Systematic Review on Treatments for Acute Pain: Surveillance Report 3

Literature Update Period: January 22, 2022, through May 6, 2022

Background and Purpose

This is the third surveillance report for the 2020 report *Treatments for Acute Pain: A Systematic Review* ([https://effectivehealthcare.ahrq.gov/products/treatments-acute-pain/research](https://effectivehealthcare.ahrq.gov/products/treatments-acute-pain/research)), covering the period January 22, 2022 through May 6, 2022. 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 last surveillance report, published in March 2022 (Surveillance Report 2), and to determine how the new evidence impacts the findings of the original 2020 report and Surveillance Reports 1 and 2. This is the final surveillance update planned for this topic.

Scope

The scope and eligibility criteria established at the time of the original report 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 on short- and long-term opioid use of prescribing opioid therapy for acute pain conditions; and factors influencing 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 January 22, 2022 through May 6, 2022. Search strategies from the original report were utilized1 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) search2 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 English-language studies and supplemented by review of reference lists of relevant articles. Search strategies are shown in Appendix A.

Randomized controlled trials were included for all KQs. Controlled observational studies (cohort, case-control, and before-after studies) were also included for opioid prescribing and effects on long-term use, accuracy and effectiveness of risk prediction instruments, and factors influencing prescribing.

As in the original review, 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, a second investigator utilizing the artificial intelligence function in Distiller SR (DistillerSR AI) provided another independent review. DistillerSR AI utilizes Natural Language Processing to train itself and make inclusion predictions using manually reviewed references. DistillerSR AI was trained using 2,132 abstracts identified in the searches conducted for Surveillance Report 1. The trained 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); 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,\textsuperscript{3} in conjunction with criteria and methods developed by the Cochrane Back Review Group.\textsuperscript{4} 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).

For Surveillance Updates 1 and 2, 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 (SOE) (meta-analysis performed if the SOE based on the original meta-analysis was low or insufficient and new evidence could increase the SOE due to increased precision, high quality, or other factors). Because this is the final surveillance update, we updated all of the meta-analyses with new data identified in any of the surveillance updates (including meta-analyses not meeting the criteria for updating described above). The SOE 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 planned to describe changes in the SOE assessments resulting from Surveillance Report 3 separately from updated findings based on new evidence identified for Surveillance Reports 1 and 2, but no new studies were identified for Surveillance Report 3. To provide an overall summary of evidence, a table detailing updated SOE assessments with new evidence from all three surveillance reports is provided.

A comprehensive list of included studies identified for all three surveillance report periods 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, quality assessments for each study are shown in Appendix F, forest plots for updated meta-analyses are shown in Appendix G, and updated SOE tables for outcomes with new evidence are available in Appendix H.

**Results**

The search for Surveillance Report 3 from January 22, 2022 to May 6, 2022, yielded 591 citations, and identified no new eligible studies (Figure 1). Surveillance Report 1 identified 13 randomized controlled trials (RCTs)\textsuperscript{5-17} and Surveillance Report 2 identified seven new trials (5 RCT\textsuperscript{18-22} and 2 pseudo-randomized [by birth year] trials).\textsuperscript{23,24}
Summary of Findings

- No new studies were identified for this update.

Summary of New Evidence

Table 1 provides the conclusions from the 2020 report and the findings from studies identified in Surveillance Reports 1 and 2, focusing on KQs and comparisons/outcomes with any new evidence, including updated meta-analyses. A table showing SOE ratings updated for areas with new evidence is shown in Appendix H; the entire strength of evidence (SOE) table from the original 2020 review is available at https://www.ncbi.nlm.nih.gov/books/NBK566513/.

