



Comparative Effectiveness Review
Number 240

Treatments for Acute Pain: A Systematic Review



Treatments for Acute Pain: A Systematic Review

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States.

The Centers for Disease Control and Prevention requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the Pacific Northwest Evidence-based Practice Center (Contract Number: 290-2015-00009-I).

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new healthcare technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for healthcare quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality.

If you have comments on this systematic review, 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.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Treatments for Acute Pain: A Systematic Review

Structured Abstract

Objectives. To evaluate the effectiveness and comparative effectiveness of opioid, nonopioid pharmacologic, and nonpharmacologic therapy in patients with specific types of acute pain, including effects on pain, function, quality of life, adverse events, and long-term use of opioids.

Data sources. Electronic databases (Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews) to August 2020, reference lists, and a Federal Register notice.

Review methods. Using predefined criteria and dual review, we selected randomized controlled trials (RCTs) of outpatient therapies for eight acute pain conditions: low back pain, neck pain, other musculoskeletal pain, neuropathic pain, postoperative pain following discharge, dental pain (surgical or nonsurgical), pain due to kidney stones, and pain due to sickle cell disease. Meta-analyses were conducted on pharmacologic therapy for dental pain and kidney stone pain, and likelihood of repeat or rescue medication use and adverse events. The magnitude of effects was classified as small, moderate, or large using previously defined criteria, and strength of evidence was assessed.

Results. One hundred eighty-three RCTs on the comparative effectiveness of therapies for acute pain were included. Opioid therapy was probably less effective than nonsteroidal anti-inflammatory drugs (NSAIDs) for surgical dental pain and kidney stones, and might be similarly effective as NSAIDs for 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. For postoperative pain, opioids were associated with increased likelihood of repeat or rescue analgesic use, but effects on pain intensity were inconsistent. 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. Heat therapy was probably effective for acute low back pain, spinal manipulation might be effective for acute back pain with radiculopathy, acupressure might be effective for acute musculoskeletal pain, an opioid might be effective for acute neuropathic pain, massage might be effective for some types of postoperative pain, and a cervical collar or exercise might be effective for acute neck pain with radiculopathy. Most studies had methodological limitations. Effect sizes were primarily small to moderate for pain, the most commonly evaluated outcome. 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. Evidence on how benefits or harms varied in subgroups was lacking.

Conclusions. Opioid therapy was associated with decreased or similar effectiveness as an NSAID for some acute pain conditions, but with increased risk of short-term adverse events. Evidence on nonpharmacological therapies was limited, but heat therapy, spinal manipulation, massage, acupuncture, acupressure, a cervical collar, and exercise were effective for specific

acute pain conditions. Research is needed to determine 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.

Contents

Evidence Summary	1
Introduction.....	1
Background	1
Purpose and Scope of the Systematic Review	2
Methods.....	3
Review Approach.....	3
Key Questions	3
Opioid Therapy	3
Nonopioid Pharmacologic Therapy	4
Nonpharmacologic Therapy.....	5
Study Selection	5
Data Extraction and Risk of Bias Assessment	6
Data Synthesis and Analysis	7
Grading the Strength of the Body of Evidence	7
Results	8
Key Question (KQ) 1. Acute Back Pain (Including Back Pain With Radiculopathy).....	9
Key Points	9
Summary of Findings.....	12
Detailed Synthesis.....	12
KQ 2. Acute Neck Pain (Including Neck Pain With Radiculopathy)	38
Key Points	38
Summary of Findings.....	39
Detailed Synthesis.....	39
KQ 3. Musculoskeletal Pain Not Otherwise Included in KQ1 or KQ2 (Including Fractures) .	42
Key Points	42
Summary of Findings.....	43
Detailed Synthesis.....	43
KQ 4. Peripheral Neuropathic Pain (Related to Herpes Zoster and Trigeminal Neuralgia).....	58
Key Points	58
Summary of Findings.....	58
Detailed Synthesis.....	58
KQ 5. Postoperative Pain (Excluding Inpatient Management of Pain Following Major Surgical Procedures).....	60
Key Points	60
Summary of Findings.....	62
Detailed Synthesis.....	62
KQ 6. Dental Pain (Surgical and Nonsurgical After Discharge)	85
Key Points	85
Summary of Findings.....	87
Detailed Synthesis.....	87
KQ 7. Kidney Stone Pain	114
Key Points	114
Summary of Findings.....	115
Detailed Synthesis.....	115
KQ 8. Sickle Cell Crisis	121

Key Points	121
Summary of Findings.....	121
Detailed Synthesis.....	121
Discussion.....	124
Key Findings and Strength of Evidence	124
Findings in Relationship to What Is Already Known	130
Applicability.....	131
Implications for Clinical and Policy Decision Making.....	131
Limitations of the Review Process.....	132
Limitations of the Evidence Base	133
Research Gaps.....	133
Conclusions	134
References	135
Abbreviations and Acronyms	153

Tables

Table 1. Opioid versus NSAID or muscle relaxant for back pain	13
Table 2. Opioid agonists versus mixed agents for back pain.....	15
Table 3. Nonopioid pharmacologic therapy versus other nonopioid pharmacologic therapy for back pain	18
Table 4. Nonopioid pharmacologic therapy versus manipulation for back pain	20
Table 5. Nonopioid pharmacologic therapy versus acupuncture for back pain.....	21
Table 6. Exercise for acute low back pain	24
Table 7. Acupuncture versus sham or usual care for acute back pain	28
Table 8. Braces or belts versus no braces or belts for acute low back pain.....	29
Table 9. Heat versus usual care, placebo, or cold therapy for acute low back pain	31
Table 10. Manipulation versus usual care, placebo, and other nonpharmacologic interventions for acute low back pain.....	35
Table 11. Nonpharmacologic interventions for acute neck pain	41
Table 12. Opioid therapy versus NSAIDs or mixed agent opioids.....	45
Table 13. NSAID versus other pharmacologic treatments for musculoskeletal pain	48
Table 14. Cold therapy versus other nonpharmacologic therapies for musculoskeletal pain.....	53
Table 15. Ultrasound versus no ultrasound or sham ultrasound for musculoskeletal pain.....	53
Table 16. Other nonpharmacologic therapies for musculoskeletal pain.....	56
Table 17. Opioid versus gabapentin for herpes zoster-related pain.....	59
Table 18. Nonopioid interventions for herpetic neuralgia	60
Table 19. Opioid therapy versus nonsteroidal anti-inflammatory drugs for postoperative pain ..	64
Table 20. Opioid therapy versus acetaminophen for postoperative pain.....	66
Table 21. Opioid agonist versus mixed agent for postoperative pain.....	68
Table 22. NSAIDs versus acetaminophen or aspirin for postoperative pain	72
Table 23. Acupuncture or acupressure versus sham or usual care	74
Table 24. Cold therapies versus no cold therapy or sham for postoperative pain	77
Table 25. Massage versus no massage for postoperative pain.....	80
Table 26. Music therapy versus silence, usual care, or relaxation for postoperative pain.....	83
Table 27. Neck stretching exercises versus no exercise for postoperative pain	84
Table 28. Transcutaneous electrical nerve stimulation or neuromuscular stimulation versus no treatment or sham.....	85

Table 29. Opioid therapy versus NSAIDs for dental pain	91
Table 30. Opioid therapy versus acetaminophen for dental pain.....	98
Table 31. Opioid agonists versus mixed agents for dental pain	101
Table 32. NSAIDs versus acetaminophen for acute dental pain	105
Table 33. Miscellaneous nonopioid pharmacologic interventions versus NSAIDs for acute dental pain.....	111
Table 34. Cold therapy versus no cold therapy for dental pain	113
Table 35. Opioid versus NSAIDs for acute renal colic	116
Table 36. Opioid versus acetaminophen and opioid agonist versus partial agonist for acute renal colic.....	118
Table 37. NSAIDs versus acetaminophen for acute renal colic	119
Table 38. Acupuncture versus NSAID or acetaminophen for acute renal colic	120
Table 39. Opioid agonist or partial agonist versus mixed agent for sickle cell pain	122
Table 40. Nonpharmacologic interventions for sickle cell pain	123
Table 41. Summary of evidence of treatments for acute pain: pain	125

Figures

Figure 1. Literature flow diagram.....	9
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Appendixes

Appendix A. Literature Search Strategies
Appendix B. Methods
Appendix C. Included Studies List
Appendix D. Forest Plots
Appendix E. Evidence Tables
Appendix F. Risk of Bias Assessment
Appendix G. Details on Strength of Evidence
Appendix H. Excluded Studies List

Evidence Summary

Main Points

- Opioids are probably less effective than nonsteroidal anti-inflammatory drugs (NSAIDs) for surgical dental pain and kidney stone pain and might be similarly effective to NSAIDs for low back pain.
- Opioids might be and NSAIDs are probably more effective than acetaminophen for surgical dental pain, but opioids are probably less effective than acetaminophen for kidney stone pain.
- An opioid might be more effective than gabapentin for acute neuropathic pain.
- Opioids are probably associated with increased risk of short-term adverse events versus nonopioid pharmacologic therapy for acute pain, including any adverse event, study withdrawal due to adverse events, nausea, dizziness, and somnolence, but serious adverse events are uncommon in randomized trials.
- Being prescribed an opioid for acute low back pain or postoperative pain might be associated with increased likelihood of use of opioids at long-term followup versus not being prescribed.
- Heat therapy is probably effective for acute low back pain, spinal manipulation might be effective for acute back pain with radiculopathy, massage might be effective for postoperative pain, and a cervical collar or exercise might be effective for acute neck pain with radiculopathy.
- Research is very limited on the comparative effectiveness of therapies for sickle cell pain, acute neuropathic pain, neck pain, and management of postoperative pain following discharge.

Background and Purpose

The purpose of this review is to evaluate the effectiveness and comparative effectiveness of opioid, nonopioid pharmacologic, and nonpharmacologic therapy in patients with specific types of acute pain, including effects on pain, function, quality of life, adverse events, and long-term use of opioids.

Methods

Electronic databases (Ovid[®] MEDLINE[®], PsycINFO[®], Embase[®], the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews) were searched through August 5, 2020 for relevant publications. Searches were supplemented by reviewing reference lists and a Federal Register Notice.

Randomized controlled trials (RCTs) of opioid therapy versus nonopioid pharmacologic or nonpharmacologic therapy, nonopioid therapy versus nonpharmacologic therapy, nonpharmacologic therapy versus inactive controls (placebo, sham therapy, attention control, or a minimal intervention), and head-to-head trials of nonopioid pharmacologic and nonpharmacologic therapy were selected using predefined criteria and dual review. Observational studies on the association between being prescribed opioids for acute pain versus no opioids and on factors influencing opioid prescribing for acute pain conditions were also included. This review focused on eight acute pain conditions: 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. The review focused on outpatient management or therapy initiated shortly before discharge (e.g., after surgery or in emergency department). Outcomes were analyzed at <1 day, 1 day to <1 week, 1 week to <2 weeks, 2 to <4 weeks, and ≥ 4 weeks. Meta-analyses were conducted on pharmacologic therapy for dental pain and kidney stone pain and likelihood of repeat or rescue medication use and adverse events. Otherwise, meta-analyses were not conducted due to small number of studies, methodological limitations and study heterogeneity. The magnitude of effects was classified as small, moderate or large using previously defined criteria, and strength of evidence was assessed.

Results

The review included 183 RCTs on the comparative effectiveness of therapies for acute pain. Most studies had methodological limitations. Evidence did not suggest an increased risk of serious harms for any intervention, though studies were not designed to assess serious harms. Effect sizes were primarily small to moderate for pain, the most commonly evaluated outcome. Evidence on how benefits or harms varied in subgroups was lacking. Main findings (focusing on effects on pain) are summarized by acute pain condition.

Low back pain (38 trials): Evidence indicated that there might be no difference between an opioid versus an NSAID and there might be no difference versus a muscle relaxant. Opioids were associated with increased risk of short-term adverse events (any adverse event, study withdrawal due to adverse events, dizziness and nausea) for both comparisons. Serious adverse events were uncommon, but studies were not designed to assess risk of overdose, opioid use disorder, or long-term harms. Being prescribed opioids might be associated with increased risk of long-term use versus not being prescribed, based on observational studies. Muscle relaxants might be associated with small to moderate improvement versus benzodiazepines. There might be no difference between an NSAID or muscle relaxant versus manipulation at 1 to <2 weeks, 2 to <4 weeks, or ≥ 4 weeks. Acupuncture might be associated with moderate decrease in pain and improved function at 2 to <4 weeks and at 4 weeks. Exercise might be associated with similar effects compared with usual care and probably associated with similar effects compared with bed rest at 1 week to 52 weeks, but might be associated with fewer sick days compared with bed rest at 3 and 12 weeks. Effects of traditional acupuncture varied depending on the type of sham control evaluated. There might be no difference between a brace versus no brace for acute pain associated with osteoporotic compression fracture at 2 to <4 weeks and at ≥ 4 weeks. Heat therapy was probably associated with moderate decrease in pain versus usual care or placebo at 1 day to <1 week and 2 to <4 weeks. There might be no difference between manipulation versus inactive controls at 1 day to <1 week and ≥ 4 weeks. Manipulation might be associated with increased likelihood of improvement in pain in patients with radiculopathy versus sham at 2 to <4 weeks and ≥ 4 weeks.

Neck pain (5 trials): No trial evaluated pharmacologic therapy for acute neck pain. For neck pain with radiculopathy, a cervical collar or exercise might be associated with moderate to large decreases in pain versus usual activity at 2 to <4 weeks and at ≥ 4 weeks; effects of a collar and exercise were similar. For whiplash neck sprain, there might be no difference between ultrasound versus sham at 1 to <2 weeks, and there might be no difference between a cervical collar versus usual activity or exercise at ≥ 4 weeks. Evidence on other nonpharmacologic therapies for nonradicular neck pain was lacking.

Other musculoskeletal pain (30 trials): Evidence on opioids versus NSAIDs was insufficient. An NSAID and acetaminophen were probably associated with similar effects for acute musculoskeletal injury (sprains, strains, minor trauma) at <1 day, at 1 day to <1 week, at 1 to <2 weeks, and at ≥ 4 weeks. There might be no difference between ultrasound versus sham for ankle sprain. Acupressure might be associated with moderate to large decreases in pain at 1 day to < 1 week and with small effects at 4 weeks compared with sham acupressure or usual care. Evidence on other nonpharmacologic therapy was insufficient.

Peripheral neuropathic pain (2 trials): An opioid might be associated with increased likelihood of improvement in pain versus gabapentin for acute herpes zoster at 1 to <2 weeks and at ≥ 4 weeks, and increased likelihood of constipation. Evidence for acute neuropathic pain was otherwise lacking.

Postoperative pain (47 trials): Trials of postoperative pain focused on treatment in the immediate postoperative period, usually prior to discharge. A multidose course of opioids was probably associated with increased likelihood of repeat or rescue medication use versus an NSAID at <1 day. Opioids might be associated with increased risk of study withdrawal due to adverse events versus acetaminophen. Being prescribed an opioid for elective or minor surgery might be associated with increased likelihood of long-term use versus not being prescribed. Legislation mandating the use of prescription drug monitoring data and an opioid risk assessment tool might not decrease opioid prescribing. Auricular acupressure might be associated with decreased pain medication use versus sham at <1 day and 1 day to <1 week. There might be no difference between cold therapy versus sham in pain at 1 day to <1 week, 2 to <4 weeks or ≥ 4 weeks, though cold therapy was associated with decreased pain medication use at <1 weeks. Massage might be associated with moderate to large decrease in pain intensity at <1 day and decreased pain medication use versus no massage. Single trials suggest that exercise or transcutaneous electrical nerve stimulation (TENS) following specific surgical procedures might reduce pain versus no exercise or sham TENS.

Dental pain (46 trials): A single dose of an opioid plus acetaminophen might be associated with decreased pain and decreased likelihood of rescue or repeat medication use at <1 day versus acetaminophen, and probably is associated with increased risk of adverse events. An opioid plus acetaminophen or NSAID is probably associated with a small to moderate increase in pain intensity versus an NSAID at <1 day and increased likelihood of rescue or repeat medication use (NSAID doses were lower in the opioid arm than the NSAID-only arm in some trials); opioids were probably associated with increased likelihood of adverse events. NSAIDs are probably associated with moderate to large decrease in pain versus acetaminophen at <1 day, decreased likelihood of rescue or repeat medication use, and decreased risk of adverse events. Evidence on nonpharmacologic therapy was insufficient.

Kidney stone pain (12 trials): A single dose of morphine is probably associated with increased likelihood of persistent pain at <1 day, decreased likelihood of pain relief, increased likelihood of rescue medication use, and increased likelihood of adverse events versus an NSAID. Findings were similar for a single dose of meperidine, though this medication is discouraged due to concerns about adverse events. NSAIDs might be associated with decreased likelihood of rescue medication use versus acetaminophen. Acupuncture might be associated with moderately increased pain intensity versus a single dose of an NSAID or acetaminophen at <1 day.

Sickle cell pain (3 trials): Evidence was insufficient from three small trials with methodological limitations.

Limitations

We excluded non-English language articles and did not search for studies published only as abstracts. We did not conduct statistical and graphical methods for assessing for small sample effects (a potential marker for publication bias) due to small numbers of trials and heterogeneity in study design methods, patient populations, and outcomes.

The evidence base had important limitations. First, there was very little evidence for sickle cell pain, acute neuropathic pain, and neck pain. Evidence was also limited for musculoskeletal pain other than low back pain and kidney stone pain. Additionally, trials were not designed to evaluate how benefits and harms varied in subgroups. Patients with a history of substance use disorder, who represent an important clinical challenge, were often excluded from trials, and trials were not designed to evaluate how benefits and harms varied according to opioid dose or amount prescribed. Evidence on the accuracy and effectiveness of risk assessment instruments was unavailable, and evidence on how risk mitigation strategies, patient education, and other factors impact prescribing of opioids was very limited.

Implications and Conclusions

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 pain for surgical dental pain, but opioids were less effective than acetaminophen for kidney stone pain. 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. With regard to nonpharmacological therapies, heat therapy is probably effective for acute low back pain, spinal manipulation is probably effective for acute back pain with radiculopathy, acupuncture might be effective for acute low back pain, massage might be effective for postoperative pain, acupressure might be effective for acute musculoskeletal pain, and a cervical collar or exercise might be effective for acute neck pain with radiculopathy. Research is needed to determine 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; and how benefits and harms of therapies vary in subgroups.

Introduction

Background

Pain is nearly universal, contributing substantially to morbidity, mortality, disability, and healthcare system burdens.^{1,2} Acute pain has been defined as “the physiologic response and experience to noxious stimuli that can become pathologic, is normally sudden in onset, time limited, and motivates behaviors to avoid actual or potential tissue injuries.”³ Acute pain usually lasts for less than 7 days but often extends up to 30 days;⁴ for some conditions, acute pain episodes may recur periodically. In some patients, acute pain persists to become chronic. Acute pain is expected and ubiquitous following surgery.⁵ Pain is the most common reason for emergency department visits and is commonly encountered in primary care, other outpatient, and inpatient settings.^{1,6,7}

The key decisional dilemma in acute pain management involves selection of interventions to provide adequate pain relief, in order to improve quality of life, improve function, and facilitate recovery, while minimizing adverse effects and avoiding overprescribing of opioids.⁸ Evidence also suggests that adequate acute pain treatment may mitigate factors that promote the transition to chronic pain.^{3,9,10} However, shortcomings in acute pain care have been documented.^{11,12} In addition to the underlying cause of pain, patient factors that impact acute pain management include age, sex, race/ethnicity, pain severity, comorbidities (including mental health and substance use), genetic factors, pregnancy, or breastfeeding status.¹³⁻¹⁶ Timing of presentation and clinical setting can also influence acute pain management. For example, postoperative pain occurs at a specific point in time and is often managed with multimodal strategies in a monitored setting prior to discharge, whereas in outpatient clinic settings, timing of presentation of acute pain is variable, and assessing treatment response is often not feasible. Additionally, access and care options may vary.^{2,8} Different acute pain conditions (e.g., musculoskeletal pain, neuropathic pain, or visceral pain) may respond differently to treatments. Therefore, a treatment that is effective for one acute pain condition and patient in a particular setting may not be effective in others.

Opioids, traditionally considered the most potent analgesics, are frequently used for acute pain. Therefore, acute pain management must be considered within the context of the current opioid crisis. Opioid prescribing quadrupled from 1999 to 2010; concurrently, the number of opioid analgesics deaths and opioid use disorder cases similarly rose sharply.¹⁷ In 2017, an estimated 47,600 Americans died from opioid overdose (approximately 17,000 from prescription opioids¹⁸). Until recently, policy efforts have focused on opioids for chronic pain, but attention has increasingly shifted to use for acute pain. Recent data suggest an association between use of opioids for acute pain and persistent long-term use, with some evidence of a dose and duration-response relationship.^{17,19-24} In addition, some studies indicate that opioids may not be more effective than nonopioid therapies for some acute pain conditions,²⁵⁻²⁹ and use of opioids may negatively affect recovery and function.^{30,31} Opioids prescribed for surgery and other acute pain conditions often go unused, a potential source for diversion and misuse.³²⁻³⁴ The 2016 Centers for Disease Control and Prevention (CDC) guideline focused on chronic pain, but included one recommendation to limit opioids for acute pain in most cases to 3 to 7 days. This recommendation was based on evidence indicating an association between use of opioids for acute pain and long-term use.³⁵ In the last several years, over 25 states have passed laws restricting prescribing of opioids for pain; nearly half of the states with limits specify that they apply to acute pain.^{20,36} Although data indicate some effects of policies in reducing opioid

prescribing, studies on clinical outcomes are lacking. Concerns include the effectiveness, availability, and insurance coverage of nonopioid treatment alternatives, potential undertreatment of acute pain, and other unintended consequences.^{37,38} A draft Agency for Healthcare Research and Quality Technical Brief (Treatment for Acute Pain: Evidence Map) identified a number of acute pain conditions for which evidence (from systematic reviews and original research) to inform treatment decisions is available, however it also noted that few reviews were sufficiently rigorous and comprehensive and that an up-to-date comprehensive systematic review would provide valuable information.³⁹

Purpose and Scope of the Systematic Review

This systematic review will assess the comparative effectiveness of treatments and harms of opioid and nonopioid treatments for surgical and nonsurgical pain related to eight acute pain conditions (back pain, neck pain, other musculoskeletal pain, neuropathic pain, postoperative pain [excluding inpatient management of pain following major surgical procedures], dental pain, kidney stones, and sickle cell crisis). The intended audience includes the CDC, policy and decision makers, and clinicians who treat acute pain. A concurrent review addresses treatments for acute pain related to episodic migraines.

Methods

Review Approach

This Comparative Effectiveness Review follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews⁴⁰ (hereafter “AHRQ Methods Guide”). All methods were determined a priori, and a protocol was published on the AHRQ website (<https://effectivehealthcare.ahrq.gov/products/treatments-acute-pain/protocol>) and registered with the PROSPERO systematic reviews registry (CRD42020165677). Below is a summary of the methods used in this review. Search strategies appear in Appendix A, and detailed methods are described in Appendix B.

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, NSAIDs, 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: 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?

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?

Study Selection

Electronic searches for evidence were conducted in August 2020 on Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from the inception of each database. Search strategies are available in Appendix A. Electronic searches were supplemented with review of reference lists of relevant studies. A Federal Register Notice was posted and a Supplemental Evidence And Data for Systematic review (SEADS) portal was available for submission of unpublished studies.

Studies were selected for inclusion using pre-established criteria based on the KQs and populations, interventions, comparators, outcomes, timing, and settings (PICOTS) of interest (Appendix B, Table B-1).⁴⁰ Briefly, this report focused on the eight acute pain (defined as pain <4 weeks in duration) conditions described above. The focus of the report was on outpatient management of acute pain; therefore, it excluded studies on inpatient management of acute pain, including inpatient management of pain following major surgical procedures. However, because acute pain is often initially managed in emergency department and acute care settings, studies in which therapy for included acute pain conditions was initiated in such settings in patients who were then discharged within one day or expected to be discharged soon were included. Studies of therapies initiated in postoperative or dental care settings were also included. In some cases (e.g., single dose studies of pharmacologic therapies or single session of nonpharmacologic therapy) therapy was not continued as an outpatient; we did not exclude such studies. Because few studies on outpatient management of sickle cell pain were expected, inpatient studies were included.

For pharmacologic therapy (opioid or nonopioid), this report focused on studies of comparative effectiveness, to address decisional dilemmas regarding the choice of pharmacologic therapy. The efficacy of pharmacologic therapy versus placebo has been addressed in other reviews. For nonpharmacologic therapy, there is more uncertainty about efficacy for acute pain. Therefore, studies comparing nonpharmacologic therapy versus inactive therapies (placebo, sham therapy, no therapy, attention control, or minimal intervention) were included, as well as head-to-head studies of comparative effectiveness. Interventions that involved combinations of different therapy were excluded, with the exception of an opioid plus acetaminophen or NSAID, since these medications are commonly administered together; this combination was classified as an opioid and analyzed separately from an opioid alone if sufficient data were available. Studies in which all patients received background therapy (i.e., not involved in the analyzed comparison) were included, as long as the background therapy could reasonably be considered usual care (e.g., non-opioid analgesics, education, or standard home exercises).

Outcomes were pain, function, quality of life (including mood and sleep), and harms. Outcomes were assessed at prespecified time periods: <1 day, 1 day to <1 week, 1 week to <2 weeks, 2 weeks to <4 weeks, and ≥ 4 weeks.

For KQs related to effectiveness and comparative effectiveness, inclusion was restricted to randomized controlled trials. Controlled observational studies (cohort, case-control, and before-after studies) were eligible to assess effects of opioid prescribing versus no prescribing on long-term use, accuracy and effectiveness of risk prediction instruments, and factors influencing prescribing.

All citations were reviewed by one investigator for potential inclusion and full text review. Excluded abstracts were reviewed by a second investigator to confirm the exclusion decision. Each full-text article was independently reviewed for eligibility by two team members. Disagreements were resolved by consensus.

Searches will be updated for new publication while the draft report is posted for public comment. Literature identified during the update search will be assessed using the process described above for the original search. Any pertinent new literature identified in the update search will be incorporated into the report prior to finalization.

Data Extraction and Risk of Bias Assessment

Data were extracted from included studies into standardized Excel spreadsheets, including study characteristics, inclusion criteria, patient characteristics, and results. Some studies reported summary data based on multiple pain measurements over a specified time period (e.g., average pain or sum of pain intensity differences). When available, we reported outcomes reported at specific time points; when necessary, data were estimated from figures provided in the studies. We extracted continuous as well as dichotomous results. We prioritized results for pain intensity in the following order: 1) mean difference in pain intensity at followup; 2) mean difference in pain intensity change from baseline; 3) mean difference in pain relief at followup; 4) other outcomes for pain intensity. Effects on pain intensity were converted when necessary to a 0 to 10 scale to facilitate interpretation across studies using different scales. Unadjusted relative risks and mean differences with 95 percent confidence intervals were calculated if necessary, using an online calculator (MedCalc).

Predefined criteria were used to assess the quality of individual controlled trials, in conjunction with the approach recommended in the chapter, AHRQ Methods Guide.⁴⁰

Data Synthesis and Analysis

Evidence tables were created to show detailed study characteristic and results, and summary tables were created to highlight the main findings. Meta-analyses were not appropriate for most comparisons and outcomes due to the small number of studies for each comparison and outcome, methodological limitations in the studies, and variability in the studies, including methods for measuring outcomes.⁴¹ Comparisons and outcomes for which meta-analyses could be conducted were limited to opioids versus NSAIDs or acetaminophen for the outcomes rescue or repeat medication use and selected harms for dental pain and kidney stone pain. Meta-analyses were conducted using Review Manager 5.3 (The Nordic Cochrane Centre, the Cochrane Collaboration, 2014).

The magnitude of effects for pain and function was classified as small, moderate, or large using the same system applied in other recent AHRQ-funded, pain-related systematic reviews conducted at our Evidence-based Practice Center (EPC).⁴²⁻⁴⁵

Grading the Strength of the Body of Evidence

The strength of evidence for each KQ/body of evidence was initially assessed by one researcher for each clinical outcome (see PICOTS) by using the approach described in the AHRQ Methods Guide (see Appendix B).⁴⁰ To ensure the consistency and validity of the assessment, the strength of evidence grade was reviewed by the entire team of investigators prior to assigning a final grade. The strength of evidence grades of high, moderate, low, or insufficient was based on the assessment of the following factors:

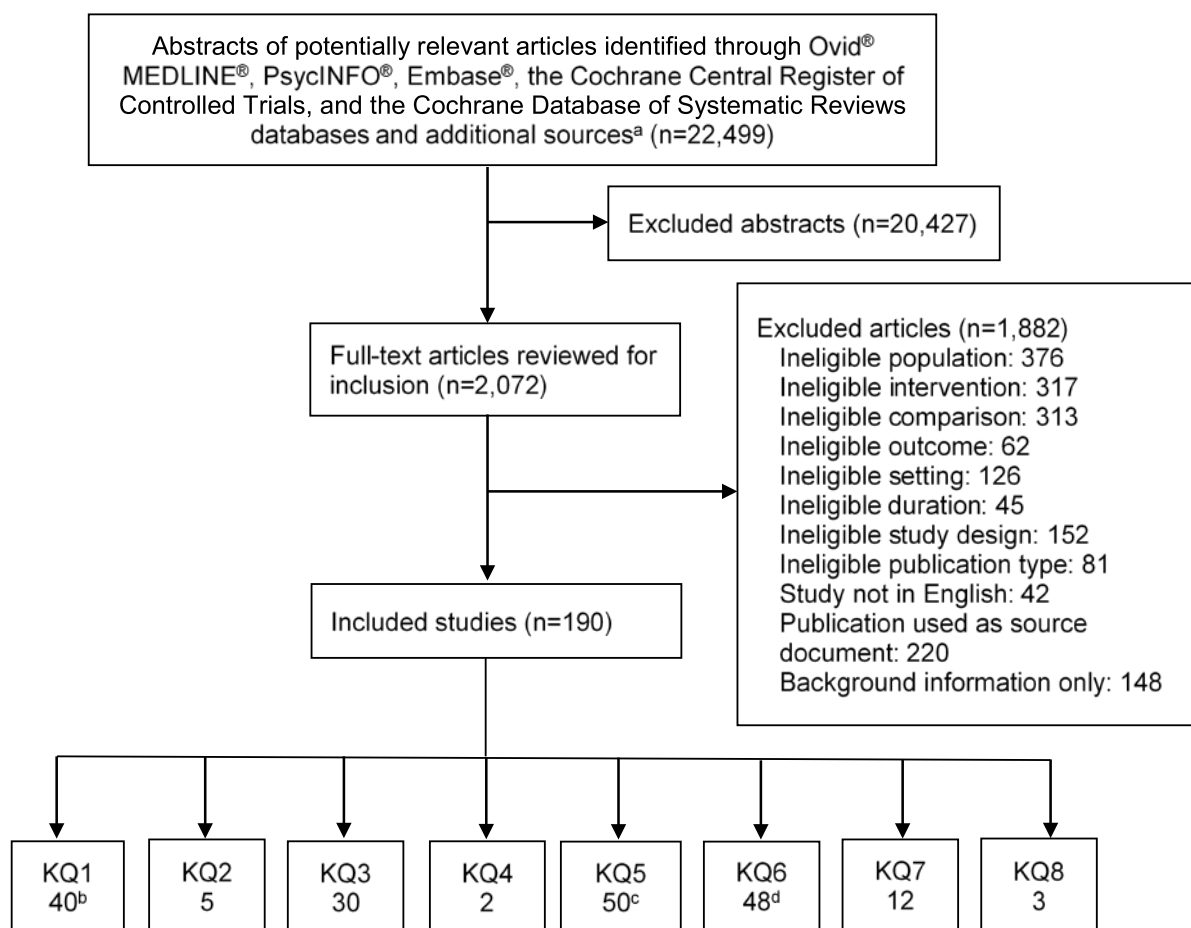
- Study limitations (low, medium, or high level of study limitations)
- Consistency (consistent, inconsistent, or unknown/not applicable)
- Directness (direct or indirect)
- Precision (precise or imprecise)
- Reporting bias (suspected or undetected)

Results

A total of 22,499 abstracts were reviewed, including 22,045 from electronic database searches and 454 from reviewing studies included in prior Evidence-based Practice Center reports and other systematic reviews. After dual review of titles and abstracts, 2,072 were selected for full-text review, of which 183 randomized controlled trials (RCTs) assessing treatments, 5 observational studies on risk of long-term opioid use, and 2 observational studies assessing effects on prescribing rates were included in this review. By pain condition, low back pain was addressed in 38 trials, neck pain in 5 trials, other musculoskeletal pain in 30 trials, neuropathic pain in 2 trials, postoperative pain in 47 trials, dental pain in 46 trials, kidney stone pain in 12 trials, and sickle cell pain in 3 trials. The search results and selection of studies are summarized in the literature flow diagram (Figure 1). Appendix C provides a list of all included studies.

Appendix D contains additional results for pooled data from studies where data were available. Detailed evidence tables for included studies and quality assessments are available in Appendixes E and F. Appendix G contains details on the strength of evidence, and Appendix H lists excluded studies along with reasons for exclusion.

Figure 1. Literature flow diagram



Abbreviations: KQ = Key Question

^a Additional sources include suggested references, reference lists, etc.

^b 38 randomized controlled trials of treatments and 2 observational studies of long-term use.

^c 47 randomized controlled trials of treatments, 2 observational studies of long-term use, and 1 observational study assessing effects on prescribing rates.

^d 46 randomized controlled trials of treatments, 1 observational study of long-term use, and 1 observational study assessing effects on prescribing rates.

Key Question (KQ) 1. Acute Back Pain (Including Back Pain With Radiculopathy)

Key Points

- Opioid vs. nonsteroidal anti-inflammatory drug (NSAID)
 - No difference in pain intensity at <1 day, pain relief at 1 day to <1 week, or functional impairment at 1 day to <1 week, based on 1 trial (strength of evidence [SOE]: low).
 - Opioid associated with increased risk of serious adverse events (relative risk [RR] 5.25, 95% confidence interval [CI] 1.20 to 22.98), study withdrawal due to adverse events (11.9% vs. 0%, $p=0.005$), and any adverse event (64% vs. 34%, RR 1.90, 95% CI 1.28 to 2.83), based on one trial (SOE: low).

- Opioid vs. muscle relaxant
 - No difference in likelihood of pain response, likelihood of functional improvement, or severity of functional impairment at 1 week or 3 months, based on one trial (SOE: low).
 - Opioid associated with increased likelihood of dizziness (15% vs. 3%, RR 5.33, 95% CI 1.60 to 17.78) and nausea or vomiting (18% vs. 4%, RR 4.75, 95% CI 1.67 to 13.50), based on one trial (SOE: moderate).
- Opioid agonist vs. mixed agent, low back pain due to vertebral compression fracture
 - No difference in pain intensity at 1 day to <1 week or at 1 to <2 weeks, based on one trial (SOE: low).
 - Estimates for adverse events were imprecise (SOE: insufficient).
- Opioid agonist vs. mixed agent, low back pain with radiculopathy
 - No difference in pain intensity at 1 to <2 weeks or likelihood of pain improvement at 1 day to <1 week or at 1 to <2 weeks, based on one trial (SOE: low).
 - Estimates for adverse events were imprecise (SOE: insufficient).
- Opioid prescribing for low back pain versus no prescribing and long-term use
 - Prescribing of opioids for low back pain associated with no difference in opioid use at 3 months in one trial, but increased risk of long-term use (through 1 to 2 years) in two observational studies (SOE: low).
- NSAID vs. acetaminophen
 - Insufficient evidence from one poor quality trial (SOE: insufficient).
- Muscle relaxant vs. benzodiazepine
 - Muscle relaxant associated with small to moderate decrease in pain at 1 day to <1 week, based on two trials (SOE: low).
 - Effects on function were inconsistent and imprecise (SOE: insufficient).
 - Carisoprodol associated with decreased likelihood of sleep impairment, based on one trial (SOE: low).
- Nonopioid pharmacologic therapy (NSAID or muscle relaxant) vs. manipulation
 - Possibly no differences in pain intensity or function at 1 to <2 weeks, 2 to <4 weeks, or ≥4 weeks, but some inconsistency at 1 to <2 weeks, based on three trials (SOE: low).
 - Sparse data for adverse events (SOE: insufficient).
- NSAID (single dose) vs. acupuncture
 - Acupuncture associated with moderate decrease in pain and improvement in function at 2 to <4 weeks and at 4 weeks, based on one trial (SOE: low).
- Acetaminophen vs. electroacupuncture
 - Insufficient evidence from one poor quality trial (SOE: insufficient).
- Exercise vs. usual care
 - No differences in pain intensity, likelihood of improvement in pain, or likelihood functional improvement at 1 week to 52 weeks, based on two trials (SOE: low).
 - Adverse events were not reported (SOE: insufficient).
- Exercise vs. bed rest
 - No differences in pain at 1 week to 52 weeks or function at 3 weeks to 6 months, based on three trials (SOE: moderate).

- Exercise associated with fewer sick days at 3 weeks and 12 weeks, based on one trial (SOE: low).
 - Sparse data for adverse events (SOE: insufficient).
- Exercise vs. advice to remain active
 - Evidence limited and somewhat inconsistent, based on two trials (SOE: insufficient).
- Exercise vs. manipulation
 - Evidence sparse and with methodological limitations, based on two trials (SOE: insufficient).
- Acupuncture vs. sham or usual care
 - Traditional Chinese acupuncture associated with decreased likelihood of persistent low back pain at 2 to <4 weeks versus nonpenetrating sham acupuncture (46.9% vs. 70.3%, RR 0.67, 95% CI 0.49 to 0.90) or usual care (46.9% vs. 72.1%, RR 0.65, 95% CI 0.48 to 0.88), but not needle sham acupuncture, based on one trial. No differences between traditional Chinese acupuncture and controls at 3 months (SOE: low).
 - Traditional Chinese acupuncture associated with increased likelihood of functional improvement at 2 to <4 weeks versus usual care (74% vs. 44%, RR 1.66, 95% CI 1.23 to 2.24) and nonpenetrating sham acupuncture (98% vs. 80%, RR 1.22, 95% CI 1.06 to 1.40), but not needle sham acupuncture, based on one trial. No differences between traditional Chinese acupuncture and controls at 3 months (SOE: low).
 - In one trial, no differences between scalp acupuncture versus nonpenetrating sham acupuncture in pain or function at 1 day to <1 week and 1 to <2 weeks; scalp acupuncture associated with moderate reduction in pain intensity and moderate improvement in function at 2 to <4 weeks and at 4 weeks (SOE: low)
 - No serious adverse events or study withdrawals due to adverse events were reported (SOE: low).
- Brace vs. no brace, osteoporotic compression fracture
 - No difference between brace versus no brace in pain or function at 2 to <4 weeks and at ≥ 4 weeks, based on 1 trial (SOE: low).
- Heat therapy vs. usual care or placebo
 - Heat therapy associated with moderate decrease in pain intensity at 1 day to <1 week (6 trials), 1 to <2 weeks (2 trials), and 2 to <4 weeks (2 trials) and moderate improvement in function at 1 day to <1 week (3 trials), 1 to <2 weeks (1 trial), and 2 to <4 weeks (1 trial) (SOE: low to moderate).
 - No serious adverse events and few non-serious adverse events (SOE: low).
- Heat therapy vs. cold therapy
 - Heat therapy associated with decreased pain intensity at 1 day to <1 week, 1 to <2 weeks, and 2 to <4 weeks, based on one trial (SOE: low).
- Manipulation vs. sham therapy, usual care, placebo, or no treatment; no radiculopathy
 - No differences in pain or function at 1 day to <1 week, 1 to <2 weeks, 2 to <4 weeks, or ≥ 4 weeks, based on six trials (SOE: low to moderate).
 - Reporting of adverse events limited, with few or no serious adverse events reported (SOE: low).
- Manipulation vs. sham manipulation; radiculopathy

- Manipulation associated with increased likelihood of reduction in back pain at day 15 (86% vs. 61%, RR 1.41, 95% CI 1.10 to 1.81), reduction in leg pain at days 15, 30 and 180 (RRs 1.20 to 1.55), being back pain free at day 180 (28% vs. 6%, RR 5.00, 95% CI 1.55 to 16.16), and being leg pain free at day 180 (55% vs. 20%, RR 2.90, 95% CI 1.60 to 5.27), based on one trial (SOE: low).
- No adverse events were reported in either group in one trial (SOE: low).

Summary of Findings

Thirty-eight trials (N=4,289) evaluated interventions for low back pain (Appendix E, Table E-1).^{26,46-82} Five trials^{26,51,53,68,82} evaluated opioid therapy (KQ 1a and 1c), 11 trials^{48,50,52,56,59,62,64,66,71,75,81} evaluated a nonopioid medication versus nonpharmacologic treatment or another nonopioid (KQ 1i and 1j), and 22 trials^{46,47,49,54,55,57,58,60,61,63,65,67,69,70,72-74,76-80} (KQ 1m and 1o) evaluated nonpharmacologic treatment versus an inactive control or another nonpharmacologic treatment. Fifteen trials^{26,46,58,61-63,66,68,69,73,74,77-79,82} excluded patients with radiculopathy, 3 trials^{51,65,76} were restricted to patients with radiculopathy, 7 trials^{48,49,57,71,72,75,80} enrolled a mixed population, and 13^{47,50,52-56,59,60,64,67,70,81} trials did not specify inclusion or exclusion of patients with radiculopathy. The trials did not enroll patients with specific causes of low back pain such as cancer, inflammatory conditions, or infection, with the exception of two trials^{47,51} of patients with vertebral compression fracture. The duration of pain was <7 days in 15 trials,^{26,46,48-50,52,53,57-59,68,69,71,72,80} ≥7 days in 11 trials,^{54,55,60-66,75,79} and not described in 12 trials.^{47,51,56,67,70,73,74,76-78,81,82} The duration of treatment ranged from 15 minutes to 12 weeks. The duration of followup was less than 1 week in 7 trials,^{56,68,70,71,73,74,77} 1 week to less than 4 weeks in 17 trials,^{46-54,58,60,61,64,69,78,81,82} and more than 4 weeks in 17 trials.^{26,47-49,55,57,59,62,63,65-67,72,75,76,79,80} Twelve trials were conducted in the United States,^{26,51-53,55,60,66,73,74,77,78,82} 15 trials in Europe,^{46,49,58,59,61,64,65,69,70,72,75,76,79,80} and 11 trials elsewhere.^{47,48,50,54,56,57,62,63,67,68,71} The mean age was 70 years in both trials of patients with vertebral compression fracture.^{47,51} In the other trials, the mean age ranged from 29 to 57. Few trials reported race or ethnicity. Five trials excluded patients with a history of substance use disorder,^{52,73,74,77,81} 17 trials excluded pregnant or breastfeeding patients,^{48,52,53,57,64,66,68-70,73-75,77,78,80,81} 2 trials excluded patients with psychiatric illness,^{52,75} and 1 trial excluded patients with other comorbidities.⁶⁸ Five trials were rated good quality,^{26,62,63,76,80} 22 trials fair quality,^{47,48,51,52,54,55,57,58,60,61,64-66,68,69,72-74,77,79,81,82} and 11 trials poor quality^{46,49,50,53,56,59,67,70,71,75,78} (Appendix F, Table F-1). Methodological limitations in the fair and poor quality trials included failure to report adequate randomization or allocation concealment methods, unblinded design, failure to report attrition, high attrition, and no intention to treat analysis.

Detailed Synthesis

Opioid Therapy

KQs 1a and 1c address the comparative effectiveness and harms 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).

Five trials evaluated opioids (with or without acetaminophen) for acute back pain (Appendix E, Table E-1). Two trials compared an opioid agonist versus tapentadol^{51,82} and three trials compared an opioid versus a nonopioid medication (NSAID or muscle relaxant).^{26,53,68} Three

trials^{26,53,68} excluded patients with radiculopathy or did not describe whether patients with radiculopathy were included or excluded, one trial⁵¹ was restricted to patients with radiculopathy, and one trial⁸² enrolled patients with acute low back pain due to vertebral compression fracture. Four trials blinded patients and caregivers to trial medications.^{26,51,68,82} One trial was rated good quality,²⁶ three trials were rated fair quality,^{51,68,82} and one trial was rated poor quality (Appendix F, Table F-1).⁵³

Opioid Versus NSAID

One fair quality (n=113)⁶⁸ and one poor quality (n=40)⁵³ trial compared codeine plus acetaminophen versus an NSAID for acute low back pain without radiculopathy (Table 1). The fair quality trial found no difference between codeine plus acetaminophen (60/600 mg every 4 to 6 hours as needed) versus ketorolac promethazine (10 mg every 4 to 6 hours as needed, maximum 40 mg daily) in pain intensity at 4 or 6 hours or the sum of pain intensity differences through 6 hours.⁶⁸ There were also no differences in the likelihood of experiencing pain relief or improved function at 4 days. The opioid plus acetaminophen combination was associated with increased risk of serious adverse events (17% vs. 3%, RR 5.25, 95% CI 1.20 to 22.98), study withdrawal due to adverse events (11.9% vs. 0%, p=0.005), and any adverse event (64% vs. 34%, RR 1.90, 95% CI 1.28 to 2.83). The smaller, poor quality trial found no differences in pain intensity at 5 or 7 days.⁵³ At 12 days, pain intensity was lower in the opioid arm (mean 0.8 vs. 2.2 on a 0 to 10 scale) but at 15 days it was lower in the NSAID arm (mean 2.5 vs. 1.0 on a 0 to 10 scale). However, results are difficult to interpret because the statistical significance of differences was not reported. Estimates for adverse events were imprecise.

