23. (pediatric\* or preschool\* or toddler\* or infan\* or child\*).ti,ab.
24. 22 not 23
25. limit 24 to english language
26. (202008\$ or 202009\$ or 20201\$ or "2020 08 \$" or "2020 09 \$" or "2020 1\$" or "2020 aug \$" or "2020 sep \$" or "2020 oct \$" or "2020 nov \$" or "2020 dec \$").dp.
27. 25 and 26
28. limit 25 to yr="2021 -Current"
29. 27 or 28

## **EBM Reviews - Cochrane Central Register of Controlled Trials, October 2021**

1. Pain/
2. Acute Pain/
3. Pain Management/
4. (acute adj3 pain).ti,ab.

5. exp back pain/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp Facial Pain/ or exp Nephrolithiasis/ or exp Anemia, Sickle Cell/ or Pain, Postoperative/
6. (back or spine or spinal or radicular or neck or musculoskeletal or fracture\* or neuropathic or neuralgia or neuropathy or sciatica or "dental pain" or "odontogenic pain" or "kidney stone\*" or urolithiasis or nephrolithiasis or "sickle cell" or "postoperative pain").ti,ab.
7. treatment outcome/
8. exp Therapeutics/
9. (dh or dt or pc or rh or th).fs.
10. (treatment or therap\* or intervention\*).ti,ab.
11. (or/1-4) and (5 or 6) and (or/7-10)
12. limit 11 to medline records
13. 11 not 12
14. conference abstract.pt.
15. "journal: conference abstract".pt.
16. "journal: conference review".pt.
17. or/14-16
18. 13 not 17
19. limit 18 to yr="2020 -Current"

#### **EBM Reviews - Cochrane Database of Systematic Reviews, 2005 to November 5, 2021**

1. (back or spine or spinal or radicular or neck or musculoskeletal or fracture\* or neuropathic or neuralgia or neuropathy or sciatica or "dental pain" or "odontogenic pain" or "kidney stone\*" or urolithiasis or nephrolithiasis or "sickle cell" or "postoperative pain").ti.
2. (treatment or therap\* or intervention\*).ti,ab.
3. 1 and 2
4. limit 3 to full systematic reviews
5. 4 not chronic.ti.
6. 5 not children.ti.
7. 5 not 6
8. 7 and adult\*.ti.
9. 6 or 8 (300)
10. ("2020" or "2021").so.
11. 9 and 10

#### **Elsevier Embase, October, 2021**

('backache'/exp OR 'musculoskeletal pain'/exp OR 'neuropathic pain'/exp OR 'neuralgia'/exp OR 'tooth pain'/exp OR 'postoperative pain'/exp OR (('sickle cell anemia'/exp OR 'sickle cell crisis'/exp) AND ('pain'/exp OR pain:ti,ab,kw))) AND 'drug therapy'/exp AND ('article'/it OR 'review'/it) AND 'human'/de AND ('cohort analysis'/de OR 'comparative study'/de OR 'controlled study'/de OR 'meta analysis'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'systematic review'/de) AND [english]/lim AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)



### **PsycINFO, 1806 to November Week 1, 2021**

1. exp Pain/
2. chronic pain/
3. 1 not 2
4. sickle cell disease/
5. exp Back Pain/
6. exp neuralgia/ or exp peripheral neuropathy/
7. Pain Management/
8. pain.ti,ab.
9. (back or spine or spinal or radicular or neck or musculoskeletal or fracture\* or neuropathic or neuralgia or neuropathy or sciatica or dental or odontogenic or kidney or urolithiasis or nephrolithiasis or "sickle cell" or postoperative).ti,ab.
10. (7 or 8) and 9
11. (acute adj3 pain).ti,ab.
12. 3 or 4 or 5 or 6 or 10 or 11
13. exp treatment outcomes/
14. treatment effectiveness evaluation/
15. 12 and (13 or 14)
16. exp clinical trials/
17. (random\* or control\* or placebo or sham or trial or blind\*).ti,ab.
18. 15 and (16 or 17)
19. limit 18 to english language
20. limit 19 to human
21. limit 20 to (childhood <birth to 12 years> or adolescence <13 to 17 years>)
22. 20 not 21
23. 22 not chronic.ti.
24. limit 23 to yr="2020 -Current"