Abbreviations: KQ = Key Question
*Additional sources include prior reports, reference lists of relevant articles, systematic reviews, etc.
†Search counts are for the surveillance report searches only. Included studies totals are from the original report and surveillance reports combined. ("New" indicates newly included in Surveillance Report 3.)
<table>
<thead>
<tr>
<th>Key Question</th>
<th>Conclusions From 2020 Report</th>
<th>Findings From Surveillance Reports</th>
<th>Updated Conclusions Following Surveillance Reports</th>
</tr>
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<tbody>
<tr>
<td>1 (Low back pain): Traditional Chinese acupuncture vs. sham or usual care</td>
<td>Pain at 2 to &lt;4 weeks: decreased (SOE: low, based on 1 RCT) with acupuncture vs. non-penetrating sham or usual care but not needle sham</td>
<td>1 RCT (n=167)^23,24 identified for Surveillance Report 1 found no difference between traditional Chinese acupuncture vs. usual care in pain, functional status, or quality of life at 2 to 4 weeks.</td>
<td>SOE: downgraded to insufficient due to inconsistency</td>
</tr>
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<td>3 (Musculoskeletal pain): Opioid plus acetaminophen vs. acetaminophen</td>
<td>No evidence.</td>
<td>One RCT (n=154)^31 identified for Surveillance Report 1 found an opioid associated with small decrease in pain but increased likelihood of adverse events and drowsiness.</td>
<td>SOE: Low for pain and adverse events</td>
</tr>
<tr>
<td>3 (Musculoskeletal pain): Topical ibuprofen vs. capsaicin</td>
<td>No evidence.</td>
<td>One RCT (n=119)^7 identified for Surveillance Report 1 was inconclusive due to poor quality.</td>
<td>SOE: Insufficient</td>
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<td>5 (Postoperative pain): Opioid vs. NSAID, multidose</td>
<td>Pain, 1 day to &lt;1 week: Inconsistent findings (SOE: insufficient, based on 4 RCTs).</td>
<td>One RCT (n=70)^8 identified for Surveillance Report 1 found opioid associated with a small increase in pain at day 1, with no difference at day 7.</td>
<td>SOE: Unchanged</td>
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<td></td>
<td>Rescue medication use, 1 day to &lt;1 week: RR 1.22 to 2.04 (SOE: moderate, based on 4 RCTs)</td>
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<tr>
<td>5 (Postoperative pain): Opioid vs. acetaminophen, multidose</td>
<td>Evidence limited and inconsistent for pain and other outcomes; each RCT evaluated outcomes at a different time point (&lt;1 day, 1 day to &lt;1 week, and 2 to &lt;4 weeks) (SOE: insufficient, based on 3 RCTs)</td>
<td>One RCT (n=80)^11 identified for Surveillance Report 1 found no difference between an opioid vs. acetaminophen in pain at day 7.</td>
<td>SOE: Unchanged</td>
</tr>
<tr>
<td>5 (Postoperative pain): Opioid vs. mixed agent</td>
<td>Pain: No difference at &lt;1 day (1 RCT, SOE: low), 1 day to &lt;1 week (6 RCTs, SOE: moderate), or 1 to &lt;2 weeks (1 RCT, SOE: low)</td>
<td>One RCT (n=91)^11 identified for Surveillance Report 1 found no difference between an opioid vs. tapentadol in pain at 1 day to &lt;1 week, 1 to &lt;2 weeks, or ≥4 weeks.</td>
<td>SOE: Unchanged at &lt;1 day and at 1 day to &lt;1 week, upgraded to moderate for 1 to &lt;2 weeks, and assessed as low for ≥4 weeks</td>
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<tr>
<td>Key Question</td>
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<td><strong>5 (Postoperative pain): Cold therapy vs. sham or no cold therapy</strong></td>
<td>Pain, &lt;1 week: No difference (SOE: low, based on 3 RCTs)</td>
<td>One RCT (n=100)(^{12}) identified for Surveillance Report 1 found continuous cooling for 7 days associated with moderate decrease in pain versus usual care at 1 day to &lt;1 week, with no differences at 1 to &lt;2 weeks or ≥4 weeks in pain intensity, function, or QoL; two RCTs (n=100(^{16}) and 137(^{14}) identified for Surveillance Report 1 reported inconsistent results for a cold pack vs. usual care in pain intensity at &lt;1 day to 1 day.</td>
<td>SOE: Unchanged for cold therapy vs. sham therapy (no new RCTs)</td>
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<td></td>
<td>Pain, function, QoL, 2 to &lt;4 weeks and ≥4 weeks: No differences (SOE: low, based on 1 RCT)</td>
<td></td>
<td>SOE: Insufficient (based on 2 RCTs) for cold therapy vs. usual care and pain intensity at &lt;1 day due to inconsistency; low (based on 1 RCT) for moderate benefit at 1 day to &lt;1 week; and low for no difference at 1 to &lt;2 weeks and ≥4 weeks</td>
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<td><strong>5 (Postoperative pain): Music therapy vs. no music therapy</strong></td>
<td>Pain, &lt;1 day and 1 day to &lt;1 week: Small to moderate decrease (SOE: low, based on 2 RCTs)</td>
<td>One RCT (n=47)(^{5}) identified for Surveillance Report 1 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.</td>
<td>SOE: Upgraded to moderate at 1 day to &lt;1 week</td>
</tr>
<tr>
<td><strong>5 (Postoperative pain): Abdominal binder vs. no binder</strong></td>
<td>No evidence</td>
<td>One RCT (n=196)(^{9}) identified for Surveillance Report 2 found an abdominal binder associated with small decrease in pain vs. no binder at 1 day to &lt;1 week, but had serious methodological limitations.</td>
<td>SOE (no prior evidence): Insufficient (based on 1 new RCT)*</td>
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<td><strong>5 (Postoperative pain): TENS vs. sham TENS</strong></td>
<td>Pain, &lt;1 day and 1 day to &lt;1 week: Small to moderate decrease (SOE: low, based on 1 RCT)</td>
<td>One RCT (n=80)(^{19}) identified for Surveillance Report 2 found TENS associated with a small decrease in pain intensity vs. sham TENS at 1 day to &lt;1 week.</td>
<td>SOE: Upgraded to moderate at 1 day to &lt;1 week</td>
</tr>
<tr>
<td><strong>5 (Postoperative pain): Preoperative education vs. no education</strong></td>
<td>No evidence</td>
<td>Three RCTs (n=445)(^{22-24}) identified for Surveillance Report 2 found preoperative education associated with decreased opioid use at 1 to 2 weeks vs. no preoperative education, with similar or decreased pain intensity.</td>
<td>SOE for opioid use (no prior evidence): Low (based on 3 new RCTs)*</td>
</tr>
<tr>
<td>Key Question</td>
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<td>6 (Dental pain): Opioid with or without acetaminophen or NSAID vs. NSAID, multidose</td>
<td>Pain, &lt;1 day and 1 day to &lt;1 week: No difference (SOE: low, based on 1 RCT [&lt;1 day] and 3 RCTs [1 day to 1 week]) Global improvement: No difference (SOE: low, based on 2 RCTs; RR 0.76, 95% CI 0.57 to 1.00)</td>
<td>One RCT (n=825)(^{15}) identified for Surveillance Report 1 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. One RCT (n=70)(^{18}) identified for Surveillance Report 2 found an opioid plus NSAID versus NSAID associated with a small, non-statistically significant decrease in pain intensity at &lt;1 day, with no difference at 1 day to 1 week. There was no difference in likelihood of a positive global assessment (an updated meta-analysis for likelihood of positive global assessment again found no difference: 4 trials, RR 1.08, 95% CI 0.87 to 1.34)</td>
<td>SOE: Unchanged</td>
</tr>
<tr>
<td>6 (Dental pain): Opioid vs. NSAID, multidose</td>
<td>Pain, &lt;1 day and 1 day to &lt;1 week: No difference (SOE: insufficient, based on 1 RCT)</td>
<td>One RCT (n=412)(^{18}) identified for Surveillance Report 1 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.</td>
<td>SOE: Upgraded to low</td>
</tr>
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<td>6 (Dental pain): Opioid with or without acetaminophen or NSAID vs. NSAID, single dose</td>
<td>Pain, &lt;1 day and 1 day to &lt;1 week: Small to moderate increase at &lt;1 day and no difference at 1 day to &lt;1 week (SOE: low, based on 12 RCTs [&lt;1 day] and 3 RCTs [1 day to &lt;1 week])</td>
<td>One RCT (n=60)(^{16}) identified for Surveillance Report 1 found a single dose of an opioid plus acetaminophen associated with a small to moderate decrease in pain intensity versus an NSAID at &lt;1 day and at 1 day to &lt;1 week, but did not report statistical significance of findings. One RCT (n=169)(^{17}) identified for Surveillance Report 2 found a single dose of an opioid plus acetaminophen associated with moderate increase in pain intensity versus an NSAID at &lt;1 day, but did not report statistical significance of findings.</td>
<td>SOE: Unchanged</td>
</tr>
<tr>
<td>Key Question</td>
<td>Conclusions From 2020 Report</td>
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<tr>
<td>6 (Dental pain): Opioid (with or without acetaminophen or NSAID) vs. NSAID</td>
<td>Opioid increased risk of: Any adverse event: 11 trials, RR 1.72 (95% CI 1.29 to 2.28) Nausea: 12 trials, RR 2.72 (95% CI 1.84 to 4.01) Dizziness: 10 trials, RR 2.97 (95% CI 1.59 to 5.54) Drowsiness: 9 trials, RR 1.76 (95% CI 1.00 to 3.10) (SOE: moderate)</td>
<td>Two RCTs (n=825 and 60) identified for Surveillance Report 1 found opioids associated with increased risk of any adverse event, nausea, dizziness, and drowsiness. Two RCTs (n=70 and 169) identified for Surveillance Report 2 found opioids associated with increased risk of any adverse event, nausea, and dizziness.</td>
<td>Updated meta-analysis Opioid increased risk of: Any adverse event: 14 trials, RR 1.85 (95% CI 1.47 to 2.33) Nausea: 15 trials, RR 3.64 (95% CI 2.44 to 5.43) Dizziness: 13 trials, RR 3.50 (95% CI 2.16 to 5.67) Drowsiness: 12 trials, RR 1.89 (95% CI 1.09 to 3.27)</td>
</tr>
<tr>
<td>6 (Dental pain): Opioid plus acetaminophen vs. acetaminophen, multidose course</td>
<td>Pain, &lt;1 day: One very small (n=20) RCT found opioid associated with large improvement (SOE: insufficient)</td>
<td>One RCT (n=39) identified for Surveillance Report 1 found no differences in pain or rescue analgesic use among patients with nonoperative dental pain.</td>
<td>SOE: Unchanged (remained insufficient due to imprecision and inconsistency)</td>
</tr>
<tr>
<td>6 (Dental pain): Opioid plus acetaminophen vs. acetaminophen, single dose</td>
<td>Pain, &lt;1 day: Inconsistent effect (SOE: moderate, based on 11 RCTs) Rescue or repeat medication use, &lt;1 day: RR 0.81 (95% CI 0.56 to 0.97) (SOE: moderate, based on 7 RCTs)</td>
<td>One RCT (n=60) identified for Surveillance Report 1 found an opioid associated with moderate to large decrease in pain intensity versus acetaminophen at &lt;1 day and 1 day to &lt;1 week, although statistical significance was not reported.</td>
<td>SOE: Unchanged</td>
</tr>
<tr>
<td>6 (Dental pain): Opioid plus acetaminophen vs. acetaminophen</td>
<td>Opioids increased risk of: Nausea: 8 trials, RR 1.55 (95% CI 0.75 to 3.18) Drowsiness: 6 trials, RR 2.03 (95% CI 0.70 to 5.93) Dizziness: 5 trials, RR 2.49 (95% CI 0.66 to 9.49) (SOE: low, based on 4 to 8 RCTs)</td>
<td>Two RCTs (n=39 and 60) identified for Surveillance Report 1 found opioids associated with increased risk of drowsiness (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%). Updated meta-analysis: Nausea: 9 trials, RR 1.86 (95% CI 0.98 to 3.54) Drowsiness: 8 trials, RR 2.36 (95% CI 0.99 to 5.63) Dizziness: 6 trials, RR 2.64 (95% CI 0.92 to 7.56)</td>
<td>SOE: Unchanged (low)</td>
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Evidence Details