Opioid Versus Muscle Relaxant

One good quality trial (n=216) compared oxycodone plus acetaminophen (5/326 1 to 2 days every 8 hours as needed) versus cyclobenzaprine (5 to 10 mg every 8 hours) for acute non-radicular low back pain (Table 1).²⁶ There were no differences in likelihood of pain response (worst pain, none or mild), likelihood of functional improvement (Roland Morris Disability Questionnaire score improved ≥ 5 points), or mean Roland Morris Disability Questionnaire score at 1 week or 3 months. There was also no difference in time to return to work, or measures of healthcare utilization. Adverse events that were serious or that led to study withdrawal were not reported. Oxycodone plus acetaminophen was associated with increased likelihood of dizziness (15% vs. 3%, RR 5.33, 95% CI 1.60 to 17.78) and nausea or vomiting (18% vs. 4%, RR 4.75, 95% CI 1.67 to 13.50); serious adverse events were not reported.

Table 1. Opioid versus NSAID or muscle relaxant for back pain

Author, Year Quality	Interventions	Type of Back Pain; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Brown, 1986 ⁵³ Poor	A. Codeine 60 mg + acetaminophen 600 mg loading dose, 30/300 mg every 4 hours B. Diflunisal 1000 mg loading dose, 500 mg every 12 hours	Low back pain 5, 7, 12, and 15 days n=40	Pain intensity (mean [SD NR] 0 to 4 categorical scale converted to 0 to 10): 2.0 vs. 2.5 at day 5, 2.5 vs. 2.2 at day 7, 0.8 vs. 2.2 at day 12, 2.5 vs. 1.0 at day 15, p=NR	NR

Author, Year Quality	Interventions	Type of Back Pain; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Innes, 1998 ⁶⁸ Fair	A. Codeine 60 mg + Acetaminophen 600 mg every 4 to 6 hours B. Ketorolac 10 mg every 4 to 6 hours	Low back pain; 4 and 6 hours for pain intensity; 4 days for other outcomes n=113	Pain intensity (mean [SD], 0 to 100 VAS converted to 0 to 10 scale): 5.24 (2.46) vs. 5.25 (2.08), MD -0.01 (95% CI -0.86 to 0.84) at 4 hours; 6.21 (2.32) vs. 6.16 (2.31), MD 0.05 (95% CI -0.81 to 0.91) at 6 hours	Proportion with "a lot" or "complete" relief of pain 4 days: 55% (95% CI 42% to 68%) vs. 53% (95% CI 40% to 66%)
Friedman, 2015 ²⁶ Good	A. Oxycodone 5 mg + acetaminophen 325 mg every 8 hours B. Cyclobenzaprine 5 mg every 8 hours Both groups received naproxen 500 mg every 12 hours	Low back pain; 1 week and 3 months n=216	Worst pain in 24 hours mild or none: 65% (70/108) vs. 60% (65/108) at 1 week, RR 1.08 (95% CI 0.88 to 1.32); 81% (87/108) vs. 75% (81/108) at 3 months, RR 1.07 (95% CI 0.93 to 1.24)	RMDQ score (mean [SD], 0 to 24 scale): 7.8 (8.5) vs. 8.2 (8.5) at 1 week, MD -0.4 (95% CI -2.7 to 1.2); 4.6 (7.7) vs. 4.5 (7.7) at 3 months, MD 0.2 (95% CI -0.9 to 2.2) RMDQ score improved ≥ 5 points: 11.1% (12/108) vs. 10.1% (11/108) at 1 week, ARD 0.9% (95% CI -2.1 to 3.9)

Abbreviations: ARD = absolute risk difference; CI = confidence interval; MD = mean difference; NR = not reported; RMDQ = Roland Morris Disability Questionnaire; RR = relative risk; VAS = visual analog scale

Opioid Agonist Versus Mixed Agent

Two fair quality trials compared an opioid agonist versus a mixed mechanism agent (tapentadol) for acute low back pain with radiculopathy⁵¹ or due to vertebral compression fracture (Table 2).⁸² Compared with patients in the radiculopathy trial, patients in the compression fracture trial were older (mean age 70 versus 45 years) and a higher proportion was female (71% versus 50%), consistent with the population affected by this condition.⁸² The vertebral compression fracture trial was terminated early after enrolling 108 of a planned 625 patients, due to slow enrollment, resulting in insufficient statistical power for statistical analysis.⁸² It found no differences between immediate-release oxycodone (30 to 90 mg daily) versus tapentadol (200 to 450 mg daily) in the sum of pain intensity differences at 5 or 10 days. The trial of patients with radiculopathy⁵¹ found no differences between immediate-release oxycodone (20 to 30 mg) versus tapentadol (200 to 300 mg) in pain intensity at 10 days or likelihood of ≥ 30 percent or ≥ 50 percent improvement in pain intensity at 5 or 10 days. The trials reported few serious adverse events (total five cases). Estimates for study withdrawal due to adverse events and specific adverse events were imprecise.

Table 2. Opioid agonists versus mixed agents for back pain

Author, Year Quality	Interventions Treatment Duration	Type of Back Pain; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Biondi, 2013 ⁵¹ Fair	A: Oxycodone 20 to 30 mg daily, titrated up to 90 mg daily B: Tapentadol 200 to 300 mg daily, titrated up to 600 mg daily 10 days	Low back pain; 10 days n=613	Pain intensity (mean [SD], Brief Pain Inventory-Short Form 0 to 10 scale): 3.9 (2.41) vs. 4.0 (2.17) on day 10, MD -0.10 (95% CI -0.46 to 0.26) ≥30% reduction in pain intensity: 55.7% (166/298) vs. 53.7% (154/287) on day 5, RR 1.04 (95% CI 0.90 to 1.20); 59.4% (177/298) vs. 61.7% (177/287), RR 0.96 (95% CI 0.84 to 1.10) on day 10 ≥50% reduction in pain intensity: 31.5% (94/298) vs. 34.1% (98/287) on day 5, RR 0.92 (95% CI 0.73 to 1.16); 46.0% (137/298) vs. 45.3% (130/287) on day 10, RR 1.01 (95% CI 0.85 to 1.21)	Global impression "much improved" or "very much improved": 67.9% (205/302) vs. 66.2% (206/311), RR 1.02 (95% CI 0.92 to 1.15)
Vorsanger, 2013 ⁸² Fair	A: Oxycodone 5 to 10 mg every 4 to 6 B: Tapentadol: 50 to 75 mg every 4 to 6 hours As needed for 10 days	Low back pain due to vertebral compression fracture; 5 days and 10 days n=87	Sum of pain intensity difference (mean [SD], 0 to 10 scale): 252.7 (208.91) vs. 227.1 (200.66) at day 5, MD 25.60 (95% CI -61.75 to 112.95); 505.0 (373.00) vs. 422.9 (382.78) at day 10, MD 82.10 (95% CI -79.01 to 243.21) to 40.77) at day 10	NR

Abbreviations: CI = confidence interval; MD = mean difference; NR = not reported; RR = relative risk; SD = standard deviation

KQs 1b and 1d ask how the comparative effectiveness and harms 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.

Evidence on how comparative effectiveness and harms of opioid therapy varied in patients with acute low back pain according to patient and prescribing factors was very limited, due to small numbers of trials for each comparison, small sample sizes, and exclusion or lack of information regarding subgroups of interest, including persons with medical or psychiatric comorbidities or substance use history. No study conducted within-study or across-study evaluations of subgroup effects. Two trials of an opioid agonist versus the mixed agent tapentadol that evaluated different populations (vertebral compression fracture, 71% female, and mean age 70 years vs. radiculopathy, 50% female, and mean age 45 years) reported consistent findings of no difference in effectiveness.^{51,82} Evidence was too limited to determine effects of different opioid doses on comparative effectiveness and harms. No trial permitted opioid refills,

and the duration of treatment was up to 15 days; the trials did not evaluate how effectiveness varied according to the amount of opioid used.

KQ 1e concerns 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).

One good quality trial of patients presenting to the emergency department with acute low back pain found that at 3 months, rates of opioid use were similarly low in 215 persons randomized to either an opioid plus acetaminophen or placebo (2% vs. 3%, absolute risk difference [ARD] -1%, 95% CI -5% to 3%). Patients in both groups received usual care with naproxen.²⁶

Two retrospective, fair quality cohort studies of patients with worker's compensation claims for acute low back pain found an association between prescribing opioid therapy for acute low back pain and continued opioid use (Appendix E, Table E-2). One study (n=8,443) found early opioid use (defined as within 15 days following onset) associated with an increased likelihood of late opioid use (defined as 5 or more opioid prescriptions from 30 to 730 days following onset) versus non-use,³¹ with a dose-response relationship observed between higher early opioid exposure and increased risk. Versus no early opioid use, the adjusted odds ratio (OR) was 2.08 (95% CI 1.55 to 2.78) for 1 to 140 mg morphine equivalents and increased to 6.14 (95% CI 4.92 to 7.66) for ≥ 450 mg. Another study (n=2,887) of acute low back pain initially evaluated in the emergency department (ED) found being prescribed an opioid within 2 days of the visit associated with increased likelihood of long-term use, defined as ≥ 3 opioid prescriptions filled between 4 days and 12 months from injury onset (adjusted RR 1.29, 95% CI 1.05 to 1.58).⁸³ It did not evaluate how risk of long-term use varied by opioid dose.

KQs 1f and 1g concern the accuracy and effectiveness of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose in patients with acute pain being considered for opioid therapy.

No study evaluated the accuracy and effectiveness of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose in patients with acute low back pain.

KQ 1h addresses the effect of the following factors on the decision to prescribe opioids for patients with acute pain being considered for opioid therapy: (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.

Substantial variations between providers in rates of prescribing opioids for acute low back pain have been described.^{84,85} However, evidence on the effects of patient education, use of risk mitigation strategies, clinician and patient values and preferences, or availability of followup on decisions to prescribe opioids for acute low back pain is lacking. One study found no difference in rates or amount of opioid prescribing in EDs before versus after a legislative requirement for provider prescription drug monitoring review was enacted.⁸⁶ However, the study did not meet inclusion criteria because the duration of low back pain was not specified; in addition, 39 percent of patients were not opioid-naïve. Another study found no effect of automated prescription drug monitoring program queries on rates or amounts of opioids prescribing in EDs, but also did not meet inclusion criteria because patients with back pain comprised less than 10 percent of the study sample and the duration of symptoms was not specified.⁸⁷

Nonopioid Pharmacologic Therapy

KQs 1i and 1k address the comparative effectiveness and harms of nonopioid pharmacologic therapy versus: (1) nonopioid pharmacologic therapy or (2) nonpharmacologic therapy.

Eleven trials evaluated nonopioid pharmacologic therapy for acute back pain (Appendix E, Table E-1).^{48,50,52,56,59,62,64,66,71,75,81} Two trials excluded patients with radiculopathy,^{62,66} three trials included patients with or without radiculopathy,^{48,71,75} and the other trials did not specify inclusion or exclusion of patients with radiculopathy. The nonopioid medication evaluated was an NSAID (diclofenac, indomethacin, mefenamic acid, or diflunisal) in seven trials,^{48,50,56,62,71,75,81} a muscle relaxant (cyclobenzaprine, carisoprodol, or tizanidine, or methocarbamol) in four trials,^{50,52,64,66} acetaminophen in two trials,^{56,59} and a benzodiazepine (diazepam) in two trials.^{52,64} Four trials compared one nonopioid medication versus another nonopioid medication,^{50,52,56,64} and seven trials compared a nonopioid medication versus nonpharmacologic therapy (electroacupuncture or manipulation).^{48,59,62,66,71,75,81} One trial was rated good quality,⁶² five trials fair quality,^{48,52,64,66,81} and five trials poor quality (Appendix F, Table F-1).^{50,56,59,71,75} Four head-to-head trials of nonopioid medications blinded patients and caregivers to treatments,^{50,52,62,64} and five trials of nonopioid medications versus nonpharmacologic therapy utilized placebo and sham treatments.^{52,59,62,66,75,81}

NSAID Versus Acetaminophen

One small (n=30) poor quality crossover trial compared various NSAIDs (indomethacin, mefenamic acid, phenylbutazone, or aspirin) versus acetaminophen for acute low back pain (presence of radiculopathy not specified) (Table 3).⁵⁶ Pain intensity at 1 week was slightly lower with NSAIDs versus acetaminophen (range 4.6 to 5.0 vs. 5.5 on a 0 to 10 scale), but differences were not statistically significant. Estimates were similar for non-aspirin NSAIDs versus aspirin. Estimates for adverse events were imprecise.

Muscle Relaxant Versus NSAID

One poor quality trial (n=87) compared cyclobenzaprine (10 mg daily) versus diflunisal (1000 mg daily) for acute low back or neck pain (presence of radiculopathy not specified)⁵⁰ (Table 3). The likelihood of a global rating of moderate or marked improvement favored cyclobenzaprine at day 2 (30% vs. 43%, RR 0.70, 95% CI 0.40 to 1.2) but the difference was not statistically significant; there was no difference at day 7 to 10 (84% vs. 79%, RR 1.06, 95% CI 0.86 to 1.30). Other outcomes and adverse events were not reported.

Muscle Relaxant Versus Benzodiazepine

Two fair quality trials (n=80 and 30) compared a muscle relaxant versus the benzodiazepine diazepam for acute low back pain (presence of radiculopathy not specified) (Table 3).^{52,64} One of the trials also included patients with thoracic back pain.⁵² The muscle relaxant was carisoprodol (1400 mg daily) in one trial⁵² and tizanidine (12 mg daily) in the other.⁶⁴ The dose of diazepam ranged from 12 to 30 mg daily in both trials.

One trial found carisoprodol associated with larger improvement in pain intensity from baseline at 7 days (mean improvement 5.5 vs. 4.6 on a 0 to 10 scale at day 7, p not reported) though effects on pain intensity at day 5 were very similar (mean improvement 4.4 vs. 4.2).⁵² Carisoprodol was also associated with greater likelihood of having slight or no pain (52% vs. 39% at day 5, 65% vs. 42% at day 7, p>0.05) and activity impairment (59% vs. 31% at day 5, 71% vs. 42% at day 7), but the differences were not statistically significant. However,

carisoprodol was associated with a statistically significant increase in likelihood of having slight or no sleep impairment at day 7 (85% vs. 61%, $p \leq 0.05$). Although results favored carisoprodol for likelihood of any adverse event, central nervous system adverse events, and drowsiness, estimates were imprecise and differences were not statistically significant.

In the other trial, tizanidine was associated with lower pain intensity versus diazepam (mean 4.3 vs. 5.7 on a 0 to 10 scale at 3 days and 2.0 vs. 3.7 at 7 days), though the statistical significance of differences was not reported.⁶⁴ The likelihood of pain improvement was higher with tizanidine (87% vs. 53% at day 3, RR 1.62, 95% CI 0.97 to 2.72 and 93% vs. 73% at day 7, RR 1.27, 95% CI 0.90 to 1.78), but the differences were not statistically significant. Effects on function were similar between the two medications. The trial only reported one adverse event in a patient randomized to tizanidine.

Table 3. Nonopioid pharmacologic therapy versus other nonopioid pharmacologic therapy for back pain

Author, Year Quality	Interventions	Type of Back Pain; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Basmajian, 1989 ⁵⁰ Poor	A. Cyclobenzaprine 10 mg daily for 7 to 10 days B. Diflunisal 1000 mg daily for 7 to 10 days	Mixed back and neck pain 2 days and 7 to 10 days n=87	NR	Global rating moderate or marked improvement: 30% (13/43) vs. 43% (19/44) on day 2, RR 0.70 (95% CI 0.40 to 1.23); 84% (37/44) vs. 79% (31/39) on days 7 to 10, RR 1.06 (95% CI 0.86 to 1.30)
Boyles, 1983 ⁵² Fair	A. Carisoprodol 1400 mg daily for 7 days B. Diazepam 20 mg daily for 7 days	Lower and thoracic back pain; 5 days and 7 days n=80	Pain intensity difference (mean improvement from baseline [SD NR], 0 to 100 VAS converted to 0 to 10 scale): 4.4 vs. 4.2 on day 5, $p=NS$; 5.5 vs. 4.6 on day 7, $p=NS$ Pain slight or none: 52% vs. 39% on day 5, $p=NS$; 65% vs. 42% on day 7, $p=NS$	Activity impairment difference (mean improvement from baseline [SD NR], 0 to 100 VAS): 45 vs. 34 at day 5, $p=NS$; 57 vs. 40 on day 7, $p \leq 0.05$ Sleep impairment (mean improvement from baseline [SD NR], 0 to 100 VAS): 42 vs. 46 on day 5, $p=NS$; 52 vs. 40 on day 7, $p=NS$ Sleep impairment slight or none: 70% vs. 52% on day 5, $p=NS$; 85% vs. 61% on day 7, $p \leq 0.05$
Evans, 1980 ⁵⁶ Poor	A: Indomethacin 150 mg x 7 days B: Mefenamic acid 1500 mg x 7 days C: Phenylbutazone 300 mg x 7 days D: Aspirin 3600 mg x 7 days E: Acetaminophen 4000 mg x 7 days	Low back pain; 7 days n=30 (crossover)	Pain intensity (mean [SD NR], 0 to 3 scale converted to 0 to 10): 5.0 vs. 4.6 vs. 4.8 vs. 4.8 vs. 5.5, $p=NS$ for all comparisons	NR

Author, Year Quality	Interventions	Type of Back Pain; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Hennies, 1981 ⁶⁴ Fair	A. Tizanidine 12 mg x 7 days B. Diazepam 12 to 30 mg x 7 days	Nonspecific back pain; 3 days and 7 days n=30	Pain intensity (mean [SD NR], 0 to 3 categorical scale converted to 0 to 10) 4.3 vs. 5.7, p=NR on day 3; 2.0 vs. 3.7, p=NR on day 7	Pain improved: 86.7% (13/15) vs. 53.3% (8/15) on day 3, RR 1.62 (95% CI 0.97 to 2.72); 92.9% (13/14) vs. 73.3% (11/15) on day 7, RR 1.27 (95% CI 0.90 to 1.78) Activities of daily living (mean [SD NR], scale NR): 0.4 vs 0.8, MD -0.4 (95% CI NR); p=NR on day 7

Abbreviations: CI = confidence interval; MD = mean difference; NR = not reported; NS = not significant; RR = relative risk; SD = standard deviation; VAS = visual analog scale

Nonopioid Pharmacologic Therapy Versus Manipulation

Four trials (N=389) compared manipulation versus nonopioid pharmacologic therapy for acute low back pain (Table 4).^{62,66,75,81} One trial was rated good quality,⁶² two trials fair quality,^{66,81} and one trial poor quality.⁷⁵ Two trials excluded patients with radiculopathy,^{62,66} one trial reported results separately for patients with and without radiculopathy,⁷⁵ and one trial did not specify inclusion or exclusion of patients with radiculopathy.⁸¹ In three trials the nonopioid was the NSAID diclofenac (dose 100 to 150 mg daily or “full dose”); the other trial⁶⁶ evaluated various muscle relaxants (carisoprodol, cyclobenzaprine, or methocarbamol). The manipulation intervention ranged from 3 to 6 sessions over 3 days to 21 sessions over 3 weeks. When described, the manipulation method was usually use of high velocity low amplitude thrust techniques.

The good quality trial (n=179) compared manipulation 12 sessions over 4 weeks versus diclofenac 100 mg daily.⁶² Patients in the diclofenac group received sham therapy with detuned (inactive) ultrasound. There were no differences between manipulation versus diclofenac in pain intensity or function at 1, 2, 4, or 12 weeks, or in time to resolution of pain. A fair quality trial (n=71) found manipulation (3 to 6 sessions over 3 days) associated with greater effects on function versus diclofenac (150 mg daily) at 7 to 9 days, based on the Roland Morris Disability Questionnaire (mean improvement from baseline 7.71 vs. 4.75 on a 0 to 24 scale, p=0.01).⁸¹ The trial also stated that manipulation was associated with greater effects on pain intensity and the 36-Item Short-Form Survey (SF-36) physical component summary score, but did not provide data. There were no statistically significant differences in rescue medication use (mean 2.22 vs. 6.41 tablets, p>0.05) or time off work (1.24 vs. 1.80 days). The poor quality trial (n=69) found manipulation (21 sessions over 3 weeks) associated with better outcomes versus diclofenac (150 mg daily) in patients with or without radiculopathy, but it evaluated outcomes using a nonvalidated composite outcome and results were poorly reported.⁷⁵

One fair quality trial (n=70) found no differences between manipulation (8 sessions over 2 weeks) versus various muscle relaxants in pain intensity, function, depression, or analgesic use at 2 or 4 weeks.⁶⁶

One trial⁸¹ reported no adverse events, and adverse events were not reported in the other trials.

Table 4. Nonopioid pharmacologic therapy versus manipulation for back pain

Author, Year Quality	Interventions	Type of Back Pain; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Hancock, 2007 ⁶² Good	A: Manipulation, 12 treatments for 4 weeks, plus placebo medication B: Diclofenac 100 mg daily plus detuned (inactive) pulsed ultrasound C: No treatment, placebo diclofenac and detuned ultrasound	Lower back pain; 2 and 12 weeks n=179	A vs. B Pain intensity difference (mean change from baseline versus placebo [95% CI], 0 to 10 NRS): 0.2 (−0.3 to 0.7) vs. −0.2 (−0.7 to 0.3) at week 1, 0.4 (−1.0 to 0.1) vs. −0.1 (−0.7 to 0.4) at week 2, −0.2 (−0.7 to 0.3) vs. −0.1 (−0.6 to 0.4) at week 4, −0.2 (−0.7 to 0.3) vs. 0.0 (−0.5 to 0.4) at week 12	A vs. B RMDQ difference (mean change from baseline versus placebo [95% CI], 0 to 24 scale): −0.7 (−2.1 to 0.6) vs. 0.5 (−0.8 to 1.8) at week 1, −1.4 (−2.7 to 0.1) vs. −0.6 (−1.9 to 0.8) at week 2, −1.0 (−2.1 to 0.1) vs. −0.7 (−1.8 to 0.4) at week 4, −0.5 (−1.7 to 0.7) vs. −0.1 (−1.3 to 1.1) at week 12
Hoiriis, 2004 ⁶⁶ Fair	A: Manipulation, Chiropractic adjustment + oral placebo, 8 visits over 2 weeks B: Muscle relaxants ^a + sham chiropractic adjustment	Lower back pain; 2 and 4 weeks n=70	Pain intensity (mean [SD], 0 to 10 VAS): 2.44 (2.22) vs. 2.73 (2.15), MD −0.29 (95% CI −1.33 to 0.75) at week 2; 1.71 (1.88) vs. 2.24 (2.23), MD −0.53 (95% CI −1.52 to 0.46) at week 4	Oswestry Low Back Pain Disability Questionnaire (mean, [SD], 0 to 100 scale): 17.02 (13.75) vs. 16.99 (12.18), MD 0.03 (95% CI −5.32 to 5.38) at week 2; 11.94 (11.93) vs. 16.04 (16.12), MD −4.10 (95% CI −9.95 to 1.75) at week 4
Postachhini, 1988 ⁷⁵ Poor	A. Manipulation, daily for 1 week, then twice daily for 2 weeks B: Diclofenac, 150 mg per day	Low back pain with and without radiculopathy; 3 weeks, 2 months, and 6 months n=69	NR	<i>No radiculopathy group</i> Composite outcome for pain, function, and flexion-strength measurements (mean change from baseline [SD NR], 5 to 32 scale, higher score indicates better status): 24.7 vs. 17.2 at week 3; 26.9 vs. 24.9, p=NS at month 2; 29.5 vs. 28.2, p=NS at month 6 <i>Radiculopathy group</i> Composite outcome as above (mean change from baseline [SD NR]): 6.3 vs. 4.7, p<0.05 at week 3; 9.2 vs. 8.7 at month 2, 12.1 vs. 10.9, p=NS at month 6
von Heyman, 2013 ⁸¹ Fair	A: Manipulation, high velocity, low amplitude (1 to 2 sessions) plus placebo diclofenac for 3 days B: Diclofenac, 50 mg three times per day + sham manipulation for 3 days	Low back pain; 7 to 9 days n=71	Results “similar” to RMDQ results, data NR	RMDQ difference (mean improvement from baseline [SD], 0 to 24 scale): 7.71 (4.88) vs. 4.75 (4.93), p=0.01 Rescue medication (mean [SD], number of tablets): 2.22 (3.73) vs. 6.41 (10.67), p=NS

Abbreviations: CI = confidence interval; MD = mean difference; NR = not reported; NRS = numeric rating scale; NS = not significant; RMDQ = Roland Morris Disability Questionnaire; SD = standard deviation; VAS = visual analog scale;

^a Cyclobenzaprine, carisoprodol, or methocarbamol

NSAID Versus Acupuncture

Two trials compared acupuncture versus diclofenac for acute low back pain with or without radiculopathy (proportion with radiculopathy not reported).^{48,71} One fair quality trial (n=58) compared a single 20 minute session of motion-style acupuncture versus a single intramuscular injection of diclofenac 75 mg in patients with acute low back pain, with or without radiculopathy.⁴⁸ At 2 to 4 weeks, acupuncture was associated with greater improvement from baseline in pain intensity (differences 1.50 and 1.66 points on a 0 to 10 scale), no differences in leg pain intensity, and greater improvement in function (differences 16.9 to 20.1 points on the 0 to 100 Oswestry Disability Index). However, at 24 weeks there were no statistically significant differences in back pain or function, though acupuncture was associated with lower leg pain intensity (difference -1.85, 95% CI -3.47 to -0.22). A small (n=44), poor quality trial found no differences between acupuncture (one session daily for 5 days) versus diclofenac 100 mg daily in pain intensity or function at 5 days.⁷¹ There were no differences in pain intensity or function at 5 days. One trial⁴⁸ reported no adverse events, and in the other trial,⁷¹ adverse events were not reported.

Acetaminophen Versus Electroacupuncture

One poor quality trial (n=41) compared electroacupuncture (two 15-minute sessions) versus acetaminophen (every 4 hours, dose not reported) for acute low back pain (inclusion of patients with radiculopathy not specified)⁵⁹ (Table 5). There was no difference between electroacupuncture versus acetaminophen in pain intensity or function (mobility score) at 1 or 2 weeks, though electroacupuncture was associated with lower pain intensity (mean 0.33 vs. 1.37 on a 0 to 10 scale at 6 weeks, $p<0.05$) and better mobility (mean 1.9 vs. 15.8 on a 0 to 100 scale, $p<0.05$) at 6 weeks. Adverse events were not reported.

Table 5. Nonopioid pharmacologic therapy versus acupuncture for back pain

Author, Year Quality	Interventions	Type of Back Pain; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Hackett, 1988 ⁵⁹ Poor	A: Electroacupuncture, two 15-minute treatments + placebo tablet B: Acetaminophen Every 4 hours (dose NR) + placebo electroacupuncture (no current)	Low back pain; 1, 2, and 6 weeks n=41	Pain intensity (mean [SD NR], 0 to 100 VAS converted to 0 to 10): 2.32 vs. 2.34 at 1 week, $p=NS$; 1.83 vs. 2.20 at 2 weeks, $p=NS$; 0.33 vs. 1.37 at 6 weeks, $p<0.05$	Mobility Score (mean [SD NR], 0 to 100 VAS): 26.5 vs. 25.2 at week 1, $p=NS$; 17.8 vs. 17.0 at week 2, $p=NS$; 1.9 vs. 15.8 at week 6, $p<0.05$
Liu, 2010 ⁷¹ Poor	A: Acupuncture, needles inserted for 30 minutes with manipulation every 10 minutes, once daily for 5 days B: Diclofenac 100 mg daily for 5 days	Low back pain with and without radiculopathy; 5 days n=44	Pain intensity (mean [SD], NRS 0 to 10 scale): 2.65 (1.22) vs. 3.02 (1.56), MD -0.37 (95% CI -1.22 to 0.48)	RMDQ (mean [SD], 0 to 24 scale): 6.45 (2.44) vs. 6.25 (2.99), MD 0.20 (95% CI -1.45 to 1.85)

Author, Year Quality	Interventions	Type of Back Pain; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Shin, 2013 ⁴⁸ Fair	A: Motion style acupuncture; single session, approximately 20 minutes B: Diclofenac: single 75 mg IM injection	Low back pain with and without radiculopathy; 2, 4, and 24 weeks n=58	Pain intensity difference, back (mean [SD], 0 to 10 NRS): 5.83 (2.61) vs. 4.17 (3.05), MD 1.66 (95% CI 0.17 to 3.15) at 2 weeks; 6.41 (2.45) vs. 4.91 (2.94), MD 1.5 (95% CI 0.08 to 2.92) at 4 weeks; 6.64 (2.47) vs. 6.84 (1.9), MD -0.21 (95% CI -1.37 to 0.95) at 24 weeks Pain intensity difference, leg (mean [SD] 0 to 10 NRS): 1.57 (2.7) vs 1.83 (2.66), MD -0.26 (95% CI -1.67 to 1.15) at 2 weeks; 1.59 (2.78) vs. 2.33 (3.06), MD -0.74 (95% CI -2.28 to 0.8) at 4 weeks; 1.64 (2.46) vs. 3.48 (3.62), MD -1.85 (95% CI -3.47 to -0.22) at 24 weeks	ODI, improvement from baseline (mean [SD], 0 to 100 scale): 56.41 (24.86) vs. 36.34 (29.1), MD 20.07 (95% CI 5.83 to 34.31) at 2 weeks; 67.72 (21.88) vs. 45.84 (29.58), MD 16.88 (95% CI 3.19 to 30.57) at 4 weeks; 73.23 (20.24) vs. 80.83 (13.58), MD -7.6 (95% CI -16.67 to 1.47) at 24 weeks

Abbreviations: CI = confidence interval; ODI = Oswestry Disability Index; MD = mean difference; NR = not reported; NRS = numeric rating scale; NS = not significant; RMDQ = Roland Morris Disability Questionnaire; SD = standard deviation; VAS = visual analog scale

KQs 1b and 1d ask how the comparative effectiveness and harms 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.

Evidence was too limited to evaluate how comparative effectiveness and harms of nonopioid therapy for acute low back pain varied in subgroups, due to few trials for each comparison, small sample sizes, methodological limitations, and exclusion or lack of information regarding relevant subgroups. No study conducted within-study or across-study evaluations of subgroup effects. Details regarding the nonopioid medications prescribed, dose, and duration of treatment are described above.

Nonpharmacologic Therapy

KQs 1m and 1n address the comparative effectiveness of nonopioid pharmacologic therapy versus: (1) inactive controls or (2) other nonpharmacologic therapies.

Twenty-six trials evaluated nonpharmacologic treatment versus an inactive control or another nonpharmacologic treatment for acute back pain (Appendix E, Table E-1).^{46,47,49,54,55,57,58,60-63,65-67,69,70,72-81} Twelve trials excluded patients with radiculopathy,^{46,58,61-63,66,69,73,74,77-79} six trials included patients with or without radiculopathy,^{49,57,65,72,75,76,80} and the other trials did not specify inclusion or exclusion of patients with radiculopathy.^{47,54,55,60,67,70,81} The nonpharmacologic therapy was heat therapy in 6 trials,^{54,70,73,74,77,78} cold therapy in one trial,⁵⁴ exercise therapy in 6 trials,^{55,57,65,67,72,79} bed rest in 4 trials,^{49,57,65,72} manipulation in 11 trials,^{55,58,60-62,66,67,69,75,76,81}

mobilization in 1 trial,^{60,65,69,72} acupuncture in 2 trials,^{63,80} braces or belts in 2 trials,^{46,47} and advice to remain active in 2 trials.^{65,72} Eleven trials compared nonpharmacologic treatment versus an inactive control (no treatment, usual care, or minimal intervention),^{46,47,49,54,57,61,62,65,69,70,72,78-80} and four trials compared one nonpharmacologic treatment versus another.^{47,54,55,60,67} Six trials compared nonpharmacologic treatment to sham therapy (designed to look or feel similar to the active nonpharmacologic treatment, but without therapeutic effects).^{58,63,66,76,80,81} Four trials were rated good quality,^{62,63,76,80} 16 trials fair quality,^{47,54,55,57,58,60,61,65,66,69,72-74,77,79,81} and 6 trials poor quality^{46,49,67,70,75,78} (Appendix F, Table F-1).

Exercise Versus Usual Care

Two fair quality trials (n=127 and 67) compared exercise therapy versus usual care in patients with acute low back pain (Table 6).^{57,79} One trial⁵⁷ enrolled a mixed population of patients with and without radiculopathy (proportion with radiculopathy 31%), and one trial⁷⁹ excluded patients with radiculopathy. The exercise intervention was one-on-one instruction in isometric flexion exercises followed by home exercises (3 times daily) in one trial⁵⁷ and group instruction in extension (McKenzie) exercises in the other trial.⁷⁹ Both trials found no differences between exercise therapy versus usual care in pain intensity or the likelihood of improvement in pain at one to 52 weeks. There were also no differences in severity of functional limitations for likelihood of functional improvement at one to 52 weeks, other than increased likelihood of achieving an Oswestry Disability Index score <20 (0 to 100 scale) at 1 week in one trial (71% vs. 47%, RR 1.52, 95% CI 1.01 to 2.29).⁷⁹ Adverse events were not reported in either trial.

Exercise Versus Bed Rest

Three fair quality trials (sample sizes 100 to 162, N=384) compared exercise therapy versus bed rest (Table 6).^{57,65,72} Two trials^{57,72} evaluated mixed populations of patients with and without radiculopathy (proportion with radiculopathy 13% and 31%), and one trial⁶⁵ restricted inclusion to patients with radiculopathy. The exercise intervention was one-on-one instruction in flexion exercise followed by home exercises (three times daily) in one trial,⁵⁷ two sessions weekly of various techniques (segmental mobilization, disc unloading and unloading, and hydrotherapy) in one trial,⁶⁵ and back mobilization exercises (one face-to-face session followed by home exercises) in one trial.⁷² Bed rest ranged from 2 to 7 days. Across the trials, there were no differences between exercise therapy versus bed rest in pain intensity or likelihood of improvement in pain at one to 52 weeks. There were also no difference in function at 3 weeks to 6 months.^{57,65,72} One trial found no differences in health-related quality of life, satisfaction with treatment, or healthcare utilization at 3 or 12 weeks, though exercise therapy was associated with fewer sick days at 3 weeks (mean 5.7 vs. 7.5 days, p not reported) and at 12 weeks (mean 7.2 vs. 9.2 days, p not reported).⁷² The trial of patients with radiculopathy reported one case of cauda equina syndrome (bed rest group), one pulmonary embolism (bed rest group), and 10 cases of recurrent radiculopathy (not reported by group).⁶⁵ Otherwise, the trials did not report adverse events.

Exercise Versus Advice To Remain Active

Two fair quality trials (sample sizes 163 and 103) compared exercise therapy versus advice to remain active.^{65,72} One trial of patients with radiculopathy found no differences between exercise (segmental mobilization, disc unloading and unloading, and hydrotherapy) versus

advice to remain active in pain intensity or function at 1 or 6 months.⁶⁵ The other trial (n=103; 13% with radiculopathy) found exercise (back mobilization) associated with worse function at 3 weeks (adjusted mean difference 6.6 points on the 0 to 100 Oswestry Disability Index, 95% CI 2.0 to 11.1) at 3 weeks and more sick days at 3 weeks (adjusted mean difference 1.8 days, 95% CI 0.1 to 3.5) and at 12 weeks (adjusted mean difference 2.5 days, 95% CI 0.2 to 4.9) versus advice to remain active.⁷² Effects on pain intensity favored exercise, but the difference was not statistically significant. There were no differences in health-related quality of life or healthcare utilization, except exercise therapy was associated with more doctor visits (mean difference 0.5, 95% CI 0.1 to 0.9).⁷² Adverse events were not reported.

Advice To Remain Active Versus Bed Rest

One poor quality trial (n=34) found advice to remain active associated with no statistically significant differences versus 48 hours of bed rest at 7 or 28 days, though effects favored advice to remain active (differences 3.7 to 9.6 points on a 0 to 100 Oswestry Disability Index).⁴⁹ There was no difference in likelihood of improvement in the Oswestry Disability Index at 7 or 28 days, though estimates were imprecise.

Exercise Versus Manipulation

A small (n=24), fair quality trial (inclusion of patients with radiculopathy not specified) found extension-oriented (McKenzie) exercises associated with decreased likelihood of symptom resolution at 1 week (17% vs. 75%, RR 0.22, 95% CI 0.06 to 0.82) and worse function at 5 days (mean 25 vs. 7 on the 0 to 100 Oswestry Disability Index, mean difference 18.0, 95% CI 8.5 to 27.5).⁵⁵ The other trial (n=60) found exercise associated with improved likelihood of favorable outcomes for pain and function, but had serious methodological limitations and was rated poor quality.⁶⁷ Adverse events were not reported by either trial.

Table 6. Exercise for acute low back pain

Author, Year Quality	Intervention	Type of Back Pain; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Erhard, 1994 ⁵⁵ Fair	A: Exercise therapy, extension-oriented (McKenzie) exercises, 3 times over 1 week B: Manipulation, thrust manipulation and hand-heel rocking once or twice per session, 3 times over 1 week	Low back pain; 3 and 5 days n=24	NR	ODI (mean [SD], 0 to 100 scale): 35 (13) vs. 20 (12), MD 15.0 (95% CI 4.4 to 25.6) on day 3; 25 (13) vs. 7 (9), MD 18.0 (95% CI 8.5 to 27.5) on day 5

Author, Year Quality	Intervention	Type of Back Pain; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Gilbert, 1985 ⁵⁷ Fair	A: Exercise therapy, isometric flexion exercises three times daily B: Bed rest, stay in bed for \geq 4 days with written instructions depicting appropriate positions C: Usual care, received same analgesics as other groups, no other treatment or instruction	Low back pain; 10 days, 6 weeks, and 12 weeks n=187	Sum of pain intensity scores through 10 days (mean [SD], scale unclear): 25.94 (7.47) vs. 24.15 (7.12) vs. 22.88 (5.88), mean difference 1.79 (95% CI -1.30 to 4.88) for A vs. B, 3.06 (95% CI 0.25 to 5.87) for A vs. C, and 1.27 (95% CI -1.38 to 3.93) for B vs. C	Sum of activity scores through 10 days (mean [SD], scale NR [lower scores indicate better result]): 21.34 (9.22) vs. 24.34 (10.04) vs. 20.90 (8.46), MD -3.00 (95% CI -7.11 to 1.11) for A vs. B, 0.44 (95% CI -3.29 to 4.17) for A vs. C, and 3.44 (95% CI -0.34 to 7.22) for B vs. C Restriction none or mild: 78.3% (47/60) vs. 71.4% (40/56) vs. 79.3% (46/58) at 6 weeks, RR 1.10 (95% CI 0.89 to 1.36) for A vs. B, RR 0.99 (95% CI 0.82 to 1.19) for A vs. C, and RR 0.90 (95% CI 0.73 to 1.11) for B vs. C; 24.2% (15/62) vs. 37.5% (21/56) vs. 34.5% (20/58) at 12 weeks, RR 0.65 (95% CI 0.37 to 1.12) for A vs. B, RR 0.70 (95% CI 0.40 to 1.24) for A vs. C, and RR 1.09 (95% CI 0.67 to 1.78) for B vs. C
Hofstee, 2002 ⁶⁵ Fair	A: Exercise therapy, instruction and advice, segmental mobilization, disc unloading and loading, and hydrotherapy; 2 sessions each week for 4 to 8 weeks B: Bed rest, remain in bed for 7 days except to use bathroom and shower C: Remain active, continue usual activities, adjusted according to pain	Low back pain; 1 and 6 months n=245	Pain intensity difference (mean change from baseline [SD NR], 0 to 100 scale converted to 0 to 10 scale): 2.42 vs. 2.59 vs. 2.34, MD 0.08 (95% CI -0.82 to 0.98) for A vs. C and 0.25 (95% CI -0.64 to 1.14) for B vs. C at 1 month; 4.68 vs. 4.82 vs. 4.78, MD -0.10 (95% CI -1.00 to 0.80) for A vs. C and 0.05 (95% CI 0.84 to 0.93) for B vs. C at 6 months	Quebec Disability Scale (mean change from baseline [SD NR], 0 to 100 scale): 15.7 vs. 11.4 vs. 16.2, MD -0.5 (95% CI -6.3 to 5.3) for A vs. C and -4.8 (95% CI -10.6 to 0.9) for B vs. C at 1 month; 34.6 vs. 32.7 vs. 35.4, MD -0.7 (95% CI -8.4 to 6.9) for A vs. C and -2.7 (95% CI -10.2 to 4.8) for B vs. C at 6 months
Hussain, 2013 ⁶⁷ Poor	A: Manipulation, 2 to 3 treatments per week over 4 weeks B: Exercise, McKenzie back extension, William flexion, raising head in crook lying position, twice daily for 4 weeks	Low back pain; 4 weeks n=60	Pain intensity 0 to 2 (0 to 5 scale): 96.7% (29/30) vs. 46.7% (14/30) RR 2.07 (95% CI 1.40 to 3.05)	ODI (mean [SD NR], scoring unclear): 244 vs. 388 at 4 weeks, p=0.001

Author, Year Quality	Intervention	Type of Back Pain; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Malmivaara, 1995 ⁷² Fair	A. Exercise, back mobilization, 1 individual, physiotherapy-led session; written instructions for home exercise every other hour during the day B. Bed rest, 2 full days, then return to routine activities as tolerated C. Usual activity as tolerated; avoid bed rest	Low back pain; 3 and 12 weeks n=162	Pain intensity (mean [SD NR], 0 to 10 NRS): 3.1 vs. 2.4 vs. 1.9 at 3 weeks, adjusted MD 0.9 (95% CI -0.001 to 1.7) for A vs. C and 0.3 (95% CI -0.4 to 0.9) for B vs. C; 1.8 vs. 2.1 vs. 1.3 at 12 weeks, adjusted MD 0.2 (95% CI -0.5 to 1.0) for A vs. C and 0.7 (95% CI 0.03 to 1.4) for B vs. C	ODI (mean [SD NR], 0 to 100 scale): 18.6 vs. 16.0 vs. 10.0 at 3 weeks, adjusted MD 6.6 (95% CI 2.0 to 11.1) for A vs. C and 3.9 (95% CI -0.2 to 8.0) for B vs. C; 10.8 vs. 11.8 vs. 7.4 at 12 weeks, adjusted MD 2.6 (95% CI -1.6 to 6.7) for A vs. C and 3.8 (95% CI 0.1 to 7.5) for B vs. C
Underwood, 1998 ⁷⁹ Fair	A. McKenzie exercises plus usual care, single 1-hour, physiotherapist-led session of passive back extension exercises; could be repeated once B. Usual care, not specified	Low back pain; 1, 2, 4, and 52 weeks n=67	Pain intensity (mean decrease from baseline [SD NR], 0 to 100 VAS converted to 0 to 10 scale: 1.51 vs. 1.26 at 1 week, MD 0.25 (95% CI -0.83 to 1.32); 2.43 vs. 1.98 at 2 weeks, MD 0.44 (95% CI -1.05 to 1.93) ; 2.64 vs. 2.70 at 4 weeks, MD -0.06 (95% CI -1.48 to 1.36); 3.58 vs. 3.67 at 52 weeks, MD -0.09 (95% CI -1.97 to 1.79)	ODI (mean decrease from baseline [SD NR], 0 to 100 scale): 8.4 vs. 9.9 at week 1, MD -1.5 (95% CI -9.9 to 6.8); 14.1 vs. 18.2 at week 2, MD -4.1 (95% CI -14.3 to 6.0) at week 2; 18.6 vs. 24.1 at week 4, MD -5.5 (95% CI -15.4 to 4.2); 21.5 vs. 27.6 at week 52, MD -6.1 (95% CI -18.0 to 5.8)

Abbreviations: CI = confidence interval; MD = mean difference; NR = not reported; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; RMDQ = Roland Morris Disability Questionnaire; SD = standard deviation; VAS = Visual Analog Scale.