### **Ovid MEDLINE(R) ALL, 1946 to November 5, 2021**

#### *Acute Pain Risk*

1. Pain/
2. Acute Pain/
3. Pain Management/
4. (acute adj3 pain).ti,ab,kf.
5. exp back pain/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp Facial Pain/ or exp Nephrolithiasis/ or exp Anemia, Sickle Cell/ or Pain, Postoperative/
6. (back or spine or spinal or radicular or neck or musculoskeletal or fracture\* or neuropathic or neuralgia or neuropathy or sciatica or "dental pain" or "odontogenic pain" or "kidney stone\*" or urolithiasis or nephrolithiasis or "sickle cell" or "postoperative pain").ti,ab,kf.
7. (or/1-4) and (5 or 6)
8. exp Analgesics, Opioid/
9. opioid\*.ti,ab,kw.

10. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol or tramadol).ti,ab,kw,sh,hw.
11. or/8-10
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict\* or misuse or diversion)).ti,ab,kf.
14. 12 or 13
15. 7 and (11 or 14)
16. Decision Support Techniques/
17. "Predictive Value of Tests"/
18. Prognosis/
19. Risk Assessment/
20. Risk Factors/
21. Proportional Hazards Models/
22. "Reproducibility of Results"/
23. "Sensitivity and Specificity"/
24. (sensitivity or specificity or accuracy).ti,ab,kf.
25. (risk and (predict\$ or assess\$)).ti,ab,kf.
26. or/16-25
27. Patient Compliance/
28. Health Services Misuse/
29. Substance Abuse Detection/
30. Drug Monitoring/
31. (urine adj7 (screen\$ or test\$ or detect\$)).ti,ab,kf.
32. Contracts/
33. Patient Education as Topic/
34. Drug Overdose/
35. or/27-34
36. risk\$.ti,ab,kf.
37. ("risk evaluation and mitigation" or "rems").ti,ab,kf.
38. Risk Reduction Behavior/ or Risk/
39. or/36-38
40. 26 or 35 or 39
41. 15 and 40
42. limit 41 to english language
43. (202008\$ or 202009\$ or 20201\$ or "2020 08 \$" or "2020 09 \$" or "2020 1\$" or "2020 aug \$" or "2020 sep \$" or "2020 oct \$" or "2020 nov \$" or "2020 dec \$").dp.
44. 42 and 43
45. limit 42 to yr="2021 -Current"
46. 44 or 45

## **EBM Reviews - Cochrane Central Register of Controlled Trials, October 2021**

### *Acute Pain Risk*

1. Pain/

2. Acute Pain/
3. Pain Management/
4. (acute adj3 pain).ti,ab.
5. exp back pain/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp Facial Pain/ or exp Nephrolithiasis/ or exp Anemia, Sickle Cell/ or Pain, Postoperative/
6. (back or spine or spinal or radicular or neck or musculoskeletal or fracture\* or neuropathic or neuralgia or neuropathy or sciatica or "dental pain" or "odontogenic pain" or "kidney stone\*" or urolithiasis or nephrolithiasis or "sickle cell" or "postoperative pain").ti,ab.
7. (or/1-4) and (5 or 6)
8. exp Analgesics, Opioid/
9. opioid\*.ti,ab,kw.
10. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol or tramadol).ti,ab,kw,sh,hw.
11. or/8-10
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict\* or misuse or diversion)).ti,ab.
14. 12 or 13
15. 7 and (11 or 14)
16. Decision Support Techniques/
17. "Predictive Value of Tests"/
18. Prognosis/
19. Risk Assessment/
20. Risk Factors/
21. Proportional Hazards Models/
22. "Reproducibility of Results"/
23. "Sensitivity and Specificity"/
24. (sensitivity or specificity or accuracy).ti,ab.
25. (risk and (predict\$ or assess\$)).ti,ab.
26. or/16-25
27. Patient Compliance/
28. Health Services Misuse/
29. Substance Abuse Detection/
30. Drug Monitoring/
31. (urine adj7 (screen\$ or test\$ or detect\$)).ti,ab.
32. Contracts/
33. Patient Education as Topic/
34. Drug Overdose/
35. or/27-34
36. risk\$.ti,ab.
37. ("risk evaluation and mitigation" or "rems").ti,ab.
38. Risk Reduction Behavior/ or Risk/
39. or/36-38
40. 26 or 35 or 39