No new studies meeting eligibility criteria were identified for Surveillance Report 3. For Key Question 6 (Dental Pain), new studies identified for Surveillance Reports 1 and 2 provided data to update meta-analyses for opioids vs. NSAIDs (global improvement [Appendix Figure G-1], any adverse event [Appendix Figure G-2], nausea [Appendix Figure G-3], drowsiness [Appendix Figure G-4], and dizziness [Appendix Figure G-5]), and opioids vs. acetaminophen (nausea [Appendix Figure G-6], drowsiness [Appendix Figure G-7], and dizziness [Appendix Figure G-8]). All updated meta-analyses were consistent with the pooled estimates and findings of the original report (Table 1). Meta-analyses were not conducted for the original report or surveillance updates on mean improvement in pain or function, because results for specific time points were estimated from graphs and variance information was missing. For pain conditions other than dental pain, new studies identified for Surveillance Reports 1 and 2 did not provide data to update meta-analyses.

Conclusions

No new studies were identified for Surveillance Report 3. The original report and Surveillance Reports 1 and 2 evaluated opioid therapy, nonopioid pharmacologic therapies, and nonpharmacologic therapies for selected acute pain conditions. For dental pain, updated meta-analyses based on randomized trials provided estimates and findings very similar to the original report (Appendix Table H-1). 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 and acute musculoskeletal 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, music therapy, TENS, 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. A new finding from Surveillance Report 2 was that preoperative education is associated with decreased opioid use with similar or reduced pain intensity versus no preoperative education (no prior trials). As previously noted, more evidence is needed to determine whether effects of pharmacologic therapy differ for acute post-surgical and nonoperative dental pain; clarify benefits and harms of treatments for sickle cell pain, acute neuropathic pain, and neck pain; and determine the association between opioid use versus non-use for specific acute pain conditions and short- or long-term opioid use.
References


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Disclaimers
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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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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) 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. They will be considered in the next version of the report.

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Appendixes

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Appendix A. Literature Search Strategies

Ovid MEDLINE(R), All 1946 to May 6, 2022

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 May 6, 2022

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 infant* 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, May 6, 2022

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 "ondotogenic 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
17. or/14-16
18. 13 not 17
19. limit 18 to yr="2020 -Current"

EBM Reviews - Cochrane Database of Systematic Reviews, 2005 to May 6, 2022

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 "ondotogenic 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, May 2022

('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 May 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 ondogenic 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 May 6, 2022

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 "ondotogenic 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, May 2022**

*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 "ondotogenic 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 May 6, 2022

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)?

I. 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

<table>
<thead>
<tr>
<th>Picots Element</th>
<th>Include</th>
<th>Exclude</th>
</tr>
</thead>
</table>
| **Population** | Adults with acute pain related to the following conditions:  
1. Acute back pain (including back pain with radiculopathy)  
2. Acute neck pain (including neck pain with radiculopathy)  
3. Other musculoskeletal pain  
4. Peripheral neuropathic pain (related to herpes zoster and, trigeminal neuralgia)  
5. Postoperative pain after discharge  
6. Dental pain  
7. Kidney stones  
8. Sickle cell crisis (episodic pain) | Adults with chronic (>3 months) and subacute pain (6 to 12 weeks); pain not associated with one of the 8 conditions; perioperative pain; children and adolescents (<18 years); headache and cancer pain, diabetic neuropathic pain, TMJ-related pain |  
*Special populations:*  
- General adult  
- Older populations >65 years  
- Patients with history of substance use disorder  
- Patients currently under treatment for opioid use disorder with opioid agonist therapy or naltrexone  
- Patients with a history of psychiatric illness  
- Patients with history of overdose  
- Pregnant/breastfeeding women  
- Patients with comorbidities (e.g., kidney disease, sleep disordered breathing)  
<p>|</p>
<table>
<thead>
<tr>
<th>Picots Element</th>
<th>Include</th>
<th>Exclude</th>
</tr>
</thead>
</table>
| Interventions | **Opioid therapy:**  
a-e. Any systemic opioid, including agonists, partial agonists, and mixed mechanism opioids.  
  