Acupuncture Versus Sham or Usual Care

Two good-quality trials^{63,80} compared needle acupuncture versus sham acupuncture or usual care for acute low back pain (Table 7). One trial⁶³ excluded patients with radiculopathy and the other trial⁸⁰ enrolled a mixed population of patients with and without radiculopathy (60% had radiculopathy). One trial⁸⁰ used traditional Chinese acupuncture techniques, and the other trial⁶³ used scalp acupuncture.

The trial (n=261)⁸⁰ of traditional Chinese acupuncture evaluated five 20-minute sessions over 14 days versus two different types of sham acupuncture (needling at nonspecific acupuncture points or use of a nonpenetrating/semiblunted needle) or usual care only (standard pharmacologic therapies, posture and exercise/activity recommendations). Acupuncture was associated with decreased likelihood of persistent low back pain at 3 weeks versus nonpenetrating sham (46.9% vs. 70.3%, RR 0.67, 95% CI 0.49 to 0.90) or usual care (46.9% vs. 72.1%, RR 0.65, 95% CI 0.48 to 0.88), with no difference versus needle (nonspecific acupoints) sham. There were no differences between acupuncture and controls in likelihood of persistent pain at 3 months. At 12 months, acupuncture was associated with decreased likelihood of persistent pain versus needle sham, though the proportion of patients with persistent pain was low in all groups (0% vs. 13%, p=0.01). For function, acupuncture was associated with increased likelihood of functional improvement (Roland Morris Disability Questionnaire improved $\geq 35\%$) versus usual care at 3 weeks (74% vs. 44%, RR 1.66, 95% CI 1.23 to 2.24) and versus

nonpenetrating acupuncture at 3 months (98% vs. 80%; RR 1.22, 95% CI 1.06 to 1.40). No differences between groups were reported at 12 months. There were no differences in the likelihood of occupational incapacity due to low back pain. No serious adverse events or withdrawals due to adverse events were reported.

The trial (n=80)⁶³ of scalp acupuncture compared five 30 minute sessions of Yamamoto's new scalp acupuncture versus sham acupuncture (nonpenetrating using the handle only) over 28 days; usual care in both groups included diclofenac. There were no differences between acupuncture versus sham acupuncture in pain intensity or severity of functional impairment at days 3 or 7. At 21 and 28 days, acupuncture was associated with decreased pain intensity (mean differences 1.69 and 1.40 points on a 0 to 10 scale) and better function (mean differences -4.10 and -4.40 points on a 0 to 24 scale). Acupuncture was also associated with better scores for SF-36 functional capacity, limitation in physical aspects, pain, and vitality subscales (differences 10.80 to 23.00 points on a 0 to 100 scale). No adverse events were reported.

Table 7. Acupuncture versus sham or usual care for acute back pain

Author, Year Quality	Interventions	Type of Back Pain; Followup Duration Sample Size	Pain Results	Function Results
Hasagawa, 2014 ⁶³ Good	A: Acupuncture (Yamamoto's new scalp acupuncture), five 30-minute sessions + 50 mg diclofenac every 8 hours as needed B: Sham acupuncture, five 30-minute sessions	Nonspecific back pain; 3, 7, 21 and 28 days n=80	Pain intensity (mean [SD], VAS 0 to 10 scale): 4.63 (2.23) vs. 5.13 (2.21) on day 3, MD -0.5 (95% CI -1.49 to 0.49); 3.83 (2.61) vs. 4.40 (2.09) on day 7, MD -0.57 (95% CI -1.62 to 0.48); 2.49 (2.40) vs. 4.18 (2.52) on day 21, MD -1.69 (95% CI -2.79 to -0.59); 1.98 (2.12) vs. 3.38 (2.26) on day 28, MD -1.40 (95% CI -2.38 to -0.42)	RMDQ (mean [SD], 0 to 24 scale): 10.30 (5.40) vs. 12.40 (4.50) at day 3, MD -2.10 (95% CI -4.31 to 0.11); 8.10 (5.50) vs. 10.20 (5.30) at day 7, MD -2.1 (-4.50 to 0.30), p=0.09; 5.30 (4.60) vs. 8.90 (5.2) at day 14, MD -3.60 (95% CI -5.78 to -1.41); 4.40 (4.40) vs. 8.50 (6.20) at day 21, MD -4.10 (95% CI -6.49 to -1.71); 4.10 (4.40) vs. 8.50 (6.20) at day 28, MD -4.40 (95% CI -6.79 to -2.01)
Vas, 2012 ⁸⁰ Good	A: Traditional Chinese acupuncture + usual care, 5 20-minute sessions over 2 weeks B: Placebo acupuncture + usual care, nonpenetrating 5 20-minute sessions over 2 weeks C: Sham acupuncture + usual care, needling nonspecific acupuncture points, 5 20-minute sessions over 2 weeks D: Usual care, no acupuncture or sham acupuncture	Low back pain; 3 weeks, 3 months, 12 months n=261	Continuing pain: 46.9% (30/64) vs. 70.3% (45/64) vs. 50.8% (33/65) vs. 72.1% (49/68), p=0.01 for A vs. B, p=0.79 for A vs. C, and p=0.01 for A vs. D at 3 weeks; 9.8% (5/51) vs. 21.6% (11/51) vs. 13.8% (8/58) vs. 16.7% (10/60), p=0.17 for A vs. B, p=0.73 for A vs. C, and p=0.44 for A vs. D at 3 months; 0% (0/51) vs. 6.1% (3/49) vs. 13.2% (7/53) vs. 0% (0/57), p=0.11 for A vs. B and p=0.01 for A vs. C	RMDQ difference (percent change from baseline [SD]): 63.9 (40.4) vs. 43.1 (58.9) vs. 65.0 (40.5) vs. 26.6 (58.9) at 3 weeks, p=0.02 for A vs. B, p=0.71 for A vs. C, and p<0.001 for A vs. D; 91.6 (17.1) vs. 76.3 (41.5) vs. 84.7 (28.9) vs. 83.0 (23.2) at 3 months, p=0.25 for A vs. B, p=0.79 for A vs. C, and p=0.10 for A vs. D; 67.4 (74.0) vs. 70.7 (55.4) vs. 75.6 (37.4) vs. 63.3 (57.4) at 12 months, p=0.99 for A vs. B, p=0.45 for A vs. C, and p=0.46 for A vs. D RMDQ improved ≥35% from baseline: 73.5% (50/68) vs. 65.2% (45/69) vs. 75.0% (51/68) vs. 44.3% (31/70) at 3 weeks, RR 1.13 (95% CI 0.90 to 1.41) for A vs. B, RR 0.98 (95% CI 0.80 to 1.20) for A vs. C, and RR 1.66 (95% CI 1.23 to 2.24) for A vs. D; 98.0% (50/51) vs. 80.4% (41/51) vs. 89.7% (52/58) vs. 95.0% (57/60) at 3 months, RR 1.22 (95% CI 1.06 to 1.40) for A vs. B, RR 1.09 (95% CI 0.99 to 1.20) for A vs. C, and RR 1.03 (95% CI 0.96 to 1.11) for A vs. D; 86.3% (44/51) vs. 83.7% (41/49) vs. 88.7% (44/53) vs. 77.2% (44/57) at 12 months, RR 1.03 (95% CI 0.87 to 1.22) for A vs. B, RR 0.97 (95% CI 0.84 to 1.13) for A vs. C, and RR 1.12 (95% CI 0.93 to 1.34) for A vs. D

Abbreviations: CI = confidence interval; MD = Mean Difference; RMDQ = Roland Morris Disability Questionnaire; RR = relative risk; SD = standard deviation; SF-36 = 36-Item Short-Form Survey; VAS = visual analog Scale.

Brace or Belt Versus No Brace or Belt

Two trials compared a back belt or brace versus no brace or belt (Table 8).^{46,47} For acute back pain due to osteoporotic compression fracture, one fair quality trial (n=60) found no differences between a rigid or soft brace versus no brace in pain intensity, function or opioid use at 2, 6, or 12 weeks.⁴⁷ Adverse events were not reported, other than one death thought unrelated to the interventions. For acute low back pain (no specific cause), a poor quality trial (n=36) found no differences between an abdominal elastic lumbar support belt versus no belt in pain or function at 1 or 3 weeks.⁴⁶

Table 8. Braces or belts versus no braces or belts for acute low back pain

Author, Year Quality	Interventions	Type of Back Pain; Followup Duration Sample Size	Pain Results	Function Results
Anders, 2019 ⁴⁶ Poor	A: Lumbar support belt: Lumbotrain abdominal elastic lumbar support belt to be worn at least 4 hours daily B: No belt	Low back pain; 1 and 3 weeks n=36	Pain: No significant overall effect (p=0.21)	ODI, baseline-adjusted (mean [95% CI], converted to 0 to 100 point scale): 33.54 (23.79 to 43.29) vs. 37.83 (26.77 to 48.90) vs. 35.95 (25.42 to 46.47), p=NS; MD (95% CI) 2.41 (−7.86 to 9.27) for A vs. C, −1.88 (−7.02 to 9.38) for B vs. C
Kim, 2014 ⁴⁷ Fair	A: Rigid brace: thoracolumbar sacral orthosis worn at all times (except when lying down) for 8 weeks followed by 2-week weaning period B: Soft brace: soft back brace worn at all times (except when lying down) for 8 weeks followed by 2-week weaning period C: No brace: instructed to walk without brace as long as comfortable	Low back pain due to acute osteoporotic thoracolumbar compression fracture; 2, 6, and 12 weeks n=60	Pain (mean [SD NR], 0 to 10 VAS): 5.7 vs. 7.1 vs. 6.0 at 2 weeks; 5.1 vs. 6.0 vs. 4.3 at 6 weeks; 3.7 vs. 4.0 vs. 4.3 at 12 weeks; no significant differences, treatment x time interaction p=0.292	RMDQ (mean [SD], 0 to 24 scale): 9.7 (19.9) vs. 5.3 (5.7), p<0.05 at day 7; 5.9 (5.6) vs. 3.2 (4.0), p=NS at day 28 RMDQ (percent with improvement from day 1): 73% (11/15) vs. 83% (15/18), p=NS at day 7; 86% (12/14) vs. 95% (19/20), p=NS at day 28 ODI (mean [SD], 0 to 100 scale): 36.0 (19.9) vs. 26.4 (21.1), p=NS at day 7; 22.9 (21.6) vs. 19.2 (15.3), p=NS at day 28 ODI (percent with improvement from day 1): 87% (13/15) vs. 83% (15/18), p=NS at day 7; 79% (11/14) vs. 95% (19/20), p=NS at day 28

Abbreviations: CI = confidence interval; ODI = Oswestry Disability Index; MD = mean difference; NR = not reported; NS = not significant; RMDQ = Roland Morris Disability Questionnaire; SD = standard deviation; VAS = visual analog scale

Heat Therapy Versus Usual Care or Placebo

Six trials (sample sizes 30 to 180, N=425)^{54,70,73,74,77,78} compared heat therapy versus usual care or placebo tablets for acute low back pain (Table 9).^{72,79} Four trials^{73,74,77,78} excluded patients with radiculopathy, and two trials^{54,70} did not specify inclusion or exclusion of patients with radiculopathy. Heat therapy interventions varied in terms of length of sessions and number of days (e.g., 20 minutes twice daily for 7 days, 8 hours for one day, 8 hours for 3 days), but was applied using a heat wrap in all trials except for one,⁵⁴ which used a hot water bag. Four trials were rated fair quality^{54,73,74,77} and two trials poor quality.^{70,78}

Heat therapy was consistently associated with decreased pain intensity versus usual care or placebo. At 1 day to <1 week, differences were 1.6 to 2.0 points on a 0 to 10 scale for pain intensity (2 trials),^{70,78} 0.94 to 1.5 points on a 0 to 5 scale for pain relief (3 trials),^{73,74,77} and 2.58

points on the McGill Pain Questionnaire in one trial⁵⁴ (scoring method and scale unclear). At 1 to 2 weeks and 2 to 4 weeks, differences in pain intensity were 1.6 to 1.8 points on a 0 to 10 scale (1 trial)⁷⁸ and 4.0 to 4.8 points on the McGill Pain Questionnaire in one trial.⁵⁴ Heat therapy was also associated with better functional status versus placebo or usual care. At 1 day to <1 week, differences ranged from 2.1 to 2.4 points on the 0 to 24 Roland Morris Disability Questionnaire (3 trials).^{73,74,78} At 1 week to <4 weeks, the difference was 4.0 to 4.6 points in one trial.⁷⁸ One trial found heat therapy associated with better sleep quality at 2 to 4 days (mean difference 0.39 on a 0 to 5 scale, mean difference 0.39, 95% CI 0.01 to 0.77),⁷³ and one trial found heat therapy associated with decreased likelihood of being woken up at night due to pain (0% vs. 58%, =0.001). Three trials reported no serious adverse events; there were a total of two non-serious adverse events.^{73,74,77}

Heat Therapy Versus Cold Therapy

One fair quality trial (n=58) compared heat versus cold therapy (Table 9).⁵⁴ The therapies were administered twice daily for twenty minutes, for seven days. Heat therapy was associated with better scores on the McGill Pain Questionnaire at day 3, 8, and 15 (mean difference -1.99 to -1.38 points). However, the scoring method for the McGill Pain Questionnaire and scale were unclear. Other outcomes and adverse events were not reported.

Table 9. Heat versus usual care, placebo, or cold therapy for acute low back pain

Author, Year Quality	Interventions	Type of Back Pain; Followup Duration Sample Size	Pain Results	Function Results
Dehghan, 2014 ⁵⁴ Fair	A: Heat therapy, hot water bag twice daily for twenty minutes for 7 days B: Cold therapy, ice pack twice daily for twenty minutes for 7 days C: Usual care, included naproxen 1000 mg per day for 7 days (all groups)	Low back pain; 3, 8 and 15 days n=87	MPQ, Overall Pain Score (mean [SD], scale NR): 7.28 (3.18) vs 9.27 (2.67) vs. 9.86 (2.26) at day 3, MD -1.99 (95% CI -3.53 to -0.44) for A vs. B and -2.58 (95% CI -4.03 to -1.13) for A vs. C; 3.72 (2.37) vs. 5.10 (2.30) vs. 7.72 (2.51) at day 8, MD -1.38 (95% CI -2.61 to -0.15) for A vs. B and -4.00 (95% CI -5.28 to -2.27) for A vs. C; 0.76 (0.38) vs. 2.20 (2.12) vs. 5.59 (2.01) at day 15, MD -1.44 (95% CI -2.24 to -0.63) for A vs. B and -4.83 (95% CI -5.59 to -4.07) for A vs. C	NR
Kettenmann, 2007 ⁷⁰ Poor	A: Heat wrap ≥4 hours per day for 4 days B: Usual care, analgesics as needed	Low back pain; 1 and 4 days n=30	Pain severity (mean [SD], 0 to 100 scale converted to 0 to 10 scale): 3.95 (1.94) vs 5.00 (2.71) at day 1, MD -1.05 (95% CI -2.81 to 0.71); 2.70 (2.32) vs 4.70 (2.71) at day 4, MD -2.00 (95% CI -38.9 to -1.1)	NR
Nadler, 2003a ⁷³ Fair	A: Heat wrap, 8 consecutive hours daily for 3 days B: Oral placebo tablet	Low back pain; 2 days, 4 to 5 days n=63	Pain relief (mean [SD], 0 to 5 scale): 2.36 (2.00) vs. 1.28 (1.36) at day 2, MD 1.11 (95% CI 0.25 to 1.97); 2.90 (1.62) vs. 1.60 (1.53) at day 4 to 5, MD 1.30 (95% CI 0.51 to 2.09)	RMDQ (mean [SD] 0 to 24 scale): 3.60 (3.90) vs 5.80 (3.96) at day 4, MD -2.20 (95% CI -4.18 to -0.22)
Nadler, 2003b ⁷⁴ Fair	A: Heat wrap, 8 consecutive hours daily for 3 days B: Oral placebo tablet	Low back pain; 1 day, 3 days, and 4 to 5 days n=180	Pain relief (mean [SD], 0 to 5 scale): 1.76 (0.96) vs 1.05 (1.04) at day 1, MD 0.71 (95% CI 0.41 to 1.00); 2.50 (1.53) vs 1.56 (1.69) at days 4 to 5, MD 0.94 (95% CI 0.47 to 1.41) Pain relief complete: 15.4% vs. 5.5% at day 5, OR 2.89 (p=0.04)	RMDQ (mean [SD] 0 to 24 scale): 5.3 vs. 7.4 at day 3, p<0.0002; 4.6 vs. 6.7 at day 5, p<0.001
Stark, 2014 ⁷⁷ Fair	A: Heat wrap for 8 continuous hours B: Oral placebo	Low back pain; 8 hours n=51	Pain relief (mean [SD NR], 0 to 5 scale, higher score=greater relief): 3.2 vs. 1.7, p<0.001 Total pain relief (mean [SD NR], sum of pain relief scores on 0 to 5 scale from 2 to 8 hours): 22.0 vs. 11.5, p<0.001	NR

Author, Year Quality	Interventions	Type of Back Pain; Followup Duration Sample Size	Pain Results	Function Results
Tao, 2005 ^{a78} Poor	A: Heat wrap during daytime hours for 3 days B: Usual care, minimal education intervention (both groups)	Low back pain; 4, 7 and 14 days n=43	Pain intensity difference (mean change from baseline [SD], 0 to 10 NRS): -3.24 vs. -1.61 at day 4, MD -1.63 (95% CI -2.99 to -0.28); -3.44 vs. -1.78 at day 7, MD -1.66 (95% CI -2.97 to -0.37); -3.85 vs. -2.22 at day 14, MD -1.63 (95% CI -2.92 to -0.34)	RMDQ difference (mean change from baseline [SD], 0 to 24 scale): -2.88 vs. -0.50 at day 4, MD -2.38 (95% CI -5.62 to 0.85); -5.32 vs. -0.72 at day 7, MD -4.60 (95% CI -8.27 to -0.94); -6.55 vs. -2.53 at day 14, MD -4.02 (95% CI -7.82 to -0.24)

Abbreviations: CI = confidence interval; MD = mean difference; MPQ = McGill Pain Questionnaire; NR = not reported; NRS = numeric rating scale; RMDQ = Roland Morris Disability Questionnaire; RR = risk ratio; SD = standard deviation

^a Pain intensity, Pain relief, and RMDQ adjusted for sex, age, baseline pain intensity, and pain medication

Spinal Manipulation Versus Sham Therapy, Usual Care, Placebo, or No Treatment

Eight trials compared spinal manipulation versus inactive treatments (sham therapy, usual care, placebo, or no treatment) for acute low back pain (Table 10).^{58,61,62,66,69,75,76,81} Five trials excluded patients with radiculopathy,^{58,61,62,66,69} one trial was restricted to patients with radiculopathy,⁷⁶ one trial enrolled a mixed population of patients with and without radiculopathy,⁷⁵ and one trial did not specify whether patients with radiculopathy were included or excluded.⁸¹ The manipulation intervention ranged from a single 15-minute session to up to 20 sessions over 4 weeks. Details of manipulation techniques were limited, but when described usually involved high velocity low amplitude thrusts. Three trials compared spinal manipulation against sham manipulation, which consisted of simulated manipulation that was similar to active manipulation but did not follow specific patterns or involve rapid thrusts,⁷⁶ placement of the hand on the paravertebral musculature with light pressure,⁶⁶ or a high velocity low amplitude maneuver applied to the sacroiliac joint area.⁸¹ Two trials were rated good quality,^{62,76} four trials fair quality,^{58,61,66,81} and one trial poor quality⁷⁵ (Appendix F, Table F-1).

In six trials of manipulation versus inactive controls that did not include patients with radiculopathy, effects on pain were inconsistent and differences were small, with no trial reporting a statistically significant difference.^{58,61,62,66,69,81} For pain intensity, at 1 day to <1 week, one trial found manipulation associated with higher pain intensity (difference 0.75 point on a 0 to 10 scale).⁶⁹ At 1 week to <2 weeks, effects of manipulation and inactive controls on pain intensity were very similar in two trials (difference 0.2 point in both trials).^{62,69} At 2 to <4 weeks, differences ranged from 0.74 point in favor of manipulation to 0.5 point in favor of inactive treatment in four trials.^{61,62,66,69} At ≥ 4 weeks, differences were 0.2 and 0.5 point in favor of manipulation in two trials.^{62,69} There was also no difference between spinal manipulation versus inactive controls in likelihood of experiencing improvement in pain at 1 day to <1 week (1 trial),⁵⁸ 2 to <4 weeks,⁶⁹ or ≥ 4 weeks.⁶⁹ For function, results favored manipulation versus inactive treatments at 1 to <2 weeks in two trials^{62,81} (difference -0.7 and -2.7 points on the 0 to 24 Roland Morris Disability Questionnaire), but results were inconsistent at 2 to <4 weeks in four trials,^{61,62,66,69} and at ≥ 4 weeks in two trials.^{62,66} One trial found no effect of manipulation on depression severity at 2 or 4 weeks.⁶⁶ There were also no differences in analgesic (NSAID) use in three trials, though estimates favored manipulation.^{66,69,81} Reporting of adverse events was very limited. One trial reported no difference between manipulation versus usual care in risk of serious adverse events (2% vs. 2%);⁶⁹ otherwise no serious adverse events were reported.

One good quality trial (n=102) compared manipulation (up to 20 sessions over 4 weeks) versus sham manipulation (maneuvers resembling manipulation but not following a specific pattern and without rapid thrusts) in patients with radiculopathy.⁷⁶ Manipulation was associated with increased likelihood of experiencing a reduction in back pain at day 15 (86% vs. 61%, RR 1.41, 95% CI 1.10 to 1.81), with no differences at day 30 or day 180. Manipulation was also associated with increased likelihood of reduction in leg pain at day 15 (82% vs. 53%, RR 1.55, 95% CI 1.16 to 2.08), day 30 (94% vs. 77%, RR 1.22, 95% CI 1.03 to 1.44), and day 180 (100% vs. 83%, RR 1.20, 95% CI 1.06 to 1.36), increased likelihood at 180 days of being back pain free at day 180 (28% vs. 6%, RR 5.00, 95% CI 1.55 to 16.16) and increased likelihood of being leg pain free at day 180 (55% vs. 20%, RR 2.90, 95% CI 1.60 to 5.27). There were no differences between manipulation versus sham in SF-36 subscales of the Kellner Rating Scale for anxiety or depression, and no statistically significant difference in NSAID use (mean difference in number of days -1.9, 95% CI -4.0 to 0.2). No adverse events were reported in either group.

One other trial evaluated⁷⁵ a mixed population of patient with and without radiculopathy, but had serious methodological limitations and only reported results using a nonvalidated composite outcome for pain, function, and flexion-strength measurements.

Manipulation Versus Mobilization

One fair quality trial (n=54) compared a single session of manipulation versus mobilization for acute low back pain (Table 10).⁶⁰ The inclusion or exclusion of patients with radiculopathy was not specified. Analyses were stratified according to duration of pain ≤ 2 weeks or 2 to 4 weeks. In patients with pain ≤ 2 weeks, there were no difference between mobilization versus manipulation on the Roland Morris Disability Questionnaire at 6 or 12 days. In patients with pain for 2 to 4 weeks, mobilization was associated with worse function at day 6 (6.0 vs. 3.75, p not reported), but there was no difference at day 12. Effects on pain were not reported, but there was no difference in the likelihood of reporting the back felt “much better.” Adverse events were not reported.

Table 10. Manipulation versus usual care, placebo, and other nonpharmacologic interventions for acute low back pain

Author, Year Quality	Interventions	Type of Back Pain; Followup Duration Sample Size	Pain Results	Function Results
Glover, 1974 ⁵⁸ Fair	A: Manipulation, one 15-minute session + 4 15-minute sham diathermy sessions B: Sham diathermy, five 15-minute sessions	Low back pain; 3 and 7 days n=84	Percent pain relief: 50% vs. 56% at day 3, $p>0.05$; 75% vs. 80% at day 7, $p>0.05$	NR
Hadler, 1987 ⁶⁰ Fair	A: Spinal mobilization, single session B: Spinal manipulation, single session	Low back pain; 6 and 12 days n=54	NR	RMDQ (mean [SD NR], 0 to 24 scale): Patients with pain for ≤ 2 weeks: 4.10 vs. 4.50, at day 6, $p>0.05$; 2.10 vs. 2.0 at day 12, $p>0.05$ Patients with pain for 2 to 4 weeks: 6.0 vs. 3.75 at day 6. $p=NR$; 5.0 vs. 4.50 at day 12, $p=NR$
Hallegraef, 2009 ⁶¹ Fair	A: Manipulation, 4 HVLA treatments over 2.5 weeks + usual care light exercise B: Usual care, 5 minutes of low intensity, low load endurance exercises twice daily	Low back pain; 2.5 weeks n=64	Pain intensity (mean [SD], 0 to 100 VAS converted to 0 to 10 scale): 1.90 (1.69) vs. 2.48 (2.01), MD -0.58 (95% CI -1.51 to 0.35)	ODI (mean [SD], 0 to 50 scale): 0.14 (0.17) vs. 0.14 (0.12), $p=0.38$
Hancock, 2007 ⁶² Good	A: Manipulation, 12 treatments for 4 weeks, plus placebo medication B: Diclofenac: 100 mg daily plus detuned (inactive) pulsed ultrasound C: No treatment, placebo diclofenac and detuned ultrasound	Low back pain; 1, 2, 4, and 12 weeks n=179	A vs. B Pain intensity difference (mean change from baseline vs. placebo [95% CI], 0 to 10 NRS): 0.2 (-0.3 to 0.7) vs. -0.2 (-0.7 to 0.3) at week 1, 0.4 (-1.0 to 0.1) vs. -0.1 (-0.7 to 0.4) at week 2, -0.2 (-0.7 to 0.3) vs. -0.1 (-0.6 to 0.4) at week 4, -0.2 (-0.7 to 0.3) vs. 0.0 (-0.5 to 0.4) at week 12	A vs. B RMDQ difference (mean change from baseline vs. placebo [95% CI], 0 to 24 scale): -0.7 (-2.1 to 0.6) vs. 0.5 (-0.8 to 1.8) at week 1, -1.4 (-2.7 to 0.1) vs. -0.6 (-1.9 to 0.8) at week 2, -1.0 (-2.1 to 0.1) vs. -0.7 (-1.8 to 0.4) at week 4, -0.5 (-1.7 to 0.7) vs. -0.1 (-1.3 to 1.1) at week 12
Hoiriis, 2004 ⁶⁶ Fair	A: Manipulation, chiropractic adjustment + oral placebo, 8 visits over 2 weeks B: Sham chiropractic adjustment + oral placebo	Low back pain; 2 and 4 weeks n=74	Pain intensity (mean [SD], 0 to 10 VAS): 2.44 (2.22) vs. 3.18 (2.4) at 2 weeks, MD -0.74 (95% CI -1.82 to 0.34); 1.71 (1.88) vs. 2.21 (2.02) at 4 weeks, MD -0.50 (95% CI -1.43 to 0.43)	ODI (mean, [SD], 0 to 100 scale): 17.02 (13.75) vs. 19.35 (13.70) at 2 weeks, MD -2.33 (95% CI -7.95 to 3.29); 11.94 (11.93) vs. 16.32 (12.95) at 4 weeks, MD -4.38 (95% CI -9.49 to 0.73)

Author, Year Quality	Interventions	Type of Back Pain; Followup Duration Sample Size	Pain Results	Function Results
Juni, 2009 ⁶⁹ Fair	A: Manipulation, HVLA thrust, mobilization, and muscle energy technique, up to 5 sessions over 2 weeks B: Usual care, advice and analgesics	Low back pain; 6, 13, 14 days and 6 months n=97	Pain intensity (mean [SD NR], 0 to 10 scale): 3.00 vs. 2.25 at day 6, p=NR; 1.95 vs. 1.75 at day 13, p=NR; 1.95 vs. 1.45 at day 14, MD 0.5 (95% CI -0.2 to 1.2) Pain intensity (mean difference between groups, 95% CI): 0.6 (-0.4 to 1.6) at 6 months	RMDQ (mean [SD], 0 to 24 scale): 5.8 vs. 5.2 at day 14, adjusted MD 0.8 (95% CI -1.5 to 3.2)
Postachhini, 1988 ⁷⁵ Poor	A: Manipulation, daily for 1 week, then twice daily for 2 weeks B: Oral placebo	Low back pain; 3 weeks and 2 and 6 months n=65	NR	<i>No radiculopathy group</i> Composite outcome for pain, function, and flexion-strength measurements (mean change from baseline [SD NR], 5 to 32 scale, higher score indicates better status): 24.7 vs. 16.5 at week 3, p<0.01; 26.9 vs. 23.8 at month 2, p=NS; 29.5 vs. 27.5 at month 6, p=NS <i>Radiculopathy group</i> Composite outcome as above (mean change from baseline [SD NR], 5 to 32 scale): 6.3 vs. 2.2 at week 3, p<0.05; 9.2 vs. 5.1 at month 2, 12.1 vs. 9.8 at month 6, p=NS
Santilli, 2006 ⁷⁶ Good	A: Manipulation, rapid thrusts and specific patterns, 5 days per week, maximum 20 sessions B: Sham manipulation, soft muscle pressing similar to manipulation but not following any specific pattern and no rapid thrusts, 5 days per week, maximum 20 sessions	Low back pain with radiculopathy; 15, 30, and 180 days n=102	Pain intensity, back (mean [SD], 0 to 10 VAS): 4.4 vs 5.6 at day 15, 3.3 vs. 4.6 at day 30, 2.2 vs. 3.3 at day 180; p=NR Pain intensity, radiating pain (mean [SD], 0 to 10 VAS): 3.6 vs. 4.1 at day 15, 2.2 vs. 3.7 at day 30, 1.3 vs. 2.5 at day 180; p=NR Reduction in back pain: 86% (44/51) vs. 61% (30/49) at day 15, RR 1.41 (95% CI 1.10 to 1.81); 94% (47/50) vs. 85% (41/48) at day 30, RR 1.10 (95% CI 0.96 to 1.26); 98% (47/48) vs. 94% (45/48) at day 180, RR 1.04 (95% CI 0.96 to 1.14)	NR

Author, Year Quality	Interventions	Type of Back Pain; Followup Duration Sample Size	Pain Results	Function Results
von Heymann, 2013 ⁸¹ Fair	A: Manipulation, HVLA thrust (1 to 2 sessions) + placebo diclofenac for 3 days B: Sham manipulation (1 to 2 sessions) + placebo diclofenac for 3 days	Low back pain; 7 to 9 days n=57	Results "similar" to RMDQ, data NR	RMDQ (mean improvement from baseline [SD], 0 to 24 scale): 7.71 (4.88) vs. 10 (5.0) at 7 to 9 days, p=0.01

Abbreviations: CI = confidence interval; HVLA = high velocity low amplitude; NR = not related; NS = not significant; ODI = Oswestry Disability Index; RMDQ = Roland Morris Disability Questionnaire; RR = relative risk; SD = standard deviation; VAS = visual analog scale

KQs 1o and 1p ask how the comparative effectiveness and harms of nonpharmacologic therapy 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.

Evidence on how the comparative effectiveness and harms of nonpharmacologic therapy varied based on patient and intervention factors was very limited. One study of manipulation versus usual care reported no subgroup effects when results were stratified by sex, age, occupation (manual vs. non-manual), pain duration (<7 or ≥ 7 days), pain intensity (<7 or ≥ 7), baseline Roland Morris Disability score (<14 or ≥ 14), or healthcare setting (ED or primary care).⁶⁹ Manipulation was associated with beneficial effects on pain and function in a trial⁷⁶ that restricted inclusion to patients with radiculopathy, but not in non-radiculopathy trials. However, it was not possible to draw strong conclusions about differential effects of manipulation by presence of radiculopathy from an indirect (between-studies) comparison involving a single radiculopathy trial.

KQ 2. Acute Neck Pain (Including Neck Pain With Radiculopathy)

Key Points

- Cervical collar vs. usual activity, neck pain with radiculopathy
 - A semi-hard cervical collar was associated with moderate to large decrease in neck pain intensity versus usual activity at 2 to <4 weeks and at ≥ 4 weeks, with no difference in disability, based on one trial (SOE: low).
- Cervical collar vs. exercise, neck pain with radiculopathy
 - A semi-hard cervical collar and exercise therapy were associated with similar effects on neck pain intensity and disability at 2 to <4 weeks and at ≥ 4 weeks, based on one trial (SOE: low).
- Exercise vs. usual activity, neck pain with radiculopathy
 - Exercise was associated with moderate decrease in neck pain intensity versus activity as usual at 2 to <4 weeks and at ≥ 4 weeks, with no difference in disability, based on one trial (SOE: low).
- Ultrasound vs. sham ultrasound, whiplash neck sprain
 - No difference in pain intensity at 1 to <2 weeks, though ultrasound was associated with a small increase in pain intensity at 2 to <4 weeks, based on one trial (SOE: low).
- Cervical collar vs. usual activity, whiplash neck sprain
 - No difference between a semi-hard cervical collar versus usual activity in pain or health status at ≥ 4 weeks, based on one trial (SOE: low).
- Cervical collar vs. exercise, whiplash neck sprain
 - No difference between a semi-hard cervical collar and exercise in pain or health status at ≥ 4 weeks, based on one trial (SOE: low).
- Exercise vs. usual activity, whiplash neck sprain.
 - No difference between exercise therapy versus usual activity in pain or health status at ≥ 4 weeks, based on one trial (SOE: low).

Summary of Findings

Five trials (N=1,020)⁸⁸⁻⁹² evaluated interventions for acute neck pain (Appendix E, Table E-3). All of the trials compared one nonpharmacologic treatment to another (KQ 2m and 2n). Four trials^{88,89,91,92} evaluated patients with acute whiplash neck sprain, and one trial⁹⁰ evaluated patients with acute cervical radiculopathy. The duration of pain was ≥ 7 days in two trials,^{89,90} and not described in three trials.^{88,91,92} The duration of treatment ranged from 1 to 6 weeks. The duration of followup was 1 week to <4 weeks in one trial,⁹¹ and ≥ 4 weeks in four trials.^{88-90,92} All five trials were conducted in Europe. The mean age ranged from 29 to 47. Few trials reported race or ethnicity. One trial excluded patients with a history of substance use disorder,⁸⁸ one trial excluded pregnant or breastfeeding patients,⁹² two trials excluded patients with psychiatric illness,^{88,91} and one trial excluded patients with fractures or dislocations of the cervical spine.⁸⁸ Three trials^{88,90,91} were fair quality, and two trials^{89,92} poor quality (Appendix F, Table F-1). Methodological limitations included failure to report adequate randomization or allocation concealment methods, failure to report attrition, high attrition, and no intention to treat analysis. It was not possible to blind patients and caregivers to study interventions.

Detailed Synthesis

Opioid Therapy

No evidence was found for opioid therapy for neck pain.

Nonopioid Pharmacologic Therapy

No evidence was found for opioid therapy for neck pain.

Nonpharmacologic Therapy

KQs 2m and 2n address the comparative effectiveness of nonpharmacologic therapy versus: (1) inactive controls or (2) other nonpharmacologic therapies.

Five trials assessed nonpharmacologic therapy for acute neck pain⁸⁸⁻⁹² (Appendix E, Table E-3). Four trials^{88-90,92} compared a cervical collar versus exercise or usual activity, and one trial⁹¹ compared ultrasound versus sham ultrasound.

Cervical Collar Versus Usual Activity

Two trials compared a cervical collar versus usual activity for acute neck pain^{89,90} (Table 11). One fair quality trial (n=135 for this comparison) compared a semi-hard cervical collar (worn during the day for 3 weeks, then weaned off over 3 weeks) versus usual activity in patients with recent onset (within 1 month) cervical radiculopathy.⁹⁰ The cervical collar was associated with lower neck pain intensity versus usual activity at 3 weeks (mean 3.80 vs. 5.50 on a 0 to 10 scale $p=0.001$) and 6 weeks (mean 3.10 vs. 5.11, $p=0.0002$). The collar was also associated with lower arm pain intensity at 3 weeks (5.03 vs. 5.91 on a 0 to 10 scale, $p=0.061$) and 6 weeks (mean 3.35 vs. 4.86, $p=0.006$), but the difference was only statistically significant at 6 weeks. Neck Disability Index scores were similar at 3 and 6 weeks and there was no difference in patient satisfaction with treatment.

Two trials evaluated patients with acute whiplash injury (N=504).^{88,89} A fair quality trial (n=303 for this comparison) found no differences between a semi-hard cervical collar versus usual activity in pain, headache severity, or SF-36 physical health summary score at 3, 6, or 12 months.⁸⁸ A poor quality trial (n=201) found no statistically significant difference in mean pain

scores between soft collar immobilization (2 hours on and 2 hours off during the day and continuous use at night) versus usual care at 6 weeks (mean 2.97 vs. 3.29 on a 0 to 10 visual analog scale [VAS], $p=0.49$) or at 6 months (mean 3.11 vs. 2.66 on a 0 to 10 VAS, $p=0.29$).⁸⁹ There was also no difference in self-reported global improvement at 6 months.

Harms were not reported by any trial.

Cervical Collar Versus Exercise

Three trials compared a cervical collar versus exercise for acute neck pain (Table 11).^{88,90,92} For acute cervical radiculopathy, one fair quality trial described above ($n=139$ for this comparison) compared a semi-hard cervical collar versus exercise therapy (face-to-face instruction and home exercise daily).⁹⁰ Differences in neck pain intensity were small and not statistically significant at 3 weeks (3.80 vs. 4.45 on a 0 to 10 scale, $p=0.212$) or 6 weeks (3.10 vs. 3.62, $p=0.321$). Results were similar for arm pain. Neck Disability Index scores were very similar at 3 and 6 weeks and there was no difference in patient satisfaction with treatment. Two trials evaluated patients with acute whiplash injury.^{88,92} A fair quality trial ($n=297$ for this comparison) found no difference between a semi-hard cervical collar versus exercise (active mobilization) in pain, neck disability, SF-36 physical or mental summary scores, or headache intensity at 3, 6, or 12 months.⁸⁸ A poor quality trial ($n=150$) compared a soft cervical collar (continuous for 1 week) versus exercise (face-to-face instruction on home mobilization exercises) for acute whiplash injury.⁹² The collar was associated with higher pain intensity versus exercise at 6 weeks (mean 1.60 vs. 1.04 on a 0 to 10 scale, $p=0.047$) and greater self-reported disability (mean 1.56 vs. 0.92 on a 0 to 10 scale, $p=0.042$). Harms were not reported by any trial.

Exercise Therapy Versus Usual Activity

Two trials described above compared exercise therapy versus usual activity (Table 11) activity.^{88,90} For acute cervical radiculopathy, a fair quality trial ($n=136$ for this comparison) found exercise therapy associated with lower neck pain intensity versus usual activity at 3 weeks (mean 4.45 vs. 5.50 on a 0 to 10 scale, $p=0.059$) and 6 weeks (mean 3.62 vs. 5.11, respectively, $p=0.007$), though the difference was of borderline statistical significance at 3 weeks.⁹⁰ Results were similar for arm pain intensity. There were no differences in Neck Disability Index scores or patient satisfaction with treatment. A fair quality trial ($n=296$ for this comparison) found no difference between exercise therapy (active mobilization) versus usual activity in pain, neck disability, SF-36 physical or mental summary scores, or headache intensity at 3, 6, or 12 months.⁸⁸ Harms were not reported in either trial.

Ultrasound Versus Sham Ultrasound

One fair quality trial ($n=54$) compared ultrasound (5 days of pulsed ultrasound followed by 5 days of continuous ultrasound) versus sham ultrasound for whiplash neck sprain (Table 11).⁹¹ Usual care in both groups included massage and exercise. There was no difference in mean pain intensity between ultrasound versus sham ultrasound at the end of treatment (mean 3.18 vs. 3.01 on a 0 to 10 scale, $p=0.742$), though ultrasound was associated with higher mean neck pain intensity at 25 days (mean 6.16 vs. 5.24 on a 0 to 10 scale, $p=0.040$). Harms were not reported.

Table 11. Nonpharmacologic interventions for acute neck pain

Author, Year Quality	Interventions	Type of Neck Pain; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Borchgrevink, 1998 ⁸⁹ Poor	A: Soft collar immobilization and sick leave for 14 days B: Usual activity for 14 days	Whiplash neck sprain; 6 weeks and 6 months n=163	Neck pain intensity (mean [SD], 0 to 100 VAS converted to 0 to 10 scale): 2.97 (2.65) vs. 3.29 (3.53) at 6 weeks, MD -0.32 (95% CI -1.24 to 0.60); 3.11 (2.16) vs. 2.66 (2.35) at 6 months, MD 0.45 (95% CI -0.22 to 1.12)	Pain during daily activities (mean [SD], 0 to 4 scale): 1.38 (0.39) vs. 1.41 (0.44) at 2 weeks, MD -0.03 (95% CI -0.15 to 0.09); 1.48 (0.45) vs. 1.34 (0.47) at 6 months, MD 0.14 (95% CI 0.004 to 0.28)
Kongsted, 2007 ⁸⁸ Fair	A: Semi-hard cervical collar during waking hours for 2 weeks followed by active mobilization for 4 weeks (maximum 2 sessions weekly) B: Active mobilization: physiotherapist- led sessions in addition to home exercises for six weeks (maximum 2 sessions weekly) C: Usual care 1 hour educational session	Whiplash neck sprain; 3, 6, and 12 months n=448	Neck pain (median [IQR], 0 to 10 VAS): 3.8 (1.2 to 6.1) vs. 3.1 (1.2 to 6.1) vs. 4.2 (1.2 to 7.0), p=0.5 at 3 months; 4.1 (1.2 To 7.0) vs. 3.0 (0.2 to 6.1) vs. 4.1 (2.1 to 6.1), p=0.2 at 6 months; 3.0 (1 to 7) vs. 3.0 (0 to 6) vs. 4.5 (0 to 8), p=0.1 at 12 months Headache (median [IQR], 0 to 10 VAS): 4.0 (0.1 to 6.0) vs. 3.0 (0.1 to 6.9) vs. 3.0 (1.0 to 8.0), p=0.6 at 3 months; 4.0 (1.0 to 7.0) vs. 2.0 (0.5 to 6.0) vs. 4.0 (1.0 to 7.0), p=0.1 at 6 months; 4.0 (0.3 to 6.9) vs. 2.0 (0.3 to 6.9) vs. 3.7 (0.3 to 6.9), p=0.3 at 12 months	SF-36 Physical health summary (median [IQR] scale unclear): 46 (34 to 56) vs. 54 (43 to 58) vs. 54 (41 to 58), p=0.6 at 12 months; Neck disability (median [IQR] 0 to 30 scale): 9 (2 to 18) vs. 7 (2 to 14) vs. 6 (2 to 18), p=0.4 at 12 months Subjects with disability >6%, , (n/N): 39% (59/152) vs. 36% (53/145) vs. 30.4% (46/151) at 12 months, RR 1.13 (95% CI 0.93 to 1.74), for A vs. C; RR 1.20 (95% CI 0.87 to 1.66) for B vs. C
Kuijper, 2009 ⁹⁰ Fair	A: Semi-hard cervical collar during the day for 3 weeks, weaned off at 6 weeks B: Exercise with focus on mobilizing and stabilizing cervical spine twice a week for 6 weeks C: No treatment	Cervical radiculopathy; 3 and 6 weeks and 6 months n=205	Neck pain (mean [SD], 0 to 100 VAS converted to 0 to 10 scale): 3.80 (2.84) vs. 4.45 (3.25) vs. 5.50 (3.18) at 3 weeks, MD -1.70 (95% CI -2.73 to -0.67) for A vs. C and -0.40 (95% CI -1.30 to 0.50) for B vs. C; 3.10 (2.82) vs. 3.62 (3.10) vs. 5.11 (3.27) at 6 weeks, MD -2.01 (95% CI -3.05 vs. -0.97) for A vs. C and -1.49 (95% CI -2.57 to -0.41) for B vs. C; median 1.00 (IQR 0.00 to 4.00) vs. 2.00 (0.00 to 4.38) vs. 1.00 (0.00 to 5.00) at 6 months	Neck disability index (mean [SD], 0 to 100 scale): 33.8 (18.7) vs. 34.6 (16.1) vs. 34.3 (18.8) at 3 weeks, MD -0.50 (95% CI -6.90 to 5.90) for A vs. C and 0.30 (95% CI 0.30 (95% CI -5.63 to 6.23) for B vs. C; 25.9 (19.1) vs. 27.8 (17.7) vs. 29.9 (20.0) at 6 weeks, MD -4.0 (95% CI -10.66 to 2.66) for A vs. C and -2.10 (95% CI -8.50 to 4.30) for B vs. C; median (IQR) 8.0 (0 to 26.0) vs. 10.0 (2.0 to 29.2) vs. 8.0 (0 to 26.) at 6 months

Author, Year Quality	Interventions	Type of Neck Pain; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Ruiz-Molinero, 2014 ⁹¹ Fair	A: Ultrasound, pulsed and continuous, 1 session per day for 10 days B: Sham ultrasound, 1 session per day for 10 days	Whiplash neck sprain; 10 and 25 days n=54	Pain intensity (mean [SD], 0 to 10 VAS): 3.18 (2.12) vs. 3.01 (1.62) at day 10, MD 0.17 (95% CI -0.86 to 1.20); 6.16 (1.89) vs. 5.24 (1.25) at day 25, MD: 0.92 (95% CI 0.04 to 1.80)	NR
Schnabel, 2004 ⁹² Poor	A: Soft cervical collar, day and night for 1 week B: Exercise therapy, mobilization of affected body regions, 2 to 5 sessions in first week, 3 sessions daily for 6 weeks	Whiplash neck sprain; 6 weeks n=150	Pain intensity (mean [SD], 0 to 10 VAS): 1.60 (2.15) vs. 1.04 (1.81), MD 0.56 (p=0.047)	Perceived disability for normal activities (mean [SD], 0 to 10 VAS): 1.56 (2.22) vs. 0.92 (1.70), MD 0.64 (p=0.042)

Abbreviations: CI = confidence interval; IQR = interquartile range; MD = mean difference; NR = not reported; SD = standard deviation; VAS = visual analog scale.