41. 15 and 40
42. limit 41 to english language
43. limit 42 to yr="2020 -Current"

**Optimized PreMEDLINE Search:**

**Ovid MEDLINE(R) In-Process & In-Data-Review Citations, 1946 to November 5, 2021**

1. (acute adj3 pain).ti,ab.
2. (((back or spine or spinal or radicular or neck or musculoskeletal or fracture\*) adj3 pain) or neuropathic or neuralgia or neuropathy or sciatica or "dental pain" or "odontogenic pain" or "kidney stone\*" or urolithiasis or nephrolithiasis or "sickle cell" or "postoperative pain").ti.
3. (treatment or therap\* or intervention\*).ti,ab.
4. (random\* or placebo\* or control\* or trial or blind\*).ti,ab.
5. (1 or 2) and 3
6. 4 and 5
7. (202008\$ or 202009\$ or 20201\$ or "2020 08 \$" or "2020 09 \$" or "2020 1\$" or "2020 aug \$" or "2020 sep \$" or "2020 oct \$" or "2020 nov \$" or "2020 dec \$").dp.
8. 6 and 7
9. limit 6 to yr="2021 -Current"
10. 8 or 9
11. limit 10 to english language
12. chronic.ti.
13. 11 not 12

## **Appendix B. Key Questions and Inclusion and Exclusion Criteria**

### **Key Questions**

Each Key Question (KQ) for this review focuses on a specific acute pain condition. The conditions and related subquestions are listed below:

KQ1: Acute back pain (including back pain with radiculopathy)

KQ2: Acute neck pain (including neck pain with radiculopathy)

KQ3: Musculoskeletal pain not otherwise included in KQ1 or KQ2 (including fractures)

KQ4: Peripheral neuropathic pain (related to herpes zoster and trigeminal neuralgia)

KQ5: Postoperative pain (excluding inpatient management of pain following major surgical procedures)

KQ6: Dental pain (surgical and nonsurgical)

KQ7: Kidney stones (including inpatient management)

KQ8: Sickle cell crisis (episodic pain)

For each condition above, we addressed the following subquestions:

### **Opioid Therapy**

a. What is the comparative effectiveness of opioid therapy versus: (1) nonopioid pharmacologic therapy (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], antidepressants, anticonvulsants) or (2) nonpharmacologic therapy (e.g., exercise, cognitive behavioral therapy, acupuncture) for outcomes related to pain, function, pain relief satisfaction, and quality of life and after followup at the following intervals: less than 1 day; 1 day to less than 1 week; 1 week to less than 2 weeks; 2 weeks to less than 4 weeks; 4 weeks or longer?

b. How does effectiveness of opioid therapy vary depending on: (1) patient demographics (e.g., age, race, ethnicity, gender); (2) patient medical or psychiatric comorbidities; (3) dose of opioids; (4) duration of opioid therapy, including number of opioid prescription refills and quantity of pills used; (5) opioid use history; (6) substance use history; (7) use of concomitant therapies?