f. Instruments, genetic/metabolic tests for predicting risk of misuse, opioid use disorder, and overdose  
g. Use of risk prediction instruments, genetic/metabolic tests  
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  
**Nonopioid pharmacological therapy:** 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).  
**Noninvasive nonpharmacological therapy:** 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]) | **Opioid therapy:**  
a-e. Transdermal patches, topical opioids  
f. Interventions to treat opioid use disorder, misuse, or overdose  
h. Studies assessing these factors for effects outside of the decision to prescribe opioids  
**Nonopioid pharm therapy:** IV lidocaine; IV ketamine or other IV therapies not likely to continue in outpatient setting; all blocks; intra-articular injections; corticosteroids  
**Noninvasive nonpharm therapy:** Other therapies not listed |
<table>
<thead>
<tr>
<th>Picots Element</th>
<th>Include</th>
<th>Exclude</th>
</tr>
</thead>
</table>
| Comparators   | **Opioid therapy:**  
|               | 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/thing 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  
|               | **Nonopioid pharmacological therapy:**  
|               | Other nonopioid pharmacological therapy or noninvasive nonpharmacological therapy  
|               | **NOTE:** Include oral vs. topical NSAID studies as well as aspirin vs. NSAID studies  
|               | **Noninvasive nonpharmacological therapy:**  
|               | Sham treatment, waitlist, usual care, attention control, and no treatment; or other noninvasive nonpharmacological therapy  
|               | **Opioid therapy:**  
|               | a-d. Other comparisons; placebo; included therapies vs. excluded therapies; dose ranging studies  
|               | **Nonopioid pharm therapy:**  
|               | placebo; included therapies vs. excluded therapies; dose ranging studies; NSAID vs. NSAID studies; selective NSAIDs vs. non-selective NSAIDs  
|               | **Noninvasive nonpharm therapy:**  
|               | historical controls; included therapies vs. excluded therapies  
| Outcomes      | **Opioid therapy:**  
|               | 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  
|               | **Nonopioid therapy:** pain, function, pain relief satisfaction, quality of life and quality of life, harms, adverse events, opioid use  
|               | **Noninvasive nonpharmacological therapy:** pain, function, pain relief satisfaction, quality of life and quality of life, harms, adverse events, opioid use  
|               | **Other outcomes:** nonclinical outcomes (e.g., non-harm lab measures, ROM); measures of utilization (i.e., costs, procedures, length of stay, cost effectiveness/modeling)  
| Time of followup | At the following intervals: <1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to 4 weeks; ≥4 weeks  
|                | **NOTE:** There will not be exclusion criteria for duration, unless duration is a matter of minutes.  
| Setting        | 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)  
|               | Other settings  

<table>
<thead>
<tr>
<th>Picots Element</th>
<th>Include</th>
<th>Exclude</th>
</tr>
</thead>
</table>
| 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; PICOTS = population, interventions, comparators, outcomes, timing, setting, study design; RCT = randomized controlled trial; ROM = range of motion; TMJ = temporomandibular joints
Appendix C. Included Studies List


Appendix D. Excluded Studies List


activation techniques: a randomized clinical trial. Odontology. 2022;Online ahead of print: doi: 10.1007/s10266-022-00700-0. PMID: 35267110. **Exclusion reason:** Wrong intervention


84. Hamilton DF, Beard DJ, Barker KL, et al. Targeting rehabilitation to improve outcomes after total knee arthroplasty in patients at risk of poor outcomes: randomised controlled trial. BMJ. 2020;371:m3576. doi: 10.1136/bmj.m3576. PMID: 33051212. **Exclusion reason:** Ineligible population


32900564. **Exclusion reason:** Ineligible intervention


177. Rhon DI, Mayhew RJ, Greenlee TA, et al. The influence of a MOBILE-based video Instruction for Low back pain (MOBIL) on


190. Sethi PM, Mandava NK, Liddy N, et al. Narcotic requirements after shoulder arthroplasty are low using a multimodal


Exclusion reason: Paper pulled for background


Appendix E. Evidence Tables

Shown in associated Excel file for Surveillance Report 2 at
Appendix F. Quality Assessment

Appendix G. Meta-Analysis Results

Figure G-1. Meta-analysis: Opioid vs. NSAID for global improvement (medication rated very good or excellent)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioid</th>
<th>NSAID</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Single dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carty 2020 Study 1</td>
<td>21</td>
<td>91</td>
<td>37</td>
</tr>
<tr>
<td>Carty 2020 Study 2</td>
<td>32</td>
<td>91</td>
<td>39</td>
</tr>
<tr>
<td>Cooper 1988</td>
<td>15</td>
<td>31</td>
<td>17</td>
</tr>
<tr>
<td>Cooper 1991</td>
<td>14</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Malmstrom 2004</td>
<td>24</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>302</td>
<td>335</td>
<td>54.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>108</td>
<td>175</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Ch^2 = 4.12, df = 4 (P = 0.32); I^2 = 3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.05 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Multidose         |        |       |        |                                  |
|                   | Events | Total | Weight |                                  |
|                   |        |       |        |                                  |
| Brown 2013        | 29     | 52    | 115    | 192  12.0% 0.76 [0.58, 1.04]      |
| Desjardins 2020   | 471    | 618   | 148    | 207  14.7% 1.07 [0.97, 1.17]      |
| Valecillo 2021    | 29     | 36    | 25     | 34   12.6% 1.10 [0.85, 1.42]      |
| Zupelani-Goncalves 2017 | 30 | 49    | 17     | 46   9.7% 1.76 [1.15, 2.72]       |
| Subtotal (95% CI) | 762    | 479   | 49.0%  | 1.68 [0.87, 1.34]                |
| Total events      | 559    | 305   |        |                                  |
| Heterogeneity: Tau^2 = 0.03; Ch^2 = 8.70, df = 3 (P = 0.02); I^2 = 69% |
| Test for overall effect: Z = 0.69 (P = 0.49) |

| Total (95% CI)    | 1084   | 814   | 100.0% | 0.83 [0.67, 1.04]              |
| Total events      | 865    | 480   |         |                                  |
| Heterogeneity: Tau^2 = 0.08; Ch^2 = 42.25, df = 8 (P < 0.00001); I^2 = 81% |
| Test for overall effect: Z = 1.59 (P = 0.11) |
| Test for subgroup differences: Ch^2 = 13.85, df = 1 (P = 0.0002), I^2 = 92.7% |

Abbreviations: NSAID = nonsteroidal anti-inflammatory drug
Figure G-2. Meta-analysis: Opioid vs. NSAID for any adverse event