KQs 2o and 2p ask how the comparative effectiveness and harms of nonpharmacologic therapy 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.

It was not possible to determine how the comparative effectiveness and harms of nonpharmacologic therapy for acute neck pain varied based on patient and intervention factors, due to small numbers of trials and methodological limitations in the trials. No trial conducted subgroup analyses.

KQ 3. Musculoskeletal Pain Not Otherwise Included in KQ1 or KQ2 (Including Fractures)

Key Points

- Opioid vs. NSAID
 - Insufficient evidence from four poor quality trials (SOE: insufficient).
- Opioid agonist vs. mixed agent
 - Inconsistent effects on pain intensity at <1 day (3 trials), no difference in pain intensity at 1 day to <1 week (1 trial) or improvement in function at 1 day to <1 week based on one trial) (SOE: low for outcomes at 1 day to <1 week).
- NSAID vs. acetaminophen, acute musculoskeletal injury
 - Similar effects on pain intensity at <1 day (4 trials), 1 day to <1 week (8 trials), 1 to <2 weeks (6 trials), and ≥4 weeks (2 trials) (SOE: moderate).
- Non-aspirin NSAID vs. NSAID
 - Insufficient evidence from four poor quality trials (SOE: insufficient).

- Ultrasound vs. sham ultrasound, ankle sprain
 - No difference in pain or other outcomes at 1 day to <1 week or ≥ 4 weeks, based on three trials (SOE: low).
- Acupressure vs. sham acupressure or usual care
 - Acupressure associated with moderate to large decrease in pain intensity versus sham acupressure or standard treatment at 1 day to <1 week, with small effects at 4 weeks (SOE: low).
- Cold therapy, transcutaneous electrical nerve stimulation, or relaxation
 - Insufficient evidence from poor quality trials (SOE: insufficient).

Summary of Findings

Thirty trials (N=2,866)⁹³⁻¹²² evaluated interventions for acute musculoskeletal pain, excluding low back and neck pain (Appendix E, Table E-4). Seven trials^{97,98,105,109,112,116,118} evaluated opioid therapy (KQ 3a and 3c), 13 trials^{93-96,99,101-103,107,108,111,120,122} evaluated a nonopioid medication versus nonpharmacologic treatment or another nonopioid (KQ 3i and 3j), and 10 trials^{100,104,106,110,113-115,117,119,121} (KQ 3m and 3n) evaluated nonpharmacologic treatment versus an inactive control or another nonpharmacologic treatment. Twelve trials^{95,99,101,104-106,109,110,113,117,119,121} evaluated patients with ankle sprain, 3 trials^{98,100,115} fractures, 1 trial⁹³ acute rotator cuff tear, and 14 trials^{94,96,97,102,103,107,108,111,112,114,116,118,120,122} various musculoskeletal pain conditions (e.g., fracture, trauma, and/or sprains/strains). The duration of pain was <7 days in 12 trials^{93,95,96,99,101-104,109,110,117,119,121,122} was <14 days in 2 trials,^{94,97} and not described in 14 trials.^{98,100,105-108,111-116,118,120} The duration of treatment ranged from a single dose or treatment session^{98,107,117,118} to 8 weeks.¹⁰⁴ The duration of followup was less than 1 week in 16 trials,^{95,98-105,107,109-111,116,118,120} 1 week to <4 weeks in 15 trials,^{94-97,99-101,106,108,112,113,117,119,121,122} and ≥ 4 weeks in 5 trials.^{93,99,104,114,115} Ten trials^{95,96,100,105,107,109,110,112,114,118} were conducted in the United States, 11 trials^{94,101,103,106,111,113,116,117,119,121,122} in Europe, and 8 trials^{93,98,99,102,104,108,115,120} elsewhere. The mean age ranged from 23 to 50. Few trials reported race or ethnicity. Four trials^{98,101,102,120} excluded patients with a history of substance use disorder, 16 trials^{93-96,98,99,101-103,105,108,112,114,116,120,122} excluded pregnant or breastfeeding patients, no trials excluded patients with psychiatric illness, and 5 trials excluded patients with other comorbidities.^{94,96,98,104,121} Three trials^{102,107,120} were rated good quality, 12 trials^{93,95,98,99,101,103,104,109,113,115,118,122} fair quality, and 15 trials^{94,96,97,100,105,106,108,110-112,114,116,117,119,121} poor quality (Appendix F, Table F-1). Methodological limitations in the fair and poor quality trials included failure to report adequate randomization or allocation concealment methods, unblinded design, failure to report attrition, high attrition, and no intention to treat analysis.

Detailed Synthesis

Opioid Therapy

KQs 3a and 3c address the comparative effectiveness and harms of opioid therapy versus: (1) nonopioid pharmacologic therapy (e.g., acetaminophen, NSAIDs, antidepressants, anticonvulsants) or (2) nonpharmacologic therapy (e.g., exercise, cognitive behavioral therapy, acupuncture).

Seven trials^{97,98,105,109,112,116,118} evaluated opioid therapy for acute musculoskeletal pain (Appendix E, Table E-4). Four trials compared an opioid versus an NSAID,^{97,105,112,116} and three trials^{98,109,118} compared an opioid agonist versus a mixed agent (buprenorphine, tramadol or

tapentadol). Three trials blinded patients to treatments.^{98,109,118} Three trials^{98,109,118} were rated fair quality, and four trials^{97,105,112,116} were rated poor quality (Appendix F, Table F-1).

Opioid Versus NSAID

Four poor quality trials compared an opioid (alone or in combination with acetaminophen) versus an NSAID for acute musculoskeletal pain (primarily sprains, strains, or fractures; or mixed musculoskeletal pain) (Table 12).^{97,105,112,116} Treatment was initiated in the ED in one trial¹⁰⁵ and in outpatient settings in three trials.^{97,112,116} The sample size for the opioid versus NSAID comparisons ranged from 35 to 113 (N=237). The duration of treatment ranged from 4 to up to 7 days. Three trials^{97,105,112} compared the combination of codeine plus acetaminophen (30 to 60 mg plus 300 mg every four to six hours; daily morphine equivalent dose 18 to 36 mg) versus diflunisal (1000 mg loading dose, then 500 mg twice to three times daily), and the third trial¹¹⁶ compared tramadol (200 to 300 mg/day) versus diclofenac (200 to 300 mg/day).

One trial found no statistically significant difference in pain intensity between an opioid versus an NSAID at 6 hours (mean difference -0.40 on a 0 to 10 scale, 95% CI -1.10 to 0.30).¹¹⁶ At five to seven days, two trials found opioids associated with a small to moderate decrease in pain intensity versus an NSAID in two trials (mean difference -0.7 and -1.0 point),^{112,116} but the difference was statistically significant in only one¹¹⁶ of the trials. A third trial found a small difference in pain intensity favoring an opioid versus an NSAID at 5 days, but did not report statistical differences.⁹⁷ Both groups had no pain at 7 days. A fourth trial found no difference between an opioid versus an NSAID in the proportion reporting no or mild pain at 1 to 7 days (90.5% to 94.7%, RR 0.96, 95% CI 0.80 to 1.14), though patients randomized to the opioid were less likely to rate pain relief as very good or excellent (38% vs. 84%, RR 0.45, 95% CI 0.25 to 0.81).¹⁰⁵ None of the trials found differences between an opioid versus NSAID in function. Evidence on adverse events was limited. Serious adverse events were not reported and withdrawal due to adverse events were few; opioids were associated with increased likelihood of any adverse event in one trial, but the difference was not statistically significant (65% vs. 28%, $p=0.06$).¹¹² Estimates for specific adverse events were imprecise.

Opioid Agonist Versus Mixed Agent

Three fair-quality trials compared an opioid agonist versus the mixed agent tramadol or versus buprenorphine for acute musculoskeletal pain (Table 12).^{98,109,118} One fair-quality trial (n=62) of patients with fracture, sprain/strain, contusion, or tendon rupture found a single dose of hydrocodone plus acetaminophen 5/500 mg (5 mg morphine equivalent dose) associated with markedly lower pain intensity at 3 hours versus tramadol 100 mg (10 mg morphine equivalent dose) (mean 2.3 vs. 5.1 on a 0 to 10 scale, $p<0.01$).¹¹⁸ However, a larger multidose trial of patients with ankle sprain (n=346) found no differences between hydrocodone plus acetaminophen versus tramadol plus acetaminophen (median 26.1 vs. 32.2 morphine equivalent dose) in pain intensity at 4 hours or 5 days, or in likelihood of experiencing ≥ 30 percent or ≥ 50 percent improvement; outcomes were nearly identical in the two groups.¹⁰⁹ There was also no difference in the likelihood of no mild or activity impairment at 5 days (73.8% vs. 65.2%, RR 1.13, 95% CI 0.99 to 1.29), and the risk of adverse events was similar, with no statistically significant differences. The third trial, which evaluated patients with extremity fracture (n=89), found no difference between a single dose of intravenous (IV) morphine (5 mg) versus sublingual buprenorphine (0.4 mg, or 15.5 mg morphine equivalents) in pain at 60 minutes.⁹⁸ No serious adverse events were reported in the trials.

Table 12. Opioid therapy versus NSAIDs or mixed agent opioids

Author, Year Quality	Interventions	Pain Condition; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Aghababian, 1986 ¹⁰⁵ Poor	A. Codeine 30 mg + acetaminophen 300 mg 1 to 2 tablets every 4 hours as needed for pain B. Diflunisal 1000mg loading dose, then 500 mg every 12 hours as needed for pain For mean of 4 days	Grade 2 ankle sprain 1 to 7 days n=40	No or mild pain: 90.5% (19/21) vs. 94.7% (18/19); RR 0.96 (95% CI 0.80 to 1.14)	Medication efficacy and tolerability "very good" or "excellent": 43% (9/21) vs. 89% (17/19); RR 0.48 95% CI 0.28 to 0.80) Pain relief 'very good' or 'excellent', % (n/N) 38% (8/21) vs. 84% (16/19); RR 0.45 (95% CI 0.25 to 0.81)
Hewitt, 2007 ¹⁰⁹ Fair	A. Hydrocodone 7.5 mg + acetaminophen 650 mg up to 4 times a day for 5 days B. Tramadol 75 mg + acetaminophen 650 mg up to 4 times a day for 5 days	Ankle sprain with partial ligament tear 4 hours and up to 5 days n=346	Pain intensity (mean [SD], 0 to 3 NRS converted to 0 to 10 scale) at day 5: 3.33 (3.63) vs. 3.33 (3.50), MD -0.00 (-0.15 to 0.16) Pain intensity difference (mean [SD], 0 to 3 NRS converted to 0 to 10 scale) at 4 hours: 3.33 (2.33) vs. 3.33 (2.33) Sum of pain intensity differences (mean [SDI], sum of hourly differences): 3.2 (2.5) vs. 3.3 (2.1), MD 0.64 (-0.78 to 2.05)	≥30% improvement in pain intensity at 4 hours: 61.7% (117/190) vs. 63.7% (128/201), MD -2.0% (-11.9% to 7.9%) ≥50% improvement in pain intensity at 4 hours: 39.9% (77/201) vs. 38.3% (76/190), MD 1.6% (-8.4% to 11.6%) No or mild activity impairment: 73.8% (144/195) vs. 65.2% (122/187), RR 1.13 (95% CI 0.99 to 1.29)
Indelicato, 1986 ⁹⁷ Poor	A: Codeine 30 mg + acetaminophen 300 mg, 1 to 2 tablets every 4 to 6 hours for 7 days B: Diflunisal 1000 mg loading dose + 500 mg every 12 hours for 7 days	Acute strains and sprains; 1, 5, and 7 days n=49	Pain (mean [SD NR], 0 to 3 converted to 0 to 10 scale): 6.7 vs. 6.3 at day 1; 1.3 vs. 2.0 at day 5; 0 vs. 0 at day 7	Patient-reported efficacy (% [n/N] rated "very good", "excellent": 28% (7/25) vs. 38% (9/24), RR 0.68 (95% CI 0.31 to 1.53)
Jalili, 2012 ⁹⁸ Fair	A: Morphine sulfate: 5 mg IV plus sublingual placebo, single dose B: Buprenorphine: 0.4 mg sublingual plus 5 mL sterile water IV placebo, single dose	Extremity fracture; 60 minutes n=89	Pain (mean [SD], 0 to 10 NRS): 2.2 (1.7) vs. 2.2 (0.7), p=0.9; MD, 0.0 (95% CI -0.55 to 0.55)	NR

Author, Year Quality	Interventions	Pain Condition; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Muncie, 1986 ¹¹² Poor	A. Codeine 60 mg + acetaminophen 650 mg every 4 hours as needed for 7 days B. Diflunisal 1000 mg loading dose, then 500 mg every 12 hours as needed for 7 days	Mild to moderate sprain or strain, or low back pain Up to 7 days n=35	Pain (mean [SD], 0 to 4 scale converted to 0 to 10 scale): 3.3 (2.8) vs. 4.0 (3.8), p=NS	Limitation of function (mean [SD]), 0 to 4 scale: 1.5 (1.3) vs. 1.9 (1.8), p=NR
Pagliara, 1997 ¹¹⁶ Poor	A. Tramadol 200 to 300 mg per day for 5 to 7 days B. Diclofenac 200 to 300 mg per day for 5 to 7 days	Musculoskeletal pain due to trauma; 6 hours and 5 to 7 days n=113	Pain intensity (mean [SD] 0 to 100 VAS converted to 0 to 10 scale) 5.7 (1.5) vs. 6.1 (2.2), at 6 hours, MD -0.40 (95% CI -1.10 to 0.30); 1.5 (1.5) vs. 2.5 (2.2), at 5 to 7 days, MD -1.0 (95% CI -1.70 to -0.30)	Patient rated efficacy (mean [SD], 0 to 100 VAS converted to 0 to 10 scale): 9.02 (1.20) vs. 7.43 (2.11), MD 1.59 (95% CI 0.95 to 2.23)
Turturro, 1998 ¹¹⁸ Fair	A. Hydrocodone 5 mg + acetaminophen 500 mg x 1 B. Tramadol 100 mg x 1	Trauma (fracture, sprain/strain, contusion, tendon rupture) 3 hours n=62	Pain intensity (mean [SD], 0 to 100 VAS converted to 0 to 10 scale): 2.3 (2.2) vs. 5.1 (2.9), p<0.01	NR

Abbreviations: AE = adverse event; CI = confidence interval; IV = intravenous; MD = mean difference; NR = not reported; NRS = numeric rating scale; NS = not significant; RR = relative risk; SD = standard deviation; VAS = visual analog scale

KQs 3b and 3d ask how the comparative effectiveness and harms 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.

Evidence on how comparative effectiveness and harms of opioid therapy for acute musculoskeletal pain vary according to patient and prescribing factors was lacking. The number of trials was small for each comparisons and most trials had small sample sizes. In addition, trials excluded patients with subgroup characteristics of interest, such as substance use history or presence of medical or psychiatric comorbidities, or did not provide information regarding these factors. No study conducted within-study or across-study evaluations of subgroup effects.

KQ 3e concerns 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).

No evidence was found for KQ 3e.

KQs 3f and 3g concern the accuracy and effectiveness of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose in patients with acute pain being considered for opioid therapy.

No study evaluated the accuracy or effectiveness of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose in patients with acute musculoskeletal pain.

KQ 3h addresses the effect of the following factors on the decision to prescribe opioids for patients with acute pain being considered for opioid therapy: (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.

Evidence on the effect of patient education, use of risk mitigation strategies, clinician and patient values and preferences, or availability of followup on decisions to prescribe opioids for postoperative pain was not available.

Nonopioid Pharmacologic Therapy

KQs 3i and 3k address the comparative effectiveness and harms of nonopioid pharmacologic therapy versus: (1) nonopioid pharmacologic therapy or (2) nonpharmacologic therapy.

Thirteen trials evaluated nonopioid pharmacologic therapy for acute musculoskeletal pain (Appendix E, Table E-4; Table 13).^{93-96,99,101-103,107,108,111,120} Eight trials compared an NSAID versus acetaminophen^{93,95,99,101-103,107,120} four trials compared a non-aspirin NSAID versus aspirin,^{94,96,108,111} and one trial compared a topical NSAID to an oral NSAID.¹²² Three trials^{102,107,120} were rated good quality, six trials fair quality,^{93,95,99,101,103,122} and four trials^{94,96,108,111} poor quality (Appendix F, Table F-1).

NSAID Versus Acetaminophen

Three good quality RCTs^{102,107,120} and five fair quality trials^{93,95,99,101,103} (N=1,139) compared an NSAID versus acetaminophen for acute musculoskeletal injury (sprains or strains, musculoskeletal injury or trauma, or rotator cuff injury). In most trials, differences between NSAIDs and acetaminophen were small and not statistically significant at <1 day (4 trials, mean difference on 0 to 10 pain scale ranged from -0.5 to -0.1 point),^{102,103,107,120} 1 day to 1 week (8 trials, mean differences ranged from -0.9 to 1.2 points),^{94,95,99,101-103,111,120} 1 to <2 weeks (6 trials, mean difference ranged from -0.8 to 0.5 point),^{94-96,99,101,102} and at ≥4 weeks (mean difference 0.2 point in two trials).^{93,99} Findings were similar when focusing on the good quality RCTs. One good quality trial (n=60) of a single dose of ibuprofen 800 mg versus acetaminophen 1000 mg found similar pain intensity at 1 hour (3.9 vs. 4.3 on a 0 to 10 scale) and no difference in rescue medication use.¹⁰⁷ Another good quality trial (n=201) compared diclofenac (25 mg every 8 hours) or indomethacin (25 mg every 8 hours) versus acetaminophen (1000 mg every 6 hours) for 3 days in patients with sprain, contusion, wound, crush, or fracture.¹²⁰ Effects on pain intensity were similar at 2 hours and 3 days; differences in mean change from baseline were 0.1 to 0.2 point on a 0 to 10 scale. The third good quality trial found no difference between a single dose of ibuprofen 800 mg versus acetaminophen 1000 mg in pain intensity at 60 minutes in patients with acute musculoskeletal injury (mean difference -0.40, 95% CI -1.9 to 1.1).¹⁰⁷ No severe adverse events were reported and there were no differences in nonsevere adverse events, though estimates were imprecise and reporting of adverse events was suboptimal.

Non-Aspirin NSAID Versus Aspirin

Four poor quality trials compared an NSAID (piroxicam 40 mg followed by 20 mg daily, flurbiprofen 150 mg daily, naproxen 750 mg daily, or diclofenac 150 mg daily) versus aspirin (2,000 to 4,000 mg daily).^{94,96,108,111} Trials were rated poor quality due to inadequate reporting of methods. In both studies, results favored the non-aspirin NSAID, though differences were not always statistically significant. One trial of professional soccer players with lower limb injuries (n=51) found no difference between flurbiprofen versus aspirin in pain at 1 day (mean 4.1 vs. 4.2, p=NS; scale not reported) but flurbiprofen was associated with decreased pain at day 6 (0.3 vs. 1.2, p<0.01).¹¹¹ Flurbiprofen was also associated with decreased time to training fitness and

match fitness (differences 0.9 to 1.2 days). The second trial (n=69) found piroxicam associated with increased likelihood of being able to accomplish activity within 16 days, though the difference was not statistically significant (80% vs. 65%, RR 1.24, 95% CI 0.92 to 1.67).¹⁰⁸ Effects on pain intensity were not reported. Piroxicam was also associated with decreased risk of any adverse event or gastrointestinal adverse events, though the difference were not statistically significant.

Table 13. NSAID versus other pharmacologic treatments for musculoskeletal pain

Author, Year Quality	Interventions	Pain Condition; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
AlRuthia, 2019 ⁹³ Fair	A: Ibuprofen, 400 to 800 mg every 6 to 8 hours as needed. Patients may increase dose to <3200 mg per day B: Acetaminophen, 500 mg every 6 to 8 hours as needed; for patients whose pain is not controlled by this dose: 1000 mg every 6 hours as needed	Acute rotator cuff disease; 6 weeks n=33	Mean difference in pain from baseline (SD), 100 point SPADI questionnaire converted to 0 to 10 scale: -1.91 (2.96) vs. -2.11 (3.49)	Mean difference in disability from baseline (SD), 100 point SPADI questionnaire: -17.30 (20.54) vs. -16.35 (39.84) Mean difference in Quick-DASH score (SD), 100 point scale: -13.41 (17.49) vs. -15.04 (24.91)
Andersen, 1984 ⁹⁴ Poor	A: Naproxen, 250 mg in the morning and 500 mg in the evening for 7 days B: Aspirin: 500 mg in the morning and at noon and 1000 mg in the evening	Soft tissue injuries 7 days n=63	Pain on movement (mean [SD NR], 0 to 100 VAS converted to 0 to 10 scale): 5.3 vs. 5.0 at day 1; 4.0 vs. 4.2 at day 3; 3.0 vs. 2.7 at day 7; all comparisons, p=NS	A vs. B Functional capacity (mean [SD NR], 1 to 4 scale): 2.5 vs. 2.7 at day 1; 2.0 vs. 2.5 at day 3; 2.0 vs. 2.2 at day 7, p=NS for all comparisons
Bondarsky, 2013 ¹⁰⁷ Good	A. Ibuprofen 800 mg x 1 B. Acetaminophen 1000 mg x 1	Acute musculoskeletal injury; 60 minutes n=60	Mean (SD) (0 to 10 scale): 3.9 (3.07) vs. 4.3 (2.79), MD -0.40 (95% CI -1.92 to 1.12)	Rescue medication use: 36.7% (11/30) vs. 33.3% (10/30), RR 1.10 (95% CI 0.55 to 2.20)
Dalton, 2006 ⁹⁵ Fair	A. Ibuprofen, 400 mg/ 3 times daily for 9 days B. Extended release acetaminophen, 1,300 mg 3 times daily for 9 days	Grade 1 or 2 lateral ankle sprain; 4 and 9 days n=255	Pain intensity on walking (least squares mean change from baseline), 0 to 100 VAS converted to 0 to 10 scale: -3.5 vs. -3.7, p=0.24 at day 4; -5.7 vs. -5.6, p=0.73 at day 9.	Satisfaction with treatment (Least squares mean change from baseline), 0 to 100 VAS (higher=more satisfied): 7.7 vs. 7.9, p=0.22 at day 4; 8.4 vs. 8.8, p=0.03 at day 9

Author, Year Quality	Interventions	Pain Condition; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Duncan, 1988 ⁹⁶ Poor	A: Diclofenac: 75 mg twice daily (150 mg daily) plus 2 placebo tablets three times daily, for 3 to 10 days B: Aspirin: 2 600 mg tablets three times daily (3.6 g daily) plus two placebo tablets twice daily, for 3 to 10 days	Acute sprains and/or strains of the knee or ankle Up to 10 days (final visit) n=96	Pain on active motion (mean difference [SEM], difference baseline to final visit, 0 to 3 scale): −1.96 (0.10) vs. −1.82 (0.10)	NR
Heere, 1998 ¹⁰⁸ Poor	A. Piroxicam 40 mg once daily for 2 days, then 20 mg once daily B. Aspirin 4000 mg daily	Sprains and tendonitis; 16 days n=69	NR	Able to accomplish activity within 16 days: 80% (28/35) vs. 65% (22/34), RR 1.24 (95% CI 0.92 to 1.67) Overall impression of efficacy good or excellent: 94.3% (33/35) vs. 82.4% (28/34), RR 1.14 (95% CI 0.96 to 1.36)
Kayali, 2007 ⁹⁹ Fair	A: Diclofenac sodium, 75 mg twice daily for 5 days B: Acetaminophen, 500 mg 3 times daily for 5 days	Grade 1 or 2 lateral ankle sprain; 2 days, 10 days, and 6 weeks n=100	Pain intensity (mean [SD NR], 0 to 100 VAS converted to a 0 to 10 scale): 2.1 vs. 1.2 at 2 days, MD 0.9; 0.98 vs. 0.63 at 10 days, MD 0.35; 0.46 vs. 0.30 at 6 weeks, MD 0.16 B vs. A MD (95% CI) : −0.88 (−1.4 to −0.35) at 2 days; −0.37 (−0.68 to −0.05) at 10 days; −0.16 (−0.40 to 0.08) at 6 weeks	NR
Lyrtsis, 2011 ¹⁰¹ Fair	A: Diclofenac, 75 mg 2 times daily for 10 days B: Acetaminophen, 500 mg 3 times daily for 10 days	Grade 2 ankle sprain of the lateral collateral ligaments; 3 and 10 days n=86	Pain intensity (mean [SD], 0 to 100 VAS converted to a 0 to 10 scale): 2.21 (1.28) vs. 2.23 (1.44) at day 3, MD −0.02 (95% CI −0.6 to 0.6); 0.69 (0.83) vs. 0.51 (0.68) at day 10, MD 0.18 (95% CI −0.1 to 0.5)	NR

Author, Year Quality	Interventions	Pain Condition; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Man, 2004 ¹⁰² Good	A: Diclofenac, 25 mg 3 times a day for 3 days B: Indomethacin, 25 mg 3 times a day for 3 days C. Acetaminophen 1000 mg 4 times a day for 3 days	Isolated soft tissue limb injury 2 hours, 1 day, and 3 days n=39	Pain intensity at rest (mean [SD], 0 to 100 VAS converted to a 0 to 10 scale: 3.0 (2.0) vs. 1.0 (1.5) vs. 1.8 (2.2) at day 1, MD 1.2 (95% CI -0.5 to 2.9) for A vs. C and -0.9 (95% CI -2.5 to 0.7) for B vs. C Change from baseline in pain intensity at rest (mean, 0 to 100 scale converted to 0 to 10 scale): -0.9 (95% CI -1.3 to -0.4) vs. -0.9 (95% CI -1.3 to -0.4) vs. -0.9 (95% CI -1.3 to -0.5) at 2 hours, MD 0.1 (95% CI -0.8 to 1.0) for A vs. C and -0.1 (95% CI -0.8 to 1.0) for B vs. C; -1.6 (95% CI -2.2 to -1.0) vs. -0.4 (95% CI -0.9 to 0.2) vs. -0.6 (95% CI -1.0 to -0.1) at 3 days, MD -0.8 (95% CI -1.9 to 0.4) for A vs. C and 0.5 (95% CI -0.6 to 1.6) for B vs. C	Requested additional analgesic after 3 days, % (n/N): 11% (1/9) vs. 30% (3/10) vs. 0% (0/14)
Muckle, 1974 ¹¹¹ Poor	A. Flurbiprofen 150 mg for 6 days B. Aspirin 1200 mg 3 times daily for 6 days	Soft tissue trauma to lower limb; 1 and 6 days n=51	Pain (mean [SD NR], total daily score, scale not reported): 4.1 vs. 4.2 at day 1, p=NR; 0.3 vs. 1.2 at day 6, p<0.01	Days to training fitness (mean [SD NR]): 3.38 vs. 4.27, p<0.05 Days to match fitness (mean [SD NR]): 4.79 vs. 6.04, p<0.05

Author, Year Quality	Interventions	Pain Condition; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Ridderikhof, 2018 ¹⁰³ Fair	A. Diclofenac, 75 mg 3 times daily for 3 days B: Acetaminophen, 1000 mg 4 times daily for 3 days	Minor musculoskeletal trauma of an extremity; 90 minutes and 3 days n=365	<p>Pain intensity at rest (mean [95% CI], 0 to 10 NRS): 4.01 (3.67 to 4.35) vs. 3.47 (3.12 to 3.82) at 90 minutes, MD -0.54 (95% CI -1.03 to -0.06); 2.95 (2.56 to 3.35) vs. 2.91 (2.52 to 3.30) at day 3, MD -0.04 (95% CI -0.59 to 0.51)</p> <p>Patients >60 years (n=14 vs. 14) Pain intensity at rest (mean [95% CI], 0 to 10 NRS): 3.79 (2.20 to 5.37) vs. 2.46 (1.24 to 3.69) at 90 minutes, MD -1.32 (95% CI -3.23 to 0.59); 2.53 (1.38 to 3.67) vs. 2.53 (0.88 to 4.19) at 3 days, MD 0.008 (95% CI -1.82 to 1.83)</p> <p>≥33% reduction in pain at rest (0 to 10 NRS), % (n/N): 92% (156/170) vs. 86% (142/166) at 90 minutes, RR 1.07 (95% CI 0.99 to 1.16); 86% (101/117) vs. 90% (98/109) at 3 days, RR 0.96 (95% CI 0.87 to 1.06)</p>	<p>Proportion "satisfied" or "very satisfied" with pain relief, % (n/N): 55% (92/166) vs 57% (98/171) at 90 minutes, RR 0.97 (95% CI 0.80 to 1.17); 74% (99/134) vs. 67% (83/123) at 3 days, RR 1.09 (95% CI 0.93 to 1.28)</p> <p>Additional opioid analgesics, % (n/N): 0.5% (1/182) vs. 0% (0/183) at 90 minutes; 9% (16/182) vs. 4% (8/183) at 3 days, RR 2.01 (95% CI 0.88 to 4.58)</p>
Woo, 2005 ¹²⁰ Good	A. Diclofenac 25 mg every 8 hours for 3 days B. Indomethacin 25 mg every 8 hours for 3 days A. Acetaminophen 1000 mg every 6 hours for 3 days	Limb injury after trauma (sprain, contusion, wound, crush, fracture); 2 hours and 3 days n=201	Pain intensity difference (mean change from baseline, 0 to 100 VAS converted to 0 to 10 scale): 0.6 vs. 0.9 vs. 0.9 at 2 hours, MD in change from baseline, -0.1 (95% CI -0.4 to 0.2) for A vs. C and -0.1 (95% CI -0.3 to 0.4) for B vs. C; 0.7 vs. 0.9 vs. 0.5 at 3 days, MD 0.1 (95% CI -0.6 to 0.4) for A vs. C and -0.2 (95% CI 0.7 to -0.4) for B vs. C	NR

Abbreviations: CI = confidence interval; DASH = Disabilities of the Arm, Shoulder, and Hand; MD = mean difference; NR = not reported; NS = not significant; RR = relative risk; SD = standard deviation; SEM = standard error of the mean; SPADI = Shoulder Pain and Disability Index; VAS = visual analog scale

Oral NSAID Versus Topical NSAID

One fair quality trial (n=100) based in the United Kingdom compared topical ibuprofen versus oral ibuprofen (400 mg) for acute soft tissue injuries.¹²² There were no differences in

median pain intensity at rest or with movement at 1 or 2 days, and the time to improvement in pain was similar in both groups.

KQs 3j and 3l ask how the comparative effectiveness and harms 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.

Evidence was too limited to evaluate how comparative effectiveness and harms of nonopioid therapy for acute musculoskeletal pain varied in subgroups, due to few trials, small sample sizes, methodological limitations, and exclusion of relevant subgroups or lack of information about them. One trial found no statistically significant differences between an NSAID versus acetaminophen in pain intensity in a subgroup analysis of patients over 60 years of age, but the number of patients was small, and estimates were imprecise.¹⁰³ No other study conducted within-study or across-study evaluations of subgroup effects. Details regarding the nonopioid medications prescribed, dose, and duration of treatment are described above.

Nonpharmacologic Therapy

KQs 3m and 3n address the comparative effectiveness of nonpharmacologic therapy versus: (1) inactive controls or (2) other nonpharmacologic therapies.

Ten trials evaluated nonpharmacologic therapy for acute musculoskeletal pain (Appendix E, Table E-4).^{100,104,106,110,113-115,117,119,121} Three trials^{106,110,117} evaluated cold therapy, one trial¹¹⁰ heat therapy, three trials^{113,119,121} ultrasound, one trial¹¹⁴ transcutaneous electrical nerve stimulation, one trial acupressure,¹⁰⁴ one trial a rib belt,¹⁰⁰ and one trial¹¹⁵ relaxation. Three trials^{104,113,115} were rated fair quality, and seven trials^{100,106,110,114,117,119,121} poor quality (Appendix F, Table F-1).

Cold Therapy Versus No Cold Therapy or Sham

Two trials compared cold therapy versus no cold therapy or sham for ankle sprain (Table 14).^{106,117} It was not possible to blind patients to use of cold, though one of the trials used a sham (non-inflated anklet without use of cold material). The trials were rated poor quality, primarily due to inadequate reporting of methods. In addition, it was unclear if one of the trials¹⁰⁶ was randomized. In that trial (n=60), 48 hours of therapy with a cold pack gel was associated with increased likelihood of recovery at 2 and 7 days versus no cold therapy (absolute difference 13.0% and 23.6%, respectively), but statistical significance testing was not reported and not calculable. At 14 days, the difference favored cold therapy but was small (8.0%). Cold therapy was also associated with decreased period of disability (9.7 vs. 14.8) of unknown statistical significance. In the other trial (n=116), there was no difference between cold therapy administered in an inflated anklet versus sham in pain relief (data not reported) or in likelihood of improving ≥ 2 points on a 5 point injury severity scale (88% vs. 79%, p=0.15).¹¹⁷ Adverse events were not reported in either trial.

Cold Therapy Versus Heat Therapy

One trial (n=37) found cold therapy (ice whirlpool or ice pack three times daily for 3 days) associated with shorter time to achieve functional milestones (walk without pain, stand without pain, climb stairs without pain, or run and jump without pain) than heat therapy (warm soak or heating pad 1 to 3 times daily for 3 days) (Table 14).¹¹⁰ However, the trial was rated poor quality, and it was not clear if it was truly randomized. In addition, results for cold therapy were

reported only stratified by time to initiation and by severity of sprain (not by overall randomization), with no evaluation of statistical significance. Adverse events were not reported.

Table 14. Cold therapy versus other nonpharmacologic therapies for musculoskeletal pain

Author, Year Quality	Interventions	Pain Condition; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Basur, 1976 ¹⁰⁶ Poor	A: Cold gel pack for 48 hours B: No cold therapy	Ankle sprain; 2, 7, and 14 days n=60	Recovery (not defined) (n/N NR): 42.1% vs. 29.1% at day 2, 84.2% vs. 60.6% at day 7, and 96.2% vs. 88.2% at day 14, p=NR	Period of disability (mean days [SD NR]): 9.7 vs. 14.8, p=NR
Hocutt, 1983 ¹¹⁰ Poor	A: Cryotherapy, ice whirlpool for 12 to 20 minutes or ice pack for 15 to 20 minutes 1 to 3 times daily 3 days B: Heat therapy, warm soak or heating pad for 15 minutes 1 to 3 times daily for ≥3 days	Grade 3 or 4 ankle sprain; Outcomes reported as time to milestones n=37	NR	A (initiating on day 0 or 1) vs. A (initiated on day 2) vs. B Walk without pain (mean [SD NR], days): 2.6 vs. 5.2 vs. 7.8 for class 3 sprain, 4.2 vs. 12.0 vs. 9.7 for class 4 sprain Stand without pain (Mean [SD NR], days): 2.7 vs. 6.2 vs. 5.7 for class 4 sprain
Sloan, 1989 ¹¹⁷ Poor	A: Inflated cooling anklet for 30 minutes while ankle elevated B: Sham therapy, non-inflated anklet without elevation	Ankle sprain; 7 days n=116	Pain improved ≥2 points on a 5 point scale: 88% vs. 79%, p=0.15	Pain relief: No difference (data not provided)

Abbreviations: NR = not reported; SD = standard deviation

Ultrasound Versus No Ultrasound or Sham Ultrasound

Three trials (N=190) compared ultrasound versus no ultrasound or sham ultrasound in patients with ankle sprains (Table 15).^{113,119,121} One trial¹¹³ was rated fair quality, and two trials^{119,121} were rated poor quality. The fair quality trial (n=51) found no differences between ultrasound (10 minutes daily for three days) versus sham ultrasound in pain or ability to bear body weight at 3 or 14 days.¹¹³ The poor quality trials (n=29 and n=110) found no differences between ultrasound versus sham ultrasound or no ultrasound on pain intensity or a composite outcome (swelling, discomfort, limp, and pain) at 1 to 4 weeks.^{119,121} Adverse events were not reported in any of the trials.

Table 15. Ultrasound versus no ultrasound or sham ultrasound for musculoskeletal pain

Author, Year Quality	Interventions	Pain Condition; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Nyanzi, 1999 ¹¹³ Fair	A: Ultrasound, 10-minute sessions daily for 3 days B: Sham ultrasound, same as above, but probes disabled	Lateral ankle ligament sprain; 3 and 14 days n=51	Pain (mean [SD], 0 to 10 VAS): 1.9 (2.5) vs. 2.2 (2.1) at day 3, 0.9 (1.4) vs. 0.7 (1.4) at day 14, p=NR at both time points	Percent of body weight in affected leg (SD): 42.8 (5.8) vs. 43.0 (6.0) at day 3, 44.7 (5.6) vs. 45.1 (4.6) at day 14

Author, Year Quality	Interventions	Pain Condition; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Williamson, 1983 ¹¹⁹ Poor	A: Ultrasound, session every other day B: No ultrasound	Lateral ankle ligament sprain; 1, 2, 3, and 4 weeks n=110	NR	Overall score for subjective assessment of swelling, patient discomfort, degree of limp, pain on inversion, pain on plantarflexion (median [IQR NR], 0 to 15 scale): 1.8 vs. 1.2 at week 1, 1.0 vs. 1.0 at week 2, 0.5 vs. 0.9 at week 3, 0 vs. 0.6 at week 4; p=NR Proportion with overall score of 0 or 1: 52% vs. 53% at week 1, 90% vs. 84% at week 2, 100% vs. 95% at week 3, 100% vs. 99% at week 4; p=NR
Zammit, 2005 ¹²¹ Poor	A: Ultrasound, 1 10- minute session every other day for 2 weeks, and 1 followup session on day 21 B: Sham ultrasound, as above, but ultrasound not turned on C: No ultrasound	Lateral ankle ligament sprain; 7, 14, and 21 days n=29	Pain intensity (mean [SD NR], 0 to 10 VAS): 1.8 vs. 2.1 vs. 2.9 at day 7, 0.8 vs. 1.2 vs. 1.7 at day 14, 0.3 vs. 0.7 vs. 0.7 at day 21; p>0.05	NR

Abbreviations: IQR = interquartile range; NR = not reported; SD = standard deviation; VAS = visual analog scale

Transcutaneous Electrical Nerve Stimulation (TENS) Versus Sham TENS

One poor-quality trial (n=100) compared TENS versus sham TENS, in patients with acute musculoskeletal injuries (sprain, laceration, fracture, or hematoma/contusion) (Table 16).¹¹⁴ Patients were randomized to four groups: TENS or sham TENS with or without the addition of codeine plus acetaminophen. TENS was worn at all times or as needed for pain for 3 days; for sham TENS the unit was not turned on. At two days, TENS was associated with decreased pain intensity versus sham TENS when each was administered without codeine plus acetaminophen (mean difference -2.44, 95% CI -3.89 to -0.99), but there was no difference between TENS versus sham TENS with codeine plus acetaminophen (mean difference 0.00, 95% CI -1.33 to 1.33). There was no difference between TENS versus sham TENS at 1 month, with or without the opioid. The only adverse event reported was mild tingling in 20 percent of overall patients (not reported by group).

Relaxation Versus Usual Care

One small (n=30), fair quality trial of patients with nonoperatively-treated, simple long or short-bone fractures found prana energization (a relaxation technique based on yoga principles) associated with decreased pain intensity at 4 weeks (mean difference -3.23 on a 0 to 10 scale, 95% CI -4.13 to -2.32) (Table 16).¹¹⁵ The intervention consisted of 30-minute sessions daily for 7 days, followed by home sessions twice daily for 3 weeks. Adverse events were not reported.

Acupressure Versus Sham Acupressure or Usual Care

One fair quality trial (n=62) compared a single session of acupressure versus sham acupressure or standard treatment without acupressure (rest ice, compression, and evaluation) for ankle sprain (Table 16).¹⁰⁴ It found acupressure associated with a moderate decrease in pain intensity at 3 days versus sham acupressure (difference -1.7 points on a 0 to 10 scale, $p<0.01$) and large decrease versus standard treatment (difference -2.1 points, $p<0.01$). At 4 weeks, effects also favored acupressure but were smaller (differences -0.79 and -0.90, $p<0.01$), with no statistically significant differences at 8 weeks (differences -0.16 and -0.31). Acupressure was also associated with small beneficial effects on the SF-36 physical and mental component summary scores at 4 weeks that were not statistically significant (differences 7.22 to 8.43 points on a 0 to 100 scale), with little difference on these summary scores at 8 weeks (differences 0.9 to 3.9 points).

Rib Belt Versus No Rib Belt

A small (n=20), poor quality trial found a rib belt associated with a pain intensity difference at day 3 versus no rib belt that was small and not statistically significant (4.4 vs. 5.2, $p>0.20$) (Table 16).¹⁰⁰ At 2 weeks, adverse events in the belt group included one case of bloody pleural effusion, two cases of asymptomatic atelectasis, and one case of contact dermatitis; there were no adverse events in the non-belt group.

Table 16. Other nonpharmacologic therapies for musculoskeletal pain

Author, Year Quality	Interventions	Pain Condition; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Lazcano, 1989 ¹⁰⁰ Poor	A: Wear rib belt at all times except bathing; duration NR B: No rib belt	Rib fracture; 3 days and 2 weeks n=20	Pain (mean [SD NR], 0 to 10 NRS): 4.4 vs. 5.2 at day 3, p>0.20	NR
Ordog, 1987 ¹¹⁴ Poor	A: TENS, worn at all times or as needed for pain in area of injury B: TENS + codeine and acetaminophen 30/300 mg, TENS as above + 1 to 2 tablets every 4 hours as needed C: Sham TENS, worn at all times or as needed for pain in area of injury D: Sham TENS + codeine and acetaminophen 30/300 mg; as above	Sprain, laceration, fracture, hematoma/contusion; 2 days and 1 month n=100	Pain intensity (mean [SD], 0 to 10 NRS): 3.04 (2.6) vs. 3.84 (2.3) vs. 5.48 (2.5) vs. 3.84 (2.38) at 2 days, MD -2.44 (95% CI -3.89 to -0.99) for A vs. C and 0.00 (95% CI -1.33 to 1.33) for B vs. D; 0.28 (0.54) vs. 0.52 (0.96) vs. 0.44 (0.65) vs. 0.52 (1.0) at 1 month, MD -0.16 (95% CI -0.50 to 0.18) for A vs. C and 0.00 (95% CI -0.56 to 0.56) for B vs. D	NR
Oswal, 2011 ¹¹⁵ Fair	A: Yoga relaxation technique (Prana energization), 30 minutes daily for 7 days, then twice daily for 3 weeks B: Usual care	Simple long or short-bone fractures 4 weeks n=30	Pain intensity (mean [SD], 0 to 10 NRS): 0.50 (0.75) vs. 3.73 (1.48), MD -3.23 (95% CI -4.13 to -2.32)	NR

Author, Year Quality	Interventions	Pain Condition; Followup Duration Sample Size	Pain Intensity Results	Other Pain and Function Results
Zhao, 2018 ¹⁰⁴ Fair	A: Acupressure plus standard treatment: pressure applied to the Yongquan point of injured foot for 10 minutes along with pressure to tenderness point on contralateral hand + standard treatment for ≥3 sessions B: Sham acupressure: pressure applied to the Yongquan point of non-injured foot and tenderness point of contralateral hand + standard treatment for ≥3 sessions C: Standard treatment: rest, ice (20 minutes in 48 hours), compression (Tubigrip compression stocking for 6 weeks), and elevation	Grade 1 or 2 ankle sprain; 1, 3, 28, and 56 days n=62	Pain score (mean, VAS 0 to 10 scale): 3.33 (95% CI 2.97 to 3.70) vs. 4.81 (95% CI 4.28 to 5.36) vs. 5.37 (95% CI 4.81 to 5.93) at 1 day, p<0.01 for A vs. B and A vs. C; 1.33 (0.70 to 1.97) vs. 3.05 (2.58 to 3.51) vs. 3.42 (2.83 to 4.01) at 3 days, p<0.01 for A vs. B and A vs. C; 0.10 (0.04 to 0.23) vs. 1.00 (0.47 to 1.53) vs. 0.89 (0.36 to 1.43) at 28 days, p<0.001 for A vs. B and A vs. C; 0.10 (0.04 to 0.23) vs. 0.41 (0.13 to 0.70) vs. 0.26 (0 to 0.5) at 56 days, p=NS for A vs. B and for A vs. C	American Orthopedic Foot and Ankle Score (mean, 0 to 100 scale): 55.9 (95% CI 50.0 to 61.7) vs. 41.6 (95% CI 34.9 to 48.2) vs. 47.5 (95% CI 39.9 to 55.1) at 1 day, p<0.01 for A vs. B and A vs. C; 70.95 (95% CI 64.9 to 77.0) vs. 60.8 (95% CI 55.5 to 66.1) vs. 65.0 (95% CI 58.5 to 71.5) at 3 days, p<0.01 for A vs. B and A vs. C; 93.2 (95% CI 90.9 to 95.6) vs. 81.1 (95% CI 75.7 to 86.6) vs. 86.2 (95% CI 81.9 to 90.4) at 28 days, p<0.01 for A vs. B and A vs. C; 99.0 (95% CI 98.2 to 99.9) vs. 96.9 (95% CI 94.7 to 99.0) vs. 97.5 (95% CI 95.3 to 99.6) at 56 days, p=NS for A vs. B and A vs. C SF-36 Physical component score (mean, 0 to 100 scale): 49.4 (95% CI 47.4 to 52.1) vs. 42.1 (95% CI 38.4 to 46.1) vs. 42.6 (95% CI 40.4 to 45.2) at 4 weeks, p=NS for A vs. B and A vs. C; 53.2 (95% CI 52.3 to 53.9) vs. 49.3 (95% CI 45.2 to 53.3) vs. 52.4 (95% CI 50.1 to 55.6) at 8 weeks, p=NS for A vs. B and A vs. C SF-36 Mental component score (mean, 0 to 100 scale): 60.1 (95% CI 62.4 to 63.1) vs. 51.7 (95% CI 47.7 to 54.5) vs. 53.2 (95% CI 50.4 to 57.7) at 4 weeks, p=NS for A vs. B and A vs. C; 66.4 (95% CI 65.5 to 67.2) vs. 62.7 (95% CI 58.4 to 65.2) vs. 63.9 (95% CI 59.1 to 67.2) at 8 weeks, p=NS for A vs. B and A vs. C

Abbreviations: CI = confidence interval; MD = mean difference; NR = not reported; NS = not significant; NRS = numeric rating scale; SD = standard deviation; SF = short form; TENS = transcutaneous electrical nerve stimulation

KQs 3o and 3p ask if the comparative effectiveness and harms of nonpharmacologic therapy 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.