- c. What are the harms of opioid therapy versus nonopioid pharmacologic therapy, or nonpharmacologic therapy with respect to: (1) misuse, opioid use disorder, and related outcomes; (2) overdose; (3) other harms including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?
- d. How do harms vary depending on: (1) patient demographics (e.g., age, gender); (2) patient medical or psychiatric comorbidities; (3) the dose of opioid used; (4) the duration of opioid therapy; (5) opioid use history; or (6) substance use history?
- e. What are the effects of prescribing opioid therapy versus not prescribing opioid therapy for acute pain on 1) short-term (<3 months) continued need for prescription pain relief, such as need for opioid refills, and 2) long-term opioid use (3 months or greater)?
- f. For patients with acute pain being considered for opioid therapy, what is the accuracy of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose?
- g. For patients with acute pain being considered for opioid therapy, what is the effectiveness of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose?
- h. For patients with acute pain being considered for opioid therapy, what is the effect of the following factors on the decision to prescribe opioids: (1) existing opioid management plans; (2) patient education; (3) clinician and patient values and preferences related to opioids; (4) urine drug screening; (5) use of prescription drug monitoring program data; (6) availability of close followup?

## **Nonopioid Pharmacologic Therapy**

- i. What is the comparative effectiveness of nonopioid pharmacologic therapy (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs, antidepressants, anticonvulsants) versus: (1) other nonopioid pharmacologic treatments, such as those in a different medication class; or (2) nonpharmacologic therapy for outcomes related to pain, function, pain relief satisfaction, and quality of life after followup at the following intervals: <1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to less than 4 weeks; 4 weeks or longer?
- j. How does effectiveness of nonopioid pharmacologic therapy vary depending on: (1) patient demographics (e.g., age, race, ethnicity, gender); (2) patient medical and psychiatric comorbidities; (3) the type of nonopioid medication; (4) dose of medication; (5) duration of treatment?
- k. What are the harms of nonopioid pharmacologic therapy versus other nonopioid pharmacologic therapy or nonpharmacologic therapy with respect to: (1) misuse, (2) overdose; (3) other harms including gastrointestinal-related harms, cardiovascular-

related harms, kidney-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cognitive harms, and psychological harms (e.g., depression)?

l. How do harms vary depending on: (1) patient demographics (e.g., age, gender); (2) patient medical comorbidities; (3) the type of nonopioid medication; (4) dose of medication; (5) the duration of therapy?

## **Nonpharmacologic Therapy**

m. What is the comparative effectiveness of nonpharmacologic therapy versus sham treatment, waitlist, usual care, attention control, and no treatment after followup at the following intervals: less than 1 day; 1 day to less than 1 week; 1 week to less than 2 weeks; 2 weeks to less than 4 weeks; 4 weeks or longer?

n. What is the comparative effectiveness of nonpharmacologic treatments (e.g., exercise, cognitive behavioral therapy, acupuncture) for outcomes related to pain, function, pain relief satisfaction, and quality of life after followup at the following intervals: less than 1 day; 1 day to less than 1 week; 1 week to less than 2 weeks; 2 weeks to less than 4 weeks; 4 weeks or longer?

o. How does effectiveness of nonpharmacologic therapy vary depending on: (1) patient demographics (e.g., age, gender); (2) patient medical and psychiatric comorbidities?

p. How do harms vary depending on: (1) patient demographics (e.g., age, gender); (2) patient medical and psychiatric comorbidities; (3) the type of treatment used; (4) the frequency of therapy; (5) the duration of therapy?

# Inclusion and Exclusion Criteria

**Table B-1. PICOTS: Inclusion and exclusion criteria**

Picots Element	Include	Exclude
Population	<p>Adults with acute pain related to the following conditions:</p> <ol style="list-style-type: none"> <li>1. Acute back pain (including back pain with radiculopathy)</li> <li>2. Acute neck pain (including neck pain with radiculopathy)</li> <li>3. Other musculoskeletal pain</li> <li>4. Peripheral neuropathic pain (related to herpes zoster and, trigeminal neuralgia)</li> <li>5. Postoperative pain after discharge</li> <li>6. Dental pain</li> <li>7. Kidney stones</li> <li>8. Sickle cell crisis (episodic pain)</li> </ol> <p>*Special populations:</p> <ul style="list-style-type: none"> <li>▪ General adult</li> <li>▪ Older populations &gt;65 years</li> <li>▪ Patients with history of substance use disorder</li> <li>▪ Patients currently under treatment for opioid use disorder with opioid agonist therapy or naltrexone</li> <li>▪ Patients with a history of psychiatric illness</li> <li>▪ Patients with history of overdose</li> <li>▪ Pregnant/breastfeeding women</li> <li>▪ Patients with comorbidities (e.g., kidney disease, sleep disordered breathing)</li> </ul>	<p>Adults with chronic (&gt;3 months) and subacute pain (6 to 12 weeks); pain not associated with one of the 8 conditions; perioperative pain; children and adolescents (&lt;18 years); headache and cancer pain, diabetic neuropathic pain, TMJ-related pain</p> <p>Mixed chronic/acute or subacute/acute populations if study does not report separate results.</p>