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioid</th>
<th>NSAID</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catty 2020 Study 1</td>
<td>23</td>
<td>6</td>
<td>3.79 [1.62, 8.88]</td>
</tr>
<tr>
<td>Catty 2020 Study 2</td>
<td>37</td>
<td>92</td>
<td>1.34 [0.90, 1.99]</td>
</tr>
<tr>
<td>Cooper 1982</td>
<td>41</td>
<td>127</td>
<td>1.23 [0.78, 1.93]</td>
</tr>
<tr>
<td>Cooper 1991</td>
<td>8</td>
<td>39</td>
<td>2.43 [0.95, 6.23]</td>
</tr>
<tr>
<td>Cooper 2021</td>
<td>34</td>
<td>87</td>
<td>2.71 [1.53, 4.77]</td>
</tr>
<tr>
<td>Dionne 1994</td>
<td>9</td>
<td>24</td>
<td>2.23 [0.99, 5.09]</td>
</tr>
<tr>
<td>Forbes 1990</td>
<td>8</td>
<td>40</td>
<td>1.19 [0.57, 2.46]</td>
</tr>
<tr>
<td>Malmstrom 2004</td>
<td>25</td>
<td>50</td>
<td>1.34 [0.85, 2.11]</td>
</tr>
<tr>
<td>Sunshine 1986</td>
<td>3</td>
<td>31</td>
<td>13.34 [0.71, 250.43]</td>
</tr>
<tr>
<td>Van Dyke 2004</td>
<td>46</td>
<td>250</td>
<td>1.71 [1.05, 2.79]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>831</td>
<td>902</td>
<td>1.72 [1.34, 2.20]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>234</td>
<td>142</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.06; Ch² = 14.38, df = 9 (P = 0.11); I² = 37%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.25 (P &lt; 0.0001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Multidose**     |        |       |                                |
| Akinbode 2019     | 25     | 45    | 51.00 [3.20, 812.96]           |
| Brown 2013        | 11     | 62    | 1.70 [0.86, 3.35]              |
| Desjardins 2020   | 263    | 619   | 1.83 [1.41, 2.39]              |
| Vallecillo 2021   | 15     | 36    | 4.72 [1.50, 14.88]             |
| **Subtotal (95% CI)** | 762 | 478 | 2.64 [1.29, 5.41] |
| **Total events**  | 314    | 71    |                                |
| Heterogeneity: Tau² = 0.30; Ch² = 9.12, df = 3 (P = 0.03); I² = 67% |
| Test for overall effect: Z = 2.66 (P = 0.008) |

| **Total (95% CI)** | 1593  | 1380 | 1.85 [1.47, 2.33] |
| **Total events**   | 546   | 213  |                                |
| Heterogeneity: Tau² = 0.06; Ch² = 24.95, df = 13 (P = 0.02); I² = 46% |
| Test for overall effect: Z = 5.19 (P < 0.00001) |
| Test for subgroup differences: Ch² = 1.25, df = 1 (P = 0.26), I² = 19.9% |
Figure G-3. Meta-analysis: Opioid vs. NSAID for nausea

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioid</th>
<th>NSAID</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>Single dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breivik 1999</td>
<td>0</td>
<td>23</td>
<td>1</td>
<td>1.6%</td>
</tr>
<tr>
<td>Catter 2020 Study 1</td>
<td>21</td>
<td>51</td>
<td>11</td>
<td>20.4%</td>
</tr>
<tr>
<td>Catter 2020 Study 2</td>
<td>2</td>
<td>11</td>
<td>2</td>
<td>5.7%</td>
</tr>
<tr>
<td>Cooper 1962</td>
<td>6</td>
<td>127</td>
<td>2</td>
<td>76</td>
</tr>
<tr>
<td>Cooper 1961</td>
<td>1</td>
<td>39</td>
<td>0</td>
<td>83</td>
</tr>
<tr>
<td>Cooper 2021</td>
<td>1</td>
<td>87</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>Dorne 1984</td>
<td>2</td>
<td>24</td>
<td>1</td>
<td>48</td>
</tr>
<tr>
<td>Forbes 1990</td>
<td>1</td>
<td>40</td>
<td>1</td>
<td>125</td>
</tr>
<tr>
<td>Malmstrom 2004</td>
<td>8</td>
<td>50</td>
<td>2</td>
<td>51</td>
</tr>
<tr>
<td>Moore 2015</td>
<td>12</td>
<td>357</td>
<td>2</td>
<td>152</td>
</tr>
<tr>
<td>Van Dyke 2004</td>
<td>25</td>
<td>250</td>
<td>7</td>
<td>188</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1190</td>
<td>1048</td>
<td>69%</td>
<td>3.97</td>
</tr>
<tr>
<td>Total events</td>
<td>114</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.10, Chi² = 11.73, df = 10 (P = 0.30); I² = 15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.40 (P &lt; 0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Multidose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioid</th>
<th>NSAID</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>Aklhade 2019</td>
<td>5</td>
<td>45</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>Brown 2013</td>
<td>6</td>
<td>62</td>
<td>4</td>
<td>152</td>
</tr>
<tr>
<td>Desjardins 2020</td>
<td>118</td>
<td>619</td>
<td>7</td>
<td>207</td>
</tr>
<tr>
<td>Valecillo 2021</td>
<td>7</td>
<td>36</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>762</td>
<td>478</td>
<td>30.33%</td>
<td>5.89</td>
</tr>
<tr>
<td>Total events</td>
<td>136</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00, Chi² = 0.72, df = 3 (P = 0.87); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.65 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 1952 1526 100.0% 3.64 [2.44, 5.43]

Total events 250 40

Heterogeneity: Tau² = 0.09, Chi² = 18.48, df = 14 (P = 0.29); I² = 15%

Test for overall effect: Z = 6.34 (P < 0.00001)

Test for subgroup differences: Chi² = 2.83, df = 1 (P = 0.09), I² = 84.7%
Figure G-4. Meta-analysis: Opioid vs. NSAID for drowsiness

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioid</th>
<th>NSAID</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breivik 1999</td>
<td>7</td>
<td>23</td>
<td>2.48 [0.71, 8.29]</td>
</tr>
<tr>
<td>Cattray 2020 Study 1</td>
<td>7</td>
<td>92</td>
<td>3.46 [0.74, 16.22]</td>
</tr>
<tr>
<td>Cattray 2020 Study 2</td>
<td>13</td>
<td>91</td>
<td>2.63 [0.98, 7.07]</td>
</tr>
<tr>
<td>Cooper 1982</td>
<td>23</td>
<td>127</td>
<td>1.06 [0.57, 1.98]</td>
</tr>
<tr>
<td>Cooper 1991</td>
<td>2</td>
<td>39</td>
<td>0.71 [0.15, 3.36]</td>
</tr>
<tr>
<td>Cooper 2021</td>
<td>0</td>
<td>87</td>
<td>0.34 [0.01, 8.35]</td>
</tr>
<tr>
<td>Forbes 1990</td>
<td>1</td>
<td>40</td>
<td>0.31 [0.04, 2.37]</td>
</tr>
<tr>
<td>Malmstrom 2004</td>
<td>4</td>
<td>50</td>
<td>4.06 [0.47, 35.25]</td>
</tr>
<tr>
<td>Moore 2015</td>
<td>5</td>
<td>367</td>
<td>5.47 [0.30, 98.39]</td>
</tr>
<tr>
<td>Thota 2021</td>
<td>6</td>
<td>30</td>
<td>17.00 [1.03, 281.51]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>946</td>
<td>844</td>
<td>1.71 [0.97, 3.03]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>70</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.22, Chi² = 12.85, df = 9 (P = 0.17); I² = 30%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.85 (P = 0.06)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Multidose**     |        |       |                                |
| Akinbode 2019     | 6      | 45    | 13.00 [0.75, 224.13]           |
| Vallecillo 2021   | 3      | 36    | 2.83 [0.31, 25.63]             |
| **Subtotal (95% CI)** | 81 | 79 | 5.03 [0.88, 26.89] |
| **Total events**  | 9      | 1     |                                |
| Heterogeneity: Tau² = 0.00, Chi² = 0.74, df = 1 (P = 0.39); I² = 0% |
| Test for overall effect: Z = 1.81 (P = 0.07) |

| **Total (95% CI)** | 1027 | 923 | 1.89 [1.09, 3.27] |
| **Total events**  | 79   | 42  |                                |
| Heterogeneity: Tau² = 0.24, Chi² = 15.38, df = 11 (P = 0.17); I² = 29% |
| Test for overall effect: Z = 2.26 (P = 0.02) |
| Test for subgroup differences: Chi² = 1.32, df = 1 (P = 0.25); I² = 24.2% |
Figure G-5. Meta-analysis: Opioid vs. NSAID for dizziness