Evidence on how the comparative effectiveness and harms of nonpharmacologic therapy for acute musculoskeletal pain varied based on patient and intervention factors was not available. The number of trials and sample sizes for each comparison were too small for between-study comparisons to be informative and no trial conducted within-study subgroup analyses.

KQ 4. Peripheral Neuropathic Pain (Related to Herpes Zoster and Trigeminal Neuralgia)

Key Points

- Opioid vs. gabapentin, herpes zoster
 - Oxycodone associated with increased likelihood of improvement in pain at 1 to <2 weeks (79.3% vs. 55.2%, RR 1.4, 95% CI 1.0 to 2.1) and at ≥ 4 weeks (86.2% vs. 62.1%, RR 1.5, 95% CI 1.1 to 2.0) (SOE: low).
 - Oxycodone associated with increased likelihood of constipation (RR 2.50, 95% CI 1.13 to 5.53), based on one trial (SOE: low).
- Topical vs. oral aspirin, herpes zoster
 - Insufficient evidence from one poor quality trial (SOE: insufficient).
- No trials of nonopioid pharmacologic therapy for acute peripheral neuropathic pain.

Summary of Findings

Evidence on the comparative effectiveness of interventions for peripheral neuropathic pain was limited to two small ($n=45$ and 30) trials (Appendix E, Table E-5).^{123,124} One trial evaluated opioid therapy (KQ 4a and 4c), and one trial evaluated nonopioid pharmacologic therapy (KQ 4i and 4j). Both trials evaluated patients with acute herpes zoster, and the duration of pain was ≥ 7 days in both trials. The mean age of patients was 49 and 66 years, and the proportion female was 30 percent and 66 percent. The trial of opioid therapy excluded patients with alcohol or drug abuse history within the last 5 years.¹²⁴ Otherwise the trials did not describe psychiatric or medical comorbidities. One trial¹²⁴ was rated fair quality, and one trial¹²³ was rated poor quality (Appendix F, Table F-1). The poor quality trial was open-label, did not report randomization and allocation concealment methods, had high attrition, and did not perform intention to treat analysis.

Detailed Synthesis

Opioid Therapy

KQs 4a and 4c address the comparative effectiveness and harms of opioid therapy versus: (1) nonopioid pharmacologic therapy (e.g., acetaminophen, NSAIDs, antidepressants, anticonvulsants) or (2) nonpharmacologic therapy (e.g., exercise, cognitive behavioral therapy, acupuncture).

Opioid Versus Gabapentin

One fair quality trial (n=45) compared oxycodone sustained-release (titrated up to 60 mg twice daily) versus gabapentin (titrated up to 600 mg three times a day) for acute herpes zoster¹²⁴ (Table 17). Oxycodone was associated with decreased average pain intensity versus gabapentin at day 1 to 8, day 1 to 14, and day 1 to 28, though differences were small (–0.5 to –0.8 point on a 0 to 10 point scale) and not statistically significant. Oxycodone was associated with increased likelihood of ≥30% improvement in pain at day 14 (79.3% vs. 55.2%, RR 1.4, 95% CI 1.0 to 2.1) and at day 28 (86.2% vs. 62.1%, RR 1.5, 95% CI 1.1 to 2.0) and increased likelihood of ≥50% improvement in pain at day 28 (72.4% vs. 48.3%, RR 1.6, 95% CI 1.0 to 2.3). Oxycodone was also associated with slightly decreased rescue medication use, though the difference was not statistically significant. There was no difference between oxycodone versus gabapentin in function. Oxycodone was associated with increased likelihood of constipation versus gabapentin (RR 2.50, 95% CI 1.13 to 5.53); there were no differences in serious adverse events, withdrawal due to adverse events, or other specific adverse events, but there were few events and estimates were imprecise.

Table 17. Opioid versus gabapentin for herpes zoster-related pain

Author, Year Quality	Interventions	Followup Duration Sample Size	Pain Intensity Results	Other Pain Results
Dworkin, 2009 ¹²⁴ Fair	A: Oxycodone, 10 mg 1 or 2 times daily titrated to up to 60 mg every 12 hours B: Gabapentin, 300 mg every night titrated to up to 600 mg every 8 hours	Days 1 to 14 and days 1 to 28; 8, 14 and 15 days n=45	Average pain intensity (adjusted mean [SD], 0 to 10 VAS): 3.5 (8.6) vs. 4.0 (8.6) at day 1 to 8, MD –0.5 (95% CI –5.0 to 4.0); 2.5 (8.6) vs. 3.3 (8.6) at day 1 to 14, MD –0.8 (95% CI –5.3 to 3.7); 0.6 (9.2) vs. 1.4 (9.2) at day 1 to 28, MD –0.8 (95% CI –5.6 to 4.0)	≥30% improvement in pain: 55.2% (16/29) vs. 34.5% (10/29) at days 8, RR 1.6 (95% CI 0.9 to 2.9); 79.3% (23/29) vs. 55.2% (16/29) at day 14, RR 1.4 (95% CI 1.0 to 2.1); 86.2% (25/27) vs. 62.1% (18/29) at day 28, RR 1.5 (95% CI 1.1 to 2.0) ≥50% improvement in pain: 24.1% (7/29) vs. 17.20% (5/29) at day 8, RR 1.4 (95% CI 0.5 to 3.9); 44.8% (13/29) vs. 27.6% (8/29) at day 15, RR 1.6 (95% CI 0.8 to 3.3); 72.4% (21/29) vs. 48.3% (14/29) at day 28, RR 1.6 (95% CI 1.0 to 2.3)

Abbreviations: CI = confidence interval; MD = mean difference; RR = relative risk; SD = standard deviation; VAS = visual analog scale

No evidence was found for other subquestions (KQs 4b and 4d to 4h) related to opioid therapy for acute peripheral neuropathic pain.

Nonopioid Pharmacologic Therapy

KQs 4i and 4k address the comparative effectiveness of nonopioid pharmacologic therapy versus: (1) nonopioid pharmacologic therapy and (2) nonpharmacologic therapy.

Topical Versus Oral Aspirin

One small (n=30), poor quality trial compared topical versus oral aspirin for acute herpes zoster¹²³ (Table 18). Oral aspirin was dosed at 375 to 750 mg daily and topical aspirin was administered as a solution three times daily. The topical aspirin was associated with decreased pain intensity at 3 hours, 1 week, and 3 weeks (differences ranged from –1.6 to –3.6 points on a 0 to 10 point pain scale), though oral aspirin was associated with decreased pain intensity at 1 day

(difference 0.9 point). Topical aspirin was associated with markedly increased likelihood of experiencing >50% improvement in pain (100% vs. 6.7%, RR 15.00, 95% CI 2.26 to 99.64).

Table 18. Nonopioid interventions for herpetic neuralgia

Author, Year Quality	Interventions	Followup Duration Sample Size	Pain Intensity Results	Other Pain Results
Balakrishnan, 2001 ¹²³ Poor	A: Topical aspirin, 75 mg aspirin/1 mL moisturizer solution, up to 10 mL of solution applied 3 times daily B: Oral aspirin, 375 to 750 mg, ^a 3 times a daily	3 hours, 1 week, and 3 weeks n=30	Pain intensity (mean [SD], 0 to 100 VAS converted to 0 to 10 scale): 1.35 (0.30) vs. 3.69 (0.65) at 3 hours, MD -2.34 (95% CI -2.72 to -1.96); 7.75 (0.37) vs. 6.82 (0.61) at 1 day, MD 0.93 (95% CI 0.55 to 1.31); 3.38 (0.67) vs. 5.0 (0.90) at 1 week, MD: -1.62 (95% CI -2.21 to -1.03); 0.68 (0.30) vs. 4.31 (0.87) at 3 weeks, MD -3.63 (95% CI -4.12 to -3.14)	Pain improved >50%: 100% (15/15) vs. 6.7% (1/15), RR 15.00 (95% CI 2.26 to 99.64)

Abbreviations: CI = confidence interval; MD = mean difference; SD = standard deviation; RR = relative risk; VAS = visual analogue scale

^a Dosage depending on patients' body mass index.

KQs 4j and 4l ask how the comparative effectiveness and harms 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.

No evidence was found for KQ 4j and 4l.

Nonpharmacologic Therapy

KQ 4m and 4n address the comparative effectiveness of nonopioid pharmacologic therapy versus: (1) inactive controls or (2) other nonpharmacologic therapies.

No evidence was found for KQ 4m and 4n.

KQ 5. Postoperative Pain (Excluding Inpatient Management of Pain Following Major Surgical Procedures)

Key Points

- Opioid vs. NSAID, single dose
 - No differences in pain or rescue medication use at <1 day, based on two trials (SOE: low).
- Opioid vs. NSAID, multidose course
 - Opioid associated with increased likelihood of repeat or rescue medication use at 1 day to 1 week (RRs ranged from 1.22 to 2.04), based on four trials; evidence on pain intensity insufficient due to inconsistency (SOE: moderate for repeat or rescue medication use, insufficient for pain intensity).
- Opioid vs. acetaminophen, single dose
 - No difference in pain intensity at <1 day and no difference in need for re-medication, based on one trial (SOE: low).

- Opioid vs. acetaminophen, multidose course
 - Evidence on comparative effectiveness limited and imprecise (SOE: insufficient).
 - Opioid 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).
- Opioid agonist vs. mixed agent
 - No difference in pain at <1 day (1 trial), 1 day to <1 week (6 trials), or 1 to <2 weeks (1 trial) (SOE: low to moderate).
- Opioid prescribing following a minor surgical procedure or elective surgery was associated with increased likelihood of opioid use at long-term followup versus no opioid prescribing, based on two observational studies (SOE: low).
- NSAID vs. acetaminophen, single dose
 - Evidence on pain intensity and use of analgesics inconsistent, based on two trials (SOE: insufficient).
- NSAID vs. acetaminophen, multidose course
 - Evidence insufficient from one poor quality trial (SOE: insufficient).
- Acupuncture vs. sham acupuncture
 - Evidence on pain intensity inconsistent, based on two trials (SOE: insufficient).
- Acupressure vs. sham acupressure
 - Acupressure associated with decreased pain medication use versus sham acupressure at <1 day and 1 day to <1 week, based on two trials, but effects on pain intensity were small and not statistically significant (SOE: low for pain medication use, insufficient for pain intensity).
- Cold therapy vs. sham therapy
 - No difference between cold therapy versus sham therapy or no cold therapy in pain intensity at 1 day to <1 week, based on three fair quality trials (SOE: low).
 - No difference between cold therapy versus sham therapy in pain intensity, function, or quality of life at 2 to <4 weeks or ≥4 weeks, based on one good quality trial, though cold therapy was associated with decreased pain medication use in the first 4 days (SOE: low).
- Massage vs. no massage
 - Massage associated with moderate to large decrease in pain intensity at <1 day (6 trials), decreased pain medication use (3 trials), and decreased anxiety (3 trials) (SOE: low).
- Music therapy vs. no music therapy
 - Music therapy was associated with moderate decrease in pain intensity versus no music therapy at <1 day (1 trial) and small to moderate decrease in pain intensity at 1 day to <1 week (1 trial) (SOE: low).
- Exercise vs. no exercise
 - One trial found exercise therapy (stretching) associated with large improvements on the Neck and Disability Index following thyroid surgery at 1 week, but there was no difference at 1 month (SOE: low).
- TENS vs. sham TENS
 - TENS associated with moderate to large decrease in pain intensity versus sham TENS following liposuction at 12 hours and at 24 hours and decreased analgesic use (1 trial) (SOE: low).

Summary of Findings

Forty-seven trials (N=6,078) evaluated interventions for postoperative pain,¹²⁵⁻¹⁷¹ excluding inpatient management of pain after major surgical procedures (Appendix E, Table E-6). Fourteen trials^{126,128,130,141,145,150,153,159,160,164,167,169-171} evaluated opioid therapy (KQ 5a and 5c), 5 trials^{131,140,152,157,163} evaluated a nonopioid medication versus nonpharmacologic treatment or another nonopioid (KQ 5i and 5j), and 28 trials^{125,127,129,132-139,142-144,146-149,151,154-156,158,161,162,165,166,168} (KQ 5m and 5n) evaluated nonpharmacologic treatment versus an inactive control or another nonpharmacologic treatment. The most common surgical procedures were cesarean sections, anterior cruciate ligament (ACL) reconstructions, knee arthroplasties, and cholecystectomies. The duration of treatment ranged from a single dose or treatment session to 6 weeks. The duration of followup was less than 1 week in 35 trials,^{125-128,131-135,137,139,140,143-147,149-152,154-158,160-165,167,169,171} 1 week to <4 weeks in six trials,^{129,130,136,153,166,170} and ≥4 weeks in seven trials.^{129,138,141,142,148,159,168} Sixteen trials^{126,130,131,139,142,144,145,150,152,157,161,163,166,169,170} were conducted in the United States, 14 trials in Europe,^{128,129,134,135,140,141,146,147,153,154,158,160,168,171} and 17 trials elsewhere.^{125,127,132,133,136-138,143,148,149,151,155,156,159,162,165,167} The mean age ranged from 22 to 70. Few trials reported race or ethnicity. Five trials^{143,145,160,167,169} excluded patients with a history of substance use disorder, 12 trials^{128,135,143,145,150,152,153,159,160,167-169} excluded pregnant or breastfeeding patients, 4 trials^{127,160,167,169} excluded patients with psychiatric illness, and 10 trials^{126,128,141,145,152,153,159,160,162,169} excluded patients with other comorbidities. Two trials^{143,168} were rated good quality, 28 trials^{126,128,130,132-135,138,141,142,145,147,149-153,157-160,162-164,167,169-171} fair quality, and 17 trials^{125,127,129,131,136,137,139,140,144,146,148,154-156,161,165,166} poor quality (Appendix F, Table F-1). Methodological limitations in the fair and poor quality trials included failure to report adequate randomization or allocation concealment methods, unblinded design, failure to report attrition, high attrition, and no intention to treat analysis.

Detailed Synthesis

Opioid Therapy

KQs 5a and 5c address the comparative effectiveness of opioid therapy versus: (1) nonopioid pharmacologic therapy (e.g., acetaminophen, NSAIDs, antidepressants, anticonvulsants) or (2) nonpharmacologic therapy (e.g., exercise, cognitive behavioral therapy, acupuncture).

Fourteen trials evaluated opioid therapy for acute postoperative pain following various surgical procedures (Appendix E, Table E-6).^{126,128,130,141,145,150,153,159,160,164,167,169-171} Five trials compared an opioid versus an NSAID,^{130,141,150,159,167} four trials compared an opioid versus acetaminophen,^{153,160,164,167} and six trials compared an opioid agonist versus a mixed agent (tramadol or tapentadol).^{126,128,145,169-171} Nine trials blinded patients and caregivers to the study medications. All of the trials were rated fair quality (Appendix F, Table F-1).^{126,128,130,145,150,159,160,164,167,169,171}

Opioid Versus NSAID

Five fair-quality trials compared an opioid (with or without acetaminophen) versus an NSAID for postoperative pain (Table 19).^{130,141,150,159,167} The surgery was arthroscopic rotator cuff repair in one trial,¹⁵⁹ cesarean section in one trial,¹⁶⁷ various orthopedic surgeries in one trial,¹⁵⁰ herniotomy in one trial,¹⁴¹ and otolaryngologic surgery in one trial.¹³⁰ Sample sizes ranged from 108 to 366 (N=1,090). The trials were conducted in the United States,^{130,150} Venezuela,¹⁶⁷ Italy,¹⁴¹ and South Korea.¹⁵⁹ Two of the studies evaluated a single dose of

medication followed by re-randomization and evaluation of a 2 or 5 day multidose course of therapy.^{150,167} The duration of treatment in the other trials was 4 days, up to 7 days, and 2 weeks.^{130,141,159} The opioid was hydrocodone in two trials (10 mg single dose, then up to 30 mg daily in one¹⁵⁰ and 5 mg every six hours in the other),¹³⁰ oxycodone in one trial (10 mg single dose, then up to 30 mg daily),¹⁶⁷ and tramadol in two trials (100 to 112 mg daily).^{141,159} Hydrocodone and oxycodone were administered with acetaminophen. The NSAID was ketorolac (30 mg daily), celecoxib (up to 600 mg daily), ibuprofen (1,155 to 2,400 mg daily) or ketoprofen (600 mg daily).

Two studies found no differences between a single dose of an opioid versus an NSAID in pain or rescue medication use at <1 day followup.^{150,167} At 1 day to <1 week in multidose trials, effects of an opioid versus an NSAID on pain intensity were inconsistent (four trials, differences ranged from 0.1 to 1.6 points on a 0 to 10 scale in favor of the NSAID),^{130,141,150,159} though opioids were associated with increased likelihood of repeat or rescue medication use (4 trials, RRs ranged from 1.22 to 2.04).^{130,150,159,167} Also at 1 day to <1 week, one trial¹⁴¹ found no difference between an opioid versus an NSAID in likelihood of pain intensity ≥ 4 on a 0 to 10 scale and one trial¹⁵⁰ found an opioid associated with better function (general activity, walking ability) and quality of life (mood, relations with others, sleep, and enjoyment of life); differences were about 1 point on a 0 to 10 scale. At 1 week, one trial found an opioid plus NSAID associated with higher pain intensity versus ibuprofen, though the difference was small and not statistically significant (3.5 vs. 2.8 on a 0 to 10 scale, $p=0.12$); the opioid plus NSAID was also associated with increased rescue medication use.¹³⁰ At 2 weeks and 24 months, one trial found no difference between an opioid versus an NSAID in pain intensity or rescue medication use.¹⁵⁹ In this trial, tramadol was associated with decreased risk of rotator cuff re-tear versus celecoxib (4.0% vs. 36.7%, RR 0.11, 95% CI 0.02 to 0.79) but the rate of re-tears for tramadol and ibuprofen were similar (4.0% vs. 7.4%, RR 0.54, 95% CI 0.05 to 5.59). Serious adverse events were otherwise not reported. One trial found no difference between an opioid versus an NSAID in likelihood of withdrawal due to adverse events.¹⁵⁰ Opioids were associated with increased risk of any adverse event in three trials (RRs ranged from 1.33 to 1.96).^{141,150,167} Two trials^{150,159} found opioids associated with increased likelihood of nausea, though the difference was small and not statistically significant in one of the trials.¹⁵⁹

Table 19. Opioid therapy versus nonsteroidal anti-inflammatory drugs for postoperative pain

Study, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity Results	Other Results
Bugada, 2015 ¹⁴¹ Fair	A. Tramadol 100 mg IV every 8 hours for first 24 hours, then tramadol 37.5 mg/acetaminophen 325 mg orally every 8 hours after discharge for 3 days B: Ketorolac 30 mg IV every 8 hours for first 24 hours, then ketorolac 10 mg orally every 8 hours after discharge for 3 days	Herniotomy; Up to 5 days, 1 month, and 3 months n=194	Pain intensity (mean [SD], 0 to 10 NRS): 2.74 (2.04) vs. 2.62 (1.90) at up to 5 days, MD 0.14 (95% CI -0.44 to 0.67) Pain intensity ≥ 4 (0 to 10 NRS): 1.1% (1/98) vs. 1.0% (1/96) at 1 month; 0% vs. 0% at 3 months	NR
Gimbel, 2001 ¹⁵⁰ Single dose component Fair	A. Hydrocodone 10 mg + acetaminophen 1000 mg x 1 B. Celecoxib 200 mg x 1	Orthopedic surgery; 4 and 8 hours n=277	Pain intensity difference (mean [SD NR], 0 to 3 VAS converted to 0 to 10 scale): 2.6 vs. 2.7 at 4 hours, p=NS, 0.9 vs. 2.0 at 8 hours; p<0.05 Sum of pain intensity differences (mean [SD NR], sum of 0 to 3 VAS from 0.25 to 8 hours): 7.1 vs. 7.8, p<0.001	Rescue medication use: 51% (69/136) vs. 44% (62/144), RR 1.18 (95% CI 0.92 to 1.51)
Gimbel, 2001 ¹⁵⁰ Multidose component Fair	A. Hydrocodone 10 mg + acetaminophen 1000 mg B. Celecoxib 200 mg	Orthopedic surgery; 2 and 5 days n=366	Maximum pain intensity (mean [SD NR], 0 to 3 VAS converted to 0 to 10 scale): 7.0 vs. 5.7 at day 2, p<0.001; 5.3 vs. 3.7 at day 5, p<0.001	No medication required, day 5: 20% (36/181) vs. 41% (76/185), RR 0.48 (95% CI 0.34 to 0.68)
Nguyen, 2019 ¹³⁰ Fair	A: Hydrocodone + acetaminophen: 5/325 mg every 6 hours as needed for up to 7 days B: Ibuprofen: 600 mg every 6 hours as needed for up to 7 days	Otolaryngology surgery (not including tonsillectomy); 1 week n=108	Pain, overall (mean, 0 to 10 NRS): 3.5 (2.8 to 4.1) vs. 2.8 (95 %CI 2.2 to 3.4), p=0.12 Pain, maximum (mean, 0 to 10 NRS): 5.7 (95% CI 5.0 to 6.5) vs. 5.3 (95% CI 4.6 to 6.1), p=0.49	Rescue medication, total pills (mean): 4.5 (95% CI 3.2 to 5.7) vs. 2.0 (95% CI 0.9 to 3.1), p=0.004

Study, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity Results	Other Results
Oh, 2018 ¹⁵⁹ Fair	A: Tramadol, 50 mg twice daily for 2 weeks B: Celecoxib, 200 mg twice daily for 2 weeks C: Ibuprofen, 385 mg three times daily for 2 weeks	Rotator cuff repair; 3 days, 2 weeks, and mean of 24 months n=162	Pain intensity (mean [SD], 0 to 10 VAS): 4.1 (1.7) vs. 3.4 (1.6) vs. 3.9 (1.9) at 3 days, MD 0.70 (95% CI 0.07 to 1.33) for A vs. B and 0.20 (95% CI -0.49 to 0.89) for A vs. C; 3.2 (1.9) vs. 2.8 (2.1) vs. 3.2 (1.9) at 2 weeks, MD 0.40 (95% CI -0.37 to 1.17) for A vs. B, and 0.00 (95% CI -0.72 to 0.72) for A vs. C; 0.8 (1.5) vs. 0.9 (1.9) vs. 0.6 (1.1) at 24 months; MD -0.10 (95% CI -1.04 to 0.84) for A vs. B and 0.20 (95% CI -0.53 to 0.93) for A vs. C	Rescue medication use: 66.7% (36/54) vs. 50.9% (27/53) vs. 54.5% (30/55) at 3 days, RR 1.31 (95% CI 0.95 to 1.81) for A vs. B and RR 1.22 (95% CI 0.90 to 1.66) for A vs. C; 38.9% (21/54) vs. 28.3% (15/53) vs. 30.9% (17/55) at 2 weeks, RR 1.26 (95% CI 0.75 to 2.11) for A vs. B and RR 1.37 (95% CI 0.80 to 2.37) for A vs. C
Sunshine, 1993 ¹⁶⁷ Single-dose component Fair	A. Oxycodone 10 mg + acetaminophen 650 mg x 1 B. Ketoprofen 50 mg x 1 C. Ketoprofen 100 mg x 1	Cesarean section; 8 hours n=144	Pain intensity difference (mean [SD NR], 0 to 3 NRS converted to 0 to 10 scale): 4.7 vs. 5.0 vs. 5.7 at 4 hours, p=NS for A vs. B, or C; 1.3 vs. 2.0 vs. 3.3 at 8 hours, p=NS for A vs. B or Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 30 scale from 1 to 8 hours): 8.73 vs. 8.34 vs. 10.34, p<0.05 for B vs. C	Global rating (mean [SD NR], 0 to 3 scale): 2.04 vs. 1.90 vs. 2.25, p=NS
Sunshine, 1993 ¹⁶⁷ Multi-dose component Fair	A: Oxycodone 5 mg + acetaminophen 325 mg every 4 hours for up to 7 days B: Ketoprofen 50 mg every 4 hours as needed for up to 7 days C: Ketoprofen 100 mg every 4 hours for up to 7 days	Cesarean section; 2 days n=224	Pain severe 2 hours after first dose on day 2: 8% (6/76) vs. 3% (2/74) vs. 7% (5/74)	Global assessment "very good" or "excellent": 39% (29/76) vs. 64% (47/74) vs. 60% (45/74), RR 0.60 (95% CI 0.43 to 0.84) for A vs. B and RR 0.63 (95% CI 0.45 to 0.88) for A vs. C

Abbreviations: CI = confidence interval; IV = intravenous; NR = not reported; NRS = numeric rating scale; NS = not significant; RR = relative risk; SD = standard deviation; VAS = visual analog scale

Opioid Versus Acetaminophen

Four fair quality trials compared an opioid versus acetaminophen (Table 20).^{153,160,164,167} One trial (n=96) compared a single dose of oxycodone plus acetaminophen (10/650 mg) versus acetaminophen (650 mg) following cesarean section.¹⁶⁷ The opioid was associated with a greater sum of pain intensity differences versus acetaminophen at 8 hours; however, the differences at 4 and 8 hours were not statistically significant. The difference in need for re-medication was also not statistically significant (72.9% vs. 87.5%).

Three trials evaluated multidose courses of an opioid versus acetaminophen. One trial each enrolled patients who underwent extremity fracture surgery,¹⁵³ hand surgery,¹⁶⁰ or Moh's surgery.¹⁶⁴ Sample sizes were 39, 73, and 140 (N=252). The opioid was tramadol (50 mg every 8 hours) plus acetaminophen (1000 mg every 6 hours) in one trial,¹⁵³ tramadol (100 mg every 8 hours) in one trial,¹⁶⁰ and codeine plus acetaminophen (30/325 every 4 hours) in one trial.¹⁶⁴ At <1 day, one trial found no difference between an opioid versus acetaminophen in pain intensity or use of additional doses.¹⁶⁴ At 1 day to <1 week, one trial found no difference between an opioid versus acetaminophen in pain intensity (mean difference 0.30, 95% CI -0.53 to 1.13) or likelihood of rescue medication use.¹⁶⁰ At 2 weeks to <4 weeks, one trial found tramadol plus acetaminophen associated with decreased pain intensity versus acetaminophen, but the difference was not statistically significant (mean difference -0.9 on a 0 to 10 scale, 95% CI -2.00 to 0.06).¹⁵³ Effects on function also favored tramadol plus acetaminophen, but the differences were small and not statistically significant. Opioids were associated with increased risk of withdrawal due to severe nausea and vomiting in one trial (17.5% vs. 0%, RR 12.81, 95% CI 0.75 to 217.60)¹⁶⁰ and increased risk of withdrawal due to any adverse event in two trials (RR 5.40, 95% CI 1.31 to 22.3 and RR 6.00, 95% CI 1.39 to 25.83).^{153,164}

Table 20. Opioid therapy versus acetaminophen for postoperative pain

Study, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity Results	Other Results
Helmerhorst, 2017 ¹⁵³ Fair	A. Tramadol 50 mg every 8 hours + acetaminophen 1000 mg every 6 hours for 2 weeks B. Acetaminophen 1000 mg every 6 hours for 2 weeks	Fracture; 2 weeks n=39	Pain intensity (mean [SD NR], 0 to 10 VAS): 3.0 vs. 3.9, MD -0.9 (95% CI -2.00 to 0.06) at 2 weeks	SMFA, function index (mean [SD NR], 0 to 100 scale, higher score=worse outcome): 37.7 vs. 44.7, p=0.12; bothersome index (mean [SD NR], 0 to 100 scale): 35.7 vs. 44.8, p=0.14 Rescue medication use: 0% (0/25) vs. 7.4% (2/27)
Rawal, 2001 ¹⁶⁰ Fair	A. Tramadol 100 mg every 6 hours for 2 days B. Acetaminophen 1000 mg every 6 hours for 2 days	Hand surgery; 1 and 2 days n=73	Pain intensity (mean [SD], 0 to 10 VAS): 2.0 (2.4) vs. 3.0 (2.7) at day 1 at bedtime, MD -1.0 (95% CI -2.14 to 0.14); 1.8 (1.7) vs. 1.5 (2.0) at day 2 at bedtime, MD 0.30 (95% CI -0.53 to 1.13)	Took rescue medication: 23% (8/34) vs. 42% (16/38) at day 1, 20% (7/34) vs. 24% (9/38) at day 2, p=NS

Study, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity Results	Other Results
Snieszek, 2001 ¹⁶⁴ Fair	A. Codeine 30 mg + acetaminophen 650 mg every 4 hours up to 4 doses B. Acetaminophen 1000 mg every 4 hours up to 4 doses	Mohs surgery; 4 and 12 hours n=140	Pain intensity change from baseline (mean [SD], 0 to 100 VAS converted to 0 to 10 scale): 2.17 (2.23) vs. 1.82 (2.25) at 4 hours, p=0.20; 0.97 (1.83) vs. 0.84 (1.37) at 12 hours, p=0.82	Additional dose used: 70% (59/70) vs. 60% (42/70), RR 1.40 (95% CI 1.13 to 1.74)
Sunshine, 1993 ¹⁶⁷ Single dose component Fair	A. Oxycodone 10 mg + acetaminophen 650 mg x 1 B. Acetaminophen 650 mg x 1	Cesarean section <1 day (8 hours) n=96	Pain intensity difference (mean [SD NR], 0 to 3 NRS converted to 0 to 10 scale): 4.7 vs. 5.0 vs. 5.7 vs. 3.7 at 4 hours, p<0.05 for B or C vs. D and p=NS for A vs. B, C, or D; 1.3 vs. 2.0 vs. 3.3 vs. 0.7 at 8 hours, p<0.05 for B or C vs. D and p=NS for A vs. B, C, or D Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 30 scale from 1 to 8 hours): 8.73 vs. 8.34 vs. 10.34 vs. 6.54, p<0.05 for A vs. D, B vs. C, and C vs. D	Re-medication: 72.9% (35/48) vs. 68.8% (33/48) vs. 57.9% (22/38) vs. 87.5% (42/48), RR 0.66 (95% CI 0.49 to 0.89) for C vs. D, otherwise p=NS

Abbreviations: CI = confidence interval; NR = not reported; NRS = numeric rating scale; NS = not significant; RR = relative risk; SD = standard deviation; SMFA=Short Musculoskeletal Function Assessment; VAS = visual analog scale

Opioid Agonist Versus Mixed Agent

Six fair quality trials compared an opioid agonist versus a mixed agent (tramadol or tapentadol) for postoperative pain (Table 21).^{126,128,145,169-171} The surgery was bunionectomy in three trials,^{126,145,169} arthroscopic shoulder surgery in one trial,¹⁷⁰ cesarean section in one trial,¹²⁸ and various orthopedic surgeries in one trial.¹⁷¹ Sample sizes ranged from 57 to 755 (N=1,462). The duration of treatment and followup ranged from two to seven days.^{126,128,145,169-171} The opioid agonist was oxycodone in five trials (dose ranged from 20 to 60 mg daily)^{126,128,145,170,171} and morphine in one trial (120 to 180 mg daily).¹⁶⁹ The mixed agent was tapentadol (dose ranged from 100 to 450 mg daily) in five trials^{126,128,145,169,170} and tramadol (100 mg twice daily) in one trial.¹⁷¹ Two trials^{128,171} compared sustained-release medications, and the others evaluated immediate-release medications. In two trials^{126,170} the daily dose in morphine equivalents was lower for the opioid agonist (30 to 90 mg or 90 to 135 mg) compared to the mixed agent (80 to 240 mg). In the other trials the doses of the opioid agonist and mixed agent were similar in daily morphine equivalents (range 30 to 180 mg).

There were no differences between an opioid agonist versus mixed agent in pain related outcomes (mean pain intensity, likelihood of improvement, or use of repeat or rescue medications) at 12 hours (1 trial),¹⁶⁹ 2 to 3 days (6 trials),^{126,128,145,169-171} or 7 days (1 trial).¹⁷⁰ One trial found oxycodone associated with increased likelihood of pain interference with sleep, but the difference was not statistically significant (26.5% vs. 17.7%, RR 1.50, 95% 0.98 to 2.30).¹⁷⁰ Otherwise, outcomes related to function or quality of life were not reported. There was no difference in risk of withdrawal due to adverse events and serious adverse events were not reported. Effects of an opioid agonist versus mixed agent on nausea were inconsistent; there were no differences in risk of other specific adverse events.

Table 21. Opioid agonist versus mixed agent for postoperative pain

Study, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity Results	Other Results
Daniels, 2009a ¹⁴⁵ Fair	A: Oxycodone 10 mg every 4 to 6 hours up to 72 hours B: Tapentadol 50 mg every 4 to 6 hours up to 72 hours C: Tapentadol 75 mg every 4 to 6 hours up to 72 hours	Bunionectomy; 48 and 72 hours n=755	Sum of pain intensity differences (least squares mean [95% CI], sum of differences from 0.5 to 72 hours on a 0 to 10 scale): 119.9 (83.52 to 156.21) vs. 89.3 (52.93 to 125.70) vs. 120.0 (83.64 to 156.33); differences of A vs. B or C within noninferiority margin ≥30% improvement in pain intensity: 75.2% vs. 77.5% vs. 76.5% at 48 hours ≥50% improvement in pain intensity: 64.4% vs. 64.7% vs. 64.0% at 48 hours	Use of rescue medication: 3.2% vs. 6.2% vs. 1.4%
Daniels, 2009b ¹²⁶ Fair	A: Oxycodone HCL 15 mg B: Tapentadol IR 50 mg; C: Tapentadol IR 75 mg D: Tapentadol IR 100 mg Day 1: 4 to 7 doses could be administered; Days 2 and 3: 4 to 6 doses could be administered	Bunionectomy; 12, 24, 48, and 72 hours n=482	Sum of pain intensity differences (mean [SD] sum of differences through 72 hours on a 0 to 10 scale): 288 (170.67) vs. 207.9 (207.57) vs. 230.5 (189.36) vs. 271.1 (154.57) ≥30% improvement in pain intensity at 48 hours: 78.4% vs. 64.7% vs. 68.3% vs. 78.8% ≥50% improvement in pain intensity at 48 hours: 72.8% vs. 58.0% vs. 56.7% v. 70.3%	Rescue medication use: 9% vs. 19% vs. 14% vs. 10% Percent reporting "much improved" or "very much improved" overall status on 1 to 7 point VRS: 88% vs. 67% vs. 77% vs. 89%
Ffrench-O'Carrol, 2019 ¹²⁸ Fair	A. Oxycodone controlled release: 10 mg every 12 hours for 2 days B. Tapentadol controlled release: 50 mg every 12 hours for 2 days	Cesarean section; 36 hours and 2 days n=68	Sum of pain intensity differences (mean [SD] sum of differences through 72 hours on a 0 to 10 scale x 24): 65.14 (70.23) vs. 74.54 (77.97), MD -11.45 (95% CI -35.35 to 12.45)	Satisfaction score (mean [SD] on 1 to 5 scale), at 2 days: 4.14 (0.84) vs. 4.34 (1.21); MD 0.032 (95% CI -0.47 to 0.53)
Viscusi, 2019 ¹⁶⁹ Fair	A: Morphine: 30 mg every 4 to 6 hours for 3 days B: Tapentadol: 75 mg every 4 to 6 hours for 3 days	Bunionectomy; 12 hours and 3 days n=189	Sum of pain intensity differences (least squares mean [SD], sum of difference on 0 to 10 NRS from 0.5 hours): 8.1 (18.2) vs. 9.9 (18.5) at 12 hours, MD -1.80 (95% CI -7.07 to 3.47); 177.1 (279.7) vs. 108.2 (281.4) at 3 days, MD 68.90 (95% CI -11.63 to 149.43)	Use of rescue medication: 64.6% (62/96) vs. 49.5% (46/93); RR 1.31 (95% CI 1.01 to 1.68) Global impression much improved or very much improved: 88.2% (82/93) vs. 84.4% (81/96)

Study, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity Results	Other Results
Vorsanger, 2013 ¹⁷⁰ Fair	A: Oxycodone 5 mg, then 5 to 10 mg every 4 to 6 hours up to 7 days B: Tapentadol 50 mg, then 50 to 100 mg every 4 to 6 hours for up to 7 days	Arthroscopic shoulder surgery; 3 and 7 days n=378	Sum of pain intensity differences (mean [SD], sum of differences on 0 to 10 scale): 41.1 (10.32) vs. 32.1 (10.19) at 3 days, least squares MD 9.0 (95% CI -18.9 to 36.9) ; 121.3 (20.43) vs. 130.6 (20.20) at 7 days, least squares MD -9.3 (-64.7, 46.0) Pain intensity improved ≥30%: 34.4% (53/154) vs. 33.5% (53/158) at day 3, 42.2% (65/154) vs. 48.1% (76/158) at day 7	Patient global impression much or very much improved: 69% (125/181) vs. 75% (144/192)
Wirz, 2005 ¹⁷¹ Fair	A: Oxycodone 10 mg twice daily for 3 days B: Tramadol 100 mg twice daily for 3 days	Orthopedic surgery; 2 and 3 days n=57	Pain intensity at rest (mean [SD NR], 0 to 100 VAS converted to 0 to 10 scale: 2.10 (1.64) vs. 1.71 (1.45) at day 2, p=0.32; 1.63 (1.54) vs. 1.06 (1.39) at day 3, p=0.16	Rescue medication use: 30.8% (8/26) vs. 35.5% (11/31)

Abbreviations: CI = confidence interval; MD = mean difference; NR = not reported; NRS = numeric SD = standard deviation; VAS = visual analog scale; VRS = verbal rating scale

KQs 5b and 5d ask how the comparative effectiveness and harms 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.

Evidence on how comparative effectiveness and harms of opioid therapy for postoperative pain vary according to patient and prescribing factors was lacking. The number of trials was small for each comparison and most trials had small sample sizes. In addition, trials excluded patients with subgroup characteristics of interest, such as substance use history or presence of medical or psychiatric comorbidities, or did not provide information regarding these factors. No study conducted within-study or across-study evaluations of subgroup effects. Evidence was too limited to determine effects of different opioid doses (converted into morphine milligram equivalents) on comparative effectiveness and harms. No trial permitted opioid refills, and the duration of treatment was up 15 days; the trials did not evaluate how effectiveness varied in subgroups defined according to the amount of opioid used.

KQ 5e concerns 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).

Two fair quality^{172,173} retrospective cohort studies found patients who received opioids after surgery were at increased likelihood of opioid use at longer-term followup (Appendix E, Table E-7; Appendix F, Table F-2). Both studies evaluated patients who were opioid-naïve prior to surgery. One study (n=391,139) evaluated patients who had undergone low-risk surgery (defined as cataract surgery, laparoscopic cholecystectomy, transurethral resection of the prostate, or varicose vein stripping).¹⁷² The analysis was based on administrative claims data and statistical adjustment was performed on age, sex, Charlson comorbidity index, socioeconomic stats, residence in long-term care facility, and hospital type. Opioids were prescribed within 7 days of surgery in 7.1 percent of patients, and opioids were prescribed at 1 year from surgery in 7.7

percent. Having opioids prescribed within 7 days of surgery was associated with increased risk of use at 1 year (adjusted OR 1.44, 95% CI 1.39 to 1.50). Estimates were similar when findings were stratified by the specific surgical procedure (adjusted ORs ranged from 1.33 to 1.62). The study was not able to adjust for factors not available in administrative claims, such as pain severity, functional status, level of psychiatric distress, or other measures of clinical status following surgery.

The other study (n=444,764) evaluated patients who underwent 20 selected elective surgeries associated with a range of expected postoperative pain.¹⁷³ The most common surgeries were laparoscopic cholecystectomy, knee arthroscopy with meniscectomy, open inguinal hernia repair, and total knee arthroplasty. Opioids were prescribed at discharge in 80.4 percent of patients. The study evaluated three definitions of opioid use at followup (“prolonged use,” “persistent use,” and the CONSORT definition). The proportion of patients with opioid fills 90 to 180 days after surgery (“prolonged use”) was 7.1 percent, the proportion with opioid use lasting 90 or more days in the period from 180 days after surgery (“persistent use”) was 1.0 percent, and the proportion meeting the CONSORT definition for persistent use (opioid use lasting 90 or more days and either 10 or more opioid fills or 120 or more days’ supply) was 0.46 percent. Having an opioid prescribed at discharge was associated with increased risk of opioid use at followup compared with no opioid prescribed, though findings were based on crude event rates without adjustment for confounders. In addition, the likelihood of persistent use increased at higher opioid doses. Prolonged opioid use was observed in 4.4 percent of patients with no opioid fill, and the proportion ranged from 6.8 percent in patients prescribed 1 to 199 mg morphine equivalent dose to 10.4 percent among those prescribed ≥ 500 mg. The CONSORT definition for persistent use was met by 0.2% of patients with no opioid fill and the proportion ranged from 0.27% at 1 to 199 mg morphine equivalent dose to 1.30% at ≥ 500 mg MED. The study was primarily designed to assess the risk of persistent opioid use for tramadol and long-acting opioids, relative to other (non-tramadol) short acting opioids. It found tramadol associated with increased risk of prolonged use (adjusted OR 1.06, 95% CI 1.00 to 1.13), persistent use (adjusted OR 1.47, 95% CI 1.25 to 1.69), and the CONSORT definition (adjusted OR 1.41, 95% CI 1.08 to 1.75), after adjustment for year, surgery, sex, race/ethnicity, socioeconomic factors, age, opioid dose, and comorbidities. Long acting opioids were associated with increased risk of persistent use (adjusted OR 1.18, 95% CI 1.02 to 1.35) and the CONSORT definition (adjusted OR 1.69, 95% CI 1.36 to 2.02), with no association with prolonged use (adjusted OR 0.95, 95% CI 0.87 to 1.03).

KQs 5f and 5g address the accuracy and effectiveness of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose for patients with acute pain being considered for opioid therapy.

No study evaluated the accuracy or effectiveness of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose in patients with postoperative pain.

KQ 5h addresses the effect of the following factors on the decision to prescribe opioids for patients with acute pain being considered for opioid therapy: (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.