Picots Element	Include	Exclude
Interventions	<p><b>Opioid therapy:</b> a-e. Any systemic opioid, including agonists, partial agonists, and mixed mechanism opioids.</p> <p>f. Instruments, genetic/metabolic tests for predicting risk of misuse, opioid use disorder, and overdose</p> <p>g. Use of risk prediction instruments, genetic/metabolic tests</p> <p>h. The following factors: (1) existing opioid management plans; (2) patient education; (3) clinician and patient values and preferences related to opioids; (4) urine drug screening; (5) use of prescription drug monitoring program data; (6) availability of close followup</p> <p><b>Nonopioid pharmacological therapy:</b> Oral, parenteral, or topical nonopioid pharmacological therapy used for acute pain (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs, skeletal muscle relaxants, benzodiazepines, antidepressants, anticonvulsants, cannabis).</p> <p><b>Noninvasive nonpharmacological therapy:</b> Noninvasive nonpharmacological therapies used for acute pain (exercise [and related therapies], cognitive behavioral therapy, meditation, relaxation, music therapy, virtual reality, acupuncture, massage, manipulation/mobilization, physical modalities [transcutaneous electrical nerve stimulation, ultrasound, braces, traction, heat, cold])</p>	<p><b>Opioid therapy:</b> a-e. Transdermal patches, topical opioids f. Interventions to <i>treat</i> opioid use disorder, misuse, or overdose</p> <p>h. Studies assessing these factors for effects <i>outside</i> of the decision to prescribe opioids</p> <p><b>Nonopioid pharm therapy:</b> IV lidocaine; IV ketamine or other IV therapies <i>not</i> likely to continue in outpatient setting; all blocks; intra-articular injections; corticosteroids</p> <p><b>Noninvasive nonpharm therapy:</b> Other therapies not listed</p>

<b>Picots Element</b>	<b>Include</b>	<b>Exclude</b>
Comparators	<p><b>Opioid therapy:</b>  a-d. Usual care, another opioid, nonopioid drug, or noninvasive, nonpharmacological therapy  e. Usual care, another opioid, nonopioid drug, or noninvasive, nonpharmacological therapy, no opioid/nothing prescribed  f. Reference standard for misuse, opioid use disorder, or overdose; or other benchmarks  g. Usual care  h. Not utilizing the factors specified in interventions (h) above  <b>Nonopioid pharmacological therapy:</b>  Other nonopioid pharmacological therapy or noninvasive nonpharmacological therapy  <b>NOTE:</b> Include oral vs. topical NSAID studies as well as aspirin vs. NSAID studies  <b>Noninvasive nonpharmacological therapy:</b>  Sham treatment, waitlist, usual care, attention control, and no treatment; or other noninvasive nonpharmacological therapy</p>	<p><b>Opioid therapy:</b>  a-d. other comparisons; placebo; included therapies vs. excluded therapies; dose ranging studies    <b>Nonopioid pharm therapy:</b>  placebo; included therapies vs. excluded therapies; dose ranging studies; NSAID vs. NSAID studies; selective NSAIDs vs. non-selective NSAIDs    <b>Noninvasive nonpharm therapy:</b>  historical controls; included therapies vs. excluded therapies</p>
Outcomes	<p><b>Opioid therapy:</b>  a-d, g, i. Pain, function, pain relief satisfaction, and quality of life, harms, adverse events (including withdrawal, risk of misuse, opioid, opioid use disorder, overdose).  e. Persistent opioid use  f. Measures of diagnostic accuracy  h. Opioid prescribing rates  <b>Nonopioid therapy:</b> pain, function, pain relief satisfaction, quality of life and quality of life, harms, adverse events, opioid use  <b>Noninvasive nonpharmacological therapy:</b> pain, function, pain relief satisfaction, quality of life and quality of life, harms, adverse events, opioid use</p>	<p>Other outcomes; nonclinical outcomes (e.g., non-harm lab measures, ROM); measures of utilization (i.e., costs, procedures, length of stay, cost effectiveness/modeling)</p>
Time of followup	<p>At the following intervals: &lt;1 day; 1 day to &lt;1 week; 1 week to &lt;2 weeks; 2 weeks to 4 weeks; ≥4 weeks  <b>NOTE:</b> There will not be exclusion criteria for duration, unless duration is a matter of minutes.</p>	
Setting	<p>Emergency department (initiation of therapy and following discharge), physician's office, outpatient or inpatient surgical center, dental clinic or oral surgery center, inpatient (sickle cell only)</p>	<p>Other settings</p>