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioid Events</th>
<th>Opioid Total</th>
<th>NSAID Events</th>
<th>NSAID Total</th>
<th>Weight M-H</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catty 2020 Study 1</td>
<td>7</td>
<td>92</td>
<td>0</td>
<td>91</td>
<td>2.3%</td>
<td>14.64 [0.66, 256.06]</td>
</tr>
<tr>
<td>Catty 2020 Study 2</td>
<td>11</td>
<td>91</td>
<td>2</td>
<td>92</td>
<td>10.6%</td>
<td>5.56 [1.27, 24.39]</td>
</tr>
<tr>
<td>Cooper 1982</td>
<td>4</td>
<td>127</td>
<td>0</td>
<td>76</td>
<td>2.8%</td>
<td>5.41 [0.30, 99.19]</td>
</tr>
<tr>
<td>Cooper 1991</td>
<td>2</td>
<td>39</td>
<td>0</td>
<td>63</td>
<td>2.6%</td>
<td>10.50 [0.52, 213.64]</td>
</tr>
<tr>
<td>Cooper 2021</td>
<td>6</td>
<td>87</td>
<td>0</td>
<td>90</td>
<td>2.8%</td>
<td>13.44 [0.77, 235.09]</td>
</tr>
<tr>
<td>Forbes 1990</td>
<td>2</td>
<td>40</td>
<td>9</td>
<td>125</td>
<td>10.0%</td>
<td>0.69 [0.16, 3.08]</td>
</tr>
<tr>
<td>Vaillantrast 2004</td>
<td>5</td>
<td>50</td>
<td>1</td>
<td>51</td>
<td>5.2%</td>
<td>5.10 [0.62, 42.12]</td>
</tr>
<tr>
<td>Moore 2015</td>
<td>9</td>
<td>387</td>
<td>2</td>
<td>182</td>
<td>10.0%</td>
<td>2.23 [0.46, 10.22]</td>
</tr>
<tr>
<td>Van Dyke 2004</td>
<td>8</td>
<td>250</td>
<td>2</td>
<td>166</td>
<td>9.8%</td>
<td>2.96 [0.64, 13.85]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1143</td>
<td>976</td>
<td></td>
<td></td>
<td></td>
<td>3.25 [1.72, 6.15]</td>
</tr>
<tr>
<td>Total events</td>
<td>54</td>
<td></td>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.00; \text{Ch}^2 = 7.95, \text{df} = 8 (P = 0.44); I^2 = 0\%

Test for overall effect: \( Z = 8.68 (P = 0.0003) \)

Multidose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioid Events</th>
<th>Opioid Total</th>
<th>NSAID Events</th>
<th>NSAID Total</th>
<th>Weight M-H</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akniode 2019</td>
<td>4</td>
<td>45</td>
<td>0</td>
<td>45</td>
<td>2.8%</td>
<td>9.00 [0.50, 152.43]</td>
</tr>
<tr>
<td>Brown 2013</td>
<td>0</td>
<td>82</td>
<td>2</td>
<td>192</td>
<td>2.5%</td>
<td>0.61 [0.03, 12.59]</td>
</tr>
<tr>
<td>Desjardins 2020</td>
<td>65</td>
<td>619</td>
<td>6</td>
<td>207</td>
<td>34.3%</td>
<td>3.62 [1.59, 8.24]</td>
</tr>
<tr>
<td>Valence 2021</td>
<td>9</td>
<td>36</td>
<td>0</td>
<td>34</td>
<td>3.0%</td>
<td>17.67 [1.06, 297.34]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>762</td>
<td>478</td>
<td></td>
<td></td>
<td></td>
<td>3.86 [1.85, 8.08]</td>
</tr>
<tr>
<td>Total events</td>
<td>76</td>
<td></td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.00; \text{Ch}^2 = 2.98, \text{df} = 3 (P = 0.40); I^2 = 0\%

Test for overall effect: \( Z = 3.99 (P = 0.0003) \)

Total (95% CI)

<table>
<thead>
<tr>
<th>Event Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1905</td>
<td>3.50 [2.16, 5.67]</td>
</tr>
</tbody>
</table>

Total events: 132

Heterogeneity: \( \tau^2 = 0.00; \text{Ch}^2 = 11.04, \text{df} = 12 (P = 0.63); I^2 = 0\%

Test for overall effect: \( Z = 5.06 (P < 0.00001) \)

Test for subgroup differences: \( \text{Ch}^2 = 0.12, \text{df} = 1 (P = 0.73); I^2 = 0\% \)
Figure G-6. Meta-analysis: Opioid vs. acetaminophen for nausea

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioid</th>
<th>Acetaminophen</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td><strong>Single dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breivik 1996</td>
<td>0</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Cooper 1980</td>
<td>24</td>
<td>172</td>
<td>3</td>
</tr>
<tr>
<td>Cooper 1981</td>
<td>2</td>
<td>42</td>
<td>37</td>
</tr>
<tr>
<td>Cooper 1991</td>
<td>1</td>
<td>39</td>
<td>2</td>
</tr>
<tr>
<td>Dorn 1994</td>
<td>2</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>Forbes 1990</td>
<td>1</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>Skoglund 1991</td>
<td>2</td>
<td>37</td>
<td>69</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>377</td>
<td>272</td>
<td>272</td>
</tr>
<tr>
<td>Total events</td>
<td>32</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00, Chi² = 2.62, df = 6 (P = 0.85); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.96 (P = 0.34)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Multidose**     |        |       |        |                          |
|                   | Events | Total | Weight |                          |
| Breivik 1996      | 2      | 10    | 10     | 4.8% 5.00 [0.27, 62.62]   |
| da Silva 2021     | 6      | 20    | 19     | 20.6% 3.60 [0.62, 15.67]  |
| **Subtotal (95% CI)** | 30    | 29    | 29     | 25.4% 4.00 [1.12, 14.32]  |
| Total events      | 10     | 2     |        |                          |
| Heterogeneity: Tau² = 0.00, Chi² = 0.03, df = 1 (P = 0.87); I² = 0% |
| Test for overall effect: Z = 2.13 (P = 0.03) |

| Total (95% CI)    | 407    | 301   | 100.0%| 1.86 [0.98, 3.54]         |
| Total events      | 42     | 12    |       |                          |
| Heterogeneity: Tau² = 0.00, Chi² = 4.51, df = 6 (P = 0.81); I² = 0% |
| Test for overall effect: Z = 1.90 (P = 0.06) |
| Test for subgroup differences: Chi² = 1.88, df = 1 (P = 0.17); I² = 48.2% |
Figure G-7. Meta-analysis: Opioid vs. acetaminophen for drowsiness