Evidence on the effect of patient education, use of risk mitigation strategies, clinician and patient values and preferences, or availability of followup on decisions to prescribe opioids for postoperative pain was limited. One study of 1,057 who underwent elective surgery in New

Hampshire found no difference in the rate of opioid prescribing before compared with after legislation mandating the use of a prescription drug monitoring program and an opioid risk assessment tool (80% vs. 77%, $p=0.29$) (Appendix E, Table E-7).¹⁷⁴ No high risk patient not subsequently prescribed opioids was identified. There was also no difference in the number of opioid pills prescribed, which had been decreasing prior to the legislation taking effect.

Nonopioid Pharmacologic Therapy

KQs 5i and 5k address the comparative effectiveness and harms of nonopioid pharmacologic therapy versus: (1) nonopioid pharmacologic therapy or (2) nonpharmacologic therapy.

Five trials evaluated nonopioid pharmacologic therapy for acute postoperative pain (Appendix E, Table E-6; Table 22).^{131,140,152,157,163} The surgery was knee arthroscopy,¹⁴⁰ strabismus surgery,¹⁵⁷ episiotomy,¹⁶³ photorefractive keratectomy,¹³¹ and gynecological surgery¹⁵² in one trial each. Three trials compared an NSAID versus acetaminophen^{140,157,163} one trial compared a non-aspirin NSAID versus aspirin,¹⁵² and one trial compared an oral NSAID versus a topical NSAID.¹³¹ Three trials^{152,157,163} were rated fair quality and two trials^{131,140} poor quality (Appendix F, Table F-1).

NSAID Versus Acetaminophen

Three trials compared an NSAID versus acetaminophen for postoperative pain.^{140,157,163} The surgery was knee arthroscopy,¹⁴⁰ strabismus surgery,¹⁵⁷ and episiotomy.¹⁶³ Sample sizes were 40, 45, and 73. Two trials evaluated a single dose of ibuprofen (400 or 650 mg) versus acetaminophen (650 or 1000 mg).^{157,163} The third trial evaluated ketoprofen (50 mg every 8 hours) or dexketoprofen (25 mg every 8 hours) versus acetaminophen (500 mg every 6 hours) for 24 hours.¹⁴⁰ Two trials were rated fair quality,^{157,163} and one trial was rated poor quality.¹⁴⁰

The two single dose trials reported inconsistent effects of an NSAID versus acetaminophen on pain intensity and use of analgesics.^{157,163} One trial¹⁶³ reported no adverse events, and the other trial¹⁵⁷ found no difference in likelihood of nausea.

The other, poor quality trial ($n=45$) found NSAIDs associated with decreased pain intensity at discharge versus acetaminophen (difference 0.7 to 1.1 points on a 0 to 10 scale, $p<0.05$).¹⁴⁰ Few patients randomized to an NSAID or acetaminophen reported maximum pain as “severe” or “worst” or required medication use after discharge. Adverse events were not reported.

Non-Aspirin NSAID Versus Aspirin

One fair quality trial ($n=157$) compared a single dose of diclofenac potassium 50 mg or 100 mg versus aspirin 650 mg following gynecological surgery.¹⁵² Effects on pain intensity favored diclofenac potassium (differences 0.7 to 1.7 points on a 0 to 10 scale at 4 or 8 hours) but the statistical significance of the difference was not reported. The difference in the sum of pain intensity differences was not statistically significant, but diclofenac was associated with decreased likelihood of repeat medication use (58% to 60% vs. 85%, RR 0.70, 95% CI 0.55 to 0.90 for 50 mg dose and RR 0.68, 95% CI 0.52 to 0.88 for 100 mg dose). Estimates for adverse events were imprecise.

Oral NSAID Versus Topical NSAID

One poor quality trial ($n=135$) of patients undergoing photorefractive keratectomy found no difference between topical ketorolac 0.4% every 12 hours versus oral naproxen 440 mg daily for

3 days in pain intensity or of additional analgesic medication (Table 22).¹³¹ No adverse events were reported in either group.

Table 22. NSAIDs versus acetaminophen or aspirin for postoperative pain

Study, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity Results	Other Results
Berti, 2000 ¹⁴⁰ Poor	A: Ketoprofen: 50 mg every 8 hours for 24 hours B: Dexketoprofen 25 mg every 8 hours for 24 hours C: Acetaminophen 500 mg every 6 hours for 24 hours	Knee arthroscopy; At discharge (median ~4 hours) and 1 day n=45	Pain intensity at discharge (mean [SD NR], 0 to 100 VAS converted to 0 to 10 scale): 1.7 vs. 1.3 vs. 2.4, p<0.05 for	Rescue medication use after discharge: 6.7% (1/15) vs. 0% (0/15) vs. 6.7% (1/15) Maximum pain "severe" or "worst" in first 24 hours after discharge: 6.7% (1/15) vs. 0% (0/15) vs. 13.3% (2/15)
Hebertson, 1995 ¹⁵² Fair	A: Diclofenac potassium 50 mg x 1 B: Diclofenac potassium 100 mg x 1 C: Aspirin 650 mg x 1	Gynecological surgery; 8 hours n=157	Pain intensity difference (mean [SD NR], 0 to 3 NRS converted to 0 to 10 scale): 3.3 vs. 3.0 vs. 2.3 at 4 hours, 1.7 vs. 2.0 vs. 0.3 at 8 hours, p=NR Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 scale from 0.5 to 8 hours): 6.2 vs. 6.3 vs. 4.8; p=NR for A or B vs. C	Global evaluation (mean [SD NR], 0 to 4 scale): 2.33 vs. 2.25 vs. 1.94; p=NS Repeat medication use: 60% (31/52) vs. 58% (30/52) vs. 85% (45/53), RR 0.70 (95% CI 0.55 to 0.90) for A vs. C and 0.68 (95% CI 0.52 to 0.88) for B vs. C
Morrison, 1994 ¹⁵⁷ Fair	A: Ibuprofen 600 mg x 1 B: Acetaminophen 650 mg x 1	Strabismus surgery; 5 hours n=40	Pain intensity (mean [SD NR], 0 to 100 VAS converted to 0 to 10 scale): 5.0 vs. 4.3 at 2 hours, 4.4 vs. 3.9 at 5 hours; p=NR	Use of analgesic medication: 30% (6/20) vs. 30% (6/20)
Ripa, 2020 ¹³¹ Poor	A. Topical ketorolac 0.4% every 12 hours for 3 days B. Oral naproxen sodium, 440 mg/day for 3 days	Photorefractive keratectomy; 5 days n=135	Pain intensity (mean [SD], 0 to 10 NRS): 0.66 (1.39) vs. 0.41 (0.83) at day 5, MD 0.25 (95% CI -0.14 to 0.64); MD 0.26 (95% CI -0.14 to 0.65) adjusted for hydrocodone + acetaminophen use	Supplemental analgesic use: 25.6% (11/43) vs. 35% (14/40), RR 0.73 (95% CI 0.38 to 1.4)
Schachtel, 1989 ¹⁶³ Fair	A: Ibuprofen 400 mg x 1 B: Acetaminophen 1000 mg x 1	Episiotomy 4 hours n=73	Pain intensity difference (mean [SD NR], 0 to 3 NRS converted to 0 to 10 scale): 3.3 vs. 2.0 at 4 hours, p<0.05 Sum of pain intensity differences (mean [SD], sum of differences on 0 to 3 scale from 0.5 to 4 hours): 4.4 (3.1) vs. 2.9 (3.2), p<0.05	Supplemental analgesic use: 22% (8/36) vs. 36% (15/37), p<0.05 Overall assessment (mean [SD], 1 to 5 scale, 5=excellent): 3.3 (1.3) vs. 2.9 (1.4), p<0.001

Abbreviations: CI = confidence interval; MD = mean difference; NR = not reported; NRS = numeric rating scale; NS = not significant; RR = relative risk; SD = standard deviation; VAS = visual analog scale

KQs 5j and 5l ask how the comparative effectiveness and harms 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.

Evidence was too limited to evaluate how comparative effectiveness and harms of nonopioid therapy for postoperative pain varied in subgroups, due to few trials, small sample sizes, methodological limitations, and exclusion of relevant subgroups or lack of information about them. No study conducted within-study or across-study evaluations of subgroup effects. Details regarding the nonopioid medications prescribed, dose, and duration of treatment are described above.

Nonpharmacologic Therapy

KQs 5m and 5n address the comparative effectiveness of nonopioid pharmacologic therapy versus: (1) inactive controls or (2) other nonpharmacologic therapies.

Twenty-eight trials evaluated nonpharmacologic therapy for acute postoperative pain following various surgical procedures (Appendix E, Table E-6).^{125,127,129,132-139,142-144,146-149,151,154-156,158,161,162,165,166,168} Two trials evaluated acupuncture,^{135,149} two trials acupressure,^{146,151} eleven trials cold therapy,^{129,132-134,136,137,139,144,155,166,168} seven trials massage,^{125,127,148,154,156,162,165} two trials music therapy,^{147,158} one trial exercise therapy,¹³⁸ two trials transcutaneous electrical nerve stimulation,^{143,161} and one trial neuromuscular stimulation.¹⁴² Two trials were rated good quality,^{143,168} 11 trials fair quality,^{132-135,138,142,147,149,151,158,162} and 15 trials poor quality (Appendix F, Table F-1).^{125,127,129,136,137,139,144,146,148,154-156,161,165,166}

Acupuncture Versus Sham Acupuncture

Two small (n=33 and 56), fair quality trials compared acupuncture versus sham acupuncture for postoperative pain (Table 23).^{135,149} One small (n=33) trial compared acupuncture twice per day with sham acupuncture after stapled hemorrhoidopexy.¹³⁵ Both the acupuncture and sham acupuncture groups also received usual care with traditional analgesia (diclofenac 50 mg three times a day and metamizol 500 mg four times a day). Sham acupuncture consisted of needle insertion in nonacupuncture points. Another small (n=56) trial compared a single 20-minute acupuncture session at two points versus sham acupuncture following cesarean section.¹⁴⁹ Sham acupuncture utilized a cotton pad to prevent contact between the acupuncture needle and skin. Effects on pain were inconsistent. In one trial,¹³⁵ acupuncture was associated with decreased pain intensity on postoperative day one (2.7 vs. 4.0 on a 0 to 10 scale, p=0.007), though pain intensity was similar on postoperative day two (1.6 vs. 2.1, p>0.05). In the other trial,¹⁴⁹ pain intensity was greater in the acupuncture arm at 24 hours (mean 3 vs. 0 on a 0 to 10 scale, p=0.71) and at 48 hours (mean 2 vs. 0, p=0.03), though the difference was only statistically significant at 48 hours. Effects on rescue analgesia use were also inconsistent. One trial¹³⁵ reported no nausea, vomiting, acupuncture site reactions, or other harms; the other trial¹⁴⁹ did not report adverse events.

Acupuncture Versus Usual Care

One of the fair quality acupuncture versus sham acupuncture trials described above also compared acupuncture versus usual care (n=34) in patients following stapled hemorrhoidopexy (Table 23).¹³⁵ The difference between acupuncture versus usual care was not statistically significant in the afternoon of postoperative day one (2.7 vs. 4.1 on a 0 to 10 scale, p=0.06) or day two (1.6 vs. 2.1, p=NS). Acupuncture was associated with decreased rescue analgesic use on

the afternoon of day 1 (6% vs. 53%, $p=0.03$), but the difference on day 2 was smaller and not statically significant (0% vs. 13%, $p=0.35$).

Acupressure Versus Sham Acupressure

Two trials compared acupressure versus sham acupressure for postoperative pain (Table 23).^{146,151} One fair quality trial ($n=90$)¹⁵¹ compared auricular acupressure (3 minutes, four times per day for 7 days) versus sham acupuncture (pressure applied to nonacupoints) following total knee arthroplasty. At 12 hours and 5 days, differences in pain intensity were small and not statistically significant, though acupressure was associated with decreased patient controlled analgesia use through 48 hours (mean 222.60 vs. 266.62 ml, mean difference -44.02 , 95% CI -71.62 to -16.42). At 7 days, the difference was slightly greater and statistically significant (mean difference -0.65 on a 0 to 10 scale, 95% CI -1.09 to -0.21). Acupressure was associated with better scores on the Hospital for Special Surgery Knee Rating Scale at 2 weeks (mean difference -6.80 , 95% CI -11.30 to -2.30 on a 0 to 100 scale), with no difference on this outcome at 3 months. Acupressure was associated with decreased risk of nausea or vomiting (17.8% vs. 71.1%, RR 0.25, 95% CI 0.13 to 0.48), dizziness or drowsiness (4.4% vs. 24.4%, RR 0.18, 95% CI 0.04 to 0.77), and urinary retention (6.7% vs. 26.7%, RR 0.25, 95% CI 0.08 to 0.83).

A small ($n=40$), poor quality trial compared acupressure to points on the body (one 30 minute session) versus sham acupressure (light stimulation to nonacupoints) following knee arthroscopy (Table 23).¹⁵¹ Acupressure was associated with lower pain intensity at 1 hour (mean 1.2 vs. 2.0 on a 0 to 10 scale, $p<0.05$) and at 1 day (mean 0.5 vs. 2.3, $p<0.0001$). One patient randomized to acupressure experienced bradycardia of less than 2 minutes duration; adverse events were otherwise not reported.

Table 23. Acupuncture or acupressure versus sham or usual care

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity	Other Results
Gamermann, 2014 ¹⁴⁹ Fair	A: Acupuncture at P6 and L14 for a 20-minute session B: Sham acupuncture (Cotton pad under needle) for a 20- minute session	Cesarean section; 24 and 48 hours $n=56$	Pain at rest (mean [SD NR], 0 to 10 VAS): 3 vs. 0 at 24 hours, $p=0.71$ at 24 hours; 2 vs. 0 at 48 hours, $p=0.03$	Satisfaction with pain relief (mean [SD NR], 0 to 10 NRS): 10.00 vs. 10.00 at 24 hours, $p=0.62$; 10.00 vs. 10.00 at 48 hours, $p=0.79$

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity	Other Results
Langenbach, 2012 ¹³⁵ Fair	A: Verum acupuncture at Du2, Du20, Bi30, Bi57, Ma44, and Pe6 twice per day B: Sham acupuncture C: Traditional analgesia (diclofenac at 50 mg orally three times a day and metamizol 500 mg orally four times a day)	Stapled hemorrhoidopexy; Postoperative days 1 and 2 n=50	Pain (mean [SD], 0 to 10 NRS): 2.7 (1.5) vs. 4.0 (1.0) vs. 4.1 (1.9) at afternoon of postoperative day 1, p=0.057 for A vs C, p=0.007 for A vs. B	Proportion using rescue analgesia: 6% (1/17) vs. 38% (6/16) vs. 53% (9/17) at afternoon of postoperative day 1, RR 0.16 (95% CI 0.02 to 1.16) for A vs. B, RR 0.11 (95% CI 0.016 to 0.78), p=0.0275 for A vs. C; 0% (0/17) vs. 13% (2/16) vs. 18% (3/17) at afternoon of postoperative day 2, RR 0.19 (95% CI 0.01 to 3.66), p=0.270 for A vs. B, RR 0.14 (95% CI 0.01 to 2.57), p=0.187 for A vs. C
Felhendler, 1996 ¹⁴⁶ Poor	A: Acupressure, stimulation to 15 classical acupoints B: Sham acupressure, light stimulation to 15 nonacupoints 30 minutes after patients awoke from anesthesia for each group	Knee arthroscopy; 1 hour and 1 day n=40	Pain intensity (median [IQR], 0 to 10 VAS): 1.2 (0.6 to 2.4) vs. 2.0 (1.5 to 3.6) at 1 hour, p<0.05; 0.5 (0.2 to 1.1) vs. 2.3 (1.4 to 2.8) at 1 day, p<0.0001	NR
He, 2013 ¹⁵¹ Fair	A: Auricular acupressure, pressure on auricular acupoints at 4 acupressure points B: Sham acupressure, Pressure on acupoints at 4 sham sites 3 minutes per point, four times per day, for 7 days for each group	Knee arthroplasty; 12 hours, 5 days, and 7 days n=90	Pain intensity (mean [SD], 0 to 10 VAS): 4.78 (1.66) vs. 4.85 (1.55) at 12 hours; 2.91 (1.12) vs. 3.51 (1.16) at 5 days, MD -0.60 (95% CI -1.08 to -0.12); 2.22 (1.02) vs. 2.87 (1.08) at 7 days, MD -0.65 (95% CI -1.09 to -0.21)	HSS Knee Rating Scale (mean [SD], 0 to 100 scale): 80.24 (10.68) vs. 73.44 (10.80) at 2 weeks, MD -6.80 (95% CI -11.30 to -2.30); 92.89 (6.99) vs. 91.91 (7.13) at 3 months, MD -0.98 (95% CI -3.94 to 1.97) PCA used through 48 hours (mean [SD], ml): 222.60 (62.59) vs. 266.62 (69.03), MD -44.02 (95% CI -71.62 to -16.42)

Abbreviations: CI = confidence interval; IQR = interquartile range; MD = mean difference; NR = not reported; NRS = numeric rating scale; HSS = Hospital for Special Surgery score; PCA = patient-controlled analgesia; SD = standard deviation; VAS = visual analog scale

Cold Therapy Versus No Cold Therapy or Sham

Eleven trials evaluated cold therapy versus no cold therapy or a sham treatment for postoperative pain. Sample sizes ranged from 19 to 131 (total N=655)^{129,132-134,136,137,139,144,155,166,168} (Appendix E, Table E-6; Table 24). The surgery was ACL repair^{132-134,137,139,144} in six trials, arthroscopic knee surgery in two trials,^{129,136} and shoulder surgery,¹⁶⁶ herniotomy,¹⁵⁵ and total knee arthroplasty¹⁶⁸ in one trial each. Cold therapy varied from a cold compress for 20 minutes to continuous application using a circulating device for up to 7 days; some devices for delivering cold therapy enabled precise temperature control. One trial was rated good quality.¹⁶⁸ It compared cold therapy using a device that maintained a consistent temperature (10 to 12 degrees Celsius) versus sham therapy using the device without cooling (21 degrees Celsius). Three trials¹³²⁻¹³⁴ were rated fair quality, and seven trials were rated poor quality (Appendix F, Table F-1).^{129,136,137,139,144,155,166,168}

The good quality trial (n=60), which evaluated patients who had undergone knee arthroplasty, found no difference between cold therapy (4 hours or more daily) versus sham therapy in pain intensity at 2 weeks (mean difference -0.30 on a 0 to 10 scale, 95% CI -1.33 to 0.73), 6 weeks (mean difference -0.40, 95% CI -1.18 to 0.38), or 12 weeks (mean difference 0.10, 95% CI -0.97 to 1.17).¹⁶⁸ There were also no differences in outcomes based on the Western Ontario and McMaster Universities Osteoarthritis Index, the Oxford Knee Scale, or the EQ-5D. However, cold therapy was associated with less tramadol use versus sham in the first 4 days (47 tablets [2350 mg] vs. 83 tablets [4150 mg]). Three fair quality trials (n=19, 78, and 71) found no differences between cold therapy versus no cold therapy or sham in pain at 1 day to <1 week.¹³²⁻¹³⁴ Differences ranged from -1.3 points on a 0 to 10 scale in favor of cold therapy to 0.50 points in favor of sham cold therapy. Two of the trials also found no differences in analgesic medication use.^{133,134}

Evidence from seven poor quality trials of cold therapy versus no cold therapy was difficult to interpret due to the methodological limitations, differences in the surgeries treated, differences in methods for administering cold therapy, and some inconsistency in results.^{129,136,137,139,144,155,166} At <1 day, cold therapy was associated with decreased pain intensity versus no cold therapy in two trials (mean differences -1.1 and -1.3 points on a 0 to 10 scale).^{139,155} At 1 day to <1 week, differences ranged from 3.1 points in favor of cold therapy to 4.2 points in favor of no cold therapy.^{129,137,139,144,155,166} At 1 week to <2 weeks effects on pain intensity ranged from 1.4 points in favor of cold therapy to no difference (0 points).^{129,136,166} One trial found no difference between cryotherapy versus no cold therapy at 6 weeks in pain at rest or on motion.¹²⁹ One trial found cold therapy associated with decreased likelihood of pain medication use at <1 day (28.2% vs. 91.5%, RR 0.22 [95% CI 0.05 to 0.90])¹⁵⁵ Effects on analgesic medication use at 1 day to <1 week were inconsistent, with two trials^{129,137} finding cold therapy associated with decreased analgesic medication use versus no cold therapy and two trials^{139,144} finding no difference. Harms were not well reported, though no serious adverse events were described.

Table 24. Cold therapies versus no cold therapy or sham for postoperative pain

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity	Other Results
Barber, 1998 ¹³⁹ Poor	A: Continuous cold-flow therapy using a constant flow unit for 3 days, then as needed for 4 days B: No cold therapy	ACL reconstruction; 6 and 7 days n=100	Pain intensity (mean [SD NR], 0 to 10 VAS): 4.10 vs. 5.22 at 8 hours, 5.33 vs. 4.39 at 6 days; p=NR	Rescue medication use (mean [SD], number of pills): 1.73 vs. 1.82 at 7 days, p=NR
Daniel, 1994 ¹⁴⁴ Poor	A: Cold therapy pad, 40 degrees F B: Cold therapy pad, 45 degrees F C: Cold therapy pad, 55 degrees F D: Cold therapy pad, 70 degrees F E: No cold therapy For cold therapy groups: continuous use during hospitalization, except 3 hours twice a day to use passive-motion machine	ACL reconstruction; Day 3 or discharge if earlier n=131	Pain (mean [SD], 0 to 10 VAS): 4.1 (2.1) vs. 4.6 (1.7) vs. 5.7 (2.0) vs. 4.9 (2.4) vs. 4.6 (2.0), p=NS	Use of parenteral meperidine (mean [SD], number of 75 mg doses): 5.5 (4.1) vs. 5.3 (4.3) vs. 4.8 (3.8) vs. 4.4 (2.6) vs. 4.8 (2.9), p=NS Use of oral codeine (mean [SD], number of 60 mg doses): 8.8 (3.0) vs. 8.6 (3.6) vs. 9.4 (3.4) vs. 9.9 (4.0) vs. 10.2 (4.5), p=NS
Dambros, 2012 ¹³² Fair	A: Cold therapy, ice pack, 20 minutes twice daily B: No cold therapy Both groups received 2 physical therapy sessions, one in the morning, and one in the afternoon	ACL reconstruction; After each physical therapy session on first day after surgery n=19	Pain (mean [SD], 0 to 10 VAS): 2.2 (2.0) vs. 2.4 (2.4) after first treatment, MD -0.20 (95% CI -2.33 to 1.93); 1.19 (1.8) vs. 2.5 (2.0) after second treatment, MD -1.31 (95% CI -3.15 to 0.53)	NR
Dervin, 1998 ¹³³ Fair	A: Cold therapy, Cryocuff with ice water B: Sham cold therapy, Cryocuff with room temperature water	ACL reconstruction; 24 hours n=78	Pain (mean [SD], 0 to 100 VAS converted to 0 to 10) at 24 hours: 3.0 (1.7) vs. 2.5 (1.3), p=NS, MD 0.50 (95% CI -0.18 to 1.18)	Morphine use (mean [SD] total infused mg/kg): 0.37 (0.23) vs. 0.35 (0.21), p=NS Codeine use (mean [SD] number of 30 mg tablets): 3.86 (2.72) vs. 3.44 (2.1), p=NS
Edwards, 1996 ¹³⁴ Fair	A: Cryotherapy, Cryocuff with ice water B: Sham cryotherapy, Cryocuff with room temperature water C: No cryotherapy, no Cryocuff	ACL reconstruction; 3 days n=71	Pain (mean [SD NR], VAS 0 to 10) at day 3: 1.2 vs. 1.8 vs. 1.7, p=N	Morphine use (mean, mg/kg of body weight) during inpatient stay: 0.65 vs. 0.60 vs. 0.65, p=NS Codeine use (mean, mg/kg of body weight) during inpatient stay: 4.14 vs. 3.91 vs. 4.31, p=NS Acetaminophen use (mean, mg/kg of body weight) during inpatient stay: 73.8 vs. 85.2 vs. 70.6, p=NS

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity	Other Results
Holmstrom, 2005 ¹²⁹ Poor	A: Cryotherapy, Cryofcuff with ice water: continuous chilling (10 to 15 degrees Celsius) and pulsing compression for 48 hours B: No cold therapy	Arthroscopic knee surgery; Day 1, day 7, and week 6 n=40	Pain at rest (mean [SD NR], 0 to 10 VAS): 3.2 vs. 3.0 at day 1; 1.0 vs. 1.3 at day 7; 0.5 vs 0.5 at 6 weeks, p=NS for all time points Pain on motion (mean [SD NR], 0 to 10 VAS): 5.7 vs. 5.8 at day 1; 2.0 vs. 3.5 at day 7; 1.8 vs. 1.8 at 6 weeks, p=NS for all time points	Morphine consumption (mean [SD NR] mg): 13.4 vs. 20.8, p=0.028 at 24 hours Mean over first 3 postoperative days: 18.7 vs. 28.4, p=NS
Koc, 2006 ¹⁵⁵ Poor	A: Cold compress, 20 minutes after surgery B: Room temperature compress, 20 minutes after surgery	Inguinal hernia; 6 and 24 hours n=40	Pain intensity (mean [SD], 0 to 10 VAS): 4.0 (0.3) vs. 5.3 (0.4) at 6 hours, p=0.02; 2.4 (0.2) vs. 3.6 (0.3) at 24 hours, p=0.007	Analgesic medication use in first 24 hours: 10% (2/20) vs. 45% (9/20), RR 0.22 (95% CI 0.05 to 0.90)
Lessard, 1997 ¹³⁶ Poor	A: Cryotherapy (cold gel packs), 20 minutes four times per day, followed by exercises B: No cryotherapy, exercises only	Minor arthroscopic knee surgery; 7 days n=45	Pain (mean [SD], McGill pain questionnaire total pain rating score, 0 to 78 scale): 8.78 (7.08) vs. 10.45 (6.97), MD -1.67 (95% CI -5.6 to 2.3) Most pain in the day (mean [SD NR], VAS 0 to 100 converted to 0 to 10 scale): 2.4 vs. 2.7, p=NS	NR
Ohkoshi, 1999 ¹³⁷ Poor	A: Cryotherapy using Icing System 2000 at 5 degrees Celsius B: Cryotherapy using Icing System 2000 at 10 degrees Celcius C: No cold therapy	ACL reconstruction; 2 days n=21	Pain (mean [SD], 0 to 100 VAS converted to 0 to 10 scale): 7.67 (1.51) vs. 3.47 (2.98) vs. 6.57 (2.05); A vs. B and B vs. C, p<0.05; MD 4.22 (95% CI 1.47 to 6.97) for A vs. B and MD -3.1 (95% CI -6.08 to -0.12) for B vs. C	Number of analgesic doses (mean [SD], 25 mg of diclofenac sodium suppositories): 1.25 (0.4) vs. 0.7 (0.8) vs. 1.5 (1.0), p=<0.05 for B vs. C

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity	Other Results
Thijs, 2019 ¹⁶⁸ Good	A: Computer-assisted cold therapy, 10 to 12 degrees Celsius, varying time and temperature through 7 days B: Sham cryotherapy: Same as intervention, except at 21 degrees Celsius	Total knee arthroplasty; 2, 6, and 12 weeks n=60	Pain intensity (mean [SD], 0 to 10 NRS): 2.8 (1.5) vs. 3.1 (2.4) at 2 weeks, MD -0.30 (95% CI -1.33 to 0.73); 1.7 (1.3) vs. 2.1 (1.7) at 6 weeks, MD -0.40 (95% CI -1.18 to 0.38); 2.0 (2.3) vs. 1.9 (1.8) at 12 weeks, MD 0.10 (95% CI -0.97 to 1.17)	WOMAC (mean [SD], 0 to 100 scale, higher score=better outcome): 69.9 (13.6) vs. 75.4 (18.3) at 2 weeks, MD -5.50 (95% CI -13.83 to 2.83); 81.6 (9.8) vs. 81.2 (12.6) at 6 weeks, MD 0.40 (95% CI -5.43 to 6.23); 90.2 (9.7) vs. 85.8 (13.6) at 12 weeks, MD 4.40 (95% CI -1.70 to 10.50) Oxford Knee Score (mean [SD], 12 to 60 scale, 12=best outcome): 29.6 (6.3) vs. 25.1 (8.1) at 2 weeks, MD 4.50 (95% CI 0.75 to 8.25); 25.8 (5.8) vs. 25.1 (8.7) at 6 weeks, MD 0.70 (95% CI -3.12 to 4.52); 21.5 (6.1) vs. 22.7 (8.1) at 12 weeks, MD -1.20 (-4.91 to 2.51)
Speer, 1996 ¹⁶⁶ Poor	A: Cold therapy, Cryo/Cuff bladder with ice water every 1 to 2 hours while awake for 24 hours; then ice 4 to 6 times daily and as needed for 10 days B: No cryotherapy	Shoulder surgery; 1 and 10 days n=50	Worst pain intensity (mean [SD] 0 to 100 VAS converted to 0 to 10 scale): 3.1 vs. 5.6 at day 1, p=0.001; 3.3 vs. 4.7 at day 10, p=0.03	NR

Abbreviations: ACL = anterior cruciate ligament; CI = confidence interval; IQR = interquartile range; MD = mean difference; NR = not reported; NRS = numeric rating scale; SD = standard deviation; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Massage Versus No Massage

Seven trials compared massage versus no massage for postoperative pain (Appendix E, Table E-6; Table 25).^{125,127,148,154,156,162,165} Sample sizes ranged from 59 to 196 (total N=792). The surgery was a laparoscopic procedure in three trials,^{154,156,165} cesarean section in three trials,^{125,127,162} and lymph node dissection in one trial.¹⁴⁸ In six trials, the intervention consisted of a single massage session to the hand or foot for 5 to 10 minutes.^{125,127,154,156,162,165} In the seventh trial, patients received 10 minute arm massages as often as needed for 3 days following lymph node dissection.¹⁴⁸ Due to the nature of the intervention, the trials could not be blinded. One trial was rated fair quality¹⁶² and the others were poor quality (Appendix F, Table F-1).

Five trials found a single massage session associated with decreased pain intensity versus no massage at <1 day (90 minutes to 3 hours or time to discharge); mean differences ranged from 1.4 to 2.6 points on a 0 to 10 scale.^{125,127,156,162,165} One other trial found no difference in pain intensity.¹⁵⁴ Three trials^{125,156,165} found a single session of massage associated with decreased pain medication use (28.2% vs. 91.5%, RR 0.31, 95% CI 0.22 to 0.44; 31.7% [foot massage] or 21.5% [foot and hand massage] vs. 89.7%, RR 0.35, 95% CI 0.24 to 0.51 and RR 0.28, 95% CI

0.18 to 0.45; and 15% vs. 70%, RR 0.21, 95% CI 0.10 to 0.46). Two trials^{156,165} found single session massage associated with decreased anxiety at <1 day (differences about 22 points on the 20 to 80 State and Continuous Anxiety Inventory, state anxiety scale), but one other trial¹⁶² found difference between massage versus no massage in anxiety.

A small (n=59) trial of multiple arm massage sessions after lymph node dissection reported effects on pain poorly.¹⁴⁸ Massage was associated with better function as measured on the Shoulder Pain and Disability Index versus no massage at 2 weeks (differences 1.7 to 2.0 points on a 0 to 10 scale for various activities).

Adverse events were not reported in the massage trials.

Table 25. Massage versus no massage for postoperative pain

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity	Other Pain and Function Results
Abbaspoor, 2014 ¹²⁵ Poor	A: Hand and foot massage (5 minutes each, 20 minutes total) B: Attention control: Investigator talked with patient for 20 minutes + usual care	Cesarean section; 1.5 hours after treatment n=80	Pain intensity (mean [SD], 0 to 10 NRS): 3.58 (0.64) vs. 6.23 (0.68), MD -2.65 (95%CI -2.94 to -2.36)	Medication use during the 1.5 h after intervention Diclofenac: 15% (6/40) vs. 70% (28/40) RR 0.21 (95% CI 0.10 to 0.46) Meperidine: 0% vs. 7.5% (3/40) No analgesic medication: 85% (34/40) vs. 22.5% (9/40), RR 3.78 995%CI 2.90 to 6.81)
Degirmen, 2010 ¹²⁷ Poor	A: Foot and hand massage: petrissage, kneading, and friction applied to the patient's hands and feet with classical massage techniques, 5 minutes per hand/foot for total of 20 minutes B: Foot massage: petrissage as above, 5 minutes per foot for total of 10 minutes C: Control: no massage	Cesarean section 60 minutes n=75	Pain intensity (mean [SD], 0 to 10 NRS): 3.64 (1.22) vs. 3.76 (1.20) vs. 5.20 (1.11); MD -0.12 (95% CI -0.81 to 0.57) for A vs. B; MD -1.56 (95% CI -2.22 to -0.90) for A vs. C; MD -1.44 (95% CI -2.10 to -0.78) for B vs. C	NR

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity	Other Pain and Function Results
Forchuk, 2004 ¹⁴⁸ Poor	A: Arm massage, suggested 10-minute sessions as needed for 3 days B: No massage	Breast cancer surgery; 1 and 3 days n=59	Pain control from massage ^c (mean [SD], %): 54.4 (37.3) vs. NR at day 1; 83.18 (28.64) vs. NR at day 3 Pain control from medication ^c (mean [SD], %): 83.18 (28.64) vs. 84.74 (16.45) at day 1; 87.81 (13.29) vs. 80.31 (12.44) at day 3	Shoulder Pain and Disability Index (mean [SD], 0 to 10 scale) at 2 weeks Wash back: 2.86 (2.98) vs. 4.89 (3.48), MD -2.03 (95% CI -3.72 to -0.34) Put on undershirt or pullover: 2.2 (3.0) vs. 4.04 (3.36), MD -1.84 (95% CI -3.50 to -0.18) Place object on high shelf: 3.03 (3.40) vs. 5.0 (3.56), MD -1.97 (95% CI -3.78 to -0.16) Remove object on high shelf: 1.23 (2.32) vs. 2.94 (3.04), MD -1.71 (95% CI -3.11 to -0.30)
Hulme, 1999 ¹⁵⁴ Poor	A: Foot massage with grapeseed oil for 5 minutes B: Usual care (standard analgesia): dose not reported	Laparoscopic sterilization; On discharge n=59	Pain (mean [SD NR], 0 to 10 NRS): 3.1 vs. 3.3, p>0.05	>3 doses of analgesia from discharge to post-operative day 1: 40.0% (12/30) vs. 48.3% (14/29), RR 0.83 (95% CI 0.46 to 1.48) Pain relief "no pain" or "very effective": 30.0% (9/30) vs. 27.6% (8/29)
Koras, 2019 ¹⁵⁶ Poor	A: Foot massage, 20 minutes when pain >4 on 0 to 10 VAS B: Usual care (standard analgesia)	Laparoscopic cholecystectomy; 2 hours n=167	Pain (mean [SD], 0 to 10 VAS): 1.3 vs. 3.6, MD: -2.3 (95% CI -2.7 to -1.9)	Pain medication use: 28.2% (24/85) vs. 91.5% (75/82), RR 0.31 (95% CI 0.22 to 0.44)
Saatsaz, 2016 ¹⁶² Fair	A: Foot massage, 5 minutes each limb, single session B: Hand and foot massage, 5 minutes each limb, single session C: Usual care	Cesarean section; 90 minutes n=156	Pain (mean [SD], 0 to 10 VAS): Post-massage: 3.62 (0.69) vs 3.56 (0.57) vs. 6.17 (0.58), MD: -2.55 (95% CI -2.80 to -2.30) for A vs. C and -2.61 (95% CI -2.83 to -2.39) for B vs. C	NR
Sozen, 2019 ¹⁶⁵ Poor	A: Foot massage, 20 minutes, single session B: Hand massage, 20 minutes, single session C: No massage	Laparoscopic cholecystectomy; 2.5 hours n=196	Pain intensity (mean [SD], 0 to 10 VAS): 1.43 (1.20) vs. 1.61 (1.40) vs. 3.44 (1.43), MD -2.01 (95% CI -2.47 to -1.55) A vs. C and -1.83 (95% CI -2.31 to -1.34) for B vs. C	Analgesic use: 31.7% (20/63) vs. 21.5% (14/65) vs. 89.7% (61/68), RR 0.35 (95% CI 0.24 to 0.51) for A vs. C and RR 0.28 (95% CI 0.18 to 0.45) for B vs. C

Abbreviations: CI = confidence interval; NR = not reported; MD = mean difference; RR = relative risk; SD = standard deviation; VAS = visual analog scale

^c Unclear how patients distinguished pain control from massage and pain control from medication

Music Therapy

Two fair quality trials compared music therapy versus no music therapy for postoperative pain (Table 26).^{147,158} One trial (n=50) found music administered in the recovery unit associated with moderate effects on pain intensity versus no music at 1 hour (mean difference -1.70 on a 0 to 10 scale, 95% CI -2.6 vs. -0.73) and decreased anxiety (mean difference -0.9 point on a 0 to 10 scale, 95% CI -1.7 to -0.1).¹⁵⁸ Music was also associated with decreased morphine use, but the difference was small (mean difference -1.9 mg, 95% CI -3.34 to -0.46). The other trial (n=98) evaluated four different types of music administered for 12 to 15 minutes for 3 days versus no music.¹⁴⁷ Effects on pain intensity favored the music intervention on day 1 (mean difference 0.68 to 1.69 points on a 0 to 10 scale) but there were no differences on day 3. There was also no difference in scores on the Profile of Mood States scale (data not provided). Harms were not reported, though not expected with this intervention.

Table 26. Music therapy versus silence, usual care, or relaxation for postoperative pain

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity	Other Results
Finlay 2016 ¹⁴⁷ Fair	A: High harmonicity and rhythmicity music B: Low harmonicity and low rhythmicity music C: Low harmonicity and high rhythmicity music D: High harmonicity and low rhythmicity music E: Control, silence using noise-canceling headphones All interventions used 12 to 15 minutes per day for 3 days	Knee arthroplasty; 1 and 3 days n=98	Brief Pain Inventory, Pain Interference (mean [SD], 0 to 10): 6.01 (2.97) vs. 7.02 (1.73) vs. 6.85 (1.68) vs. 6.05 (1.83) vs. 5.33 (1.64) at day 1, MD: 0.68 (95% CI -0.88 to 2.24) for A vs. E, 1.69 (95% CI 0.62 to 2.76) for B vs. E, 1.52 (95% CI 0.43 to 2.61) for C vs. E, 0.72 (95% CI -0.38 to 1.82) for D vs. E; 5.15 (2.00) vs. 5.80 (2.19) vs. 6.10 (1.64) vs. 4.36 (2.70) vs. 4.94 at day 3, MD 0.21 (95% CI -1.20 to 1.62) for A vs. E, 0.86 (95% CI -0.55 to 2.27) for B vs. E, 1.16 (95% CI -0.16 to 2.48) for C vs. E, -0.58 (95% CI -2.16 to 1.00) for D vs. E	NR
Nilsson 2005 ¹⁵⁸ Fair	A: Music CD upon arrival in PACU and for 1 hour after B: Sham CD player (numbers shown, no sound)	Hernia repair; 1 hour n=50	Pain intensity (mean [SD], 0 to 10 NRS): 2.1 (1.5) vs. 3.8 (1.9) at 1 hour, MD -1.70 (95% CI -2.6 to -0.73)	Use of analgesic medication: 30% (6/20) vs. 30% (6/20)

Abbreviations: CI = confidence interval; MD = mean difference; NR = not reported; NRS = numeric rating scale; SD = standard deviation

Exercise Versus No Exercise

One fair quality trial (n=80) compared neck stretching exercises versus no exercise following thyroidectomy patients (Table 27).¹³⁸ Five repetitions of eight exercises were performed three times daily for 1 month. There was no difference between exercise versus no exercise in pain with neck movement at 1 week or 1 month, but pain intensity was very low in both groups. Exercise was associated with better Neck and Disability Score at 1 week (mean difference -2.15 on a 0 to 10 scale, 95% CI -2.69 to -1.61), but there was no effect at 1 month (mean difference: -0.18, 95% CI -0.40 to 0.04).

Table 27. Neck stretching exercises versus no exercise for postoperative pain

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity
Ayhan, 2016 ¹³⁸ Fair	A: 5 sets, 8 different neck exercises, three times a day for one month B: Resume pre-op neck motion	Thyroidectomy; 1 week and 1 month n=80	Neck Pain and Disability Score (mean [SD], 0 to 100 scale converted to 0 to 10): 0.88 (1.22) vs. 3.03 (1.21) at 1 week, MD -2.15 (95% CI -2.69 to -1.61); 0.17 (0.27) vs. 0.35 (0.66) at 1 month, MD -0.18 (95% CI -0.40 to 0.04) Pain with neck movement (median [IQR], 0 to 14 scale): 0 (0.20) vs. 0.35 (0.58) at 1 week, 0 (0.0) vs. 0 (1.8) at 1 month

Abbreviations: CI = confidence interval; IQR = interquartile range; MD = mean difference; SD = standard deviation;

TENS Versus Sham or No TENS

Two small trials (n=12 and 42) evaluated transcutaneous electrical nerve stimulation for postoperative pain (Table 28).^{143,161} One fair quality trial (n=42) found TENS associated with decreased pain intensity versus sham TENS following liposuction at 12 hours (median 0 vs. 3.0 on a 0 to 10 scale, p=0.001) and at 24 hours (median 0 vs. 2.0, p=0.001), though pain scores were low in both groups.¹⁴³ TENS was also associated with decreased analgesic use (19.0% vs. 100% at 24 hours, RR 0.19, 95% CI 0.08 to 0.46). A very small (n=12), poor quality trial of patients following cholecystectomy found TENS associated with decreased morphine use versus no TENS, but estimates were imprecise and differences were not statistically significant.¹⁶¹ One trial¹⁶¹ reported minor skin reactions at the TENS electrode sites and one trial¹⁴³ reported drowsiness and nausea in patients randomized to sham TENS. No serious adverse events were reported.

Neuromuscular Stimulation Versus Sham Neuromuscular Stimulation

One small (n=29) trial compared neuromuscular stimulation (two 20-minute sessions daily) versus sham stimulation following total hip arthroplasty (Appendix E, Table E-6; Table 28).¹⁴² It was rated poor quality; methodological limitations included high loss to followup and lack of intention to treat analysis (Appendix F, Table F-1). Neuromuscular stimulation was not associated with decreased pain intensity at discharge or at 6 weeks, less use of opioids, or improved function versus sham stimulation. Device malfunctions occurred in 7.5 percent (3/40) of patients randomized to neuromuscular stimulation.

Table 28. Transcutaneous electrical nerve stimulation or neuromuscular stimulation versus no treatment or sham

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity	Other Results
Castellano, 2016 ¹⁴² Poor	A: NMES, 2 20-minute sessions daily B: Sham stimulation, subclinical level of stimulation for 2 20-minute sessions daily	Total hip arthroplasty; At discharge and 6 weeks n=29	Pain intensity change from baseline (mean [SD NR], 0 to 10 VAS): 0.07 vs. -0.21 at discharge, $p>0.05$; -1.73 vs. -2.21 at 6 weeks, $p>0.05$	Use of opioids (mean [SD NR], days): 3.13 vs. 3.36, $p=NS$
da Silva, 2015 ¹⁴³ Fair	A: TENS, one 30-minute session B: Sham TENS, one 30-minute session with no current	Liposuction; 12 and 24 hours n=42	Pain intensity: (median [IQR], 0 to 10 VAS): 0 (0 to 0) vs. 3.0 (3.0 to 5.0) at 12 hours, $p=0.001$; 0 (0 to 0) vs. 2.0 (2.0 to 3.0) at 24 hours, $p=0.001$	Request for analgesics: 8.7% (2/21) vs. 95.2% (20/21) at 12 hours, RR 0.25 (95% CI 0.06 to 1.04); 19.0% (4/21) vs. 100% (21/21) at 24 hours, RR 0.19 (95% CI 0.08 to 0.46)
Rosenberg, 1978 ¹⁶¹ Poor	A: TENS, duration and number of sessions per patient B: No TENS	Cholecystectomy ; Day of surgery and 2 days after surgery n=12	NR	Opioid use (mean [SD], morphine equivalents/day): 8.5 (2.4) vs. 11.5 (15.9) day of surgery, MD -3.00 (95% CI -17.65 to 11.65); 5.5 (15.9) vs. 19.0 (36.7) postoperative day 2, MD -13.50 (95% CI -49.93 to 22.93); 7.5 (7.3) vs. 19.0 (17.1) total, MD -11.50 (95% CI -28.47 to 5.47)

Abbreviations: ACL = anterior cruciate ligament; CI = confidence interval; IQR = interquartile range; MD = mean difference; NMES = neuromuscular electrical stimulation; NR = not reported; RR = relative risk; SD = standard deviation; TENS = Transcutaneous Electrical Nerve Stimulation; VAS = visual analog scale

KQs 5o and 5p ask how the comparative effectiveness and harms of nonpharmacologic therapy 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.