<b>Picots Element</b>	<b>Include</b>	<b>Exclude</b>
Study design	All KQs: RCTs; in addition: e. cohort studies (for long-term opioid use) f. studies assessing diagnostic accuracy h. cohort studies and before-after studies assessing effects on prescribing rates	For all KQs, exclude uncontrolled observational studies, case series, and case reports; studies with historical controls

Abbreviations: IV = intravenous; KQ = key question; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial; ROM = range of motion; TMJ = temporomandibular joints

## Appendix C. Included Studies List

1. Akgol Gur ST, Dogruyol S, Kocak AO, et al. Topical capsaicin versus topical ibuprofen in acute musculoskeletal injuries: a randomized, double-blind trial. *Hong Kong Journal of Emergency Medicine*. 2020;00(0):1-7. doi: 10.1177/1024907920975368. PMID: n/a.
2. Bloom DA, Kirby DJ, Thompson K, et al. Effect of acetaminophen on postoperative percocet use in hip arthroscopy: a randomized controlled trial. *Arthroscopy*. 2021;37(2):530-6. doi: 10.1016/j.arthro.2020.09.046. PMID: 33045334.
3. Brouwers HFG, de Vries AJ, van Zuilen M, et al. The role of computer-assisted cryotherapy in the postoperative treatment after total knee arthroplasty: positive effects on pain and opioid consumption. *Knee Surg Sports Traumatol Arthrosc*. 2021 doi: 10.1007/s00167-021-06568-x. PMID: 33903923.
4. Cope AG, Wetzstein MM, Mara KC, et al. Abdominal ice after laparoscopic hysterectomy: a randomized controlled trial. *J Minim Invasive Gynecol*. 2021;28(2):342-50.e2. doi: 10.1016/j.jmig.2020.06.027. PMID: 32622918.
5. da Silva PB, Mendes AT, Cardoso MBF, et al. Comparison between isolated and associated with codeine acetaminophen in pain control of acute apical abscess: a randomized clinical trial. *Clin Oral Investig*. 2021;25(3):875-82. doi: 10.1007/s00784-020-03374-6. PMID: 32651644.
6. Desjardins P, Alvarado F, Gil M, et al. Efficacy and safety of two fixed-dose combinations of tramadol hydrochloride and diclofenac sodium in postoperative dental pain. *Pain Med*. 2020;21(10):2447-57. doi: 10.1093/pm/pnaa124. PMID: 32488263.
7. Frants A, Garber D, Lafer MP, et al. Prospective randomized trial comparing opioids versus nonsteroidal antiinflammatory drugs for postoperative analgesia in outpatient rhinoplasty. *Plast Reconstr Surg*. 2021;147(1):56-62. doi: 10.1097/PRS.0000000000007427. PMID: 33370050.
8. Friedman BW, Irizarry E, Feliciano C, et al. A randomized controlled trial of oxycodone/acetaminophen versus acetaminophen alone for emergency department patients with musculoskeletal pain refractory to ibuprofen. *Acad Emerg Med*. 2021;28(8):859-65. doi: 10.1111/acem.14231. PMID: 33576545.
9. Laframboise-Otto JM, Horodyski M, Parvataneni HK, et al. A randomized controlled trial of music for pain relief after arthroplasty surgery. *Pain Manag Nurs*. 2021;22(1):86-93. doi: 10.1016/j.pmn.2020.09.003. PMID: 33129705.
10. Rian T, Skogvoll E, Hofstad J, et al. Tapentadol vs oxycodone for postoperative pain treatment the first 7 days after total knee arthroplasty: a randomized clinical trial. *Pain*. 2021;162(2):396-404. doi: 10.1097/j.pain.0000000000002026. PMID: 32773594.
11. Skonnord T, Skjeie H, Brekke M, et al. Acupuncture for acute non-specific low back pain: a randomised, controlled, multicentre intervention study in general practice - the Acuback study. *BMJ Open*. 2020;10(8):e034157. doi: 10.1136/bmjopen-2019-034157. PMID: 32764081.
12. Suwannalert P, Chanthasenont A, Pongrojapaw D. Effect of applying cold gel pack on reduction of postoperative pain in cesarean section, low midline skin incision: a randomized controlled trial. *J Obstet Gynaecol Res*. 2021;47(8):2653-8. doi: 10.1111/jog.14855. PMID: 34008228.
13. Thota L, Bansal R, Thota G, et al. Efficacy of routinely used analgesics in management of pulpal pain postoperatively a clinical study. *J Pharm Bioallied Sci*. 2021;13(Suppl 1):S684-S7. doi: 10.4103/jpbs.JPBS\_782\_20. PMID: 34447181.