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioid</th>
<th>Acetaminophen</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Single dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooper 1990</td>
<td>26</td>
<td>172</td>
<td>37</td>
<td>24.9%</td>
</tr>
<tr>
<td>Cooper 1991</td>
<td>0</td>
<td>42</td>
<td>37</td>
<td>12.0%</td>
</tr>
<tr>
<td>Forbes 1990</td>
<td>2</td>
<td>38</td>
<td>37</td>
<td>11.5%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>293</strong></td>
<td><strong>152</strong></td>
<td><strong>355</strong></td>
<td><strong>66.4%</strong></td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 1.05, Chi² = 4.92, df = 3 (P = 0.16); I² = 39%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.81 (P = 0.42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Multidose        |        |          |       |         |                      |                      |
|                  | Events | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Breivik 1998     | 3      | 10      | 10   | 12.8%  | 7.00 [0.41, 120.16]  |                      |
| da Silva 2021    | 3      | 20      | 19   | 20.6%  | 2.65 [0.32, 25.07]   |                      |
| **Subtotal (95% CI)** | **30** | **29** | **59** | **33.8%** | **3.97 [0.71, 22.33]** |                      |
|                  | 6      | 1       |       |         |                      |                      |
| Heterogeneity: Tau² = 0.00, Chi² = 0.25, df = 1 (P = 0.62); I² = 0% |
| Test for overall effect: Z = 1.56 (P = 0.12) |

| Total (95% CI)   | 323    | 181     | 100.0% | 2.64 [0.92, 7.56] |
|                  | 98     | 6       |         |                      |
| Heterogeneity: Tau² = 0.16, Chi² = 5.47, df = 5 (P = 0.36); I² = 9% |
| Test for overall effect: Z = 1.81 (P = 0.07) |
| Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.55); I² = 0% |
Figure G-8. Meta-analysis: Opioid vs. acetaminophen for dizziness

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioid</th>
<th>Acetaminophen</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Single dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breivik 1999</td>
<td>7</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Cooper 1980</td>
<td>42</td>
<td>172</td>
<td>1</td>
</tr>
<tr>
<td>Cooper 1981</td>
<td>6</td>
<td>42</td>
<td>7</td>
</tr>
<tr>
<td>Cooper 1991</td>
<td>2</td>
<td>39</td>
<td>3</td>
</tr>
<tr>
<td>Forbes 1990</td>
<td>1</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>Thota 2021</td>
<td>8</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>346</td>
<td>206</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>86</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: \( \tau^2 = 1.46 \); \( \chi^2 = 13.42, df = 5 \) (P = 0.02); \( I^2 = 63\% \)
| Test for overall effect: \( Z = 1.37 \) (P = 0.17) |

| Multidose        |        |               |        |               |        |                                    |
|                  |        |               |        |               |        |                                    |
| Breivik 1996     | 4      | 10            | 1      | 10            | 11.2%  | 4.00 [0.54, 29.80]                 |
| da Silva 2021    | 7      | 19            | 3      | 19            | 18.2%  | 2.22 [0.67, 7.34]                  |
| **Subtotal (95% CI)** | 30    | 29            |        | 29            | 29.3%  | 2.59 [0.93, 7.24]                  |
| Total events     | 11     | 4             |        |               |        |                                    |
| Heterogeneity: \( \tau^2 = 0.00 \); \( \chi^2 = 0.25, df = 1 \) (P = 0.82); \( I^2 = 0\% \)
| Test for overall effect: \( Z = 1.81 \) (P = 0.07) |

| Total (95% CI)   | 376    | 235           | 100.0% | 2.36 [0.99, 5.63] |
| Total events     | 77     | 17            |        |                 |
| Heterogeneity: \( \tau^2 = 0.71 \); \( \chi^2 = 13.66, df = 7 \) (P = 0.06); \( I^2 = 49\% \)
| Test for overall effect: \( Z = 1.94 \) (P = 0.05) |
| Test for subgroup differences: \( \chi^2 = 0.01 \), \( df = 1 \) (P = 0.94); \( I^2 = 0\% \) |
## Appendix H. Strength of Evidence Tables

**Table H-1. Strength of evidence and key findings for new evidence***

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcomes</th>
<th>Timing of Outcomes</th>
<th>Number of Studies</th>
<th>Number of Subjects</th>
<th>Directness</th>
<th>Precision</th>
<th>Quality</th>
<th>Consistency</th>
<th>Findings</th>
<th>SOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KQ 1: Acute low back pain</strong></td>
<td>Pain, function</td>
<td>2 to &lt;4 w</td>
<td>2 (1 new)</td>
<td>428 (179 added)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Fair</td>
<td>Inconsistent</td>
<td>Effects on pain and function inconsistent</td>
<td>Insufficient (previously low)</td>
</tr>
<tr>
<td><strong>Traditional Chinese acupuncture vs. sham or usual care</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KQ 3: Other musculoskeletal pain</strong></td>
<td>Pain</td>
<td>&lt;1 day</td>
<td>1 (new)</td>
<td>154</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Good</td>
<td>Unable to assess (1 study)</td>
<td>Opioid associated with small decrease in pain intensity</td>
<td>Low*</td>
</tr>
<tr>
<td><strong>Opioid plus acetaminophen vs. acetaminophen</strong></td>
<td>Adverse events (any adverse event, drowsiness)</td>
<td>&lt;1 day</td>
<td>1 (new)</td>
<td>154</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Good</td>
<td>Unable to assess (1 study)</td>
<td>Opioid associated with increased likelihood of adverse events and drowsiness</td>
<td>Low*</td>
</tr>
<tr>
<td><strong>KQ 3: Other musculoskeletal pain</strong></td>
<td>Pain</td>
<td>&lt;1 day, 1 day to &lt;1 week</td>
<td>1 (new)</td>
<td>119</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Poor</td>
<td>Unable to assess (1 study)</td>
<td>Inconclusive due to poor quality</td>
<td>Insufficient*</td>
</tr>
<tr>
<td><strong>Topical ibuprofen vs. capsaicin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KQ 5: Postoperative pain</strong></td>
<td>Pain</td>
<td>1 d to &lt;1 w</td>
<td>5 (1 new)</td>
<td>900 (70 added)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Fair</td>
<td>Inconsistent</td>
<td>Unable to determine due to inconsistency</td>
<td>Insufficient</td>
</tr>
<tr>
<td><strong>Opoid vs. NSAID, multidose course, various surgeries</strong></td>
<td>Rescue medication use</td>
<td>1 d to &lt;1 w</td>
<td>5 (1 new)</td>
<td>930 (70 added)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Fair</td>
<td>Consistent</td>
<td>RR 1.22 to 2.04</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