Evidence on how the comparative effectiveness and harms of nonpharmacologic therapy for postoperative pain varied based on patient and intervention factors was lacking. The number of trials and sample sizes for each comparison were too small for between study comparisons to be informative and no trial conducted within-study subgroup analyses.

KQ 6. Dental Pain (Surgical and Nonsurgical After Discharge)

Key Points

- Opioid plus acetaminophen or NSAID vs. NSAID, primarily surgical pain
 - A single dose of an opioid plus acetaminophen or NSAID was associated with small to moderate increase in pain intensity versus an NSAID at <1 day (12 trials) and increased likelihood of rescue or repeat medication use (9 trials, RR 1.35, 95% CI 1.23 to 1.48) (SOE: low for pain intensity, moderate for rescue or repeat medication use).

- No difference between a multidose course of therapy with an opioid plus acetaminophen or an NSAID versus an NSAID in pain intensity at 1 day to <1 week, based on 3 trials (SOE: low).
- Opioid versus NSAID, surgical or nonsurgical dental pain
 - Insufficient evidence due to inconsistent results from six trials (SOE: insufficient).
- Opioid (with or without acetaminophen) versus NSAID, primarily surgical pain
 - Opioid 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) (SOE: moderate).
- Opioid plus acetaminophen vs. acetaminophen, single dose, surgical pain
 - Inconsistent effects of opioid plus acetaminophen versus acetaminophen on pain intensity at <1 day (11 trials), but opioid plus acetaminophen associated with larger sum of pain intensity differences at <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).
- Opioid vs. acetaminophen, single dose, surgical pain
 - Similar effects on pain intensity at <1 day (2 trials) and likelihood of rescue medication use based on one trial (SOE: low).
- Opioid (with or without acetaminophen) vs. acetaminophen, surgical pain
 - Opioid may be associated with increased likelihood of any adverse event (8 trials), nausea (8 trials), drowsiness (6 trials), and dizziness (5 trials), but differences were not statistically significant, and estimates were imprecise (SOE: low).
- Opioid agonist versus tramadol, surgical or nonsurgical pain
 - Insufficient evidence from two trials with inconsistent results (SOE: insufficient).
- NSAID versus acetaminophen, single dose, surgical pain
 - NSAIDs were associated with moderate to large decrease in pain intensity versus acetaminophen at <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).
 - NSAIDs may 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).
- Pregabalin versus NSAID, surgical pain
 - Insufficient evidence to determine effects on pain intensity, based on 1 trial (SOE: insufficient).
 - Pregabalin 300 mg associated with increased risk of any adverse event versus ibuprofen (RR 5.55, 95% CI 2.56 to 12.03) (SOE: low).
- Non-aspirin NSAID versus aspirin, surgical pain
 - Non-aspirin NSAID associated with a moderate to large decrease in pain intensity versus aspirin at <1 day, based on two trials (SOE: low).
- Acupuncture versus sham acupuncture, surgical pain
 - Insufficient evidence from one poor quality trial (SOE: insufficient).
- Cold therapy versus no cold therapy, surgical pain
 - Insufficient evidence on pain intensity at 1 day to <1 week, based on four trials (SOE: insufficient).

Summary of Findings

Forty-six trials (N=7,119) evaluated interventions for dental pain (Appendix E, Table E-8).¹⁷⁵⁻²¹⁸ Twenty-five trials evaluated opioid therapy (KQ 6a and 6c),^{175,177,179,181,184-192,194,195,201,205,207,210-213,215,218} 15 trials evaluated a nonopioid medication versus nonpharmacologic treatment or another nonopioid (KQ 6i and 6j),^{176,178,180,182,193,197,198,202-204,206,208,209,216,219} and 6 trials (KQ 6m and 6n) evaluated nonpharmacologic treatment versus an inactive control or another nonpharmacologic treatment.^{183,196,199,200,214,217} The most common dental procedure was third molar extraction (40 trials).^{175-178,180-203,207-209,212-219} Other procedures were root canals,^{179,205} apical periodontitis,²¹⁰ periradicular abscess surgery,²¹¹ and various oral surgery procedures.²⁰⁴ For dental conditions associated with pain prior to surgery, the duration of pain was not reported. Thirty-five trials evaluated single doses of medications.^{176-178,180-182,184,186,188-195,197,198,201-205,207-210,212,213,215,216,219} In the other trials, the duration of treatment ranged from 45 minutes to 4 days. The duration of followup was less than one week in 44 trials.^{175-182,184-199,201-219} and 1 week to <4 weeks in 2 trials.^{183,200} Twenty-eight trials were conducted in the United States,^{177-180,182,187-195,197,200-204,207-209,213,215,216,219} 7 trials in Europe,^{176,181,185,186,196,198,212} and 11 trials elsewhere.^{175,183,184,199,205,206,210,211,214,217,218} The mean age ranged from 18 to 43 years. Few trials reported race or ethnicity. Eleven trials excluded patients with a history of substance use disorder,^{175,178,190,194,201,203,207,209,213,215,218} 28 trials excluded pregnant or breastfeeding patients,^{175,177-181,183,187,190,194-198,200,201,203,206-211,213-215,218} 1 trial excluded patients with psychiatric illness,^{178,215} and 11 trials excluded patients with other comorbidities.^{176,178,182,190,194,201,203,206,208,211,218} Three trials were rated good quality,^{181,186,202} 33 trials fair quality,^{175-180,182,184,186-189,192,193,196-198,201,203-205,207-210,212-216,218-220} and 10 trials poor quality (Appendix F, Table F-1).^{183,190,191,194,195,199,200,206,211,217} Methodological limitations in the fair and poor quality trials included failure to report adequate randomization or allocation concealment methods, unblinded design, failure to report attrition, high attrition, and no intention to treat analysis. In most trials, results for pain intensity and pain intensity differences at 4 hours and at 6 to 8 hours were estimated from graphs; the statistical significance of differences were usually not reported or calculable (e.g., standard deviations not provided).

Detailed Synthesis

Opioid Therapy

KQs 6a and 6c address the comparative effectiveness and harms of opioid therapy versus: (1) nonopioid pharmacologic therapy (e.g., acetaminophen, NSAIDs, antidepressants, anticonvulsants) or (2) nonpharmacologic therapy (e.g., exercise, cognitive behavioral therapy, acupuncture).

Twenty-five trials evaluated opioid therapy for acute dental pain (Appendix E, Table E-8).^{175,177,179,181,184-192,194,195,201,205,207,210-213,215,218} 11 trials compared an opioid versus acetaminophen,^{184-186,188,190-192,194,195,212,213} 18 trials an opioid versus an NSAID,^{175,177,179,181,186,187,189-191,194,195,201,205,210,213,215,218} and 2 trials an opioid agonist versus a mixed agent (tramadol).^{207,211} 23 trials blinded patients and caregivers to the study medications.^{175,177,179,181,190,194,195,205,207,210-213,215,218} Two trials were rated good quality,^{181,186} 18 trials fair quality,^{175,177,179,184,185,187-189,192,201,205,207,210,212,213,215,218} and 5 trials poor quality (Appendix F, Table F-1).^{190,191,194,195,211}

Opioid Versus NSAID

Eighteen trials compared an opioid (alone or in combination with acetaminophen or an NSAID) versus an NSAID for acute dental pain (Table 29).^{175,177,179,181,186,187,189-191,194,195,201,205,210,213,215,218} Dental pain was due to third molar extraction in fifteen trials,^{175,177,181,186,187,189-191,194,195,201,213,215,218} root canal instrumentation for irreversible pulpitis in two trials,^{179,205} and acute apical periodontitis in one trial.²¹⁰ The sample size for the opioid versus NSAID comparisons ranged from 37 to 541 (N=2,676). Fourteen trials were single dose studies, and four trials^{175,179,187,218} evaluated three or four days of therapy. In the single dose trials, the duration of followup ranged from ninety minutes to 24 hours. Eight trials evaluated multiple opioid or NSAID arms.^{179,181,189,191,194,195,213,215} The opioid was codeine in 13 trials (dose 60 mg in 11 trials,^{175,186,187,189-191,194,195,201,213} 50 mg in 1 trial,²¹⁸ and 15 mg in 1 trial²¹⁰), oxycodone in 1 trial (5 mg),²¹⁵ and tramadol in 4 trials^{175,179,181,205} (100 mg). In 11 trials, the opioid was administered with acetaminophen (dose 325 to 1000 mg),^{177,186,187,190,191,194,195,201,210,213} five trials evaluated the opioid administered with an NSAID (ibuprofen 400 mg, aspirin 650 mg, diclofenac 50 mg, flurbiprofen 50 mg [after 100 mg loading dose], and dexketoprofen trometamol 12.5 or 25 mg),^{179,181,189,215,218} and six trials evaluated an opioid alone.^{175,179,181,189,205,215} The opioid was compared with the NSAID ibuprofen in five trials (400 or 600 mg),^{181,187,189,195,215} naproxen or naproxen sodium in four trials (440, 500 or 550 mg),^{177,201,205} diclofenac in two trials (50 or 100 mg),^{186,218} flurbiprofen in four trials (50 or 100 mg),^{179,191,194,213} and aspirin (650 mg),¹⁸⁹ meclofenamate sodium (100 mg),¹⁹⁰ ketorolac or ketorolac tromethamine (10 or 20 mg),^{195,210} or dexketoprofen trometamol (12.5 or 25 mg)¹⁸¹ in one trial each.

All of the trials used a blinded design with matching placebo, with the exception of one that blinded without using a placebo¹⁷⁵ and two trials^{191,201} in which blinding status was unclear. One trial²¹⁸ used a crossover design, and the others were parallel group trials. Two trials was rated good quality,^{181,186} twelve trials fair quality,^{175,177,179,187,189,201,205,210,213,215,218} and four trials poor quality (Appendix F, Table F-1).^{190,191,194,195}

Fifteen trials evaluated effects of an opioid plus acetaminophen or NSAID versus an NSAID alone on pain intensity (based on the pain intensity difference [PID] or mean pain intensity).^{177,179,181,186,187,189-191,194,195,210,213,215} The trials varied in timing of outcome assessment. One trial of patients with apical periodontitis (n=63) found codeine plus acetaminophen associated with a large reduction in pain intensity versus ketorolac tromethamine at 90 minutes (mean 4.34 vs. 1.00 on a 0 to 10 scale, p=0.05);²¹⁰ longer-term followup was not reported. Nine trials (N=1,556) evaluated pain intensity at 4 hours in patients who underwent third molar extraction. In six trials, an opioid plus acetaminophen or an NSAID was associated with lesser effects on pain intensity than an NSAID alone (differences ranged from 0.2 to 2.1 points on a 0 to 10 scale).^{189-191,194,195,213} In one trial, oxycodone plus ibuprofen combination therapy was associated with lesser effects on pain intensity at 4 hours than an opioid alone by 4.0 points, but only by 0.5 points compared with ibuprofen alone.²¹⁵ Another trial found that differences between an opioid plus NSAID versus an NSAID alone in pain intensity at 4 hours varied between various dose combinations of tramadol (37.5 or 75 mg) and dexketoprofen trometamol (12.5 or 25 mg) versus dexketoprofen (12.5 or 25 mg) or ibuprofen (400 mg) (differences ranged from -3.0 to 2.0 points on a 0 to 10 scale).¹⁸¹ In the ninth trial, opioid combination therapy was favored by 1.0 point.¹⁸⁶ Three trials (N=465) did not report effects on pain intensity but found codeine plus acetaminophen associated with less pain relief versus naproxen sodium at 4 hours (mean 0.8 to 3.8, p values not reported).^{177,201} Four trials (N=375) found single dose codeine plus

acetaminophen associated with lesser effects on pain intensity at 6 hours (after analgesia had peaked) versus an NSAID alone (differences 0.1 to 2.7 points on a 0 to 10 scale).^{191,194,195,213} One trial (n=25) found tramadol plus an NSAID associated with lower pain intensity versus an NSAID alone at 6 hours (2.3 vs. 3.8 on a 0 to 10 scale).¹⁷⁹ One trial (n=45) found little difference between single dose codeine plus acetaminophen versus diclofenac in pain intensity at 8 hours (3.3 versus 3.5, p not reported).¹⁸⁶ Two trials (N=300) of patients who underwent third molar extraction found no difference between a course of therapy with codeine plus acetaminophen or an NSAID versus an NSAID alone in pain intensity at 3 to 4 days;^{187,218} one of the trials found codeine plus acetaminophen associated with lesser effects on pain relief at <1 day.²²⁰ One trial (n=25) of patients with endodontic pain following a root canal found a course of tramadol plus flurbiprofen associated with decreased pain intensity versus flurbiprofen alone at 2 days (0 vs. 0.8 on a 0 to 10 scale).¹⁷⁹

Ten trials^{177,189-191,194,195,201,213,215} (N=1,550) of patients who underwent third molar extraction tended to find lesser effects on the sum of pain intensity differences (SPID) for an opioid plus acetaminophen or an NSAID versus an NSAID alone, though there was some inconsistency. One trial¹⁸⁶ (n=45) found codeine plus acetaminophen associated with lower average pain intensity (mean of all measurements) versus diclofenac (2.5 vs. 3.8 on a 0 to 10 scale, p=0.02). An opioid plus acetaminophen or an NSAID was associated with increased likelihood of rescue or repeat medication use versus an NSAID (9 trials, N=1,180, pooled RR 1.35, 95% CI 1.23 to 1.48, I²=0%; ARD 15%, 95% CI 9% to 22%; Appendix D, Figure D-1).^{177,186,187,190,191,195,201,213} Effects on the likelihood of being rated “very good” or “excellent” favored opioids, but the difference was of borderline statistical significance (7 trials, N=983, pooled RR 0.76, 95% CI 0.57 to 1.00, I²=74%; Appendix D, Figure D-2).^{177,187,190,191,201,218} Findings for rescue or repeat medication use and likelihood of being rated “very good” or “excellent” were similar when poor quality trials were excluded from the pooled analyses. One trial (n=136) found single dose codeine plus acetaminophen associated with decreased likelihood of 50% pain relief versus an NSAID (13% vs. 36%, RR 0.37, 95% CI 0.16 to 0.87).¹⁹⁵ Quality of life and function were not reported in the trials.

Six trials (N=1,011) compared an opioid alone versus an NSAID.^{175,179,181,189,205,215} One trial (n=50) of patients who underwent root canal instrumentation found a single dose of tramadol associated with higher pain intensity than naproxen at 6 hours (mean difference 2.4 on a 0 to 10 scale, 95% CI 1.2 to 3.6) and 24 hours (mean difference 1.5, 95% CI 0.5 to 2.5).²⁰⁵ Another small trial (n=24) of patients with endodontic pain following root canal found a course of tramadol and flurbiprofen associated with similar pain intensity at 6 hours and 2 days.¹⁷⁹ Three trials compared a single dose of opioid alone versus an NSAID in patients who underwent third molar extraction.^{181,189,215} Results for pain intensity were somewhat inconsistent. One trial (n=298) that compared different doses of tramadol (37.5 or 75 mg) versus dextketoprofen trometamol (12.5 mg or 25 mg) or ibuprofen (400 mg) found that differences in pain intensity at 4 hours ranged from -2.7 to 0.3 points on a 0 to 10 scale.¹⁸¹ One trial (n=117) found a single dose of codeine associated with a larger PID than ibuprofen or aspirin (differences 0.4 to 0.8 on a 0 to 10 scale, p not reported), though the difference was small.¹⁸⁹ The third trial (n=435) found a single 5 mg dose of oxycodone associated with a smaller PID than a single dose of ibuprofen (-0.4 vs. 2.6 at 6 hours, p not reported).²¹⁵ One other trial (n=87) that evaluated a course of therapy after third molar extraction found tramadol associated with higher pain intensity at 4 hours (5.2 vs. 2.4 on a 0 to 10 scale, p=0.001), but differences were smaller and not statistically significant at 8 hours (3.2 vs. 2.3) or 2 days (0.8 vs. 0.4).¹⁷⁵

Opioids (with or without acetaminophen or an NSAID) were associated with increased risk of any adverse event versus an NSAID alone (11 trials, N=1,900, pooled RR 1.72, 95% CI 1.29 to 2.28, $I^2=47\%$; ARD 14%, 95% CI 7% to 22% Appendix D, Figure D-3),^{175,177,187,189,191,194,195,201,213,215} nausea (12 trials, N=2,405, pooled RR 2.72, 95% CI 1.84 to 4.01, $I^2=0\%$; ARD 5%, 95% CI 2% to 7%; Appendix D, Figure D-4),^{175,177,181,186,187,189,191,194,195,201,215} dizziness (10 trials, N=2,286, pooled RR 2.97, 95% CI 1.59 to 5.54, $I^2=0\%$; ARD 3%, 95% CI 1% to 6%; Appendix D, Figure D-5),^{175,177,181,187,189,191,195,201,215} and drowsiness (9 trials, N=1,643, pooled RR 1.76, 95% CI 1.00 to 3.10, $I^2=29\%$; ARD 3%, 95% CI -1% to 8%, Appendix D, Figure D-6).^{175,177,181,186,189,191,195,201} The estimate for headache was imprecise (9 trials, N=1,832, pooled RR 0.99, 95% CI 0.46 to 2.11, $I^2=24\%$ Appendix D, Figure D-7).^{177,181,186,189,191,194,195,201} The number of adverse events in most trials was small, and all trials except for two were single dose studies.^{175,187} The larger multidose trial (n=254), which evaluated dosing every 6 hours for three days, found codeine plus acetaminophen associated with increased risk of headache (6.5% vs. 0.5%, RR 12.41, 95% CI 1.41 to 108.77), nausea (9.7% vs. 2.1%, RR 4.65, 95% CI 1.35 to 15.93), and vomiting (8.1% vs. 0.5%, RR 15.48, 95% CI 1.84 to 130.02) versus ibuprofen.¹⁸⁷ In this trial, the difference in risk of study withdrawal due to adverse events was not statistically significant (4.8% vs. 0.5%, RR 9.29, 95% CI 0.98 to 87.71).

Table 29. Opioid therapy versus NSAIDs for dental pain

Study, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity Results	Other Results
Akinbade, 2019 ¹⁷⁵ Fair	A. Tramadol 100 mg every 8 hours for 48 hours B. Celecoxib 400 mg followed by 200 mg every 12 hours for 48 hours	Third molar extraction; <1 day (4, 8, and 16 hours) <1 week (1 and 2 days) n=87	Pain, (median [range], 0 to 100 VAS converted to 0 to 10 scale: 5.2 (0.5 to 10.0) vs. 2.4 (0 to 0.97) at 4 hours (p=0.001); 3.2 (0 to 9.8) vs. 2.3 (0 to 8.3) at 8 hours (p=0.12); 1.6 (0 to 7.8) vs. 1.5 (0 to 9.8) at 16 hours (p=0.63); 1.0 (0 to 7.9) vs. 0.7 (0 to 9.8) at 1 day (p=0.21); 0.8 (0 to 8.0) vs. 0.4 (0 to 8.9) at day 2 (p=0.19)	NR
Breivik, 1999 ¹⁸⁶ Good	A: Codeine 60 mg + acetaminophen 1000 mg x 1 B: Diclofenac 100 mg x 1	Third molar extraction; <1 day (8 hours) n=45	Pain (mean [SD NR], 0 to 100 VAS converted to 0 to 10 scale): 2.1 vs. 3.1 at 4 hours, 3.3 vs. 3.5 at 8 hours, p=NR Average pain (mean [SD], of all values from 0.5 to 8 hours, 0 to 100 VAS converted to 0 to 10 scale): 2.5 (1.8) vs. 3.8 (1.8), p=0.02 for A vs. B	Rescue medication use (codeine + acetaminophen): 35% (8/23) vs. 36% (8/22) vs. 45% (10/22), RR 0.96 (95% CI 0.44 to 2.10)
Brown, 2013 ¹⁸⁷ Daniels, 2011 ²²⁰ Fair	A: Codeine 60 mg + acetaminophen 600 mg every 6 hours x 1 day, then every 6 hours as needed x 2 days B: Ibuprofen 600 mg q 6 hours x 1 day, then every 6 hours as needed x 2 days	Third molar extraction; 3 days n=254	Average pain, difference versus placebo (least square mean [95% CI], 0 to 10 NRS): -0.87 (-1.63 to -0.11) vs. -1.11 (-1.75 to -0.48) at day 2, MD 0.24 (95% CI -0.96 to 1.44); -0.45 (-1.18 to 0.29) vs. -0.28 (-0.89 to 0.33) at day 3, MD -0.17 (95% CI -1.33 to 0.99) Pain relief (mean [SD NR], 0 to 4 categorical scale converted to 0 to 10): 5 vs. 7.5 at 4 hours; 4.6 vs. 6.8 at 6 hours; 5.4 vs. 6.2 at 24 hours	Rescue medication use (acetaminophen): 23% (14/62) vs. 23% (44/192) day 2, RR 0.99 (95% CI 0.58 to 1.67); 20% (12/62) vs. 18% (34/192) day 3, RR 1.09 (95% CI 0.60 to 1.98) Global assessment "very good" or "excellent": 47% (29/62) vs. 64% (123/192) at day 2, RR 0.73 (95% CI 0.55 to 0.97); 47% (29/62) vs. 60% (115/192) at day 3, RR 0.78 (95% CI 0.58 to 1.04)
Cattry, 2020 – Study 1 ¹⁷⁷ Fair	A: Codeine 60 mg + acetaminophen 600 mg x 1 B: Naproxen sodium 440 mg x 1	Third molar extraction; <1 day (8 hours) n=181	Sum of pain intensity differences (least square mean [SD] sum of differences on 0 to 3 categorical scale from 0.5 to 8 hours): 2.1 (6.0) vs. 4.3 (6.0), p<0.05 Pain relief (mean [SD NR], 0 to 4 categorical scale converted to 0 to 10): 1.7 vs. 0.9 at 4 hours (p<0.05); 2.5 vs. 0.8 at 8 hours, p<0.05	Rescue medication use (not specified): 85% (77/91) vs. 62% (56/90), RR 1.36 (95% CI 1.13 to 1.63) Global assessment "very good" or "excellent": 23% (21/91) vs. 41% (37/90), RR 0.56 (95% CI 0.36 to 0.88)

Study, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity Results	Other Results
Cattry, 2020 – Study 2 ¹⁷⁷ Fair	A: Codeine 60 mg + acetaminophen 600 mg x 1 B: Naproxen sodium 440 mg x 1	Third molar extraction; <1 day (8 hours) n=183	Sum of pain intensity differences (least square mean [SD] sum of differences on 0 to 3 categorical scale from 0.5 to 8 hours): 2.0 (4.9) vs. 2.8 (6.0), p>0.05 Pain relief (mean [SD NR], 0 to 4 categorical scale converted to 0 to 10): 4.0 vs. 2.5 at 4 hours (p<0.05); 2.8 vs. 1.2 at 8 hours, p<0.05	Rescue medication use (not specified): 77% (70/91) vs. 55% (51/92), RR 1.39 (95% CI 1.12 to 1.72) Global assessment “very good” or “excellent”: 35% (32/91) vs. 42% (39/92), RR 0.83 (95% CI 0.57 to 1.20)
Cooper, 1982 ¹⁸⁹ Fair	A: Codeine 60 mg x 1 B: Codeine 60 mg + ibuprofen 400 mg x 1 C: Codeine 60 mg + aspirin 650 mg x 1 D: Ibuprofen 400 mg x 1 E: Aspirin 650 mg x 1	Third molar extraction; <1 day (4 hours) n=203	Pain intensity difference (mean [SD NR], 0 to 3 categorical scale converted to 0 to 10 scale) at 4 hours: 0.2 vs. 1.2 vs. 0.7 vs. 1.0 vs. 0.6, p=NR Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 categorical scale from 1 to 4 hours): 0.95 vs. 4.71 vs. 3.33 vs. 3.76 vs. 1.76, p=NR	NR
Cooper, 1988 ¹⁹⁰ Poor	A: Codeine 60 mg + acetaminophen 600 mg x 1 B: Meclofenamate sodium 100 mg x 1	Third molar extraction; <1 day (6 hours) n=67	Pain intensity difference (mean [SD NR], 0 to 3 NRS converted to 0 to 10 scale): 2.8 vs. 3.4 at 4 hours, 1.7 vs. 1.8 at 6 hours p=NR Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 NRS from 0.5 to 6 hours): 5.26 vs. 5.61, p=NR	Repeat medication use: 58% (18/31) vs. 53% (19/36); RR 1.10 (95% CI 0.72 to 1.69) Medication rated 'very good' or 'excellent': 49% (15/31) vs. 47% (17/36); RR 1.02 (95% CI 0.62 to 1.69)
Cooper, 1991 ¹⁹¹ Poor	A: Codeine 60 mg + acetaminophen 650 mg x 1 B: Flurbiprofen 50 mg x 1 C: Flurbiprofen 100 mg x 1	Third molar extraction; <1 day (6 hours) n=122	Pain intensity difference (mean [SD NR], 0 to 3 categorical converted to 0 to 10): 2.3 vs. 2.5 vs. 3.3 at 4 hours, p=NR; 1.6 vs. 1.7 vs. 3.0 at 6 hours, p=NR Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 scale from 1 to 6 hours): 4.54 vs. 4.33 vs. 6.37, p=NS	Repeat medication use: 79.5% (31/39) vs. 69.0% (29/42) vs. 58.5% (24/41) Medication rated "very good" or "excellent": 35.8% (14/39) vs. 40.5% (17/42) vs. 53.6% (22/41)
Doroschak, 1999 ¹⁷⁹ Fair	A. Tramadol 100 mg every 6 hours + flurbiprofen 100 mg then B. Tramadol 100 mg every 6 hours 50 mg every 6 hours C. Flurbiprofen 100 mg then 50 mg every 6 hours	Endodontic pain following a root canal; <1 day (6 hours), <1 week (2 days) n=37	Pain intensity (mean [SD NR], 0 to 100 VAS converted to a 0 to 10 scale: 2.3 vs. 3.7 vs. 3.8 at 6 hours, and 0 vs. 0.3 vs. 0.8 at day 2	NR

Study, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity Results	Other Results
Dionne, 1994 ¹⁹⁴ Poor	A: Codeine 60 mg + acetaminophen 650 mg x 1 B: Flurbiprofen 50 mg x 1 C: Flurbiprofen 100 mg x 1	Third molar extraction; <1 day (6 hours) n=72	Pain intensity difference (mean [SD NR], 0 to 3 categorical converted to 0 to 10): 3.7 vs. 5.2 vs. 6.0 at 4 hours, p<0.05 for B vs. C, p=NS for A vs. C; 2.8 vs. 4.7 vs. 5.5 at 6 hours, p<0.05 for B vs. C, p=NS for A vs. C Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 scale from 1 to 6 hours): 6.1 vs. 8.4 vs. 9.4, p<0.05 for A or B vs. C	NR
Forbes, 1990 ¹⁹⁵ Poor	A: Codeine 60 mg + acetaminophen 600 mg x 1 B: Ketorolac 10 mg x 1 C: Ketorolac 20 mg x 1 D: Ibuprofen 400 mg x 1	Third molar extraction; <1 day (6 hours) n=136	Pain intensity difference (mean [SD NR], 0 to 3 categorical scale converted to 0 to 10): 1.40 vs. 3.33 vs. 3.03 vs. 3.53 at 4 hours, p≤0.01 for A vs. B, C, or D; 0.80 vs. 1.83 vs. 2.56 vs. 1.86 at 6 hours, p<0.01 for A vs. C, p=NS for A vs. B or D Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 scale from 1 to 6 hours): 2.84 vs. 5.84 vs. 5.69 vs. 5.31, p=NS	50% pain relief: 21.0% (8/38) vs. 64.5% (20/31) vs. 68.6% (24/35) vs. 59.4% (19/32) at 4 hours, p<0.01 for A vs. B, C or D; 13.2% (5/38) vs. 32.3% (10/31) vs. 42.9% (15/35) vs. 31.2% (10/32) at 6 hours, p<0.01 for A vs. C p=NS for A or B or D Repeat medication use: 84.2% (32/38) vs. 51.6% (16/31) vs. 57.1% (20/35) vs. 62.5% (20/32)
Malmstrom, 2004 ²⁰¹ Fair	A: Codeine 60 mg + acetaminophen 600 mg x 1 B: Naproxen sodium 550 mg x 1	Third molar extraction; 1 day n=101	Pain relief (mean [SD NR], 0 to 4 categorical scale converted to 0 to 10 scale): 3.2 vs. 7.0 at 4 hours, 3.0 vs. 5.5 at 20 hours, 3.0 vs. 5.2 at 1 day; p=NR Sum of pain intensity differences (mean [SD], sum of differences on 0 to 4 scale at 0.25 to 8 hours): 5.1 (6.01) vs. 11.7 (6.0), MD -6.60 (95% CI -9.00 to -4.20)	Perceptible pain relief (not defined): 60% (30/50) vs. 90.2% (46/51), RR 0.65 (95% CI 0.51 to 0.83) Rescue medication use (hydrocodone 5 mg + acetaminophen 500 mg): 76.0% (38/50) vs. 52.9% (27/51), RR 1.44 (95% CI 1.06 to 1.94) Response 'good,' 'very good' or 'excellent': 48% (24/50) vs. 84% (43/51) at 8 hours, RR 0.57 (95% CI 0.42 to 0.78)
Mehrvarzfar, 2012 ²⁰⁵ Fair	A: Tramadol 100 mg x 1 B: Naproxen 500 mg x 1	Root canal instrumentation for irreversible pulpitis; 1 day n=50	Pain intensity (mean [SD], 0 to 10 VAS): 3.2 (2.6) vs. 0.8 (1.1) at 6 hours, MD 2.4 (95% CI 1.2 to 3.6); and 2.1 (1.4) vs. 0.5 (0.5) at 12 hours, MD 1.6 (1.0 to 2.2); 2.2 (2.2) vs. 0.7 (1.0) at 24 hours, MD 1.5 (95% CI 0.5 to 2.5)	NR

Study, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity Results	Other Results
Moore, 2015 ¹⁸¹ Good	A: Tramadol hydrochloride 37.5 mg + dexketoprofen trometamol 12.5 mg x 1 B: Tramadol hydrochloride 75 mg + dexketoprofen trometamol 12.5 mg x 1 C: Tramadol hydrochloride 37.5 mg + dexketoprofen trometamol 25 mg x 1 D: Tramadol hydrochloride 75 mg + dexketoprofen trometamol 25 mg x 1 E: Tramadol hydrochloride 37.5 mg x 1 F: Tramadol hydrochloride 75 mg x 1 G: Dexketoprofen trometamol 12.5 mg x 1 H: Dexketoprofen trometamol 25 mg x 1 I: Ibuprofen 400 mg x 1	Third molar extraction; <1 day (4, 6, 8, and 24 hours); 1 day to <1 week (24 hours) n=544	A vs. B vs. C vs. D vs. E vs. F vs. G. vs. H. vs. I Pain intensity (mean [SD NR], 0 to 3 categorical scale converted to 0 to 10): 5.3 vs. 3.7 vs. 6.7 vs. 4.3 vs 4.0 vs. 5.0 vs. 6.7 vs. 6.7 vs. 4.7 at 4 hours, 6.7 vs. 5.3 vs. 7.3 vs. 5.7vs. 5.7 vs. 6.7 vs. 7.7 vs. 7.0 vs. 5.0 at 6 hours, 7.0 vs. 6.0 vs. 7.3 vs. 5.7 vs. 6.3 vs. 7.0 vs. 7.3 vs. 7.0 vs. 6.0 at 8 hours, 7.3 vs. 6.3 vs. 7.3 vs. 6.0 vs. 6.7 vs. 6.7 vs. 7.3 vs. 7.0 vs. 7.0 at 24 hours Sum of Pain Intensity Difference (mean [SD], sum of difference on 0 to 3 scale from 4 to 12 hours): 5.6 (6.1) vs. 9.0 (8.8) vs. 8.6 (7.6) vs. 10.1 (8.4) vs. 2.4 (4.6) vs. 3.8 (6.3) vs. 4.8 (6.2) vs. 6.0 (7.0) vs. 7.4 (9.3)	A vs. B vs. C vs. D vs. E vs. F vs. G. vs. H. vs. I Experienced ≥50% maximum total pain relief: 12% (7/60) vs. 36% (22/62) vs. 29% (18/63) vs. 38% (23/61) vs. 5.1% (3/59) vs. 15% (9/59) vs.10% (6/60) vs. 13% (8/60) vs. 25% (15/60) Proportion of patients rating the study medication as 'very good' or 'excellent', % (n/N): 27% (16/60) vs. 47% (29/62) vs. 46% (29/63) vs. 51% (31/61) 25% (15/59) vs. 14% (8/59) vs. 33% (20/60) vs.28% (17/60) vs. 33% (20/60) Rescue medication use (paracetamol) at 24 hours: 75% (45/60) vs. 58% (36/62) vs. 49% (31/63) vs. 54% (33/61) vs. 73% (43/59) vs. 66% (39/59) vs. 65% (39/60) vs. 62% (37/60) vs. 65% (39/60)
Sadeghein, 1999 ²¹⁰ Fair	A: Codeine 15 mg + acetaminophen 325 mg x 1 B: Ketorolac tromethamine 10 mg x 1	Acute apical periodontitis; <1 day (90 minutes) n=63	Pain intensity (mean [SD NR], 0 to 10 VAS): 4.34 vs 1.00, p=0.05	NR

Study, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity Results	Other Results
Sunshine, 1986 ²¹³ Fair	A: Codeine 60 mg + acetaminophen 650 mg x 1 B: Flurbiprofen 50 mg x 1 C: Flurbiprofen 100 mg x 1	Third molar extraction; <1 day (6 hours) n=91	Pain intensity difference (mean [SD NR], 0 to 3 categorical scale transformed to 0 to 10): 2.03 vs. 3.76 vs. 3.90 at 4 hours, p=NS for A vs. B or C; 1.30 vs. 3.33 vs. 3.56 at 6 hours, p=NS for A vs. B or C Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 scale from 0.5 to 6 hours): 4.66 vs. 7.01 vs. 6.85, p=NS for A vs. B or C	Rescue medication use: 92.0% (9/31) vs. 19.4% (6/31) vs. 13.8% (4/29)
Van Dyke, 2004 ²¹⁵ Fair	A: Oxycodone 5 mg + ibuprofen 400 mg x 1 B: Oxycodone 5 mg C: Ibuprofen 400 mg x 1	Third molar extraction <1 day (6 hours) n=435	Pain intensity difference (mean [SD NR], 0 to 3 categorical scale converted to 0 to 10 scale): 3.6 vs. -0.4 vs. 3.1 at 4 hours, 3.0 vs. -0.4 vs. 2.6 at 6 hours; p=NR Sum of pain intensity differences (mean [SD], sum of differences on 0 to 3 scale from 0.25 to 6 hours): 6.54 (0.42) vs. 0.14 (0.60) vs. 5.41 (0.44); p=0.002 for A vs. C, p=NS for B vs. C	Pain improved ≥50% after 1 hour: 74.9% (140/186) vs. 19.0% (12/63) vs. 59.1% (110/186), p<0.05 for A vs. C and p<0.001 for B vs. C Global evaluation (mean [SD], 0 to 4 scale): 2.63 (0.10) vs. 0.66 (0.16) vs. 2.26 (0.10); p<0.01 for A vs. C and p<0.001 for B vs. C
Zupelari- Goncalves, 2017 ²¹⁸ Fair	A: Codeine 50 mg + diclofenac 50 mg every 8 hours x 4 days B: Diclofenac 50 mg x 1 every 8 hours x 4 days	Third molar extraction; 4 days n=46	Pain (median [IQR], 0 to 100 VAS converted to 0 to 10 scale): 0 (0 to 0) vs. 1.8 (0 to 4.7) at 18 hours, 1.0 (0 to 2.5) vs. 1.0 (0 to 2.5) at 4 days, p=NS	Rescue medication use (mean [SD], tablets): 3.0 (3.3) vs. 5.0 (3.4), p≤0.05 Global efficacy “very good” or “excellent”: 65% (30/46) vs. 37% (17/46), RR 1.76 (95% CI 1.15 to 2.72)

Abbreviations: CI = confidence interval; IQR = interquartile range; MD = mean difference; NR = not reported; NS = not significant; RR = relative risk; SD = standard deviation; VAS = visual analog scale;

Note: Pain intensity difference=pain at followup minus pain at baseline

Opioid Versus Acetaminophen

Eleven trials compared an opioid (alone or in combination with acetaminophen) versus acetaminophen for acute dental pain (Appendix E, Table E-8; Table 30).^{184-186,188,190-192,194,195,212,213} Dental pain was due to third molar extraction in all of the trials; one of the trials¹⁸⁴ also included patients undergoing other extractions and procedures. The sample size for the opioid versus acetaminophen arms ranged from 20 to 209 (N=891). All trials were single dose studies, with the exception of one trial¹⁸⁵ in which three doses were taken over six hours. The duration of followup ranged from four to eight hours. All trials evaluated an opioid in combination with acetaminophen; two trials also evaluated an opioid alone.^{184,192} The opioid was codeine in 10 trials^{184-186,188,190,191,194,195,212,213} (dose 60 mg) and oxycodone in 1 trial¹⁹² (dose 5 or 10 mg). The dose of acetaminophen administered with an opioid was 1000 mg in five trials^{184-186,192,212} and 500 to 650 mg in seven trials^{188,190-192,194,195,213} (one of the trials¹⁹² evaluated acetaminophen 500 and 1000 mg). The dose of acetaminophen in the non-opioid arm was 1000 mg in 5 trials,^{184-186,192,212} 600 or 650 mg in six trials,^{188,190,191,194,195,213} one of the 1000 mg dose trials²¹² also had a 2000 mg arm.

All of the trials used a parallel group design and used a blinded design, except for one trial¹⁹¹ in which blinding status was unclear. One trial was rated good quality,¹⁸⁶ six trials fair quality,^{184,185,188,192,212,213} and four trials^{190,191,194,195} poor quality (Appendix F, Table F-1).

Eleven trials (N=828) evaluated effects of an opioid plus acetaminophen versus acetaminophen alone on pain intensity at 4 hours, based on the PID or mean pain intensity.^{184-186,188,190-192,194,195,212,213} In seven of the trials, an opioid plus acetaminophen was associated with greater reduction in pain intensity versus acetaminophen alone; in most of the trials, the magnitude of the effect was moderate (range 0.8 to 2.9 points on a 0 to 10 scale).^{184-186,190-192,194} In the other four trials, effects of an opioid plus acetaminophen and acetaminophen alone on pain intensity were similar (range -0.2 to 0.3 point).^{188,195,212,213} The trial that evaluated three doses over six hours reported the largest effects in favor of the opioid combination on pain intensity; the difference in this trial was statistically significant (n=20, PID 4.8 vs. 2.0, p<0.01).¹⁸⁵ Eight trials (N=546) evaluated effects of an opioid plus acetaminophen versus acetaminophen alone on pain intensity at 6 to 8 hours^{185,186,190,191,194,195,212,213} (subsequent to peak analgesic effects in most single dose trials). Results were inconsistent, with differences ranging from 3 points on a 0 to 10 scale in favor of acetaminophen to 2.5 points in favor of an opioid plus acetaminophen. An opioid plus acetaminophen was associated with larger SPID versus acetaminophen in 10 trials (N=898),^{184,185,188,190-192,194,195,212,213} though the difference was statistically significant in only one trial.¹⁸⁵ An opioid plus acetaminophen was also associated with less average pain (mean of all assessments) (1 trial, n=45, 2.5 vs. 3.7 on a 0 to 10 scale, p=0.03),¹⁸⁶ and decreased likelihood of rescue or repeat medication use (7 trials, N=484, pooled RR 0.81, 95% CI 0.67 to 0.97, I²=39%; ARD -12%, 95% CI -19% to -5%; Appendix D, Figure D-8).^{184,186,188,190,191,195,213} Effects on likelihood of rescue or repeat medication use were similar when poor quality trials were excluded (4 trials, N=267, pooled RR 0.62, 95% CI 0.45 to 0.86, I²=0%).^{184,186,188,213} One trial¹⁹⁵ (n=74) found no difference in the likelihood of 50 percent pain relief, though two trials^{190,191} (n=143) found an opioid plus acetaminophen more likely to be rated “very good” or “excellent” (49% vs. 28%, RR 0.45, 95% CI 0.09 to 2.20 and 36% vs. 8.1%, RR 4.42, 95% CI 1.38 to 14.17). Quality of life and function were not reported in the trials.

Two trials (N=149) compared an opioid alone versus acetaminophen.^{184,192} Effects on pain intensity at 4 hours were below the threshold for small (differences ranged from 0.23 point on a 0 to 10 scale favoring the opioid to 0.1 point favoring acetaminophen). Differences in the SPID

were also small or not statistically significant. One trial (n=62) found no difference between an opioid versus acetaminophen in likelihood of rescue medication use (RR 1.08, 95% CI 0.77 to 1.54).¹⁸⁴

There were no statistically significant differences between an opioid (alone or in combination with acetaminophen) versus acetaminophen alone in risk of any adverse event (8 trials, N=774, pooled RR 1.43, 95% CI 0.87 to 2.37, $I^2=65\%$; Appendix D, Figure D-9),^{184,188,191,192,194,195,212,213} nausea (8 trials, N=669, pooled RR 1.55, 95% CI 0.75 to 3.18, $I^2=0\%$; Appendix D, Figure D-10),^{185,186,188,191,192,194,195,212} drowsiness (6 trials, N=512, pooled RR 2.03, 95% CI 0.70 to 5.93, $I^2=53\%$; Appendix D, Figure D-11),^{185,186,188,191,192,195} dizziness (5 trials, N=465, pooled RR 2.49, 95% CI 0.66 to 9.49, $I^2=27\%$; Appendix D, Figure D-12),^{185,188,191,192,195} or headache (4 trials, N=415, pooled RR 0.67, 95% CI 0.20 to 2.18, $I^2=0\%$; Appendix D, Figure D-13).^{188,191,192,194} However, most estimates favored acetaminophen, the number of adverse events in most trials was small, estimates were imprecise, and statistical heterogeneity was large for some outcomes. In addition, all trials except for one were single dose studies, and the single multiple dose trial was very small (n=20).¹⁸⁵ Serious adverse events were not reported.