## Appendix D. Excluded Studies List

1. Abo Elfadl GM, Osman AM, Ghalyoom MF, et al. Preoperative duloxetine to prevent postoperative shoulder pain after gynecologic laparoscopy: a randomized controlled trial. *Braz J Anesthesiol*. 2021; doi: 10.1016/j.bjane.2021.07.035. PMID: 34411629. **Exclusion reason:** Ineligible population
2. Abushanab D, Al-Badriyeh D. Efficacy and safety of ibuprofen plus paracetamol in a fixed-dose combination for acute postoperative pain in adults: meta-analysis and a trial sequential analysis. *CNS Drugs*. 2021;35(1):105-20. doi: 10.1007/s40263-020-00777-7. PMID: 33428176. **Exclusion reason:** Background only
3. Actrn. A comparison of clinic-delivered and telehealth-delivered post-operative rehabilitation and functional assessment following total knee arthroplasty. <http://www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12620001168943>. 2020 **Exclusion reason:** Ineligible publication type/not a study
4. Akdogan M, Utebey G, Atilla HA, et al. Effects of preoperative pregabalin on postoperative pain control in total knee arthroplasty surgery. *J Invest Surg*. 2021;34(8):848-52. doi: 10.1080/08941939.2019.1704317. PMID: 31913778. **Exclusion reason:** Ineligible intervention
5. Akpinar KE, Kaya F. Effect of different clinical practices on postoperative pain in permanent mandibular molar teeth with symptomatic apical periodontitis: a randomized controlled clinical trial. *Niger J Clin Pract*. 2021;24(1):8-16. doi: 10.4103/njcp.njcp\_16\_20. PMID: 33473019. **Exclusion reason:** Ineligible intervention
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## **Appendix E. Evidence Tables**

Shown in associated Excel files for surveillance report 1 at  
<https://effectivehealthcare.ahrq.gov/products/treatments-acute-pain/research>.

## **Appendix F. Quality Assessment**

Shown in associated Excel files for surveillance report 1 at  
<https://effectivehealthcare.ahrq.gov/products/treatments-acute-pain/research>.