*SOE indicates the strength of evidence (Low, Moderate). Adverse events (any adverse event, drowsiness)
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcomes</th>
<th>Timing of Outcomes</th>
<th>Number of Studies</th>
<th>Number of Subjects</th>
<th>Directness</th>
<th>Precision</th>
<th>Quality</th>
<th>Consistency</th>
<th>Findings</th>
<th>SOE</th>
</tr>
</thead>
</table>
| KQ 5: Postoperative pain  
Opioid vs. mixed agent | Pain                                         | <1 d, 1 d to <1 w, 1 to <2 w | 2 (1 new) for <1 d and 1 to <2 w; 7 (1 new) for 1 d to <1 w | 1,553 (91 added) | Direct | Imprecise | Fair    | Unable to assess (<1 d and 1 to <2 w); consistent (1 to <2 w) | No difference | Low (<1 day and 1 to <2 w); moderate (1 d to <1 w, previously low) |
| KQ 5: Postoperative pain  
Cold therapy vs. sham or usual care, various surgeries | Pain intensity | 1 w | 6 (3 new) | 505 (337 added) | Direct | Imprecise | Fair    | Inconsistent (<1 day); unable to assess (1 d to <1 w, 1 study) | Unable to determine at <1 day (inconsistently); low for moderate benefit at 1 day to <1 weeks | Insufficient (<1 d); low (1 d to <1 w) |
|                          | Pain intensity; function, QoL | ≥4 w | 2 (1 new) | 160 (100 added) | Direct | Imprecise | Fair    | Consistent | No difference | Low                                       |
| KQ 5: Postoperative pain  
Music therapy vs. no music therapy | Pain                                         | <1 d, 1 d to <1 w | 3 (1 new) | 195 (47 added) | Direct | Imprecise | Fair    | Consistent | Small to moderate decrease in pain intensity | Moderate (previously low) |
| KQ 5: Postoperative pain  
TENS vs. sham TENS | Pain intensity, analgesic use | 1 d to <1 w | 2 (1 new) | 122 (80 added) | Direct | Imprecise | Fair    | Consistent | Small to moderate decrease at 1 d to <1 w | Moderate (previously low) |
| KQ 5: Postoperative pain  
Abdominal binder vs. no abdominal binder | Pain                                         | 1 d to <1 w | 1 (new) | 196 | Direct | Precise | Poor    | Unable to assess (1 study) | Unable to determine due to serious methodological limitations | Insufficient* |

*Insufficient
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcomes</th>
<th>Timing of Outcomes</th>
<th>Number of Studies</th>
<th>Number of Subjects</th>
<th>Directness</th>
<th>Precision</th>
<th>Quality</th>
<th>Consistency</th>
<th>Findings</th>
<th>SOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KQ 5: Postoperative pain</strong> Preoperative education vs. no education</td>
<td>Pain, opioid use</td>
<td>1 w to 2 w</td>
<td>3 (new)</td>
<td>445</td>
<td>Direct</td>
<td>Precise</td>
<td>Fair</td>
<td>Consistent</td>
<td>Decreased opioid use at 1 to 2 weeks, with similar or decreased pain intensity</td>
<td>Low*</td>
</tr>
<tr>
<td><strong>KQ 6: Dental pain</strong> Opioid + acetaminophen vs. acetaminophen, multidose</td>
<td>Pain rescue medication use</td>
<td>&lt;1 d</td>
<td>2 (1 new)</td>
<td>59 (39 added)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Fair</td>
<td>Inconsistent</td>
<td>Unable to assess, due to imprecision and inconsistency</td>
<td>Insufficient</td>
</tr>
<tr>
<td><strong>KQ 6: Dental pain</strong> Opioid + acetaminophen vs. acetaminophen, single dose</td>
<td>Pain</td>
<td>&lt;1 d</td>
<td>12 (1 new)</td>
<td>888 (60 added)</td>
<td>Direct</td>
<td>Precise</td>
<td>Fair</td>
<td>Inconsistent</td>
<td>Opioids associated larger sum of pain intensity differences than acetaminophen, though magnitude varied</td>
<td>Moderate (for sum of pain intensity differences)</td>
</tr>
<tr>
<td><strong>KQ 6: Dental pain</strong> Opioid (with or without acetaminophen) vs. acetaminophen</td>
<td>Nausea, drowsiness, dizziness</td>
<td>&lt;1 d</td>
<td>6 to 9 (1 to 2 new)</td>
<td>504 to 708 (39 to 60 added)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Fair</td>
<td>Consistent</td>
<td>Increased risk with opioid <strong>Nausea</strong>: 9 trials, RR 1.86 (95% CI 0.98 to 3.54) <strong>Drowsiness</strong>: 8 trials, RR 2.36 (95% CI 0.99 to 5.63) <strong>Dizziness</strong>: 6 trials, RR 2.64 (95% CI 0.92 to 7.56)</td>
<td>Low</td>
</tr>
<tr>
<td>Intervention</td>
<td>Outcomes</td>
<td>Timing of Outcomes</td>
<td>Number of Studies</td>
<td>Number of Subjects</td>
<td>Directness</td>
<td>Precision</td>
<td>Quality</td>
<td>Consistency</td>
<td>Findings</td>
<td>SOE</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
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<td>-----------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>KQ 6: Dental pain</td>
<td>Pain</td>
<td>&lt;1 d, 1 d to &lt;1 w</td>
<td>14 (&lt;1 d, 2 new); 4 (1 d to &lt;1 w, 1 new)</td>
<td>826 to 2,021; 986 to 2,250; 60 to 229 (60 to 229 added)</td>
<td>Direct</td>
<td>Precise</td>
<td>Fair</td>
<td>Inconsistent</td>
<td>Small to moderate increase in pain intensity with opioids</td>
<td>Low</td>
</tr>
<tr>
<td>KQ 6: Dental pain</td>
<td>Any AE, nausea, dizziness, drowsiness</td>
<td>&lt;1 d, 1 d to &lt;1 w</td>
<td>12 to 15 (4 new)</td>
<td>1,950 to 3,478 (1,073 to 1,133 added)</td>
<td>Direct</td>
<td>Precise</td>
<td>Fair</td>
<td>Consistent</td>
<td>Increased risk with opioids</td>
<td>Moderate</td>
</tr>
<tr>
<td>KQ 6: Dental pain</td>
<td>Pain</td>
<td>&lt;1 d, 1 d to &lt;1 w</td>
<td>2 (1 new)</td>
<td>449 (412 added)</td>
<td>Direct</td>
<td>Precise</td>
<td>Fair</td>
<td>Consistent</td>
<td>No difference</td>
<td>Low</td>
</tr>
<tr>
<td>KQ 6: Dental pain</td>
<td>Pain intensity</td>
<td>&lt;1 d</td>
<td>15 (1 new)</td>
<td>2,563</td>
<td>Direct</td>
<td>Precise</td>
<td>Fair</td>
<td>Consistent</td>
<td>Moderate to large decrease in pain with NSAID</td>
<td>Moderate</td>
</tr>
</tbody>
</table>