Table 30. Opioid therapy versus acetaminophen for dental pain

Study, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity Results	Other Results
Bentley, 1987 ¹⁸⁴ Fair	A. Codeine 60 mg x 1 B. Codeine 60 mg + acetaminophen 1000 mg x 1 C. Acetaminophen 1000 mg x 1	Extraction or other procedure involving reflection of the mucoperiosteal flap and removal of bone; <1 day (5 hours) n=103	Pain intensity (mean [SD NR], 0 to 9 NRS converted to 0 to 10 scale): 1.1 vs. 1.8 vs. 1.0 at 4 hours, 1.1 vs. 1.5 vs. 0.8 at 5 hours, p=NR Sum of pain intensity differences (mean [SD] of differences on 0 to 9 NRS at 1 to 5 hours): 4.33 (11.80) vs. 9.71 (10.49) vs. 6.17 (8.48); MD -5.38 (95% CI -11.25 to 0.49) for A vs. B, MD -1.84 (95% CI -7.05 to 3.37) for A vs. C, MD 3.54 (95% CI -0.65 to 7.73) for B vs. C	Rescue medication use through 4 hours: 70% (15/21) vs. 38% (16/41) vs. 67% (27/41), RR 1.83 (95% CI 1.15 to 2.92) for A vs. B, RR 1.08 (95% CI 0.77 to 1.54) for A vs. C, and RR 0.59 (95% CI 0.38 to 0.92) for B vs. C
Breivik, 1998 ¹⁸⁵ Fair	A. Codeine + acetaminophen 60/1000 mg every 3 hours x 3 days B. Acetaminophen 1000 mg every 3 hours x 3 days	Third molar extraction; <1 day (8 hours) n=20	Pain intensity (mean [SD NR], 0 to 100 VAS converted to 0 to 10 scale): 1.6 vs. 4.5 at 4 hours, p<0.01; 1.0 vs. 4.8 at 8 hours, p<0.005 Pain intensity difference (mean [SD NR], 0 to 100 VAS converted to 0 to 10 scale): 4.8 vs. 2.0 at 4 hours, p<0.01; 2.1 vs. 5.1 at 8 hours, p<0.05 Sum of pain intensity differences (median [IQR], sum of differences on 0 to 100 VAS from 0 to 8 hours): 551 (148) vs. 318 (252), p=0.01	NR
Breivik, 1999 ¹⁸⁶ Good	A. Codeine 60 mg + acetaminophen 1000 mg x 1 B. Acetaminophen 1000 mg x 1	Third molar extraction; <1 day (8 hours) n=45	Pain intensity (mean [SD NR], 0 to 100 VAS converted to 0 to 10 scale): 2.1 vs. 3.1 at 4 hours; 3.3 vs. 3.5 vs. 5.8 at 8 hours, p=NR Average pain (mean [SD] of all values from 0.5 to 8 hours, 0 to 100 VAS converted to 0 to 10 scale): 2.5 (1.8) vs. 3.7 (2.4), p=0.03	Rescue medication use: 35% (8/23) vs. 45% (10/22), RR 0.77 (95% CI 0.37 to 1.58)
Cooper, 1980 ¹⁹² Fair	A. Oxycodone 5 mg x 1 B. Oxycodone 5 mg + acetaminophen 500 mg x 1 C. Oxycodone 5 mg + acetaminophen 1000 mg x 1 D. Oxycodone 10 mg + acetaminophen 1000 mg x 1 E. Acetaminophen 1000 mg x 1	Third molar extraction <1 day (4 hours) n=209	Pain intensity difference (mean [SD NR], 0 to 3 categorical scale converted to 0 to 10 scale) at 4 hours: 1.03 vs. 1.93 vs. 2.56 vs. 3.26 vs. 0.80, p=NR Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 categorical scale from 1 to 4 hours): 1.38 vs. 3.00 vs. 3.55 vs. 4.49 vs. 1.49, p=NR	Observations with 50% pain relief (mean [SD NR]): 1.12 vs. 2.00 vs. 2.15 vs. 2.56 vs. 0.95, p=NR

Study, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity Results	Other Results
Cooper, 1981 ¹⁸⁸ Fair	A. Codeine 60 mg + acetaminophen 650 mg x 1 B. Acetaminophen 650 mg x 1	Third molar extraction; <1 day (4 hours) n=79	Pain intensity difference (mean [SD NR], 0 to 3 NRS converted to 0 to 10 scale) at 4 hours: 1.60 vs. 1.90, p=NR Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 NRS from 1 to 4 hours): 3.05 vs. 2.84, p=NR	Observations with 50% relief: 58% vs. 55%, p=NR Repeat use of medication: 5% (2/37) vs. 12% (5/42), RR 0.45 (95% CI 0.09 to 2.20)
Cooper, 1988 ¹⁹⁰ Poor	A. Codeine 60 mg + acetaminophen 600 mg x 1 B. Acetaminophen 600 mg x 1	Third molar extraction; <1 day (6 hours) n=67	Pain intensity difference (mean [SD NR, 0 to 3 NRS converted to 0 to 10 scale): 2.8 vs. 1.5 at 4 hours, 1.7 vs. 0.3 at 6 hours p=NR Sum of pain intensity differences (mean [SD NR] sum of differences on 0 to 3 NRS from 0.5 to 6 hours): 5.26 vs. 2.86, p=NR	Repeat medication use: 58% (18/31) vs. 78% (28/36), RR 0.75 (95% CI 0.53 to 1.06) Medication rated "very good" or "excellent": 49% (15/31) vs. 28% (10/36), RR 1.74 (95% CI 0.92 to 3.30)
Cooper, 1991 ¹⁹¹ Poor	A: Codeine 60 mg + acetaminophen 650 mg x 1 B: Acetaminophen 650 mg x 1	Third molar extraction; <1 day (6 hours) n=76	Pain intensity difference (mean [SD NR], 0 to 3 categorical converted to 0 to 10): 2.3 vs. 1.2 at 4 hours, p=NR; 1.6 vs. 0.7 at 6 hours, p=NR Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 scale from 1 to 6 hours): 4.54 vs. 2.41, p=NS	Repeat medication use: 79.5% (31/39) vs. 94.6% (35/37) Medication rated "very good" or "excellent": 35.8% (14/39) vs. 8.1% (3/37), RR 4.42 (95% CI 1.38 to 14.17)
Dionne, 1994 ¹⁹⁴ Poor	A: Codeine 60 mg + acetaminophen 650 mg x 1 B: Acetaminophen 650 mg x 1	Third molar extraction; <1 day (6 hours) n=51	Pain intensity difference (mean [SD NR], 0 to 3 categorical converted to 0 to 10): 3.7 vs. 2.7 at 4 hours, p=NS; 2.8 vs. 2.7 at 6 hours, p=NS Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 scale from 1 to 6 hours): 6.1 vs. 5.4, p=NS	NR
Forbes, 1990 ¹⁹⁵ Poor	A: Codeine 60 mg + acetaminophen 600 mg x 1 B: Acetaminophen 600 mg x 1	Third molar extraction; <1 day (6 hours) n=74	Pain intensity difference (mean [SD NR], 0 to 3 categorical scale converted to 0 to 10): 1.40 vs. 1.20 at 4 hours, p=NS; 0.80 vs. 0.47 at 6 hours, p=NS Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 scale from 1 to 6 hours): 2.84 vs. 2.47, p=NS	50% pain relief: 21.0% (8/38) vs. 27.8% (10/36) at 4 hours, p=NS; 16.7% (6/36) vs. 13.2% (5/38) at 6 hours, p=NS Repeat medication use: 84.2% (32/38) vs. 83.3% (30/36)

Study, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity Results	Other Results
Skoglund, 1991 ²¹² Fair	A. Codeine 60 mg + acetaminophen 1000 mg x 1 B. Acetaminophen 1000 mg x 1 C. Acetaminophen 2000 mg x 1	Third molar extraction; <1 day (6 hours) n=106	Pain intensity difference (mean [SD NR], 0 to 100 VAS converted to 0 to 10 scale): 2.1 vs. 2.3 vs. 1.8 at 4 hours, 1.3 vs. 1.1 vs. 1.4 at 6 hours, p=NR Sum of pain intensity differences (mean [SD], sum of differences on 0 to 100 VAS from 1 to 6 hours): 132.6 (147.8) vs. 124.5 (169.4) vs. 95.1 (167.5); p<0.001 for A vs. B, p=NS for A vs. C and B vs. C	NR
Sunshine, 1986 ²¹³ Fair	A: Codeine 60 mg + acetaminophen 650 mg x 1 B: Acetaminophen 650 mg x 1	Third molar extraction; <1 day (6 hours) n=61	Pain intensity difference (mean [SD NR], 0 to 3 categorical scale transformed to 0 to 10): 2.03 vs. 2.23 at 4 hours, p=NS; 1.30 vs. 0.67 at 6 hours, p=NS Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 scale from 0.5 to 6 hours): 4.66 vs. 4.23, p=NS	Rescue medication use: 29.0% (9/31) vs. 46.7% (14/30)

Abbreviations: CI = confidence interval; IQR = interquartile range; MD = mean difference; NR = not reported; NRS = numeric rating scale; NS = not significant; RR = relative risk; SD = standard deviation; VAS = visual analog scale

Opioid Agonist Versus Mixed Agent

Two trials compared a pure opioid agonist versus a mixed agent (tramadol) in patients with dental pain (Appendix E, Table E-8; Table 31).^{207,211} One fair-quality trial (n=172) of patients who underwent third molar extraction found single dose codeine 60 mg associated with smaller effects on pain intensity versus tramadol 50 or 100 mg (difference 0.6 and 1.3 points, respectively, on a 0 to 10 scale; p not reported) and a smaller SPID through 6 hours.²⁰⁷ Differences in rescue medication use were not statistically significant (80% vs. 69% vs. 73%; RR 1.15, 95% CI 0.89 to 1.49 for codeine versus tramadol 50 mg and RR 1.10, 95% CI 0.86 to 1.41 for codeine versus tramadol 100 mg). This trial also evaluated codeine plus acetaminophen and found similar effects compared with tramadol 50 or 100 mg. A small (n=20), poor quality trial of patients with periradicular abscess found no difference between codeine (pure opioid agonist) plus acetaminophen versus tramadol (mixed agent) plus acetaminophen in pain intensity (median 1.0 vs 1.0 on a 0 to 10 scale at 6 hours, p=0.59; 0.6 vs. 0.6 at 12 hours, p=0.54, and 0 vs. 0 at 3 days, p=0.43).²¹¹ In both trials, estimates for adverse events did not indicate differences.

Table 31. Opioid agonists versus mixed agents for dental pain

Study, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity Results	Other Results
Moore, 1998 ²⁰⁷ Fair	A: Codeine 60 mg + aspirin 650 mg x 1 B: Codeine 60 mg x 1 C: Tramadol 50 mg x 1 D: Tramadol 100 mg x 1	Third molar extraction; <1 day (4 and 8 hours) n=172	Pain intensity difference (mean [SD NR], 0 to 3 categorical scale converted to 0 to 10 scale): 1.1 vs. 0.3 vs. 0.9 vs. 1.6 at 4 hours, p=NR; 0.7 vs. 0.5 vs. 1.1 vs. 1.4 at 8 hours, p=NR Sum of pain intensity differences (mean [SD], sum of difference on 0 to 3 scale from 0.5 to 6 hours): 2.2 (0.45) vs. 0.6 (0.31) vs. 1.5 (0.47) vs. 2.3 (0.61), p<0.05 for A and D vs. placebo, p=NS for B and C vs. placebo	Rescue medication use: 73.7% (23/38) vs. 80.0% (24/30) vs. 69.4% (34/49) vs. 72.9% (35/48); RR 1.15 (95% CI 0.89 to 1.49) for B vs. C and RR 1.10 (95% CI 0.86 to 1.41) for B vs. D
Santini, 2017 ²¹¹ Poor	A: Codeine 30 mg + acetaminophen 500 mg every 4 hours x 3 days B: Tramadol 37.5 mg + acetaminophen 500 mg every 4 hours x 3 days	Third molar extraction; 12 hours and 3 days n=20	Pain (median [IQR], 0 to 10 VAS): 1.0 (0 to 6.0) vs. 1.0 (0.5 to 6.2) at 6 hours, p=0.59; 0.6 (0 to 3.6) vs. 0.6 (0 to 6.2) at 12 hours, p=0.54, 0 (0 to 0.4) vs. 0 (0 to 2.0) at 3 days, p=0.43	NR

Abbreviations: CI = confidence interval; IQR = interquartile range; NR = not reported; NS = not significant; RR = relative risk; SD = standard deviation; VAS = visual analog scale

KQs 6b and 6d ask how the comparative effectiveness and harms 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.

Evidence on how comparative effectiveness and harms of opioid therapy for dental pain vary according to patient and prescribing factors was lacking. The trials did not describe substance use history or presence of medical or psychiatric comorbidities. Most trials were conducted in populations of younger persons undergoing third molar surgery. This surgery is typically

performed for third molar impaction, a condition that usually is not painful. Two trials evaluated older populations of patients with painful dental conditions (irreversible pulpitis or acute apical periodontitis),^{205,210} but there was insufficient evidence to determine how presence of nonsurgical pain, antecedent pain or age impacted findings. Evidence was too limited to determine effects of different opioid doses (converted into morphine milligram equivalents) on comparative effectiveness and harms. Most trials evaluated single doses of opioids, and no trial permitted opioid refills.

KQ 6e concerns 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).

One retrospective cohort study (n=70,942) of opioid-naïve patients who underwent third molar extraction found a filled perioperative opioid prescription (from 7 days prior to 3 days after the surgery) associated with increased risk of persistent opioid use (adjusted OR 2.69, 95% CI 2.10 to 3.44) (Appendix E and F; Tables E-9 and F-2).²²¹ The analysis adjusted for age, sex, insurance status, income, chronic conditions, perioperative medications, and third molar impaction status. Persistent use was defined as at least one opioid prescription filled during postprocedure days 4 to 90 and 91 to 365.

KQs 6f and 6g address the accuracy and effectiveness of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose for patients with acute pain being considered for opioid therapy.

No study evaluated the accuracy or effectiveness of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose in patients with acute dental pain.

KQ 6h addresses the effect of the following factors on the decision to prescribe opioids for patients with acute pain being considered for opioid therapy: (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.

Evidence on the effect of patient education, use of risk mitigation strategies, clinician and patient values and preferences, or availability of followup on decisions to prescribe opioids for postoperative pain was limited. One before-after study (n=6,204) found that among patients who received pain medication, the likelihood of receiving opioid analgesics was decreased in two assessment periods following implementation of mandatory use of prescription drug monitoring data prior to prescribing a controlled substance, compared with before implementation (OR 0.37, 95% CI 0.31 to 0.45 and OR 0.24, 95% CI 0.20 to 0.30) (Appendix E, Table E-9).²²² In addition to use of a before-after study design, the study did not control for potential confounders.

Nonopioid Pharmacologic Therapy

KQs 6i and 6k address the comparative effectiveness and harms of nonopioid pharmacologic therapy versus: (1) nonopioid pharmacologic therapy or (2) nonpharmacologic therapy?

Seventeen trials evaluated nonopioid pharmacologic therapy for acute dental pain (Appendix E, Table E-8).^{176,178,180,182,186,190,191,193-195,197,198,202-204,206,208,209,213,216,219} Dental pain was related to third molar extraction in 19 trials,^{176,178,180,182,186,190,191,193-195,197,198,202,203,208,209,213,216,219} various oral surgeries in 1 trial,²⁰⁴ and mouth flap surgery for periodontitis in 1 trial.²⁰⁶ Seventeen trials compared an NSAID versus acetaminophen,^{176,178,180,182,186,190,191,193-195,197,202,204,209,213,216,219} one trial pregabalin versus an NSAID,¹⁹⁸ two trials a non-aspirin versus aspirin NSAID,^{203,208} and one trial an oral versus topical NSAID.²⁰⁶ Two trials were rated good quality,^{186,202} fourteen trials

were rated fair quality^{176,178,180,182,193,197,198,203,204,208,209,213,216,219} and five trials poor quality (Appendix F, Table F-1).^{190,191,194,195,206}

NSAID Versus Acetaminophen

Seventeen trials compared an NSAID versus acetaminophen for acute dental pain (Table 32).^{186,190,191,193-195,197,202,204,209,213,216} Dental pain was due to third molar extraction in all trials except for one,²⁰⁴ which evaluated dental pain related to extractions and other dental procedures. The sample size ranged from 38 to 612 (N=3,152). All trials were single dose studies with duration of followup that ranged from 6 to 12 hours. Fourteen trials were conducted in the United States, and two trials in Europe. The NSAID was ibuprofen in nine trials^{178,182,193,195,197,202,204,209,219} (200 mg in one trial, 250 mg in one trial, 400 mg in five trials), flurbiprofen in three trials (50 or 100 mg),^{191,194,213} ketoprofen in two trials (25 or 100 mg),^{176,209} and ketorolac (10 or 20 mg),¹⁹⁵ diclofenac (100 mg),¹⁸⁶ meclofenamate (100 mg),¹⁹⁰ aspirin (1000 mg)²¹⁶ and naproxen sodium (440 mg)¹⁸⁰ in one trial each (two trials evaluated two different types of NSAIDs). Two trials of ibuprofen used a solubilized (“liquigel”) formulation rather than a standard solid tablet,^{197,209} and one trial evaluated ibuprofen sodium and ibuprofen with poloxamer.¹⁷⁸ The dose of acetaminophen was 1000 mg in twelve trials^{176,178,180,182,186,193,197,202,204,209,216,219} and 600 to 650 mg in five trials.^{190,191,194,195,213}

All of the trials used a parallel group design and were blinded using matching placebo, with the exception of one trial¹⁹¹ in which blinding was unclear. Two trials were rated good quality,^{186,202} 11 trials fair quality,^{176,178,180,182,193,197,204,209,213,216,219} and four trials poor quality (Appendix F, Table F-1).^{190,191,194,195} Methodological limitations in the fair and poor quality trials included failure to report randomization and allocation concealment methods or unclear blinding of outcome assessors; the poor quality trials also did not conduct intention to treat analysis. In most trials, results for pain intensity and PID at 4 hours and at 6 to 8 hours had to be estimated from graphs; the statistical significance of differences were usually not reported or calculable (e.g., standard deviations not provided).

Fifteen trials (N=2,506) evaluated effects of an NSAID versus acetaminophen on pain intensity at 4 hours, based on the PID or mean pain intensity.^{176,178,180,182,186,190,191,193-195,197,202,204,213,219} In thirteen trials, effects on pain intensity favored the NSAID, with differences that ranged from moderate to large (1.2 to 3.3 points on a 0 to 10 scale).^{176,178,180,182,190,191,193-195,197,204,213,219} In the other two trials, NSAIDs and acetaminophen were associated with similar effects on pain intensity (differences 0 and 0.2 points).^{186,202} The largest trial (n=612), which evaluated patients undergoing extractions and other dental procedures, found NSAIDs associated with moderate effects versus acetaminophen on pain intensity (mean difference in PID 1.33 points on a 0 to 10 scale, 95% CI 0.87 to 1.79).²⁰⁴ Fourteen trials (N=2,503) also evaluated effects of an NSAID versus acetaminophen on pain intensity at 6 to 8 hours (subsequent to the typical peak analgesic effect of a single dose).^{178,180,182,186,190,191,193-195,197,202,204,213,219} Thirteen of the trials found that effects on pain intensity favored NSAIDs at 6 to 8 hours (differences 1.0 to 2.8 on a 0 to 10 scale);^{186,190,191,193-195,197,204,213,219} the other trial²⁰² found NSAIDs and acetaminophen associated with similar effects on pain intensity at 8 hours. One trial (n=200) did not report pain intensity but reported pain relief.²⁰⁹ It found ibuprofen liquigel and ketoprofen associated with greater pain relief versus acetaminophen at 4 hours (differences 0.9 and 0.4 on a 0 to 4 scale, respectively; p not reported). Ibuprofen, but not ketoprofen, was associated with greater pain relief than acetaminophen at 6 hours (differences 0.7 and 0.1, respectively; p not reported).

Fifteen trials (N=2,868) evaluated effects of an NSAID versus acetaminophen on the SPID.^{176,180,182,190,191,193-195,197,202,204,209,213,216,219} The SPID is difficult to interpret and not directly comparable across trials, because it varies depending on the pain intensity scale used, the number and timing of measurements, and the duration of followup. NSAIDs were associated with larger SPID versus acetaminophen in 13 trials; most trials^{176,180,182,190,193,197,204,209,219} found that the differences were statistically significant. In one trial (n=408), aspirin 1000 mg was associated with a smaller SPID than acetaminophen 1000 mg (5.9 [SD 5.1] vs. 7.9 [SD 4.9], $p<0.001$).²¹⁶ One other trial²⁰² (n=103) found no statistically significant difference between ibuprofen versus acetaminophen in the sum of pain relief plus pain intensity differences through 8 hours, and one trial¹⁸⁶ (n=44) found no difference between diclofenac versus acetaminophen in average pain (mean of all measurements) through 8 hours (3.8 vs. 3.7, $p>0.05$). NSAIDs were associated with decreased likelihood of rescue or repeat medication use versus acetaminophen (11 trials, N=2,014, pooled RR 0.64, 95% CI 0.58 to 0.71, $I^2=15\%$; ARD -22%, 95% CI -27% to -17%; Figure D-14)^{178,186,190,191,193,195,197,204,209,213,219} and increased likelihood of being rated “very good” or “excellent” (6 trials, N=936, pooled RR 1.61, 95% CI 1.37 to 1.88, $I^2=21\%$; ARD 25%, 95% CI 18% to 32%; Figure D-15).^{178,190,191,193,197,219} Three trials^{178,195,204} (N=926) found NSAIDs associated with greater likelihood of more than 50 percent pain improvement (45% vs. 30%, RR 1.50, 95% CI 1.21 to 1.85, 36% vs. 17%, RR 2.14, 95% CI 0.98 to 4.66, and 91% vs. 75%, RR 1.22, 95% CI 1.06 to 1.39), and one trial²⁰⁹ (n=200) found ibuprofen liquigel associated with greater likelihood of complete pain relief (73% vs. 48%, RR 1.51, 95% CI 1.13 to 2.01). One trial (n=333) found ibuprofen and acetaminophen associated with similar likelihood of experiencing meaningful pain relief as defined by the patient (79% vs. 72%, RR 1.11, 95% CI 0.98 to 1.26).¹⁸² Effects on quality of life or function were not reported, other than one trial that found ibuprofen associated with less pain interference with daily activities, based on the Rainier scale (difference 5.3 to 7.3 points, scale not reported).¹⁷⁸

Table 32. NSAIDs versus acetaminophen for acute dental pain

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity	Other Results
Akural, 2009 ¹⁷⁶ Fair	A. Ketoprofen, 100 mg x 1 B. Acetaminophen, 1000 mg x 1	Third molar extraction; <1 day (10 hours) n=38	Pain intensity difference at rest (mean [SD NR], 0 to 10 NRS): 1.9 vs. 0.7 at 4 hours Sum of pain intensity difference at rest (mean [SD], sum of differences on 0 to 10 NRS from 0.25 to 10 hours): 14.91 (19.50) vs. -4.22 (19.92), p<0.05	NR
Breivik, 1999 ¹⁸⁶ Good	A: Diclofenac 100 mg x 1 B: Acetaminophen 1000 mg x 1	Third molar extraction; <1 day (8 hours) n=44	Pain (mean [SD NR], 0 to 100 VAS converted to 0 to 10 scale): 3.1 vs. 3.1 at 4 hours, 3.5 vs. 5.8 at 6 hours, p=NR Average pain (mean [SD] of all values from 0.5 to 8 hours, 0 to 100 VAS converted to 0 to 10 scale): 3.8 (1.8) vs. 3.7 (2.4), p>0.05	Rescue medication use: 36% (8/22) vs. 45% (10/22), RR 0.80 (95% CI 0.39 to 1.64)
Cooper, 1988 ¹⁹⁰ Poor	A: Meclofenamate sodium 100 mg x 1 B: Acetaminophen 600 mg x 1	Third molar extraction; <1 day (6 hours) n=72	Pain intensity difference (mean [SD NR], 0 to 3 NRS converted to 0 to 10 scale): 3.4 vs. 1.5 at 4 hours, 1.8 vs. 0.3 at 6 hours; p=NR Sum of pain intensity differences (mean [SD NR] sum of differences on 0 to 3 NRS from 0.5 to 6 hours): 5.61 vs. 2.86, p<0.05	Medication rated "very good" or "excellent": 47% (17/36) vs. 28% (10/36), RR 1.70 (95% CI 0.91 to 3.19) Repeat medication use: 53% (19/36) vs. 78% (28/36), RR 0.68 (0.48 to 0.97)
Cooper, 1989 ¹⁹³ Fair	A: Ibuprofen 400 mg x 1 B: Acetaminophen 1000 mg x 1	Third molar extraction; <1 day (6 hours) n=120	Pain intensity difference (mean [SD NR], 0 to 3 NRS converted to 0 to 10 scale): 3.0 vs. 1.5 at 4 hours, 2.1 vs. 0.5 at 6 hours, p=NR Sum of pain intensity differences (mean [SD] sum of difference from 0.5 to 6 hours on 0 to 3 NRS): 5.7 (0.7) vs. 3.4 (0.7), p<0.05	Medication rated "excellent" or "very good": 52% (32/61) vs. 27% (16/59), RR 1.94 (95% CI 1.19 to 3.13) Repeat medication use within 4 hours: 30% (18/61) vs. 51% (30/59), RR 0.58 (95% CI 0.37 to 0.92)
Cooper, 1991 ¹⁹¹ Poor	A: Flurbiprofen 50 mg B: Flurbiprofen 100 mg C: Acetaminophen 650 mg	Third molar extraction; <1 day (6 hours) n=120	Pain intensity difference (mean [SD NR], 0 to 3 categorical converted to 0 to 10): 2.5 vs. 3.3 vs. 1.2 at 4 hours, p=NR; 1.7 vs. 3.0 vs. 0.7 at 6 hours, p=NR Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 scale from 1 to 6 hours): 4.33 vs. 6.37 vs. 2.41, p<0.05 for B vs. C	Repeat medication use: 69.0% (29/42) vs. 58.5% (24/41) vs. 94.6% (35/37) Medication rated "very good" or "excellent": 40.5% (17/42) vs. 53.6% (22/41) vs. 35.8% (14/39)

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity	Other Results
Daniels, 2009 ^{c178} Fair	A: Ibuprofen 512 mg x 1 B: Ibuprofen 400 mg + poloxamer 407 120 mg x 1 C: Acetaminophen: 1000 mg x 1	Third molar extraction; <1 day (6 hours) n=240	Pain intensity difference, (mean [SD NR], 0 to 3 categorical scale converted to 0 to 10 scale): 3.8 vs. 4.0 vs. 2.2 at 4 hours, 3.0 vs. 3.0 vs. 1.8 at 6 hours	Pain interference with daily activities (mean [SD NR], Rainier scale, range not reported): 15.1 vs. 17.1 vs. 22.4 at 6 hours, p=0.004 for A vs. C and p=0.01 for B vs. C Rescue medication use: 32.5% (26/80) vs. 22.5% (18/80) vs. 43.8% (35/80), RR 0.73, 95% CI 0.49 to 1.09 for A vs. C and RR 0.51, 95% CI 0.32 to 0.81 for B vs. C Proportion reporting ≥50% pain relief: 93.8% (75/80) vs. 88.8% (71/80) vs. 75.0% (60/80), RR 1.25 (95% CI 1.09 to 1.44) for A vs. C and RR 1.18 (95% CI 1.02 to 1.37) for B vs. C Proportion rated score “good”, “very good”, or “excellent”: 81.3% (65/80) vs. 84.8% (68/80) vs. 53.8% (43/80), RR 1.51 (95% CI 1.20 to 1.90) for A vs. C and RR 1.58 (95% CI 1.27 to 1.98) for B vs. C
Dionne, 1994 ¹⁹⁴ Poor	A: Flurbiprofen 50 mg x 1 B: Flurbiprofen 100 mg x 1 C: Acetaminophen 650 mg x 1	Third molar extraction; <1 day (6 hours) n=75	Pain intensity difference (mean [SD NR], 0 to 3 categorical converted to 0 to 10): 5.2 vs. 6.0 vs. 2.7 at 4 hours, p<0.05 for A or B vs. C; 4.7 vs. 5.5 vs. 2.7 at 6 hours, p<0.05 for A or B vs. C Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 scale from 1 to 6 hours): 8.4 vs. 9.4 vs. 5.4, p<0.05 for A or B vs. C	NR
Forbes, 1990 ¹⁹⁵ Poor	A: Ketorolac 10 mg x 1 B: Ketorolac 20 mg x 1 C: Ibuprofen 400 mg x 1 D: Acetaminophen 600 mg x 1	Third molar extraction; <1 day (6 hours) n=134	Pain intensity difference (mean [SD NR], 0 to 3 categorical converted to 0 to 10): 3.33 vs. 3.03 vs. 3.53 vs. 1.20 at 4 hours, p<0.01 for A, B, or C vs. D; 1.83 vs. 2.56 vs. 1.86 vs. 0.47 at 6 hours, p<0.01 for B vs. D, p=NS for A or C vs. D Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 scale from 1 to 6 hours): 5.84 vs. 5.69 vs. 5.31 vs. 2.47, p<0.01 for A, B, or C vs. D	≥50% pain relief: 64.5% (20/31) vs. 68.6% (24/35) vs. 59.4% (19/32) vs. 27.8% (10/36) at 4 hours, p<0.01 for A, B, or C vs. D; 32.3% (10/31) vs. 42.9% (15/35) vs. 31.2% (10/32) vs. 16.7% (6/36) at 6 hours, p<0.01 for B vs. D, p=NS for A or C vs. D Repeat medication use: 51.6% (16/31) vs. 57.1% (20/35) vs. 62.5% (20/32) vs. 83.3% (30/36)

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity	Other Results
Hersh, 2000 ¹⁹⁷ Fair	A: Ibuprofen liquigel 200 mg x 1 B: Ibuprofen liquigel 400 mg x 1 C: Acetaminophen 1000 mg x 1	Third molar extraction; <1 day (6 hours) n=183	Pain intensity difference (mean [SD NR, 0 to 3 NRS converted to 0 to 10 scale): 3.7 vs. 4.7 vs. 2.3 at 4 hours, p<0.01 for A vs. C and p<0.001 for B vs. C; 2.7 vs. 3.3 vs. 1.3 at 6 hours, p<0.01 for A vs. C and p<0.001 for B vs. C Sum of pain intensity differences (mean [SD], sum of differences on 0 to 3 NRS from 0.25 to 6 hours): 6.93 (4.61) vs. 8.07 (3.84) vs. 5.05 (4.60), p<0.001 for A or B vs. C	Medication rated "very good" or "excellent": 63% (38/61) vs. 79% (47/59) vs. 52% (33/63); RR 0.78 (95% CI 0.62 to 0.99) for A vs. B, RR 1.19 (95% CI 0.88 to 1.61) for A vs. C, RR 1.52 (95% CI 1.16 to 1.99) Rescue medication use: 31% (19/61) vs. 23% (14/59) vs. 51% (32/63); RR 1.31 (95% CI 0.73 to 2.37) for A vs. B, RR 0.61 (95% CI 0.39 to 0.96) for A vs. C, RR 0.47 (95% CI 0.28 to 0.78) for B vs. C
Kiersch, 1994 ¹⁸⁰ Fair	A: Naproxen sodium 440 mg x 1 B: Acetaminophen 1000 mg x 1	Third molar extraction; <1 day (12 hours) n=181	Pain intensity difference (mean [SD NR], 0 to 100 VAS converted to 0 to 10 scale): 2.4 vs. 0.6 at 4 hours, 2.2 vs. -0.1 at 6 hours, 1.3 vs. -0.7 at 12 hours Sum of pain intensity difference (mean [SD NR], sum of differences on 0 to 3 NRS from 4 to 12 hours): 5.7 vs. -0.06, p<0.001 Sum of pain intensity difference (mean [SD], sum of differences on 0 to 100 VAS from 4 to 12 hours): 224.7 vs. 11.7, p<0.001 at 12 hours	NR
Mehlisch, 1990 ²⁰⁴ Fair	A: Ibuprofen 400 mg x 1 B: Acetaminophen 1000 mg x 1	Various oral surgery procedures; <1 day (6 hours) n=612	Pain intensity difference (mean [SD], 1 to 4 NRS converted to 0 to 10 scale): 3.26 (2.90) vs. 1.93 (2.90) at 4 hours, MD 1.33 (95% CI 0.87 to 1.79); 2.40 (3.50) vs. 0.13 (3.50) at 6 hours, MD 2.27 (95% CI 1.71 to 2.83) Sum of pain intensity differences (mean [SD], sum of differences on 1 to 4 scale from 0.5 to 6 hours): 5.84 (4.37) vs. 4.14 (2.97), MD -1.70 (95% CI -2.29 to -1.11)	Pain improved >50%: 45% (138/306) vs. 30% (92/306), RR 1.50 (95% CI 1.21 to 1.85) Repeat medication use: 41% (125/306) vs. 57% (174/306), RR 0.72 (95% CI 0.61 to 0.85)
Mehlisch, 1995b ²¹⁹ Fair	A: Ibuprofen lysine 400 mg x 1 B: Acetaminophen 1000 mg x 1	Third molar extraction; <1 day (6 hours) n=199	Pain intensity differences (mean [SD NR], 0 to 3 categorical scale converted to 0 to 10 scale): 4.2 vs. 2.5 at 4 hours, p≤0.05; 3.3 vs. 2.0, at 6 hours, p≤0.05 Sum of pain intensity differences (mean [SD] sum of 0 to 3 pain intensity from 0.25 to 6 hours) : 6.46 (3.72) vs. 3.95 (4.47), p<0.05	Medication rated 'very good' or 'excellent': 66% (65/98) vs. 31% (31/101), RR 2.16 (95% CI 1.56 to 2.99) Repeat medication: 26% (25/98) vs. 60% (61/101), RR 0.42 (95% CI 0.29 to 0.61)

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity	Other Results
Mehlisch, 2010 ²⁰² Good	A: Ibuprofen 400 mg x 1 B: Acetaminophen 1000 mg x 1	Third molar extraction; <1 day (8 hours) n=103	Pain intensity difference (mean [SD NR], 0 to 3 NRS converted to 0 to 10 scale): 2.8 vs. 2.2 at 4 hours, p=NS; 1.5 vs. 1.6 at 8 hours, p=NS Sum of pain relief and intensity differences (mean [SD] sum of 0 to 3 pain intensity and pain relief (scale NR) differences from 0.25 to 8 hours): 18.0 (14.1) vs. 15.5 (15.0), p=NS	NR
Olson, 2001 ²⁰⁹ Fair	A: Ibuprofen liquigel 400 mg x 1 B: Ketoprofen 25 mg x 1 C: Acetaminophen 1000 mg x 1	Third molar extraction; <1 day (6 hours) n=200	Sum of pain intensity differences (mean [SD] sum of 0 to 3 NRS from 0.25 to 6 hours): 11.77 (4.2) vs. 9.64 (4.4) vs. 8.36 (4.7); MD 3.41 (95% CI 1.88 to 4.94) for A vs. C and MD 1.28 (95% CI -0.28 to 2.84) for B vs. C Pain relief (mean [SD NR] on 0 to 4 scale, 4=complete relief): 3.0 vs. 2.5 vs. 2.1 at 4 hours, 2.6 vs. 2.0 vs. 1.9 at 6 hours, p=NR	Meaningful pain relief (pain relief or pain intensity score ≥ 1): 95.8% (64/67) vs. 98.5% (66/67) vs. 87.9% (58/66); RR 1.09 (95% CI 0.98 to 1.21) for A vs. C; RR 1.12 (95% CI 1.02 to 1.23) for B vs. C Complete pain relief (pain relief score=4): 73.1% (49/67) vs. 58.2% (39/67) vs. 48.5% (32/66); RR 1.51 (95% CI 1.13 to 2.01) for A vs. C and RR 1.20 (95% CI 0.87 to 1.65) for B vs. C Rescue medication use: 21% (14/67) vs. 30% (20/67) vs. 38% (25/66); RR 0.55 (95% CI 0.32 to 0.96) for A vs. C and RR 0.79 (95% CI 0.49 to 1.27) for B vs. C
Searle, 2020 ¹⁸² Fair	A: Ibuprofen 250 mg x1 B: Acetaminophen 650 mg x 1	Third molar extraction; <1 day (8 hours) n=333	Pain intensity difference (mean [SD], 0 to 10 NRS): 4.2 vs. 2.7 at 4 hours, p<0.05; 3.7 vs. 2.1 at 6 hours, 1.7 vs. 1.3 at 12 hours, p<0.05 Sum of pain intensity differences (least square mean [SE] using analysis of covariance model, sum of differences on 0 to 10 scale from 0.25 to 8 hours): 28.7 (1.5) vs. 19.6 (1.6), p<0.001	Meaningful pain relief as defined by patient): 79.4% (139/175) vs. 71.5% (118/165); RR 1.11 (95% CI 0.98 to 1.26) Treatment failure (rescue medication use or dropout due to adverse event or lack of efficacy) at 8 hours: 60.0% (105/175) vs. 63.6% (105/165), RR 0.94 (95% CI 0.80 to 1.11)

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity	Other Results
Sunshine, 1986 ²¹³ Fair	A: Flurbiprofen 50 mg x 1 B: Flurbiprofen 100 mg x 1 C: Acetaminophen 1000 mg x 1	Third molar extraction; <1 day (6 hours) n=90	Pain intensity difference (mean [SD NR], 0 to 3 categorical scale converted to 0 to 10): 3.76 vs. 3.90 vs. 2.23 at 4 hours, p=NS for A or B vs. C; 3.33 vs. 3.56 vs. 0.67 at 6 hours, p≤0.05 for A or B vs. C Sum of pain intensity differences (mean [SD NR], sum of differences on 0 to 3 scale from 0.5 to 6 hours): 7.01 vs. 6.85 vs. 4.23, p=NS for A or B vs. C	Rescue medication use: 19.4% (6/31) vs. 13.8% (4/29) vs. 46.7% (14/30)
Voelker, 2016 ²¹⁶ Fair	A: Aspirin 1000 mg x 1 B: Acetaminophen 1000 mg x 1	Third molar extraction; <1 day (6 hours) n=408	Sum of pain intensity difference (mean [SD] sum of 0 to 10 NRS from 5 minutes to 6 hours): 5.9 (5.1) vs. 7.9 (4.9), p<0.001	NR

Abbreviations: CI = confidence interval; MD = mean difference; NR = not reported; NRS = numeric rating scale; NS = not significant; RR = relative risk; SD = standard deviation; VAS = visual analog scale

Note: Pain intensity difference = pain at followup minus pain at baseline.

NSAIDs were associated with decreased risk of any adverse event versus acetaminophen (12 trials, N=2,512, pooled RR 0.85, 95% CI 0.72 to 1.00, $I^2=0\%$; Figure D-16).^{178,180,191,193-195,197,202,204,213,216,219} NSAIDs were also associated with decreased risk of nausea versus acetaminophen (13 trials, N=2,230, pooled RR 0.75, 95% CI 0.57 to 0.98, $I^2=0\%$; ARD -2%, 95% CI -4% to 0%; Figure D-17).^{176,178,180,182,185,191,193-195,197,202,209,216} There was no statistically significant difference in risk of drowsiness (7 trials, N=1,459, pooled RR 1.17, 95% CI 0.60 to 2.30, $I^2=28\%$; Figure D-18),^{180,186,191,193,195,204,209} dizziness (8 trials, N=1,750, pooled RR 0.59, 95% CI 0.33 to 1.05, $I^2=6\%$; Figure D-19),^{178,180,182,193,195,197,202,216} or headache (12 trials, N=2,762, pooled RR 0.96, 95% CI 0.65 to 1.42, $I^2=0\%$; Figure D-20).^{178,180,182,191,193-195,197,202,204,209,216} However, pooled estimates favored NSAIDs for drowsiness and dizziness, the number of adverse events in most trials was small, estimates were imprecise, and all of the trials were single dose studies. The largest trial (n=617) found no difference between ibuprofen versus acetaminophen in risk of any adverse event (10% vs. 10%, RR 1.04, 95% CI 0.65 to 1.66), gastrointestinal adverse events (4% vs. 5%, RR 0.82, 95% CI 0.40 to 1.68), sleepiness (3% vs. 2%, RR 1.68, 95% CI 0.62 to 4.57), or headache (1% vs. 1%, RR 2.02, 95% CI 0.37 to 10.95).²⁰⁴ One trial found no difference between an NSAID versus acetaminophen in risk of severe adverse events (28% vs. 35%, RR 0.78, 95% CI 0.43 to 1.41).²⁰¹ One trial¹⁸⁰ reported NSAIDs and acetaminophen associated with low rates of discontinuation from participation due to adverse events (1.1% vs. 2.2%), and one trial¹⁸² reported no discontinuations due to adverse events. Serious adverse events were not reported.

Pregabalin Versus NSAID

One fair-quality trial (n=148) compared single dose pregabalin 50 mg, pregabalin 300 mg, and ibuprofen 400 mg in patients who underwent third molar extraction¹⁹⁸ (Table 33). Pregabalin 50 mg was not associated with improved pain intensity at any time point through 12 hours. Pregabalin 300 mg and ibuprofen were associated with slightly smaller PID at 4 hours and slightly larger PID at 12 hours (difference ~0.1 point), but the scale was not reported. Pregabalin 300 mg was associated with increased risk of any adverse event versus ibuprofen (68% vs. 12%, RR 5.55, 95% CI 2.56 to 12.03); specific adverse events were not reported.

Non-Aspirin Versus Aspirin NSAID

Two fair quality trials (n=156 and 204) compared a single dose of a non-aspirin NSAID (diclofenac) versus aspirin following third molar extraction (Appendixes E and F, Tables E-8 and F-1; Table 33).^{203,208} In both trials, a single dose of diclofenac (25 to 100 mg) was associated with larger reductions in pain intensity than aspirin (650 mg) at 4 hours (differences 1.8 to 3.5 on a 0 to 10 scale) and larger SPIDs. However, there was no difference in repeat medication use between diclofenac 25, 50, or 100 mg versus aspirin in one of the trials (61% vs. 47% vs. 38% vs. 51%, respectively; RR 0.73, 95% CI 0.47 to 1.14 for diclofenac 100 mg versus aspirin). Adverse events were similar between diclofenac and aspirin.

Oral Versus Topical NSAID

One small (n=30), poor quality trial of patients who underwent third molar extraction found no difference between oral diclofenac versus diclofenac mouthwash in pain intensity (mean difference -0.50, 95% CI -1.70 to 0.70 on a 0 to 10 scale at day 1; mean difference -0.37, 95% CI -1.29 to 0.55 at day 2) (Table 33).²⁰⁶ Other outcomes were not reported.

Table 33. Miscellaneous nonopioid pharmacologic interventions versus NSAIDs for acute dental pain

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity	Other Results
Hill, 2001 ¹⁹⁸ Fair	A: Pregabalin 50 mg x 1 B: Pregabalin 300 mg x 1 C: Ibuprofen 400 mg x 1	Third molar extraction; <1 day (4 hours and 12 hours) n=148	Pain intensity difference (mean [SD NR], scale NR): 0 vs. 0.6 vs. 0.7 at 4 hours, p>0.05; -0.1 vs. 0.1 vs. 0 at 12 hours, p>0.05	Patient global assessment (mean [SD], 0 to 4 scale): 2.25 vs. 3.50 vs. 3.25, p=NR
Mehlisch, 1995a ²⁰³ Fair	A: Diclofenac 50 mg x 1 B: Diclofenac 100 mg x 1 C: Aspirin 650 mg x 1	Third molar extraction; <1 day (30 minutes and hourly for 8 hours) n=156	Pain intensity difference (mean [SD NR], 0 to 3 categorical scale converted to 0 to 10 scale): 3.7 vs. 4.7 vs. 1.7 at 4 hours, p<0.05 for B vs. C; 1.0 vs. 2.3 vs. -0.7 at 8 hours, p<0.05 for B vs. C Sum of pain intensity differences (mean [SD], 0 to 3 scale differences from 0.5 to 8 hours): 6.3 (2.2) vs. 8.1 (2.2) vs. 4.0 (2.9); MD 2.3 (95% CI 1.3 to 3.3) for A vs. C and MD 4.10 (95% CI 3.11 to 5.19) for B vs. C	Overall rating "very good" or "good": 75% (40/53) vs. 85% (44/52) vs. 53% (27/51); RR 1.4 (95% CI 1.1 to 1.9) for A vs. C and RR 1.6 (95% CI 1.2 to 2.1) for B vs. C
Nelson, 1994 ²⁰⁸ Fair	A: Diclofenac 25 mg x 1 B: Diclofenac 50 mg x 1 C: Diclofenac 100 mg x 1 D: Aspirin 650 mg x 1	Third molar extraction; <1 day (30 minutes and hourly for 8 hours) n=204	Pain intensity difference (mean [SD NR], 0 to 3 categorical rating scale converted to 0 to 10 scale): 2.3 vs. 2.7 vs. 4.0 vs. 0.5 at 4 hours, p=NS; 1.0 vs. 0.7 vs. 2.7 vs. 0.7 at 8 hours, p<0.05 for C vs. D, p=NS for A or B vs. D Sum of pain intensity differences (mean [SD], sum of differences on 0 to 3 scale at 0.5 to 8 hours): 4.3 vs. 4.9 vs. 8.1 vs. 4.0, p<0.05 for C vs. D, p=NS for A or B vs. C	Repeat medication use: 61% (31/51) vs. 47% (24/51) vs. 38% (19/51) vs. 51% (26/51); RR 0.73 (95% CI 0.47 to 1.14) for C vs. D.
Mishra, 2017 ²⁰⁶ Poor	A: Diclofenac tablet 50 mg twice daily for 3 days B: Diclofenac mouth wash, rinse 15 mL 0.074% solution for 30 seconds twice daily for 3 days	Mouth flap surgery for periodontitis; 1 and 2 days n=30	Pain intensity (mean [SD], 0 to 10 VAS): 1.50 (1.51) vs. 2.00 (1.69) at day 1, MD -0.50 (95% CI -1.70 to 0.70); 1.13 (1.25) vs. 1.50 (1.20) at day 2, MD -0.37 (95% CI -1.29 to 0.55)	NR

Abbreviations: CI = confidence interval; MD = mean difference; NR = not reported; NS = not significant; RR = relative risk; SD = standard deviation; VAS = visual analog scale

KQs 6j and 6l ask how the comparative effectiveness and harms 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.

Evidence was too limited to evaluate how comparative effectiveness and harms of nonopioid therapy for acute dental pain varied in subgroups, due to few trials, small sample sizes, methodological limitations, and exclusion of relevant subgroups or lack of information about them. No study conducted within-study or across-study evaluations of subgroup effects. Details regarding the nonopioid medications prescribed, dose, and duration of treatment are described above.

Nonpharmacologic Therapy

KQs 6m and 6n address the comparative effectiveness of nonopioid pharmacologic therapy versus: (1) inactive controls or (2) other nonpharmacologic therapies.

Six trials evaluated nonpharmacologic therapy for acute dental pain (Appendix E, Table E-8).^{183,196,199,200,214,217} One trial evaluated acupuncture²⁰⁰ and five trials cold therapy.^{183,196,199,214,217} Two trials were rated fair quality,^{196,214} and four trials poor quality (Appendix F, Table F-1).^{183,199,200,217}

Acupuncture Versus Sham Acupuncture

One small (n=19) trial found two sessions of acupuncture following third molar extraction associated with decreased pain intensity versus sham acupuncture at 5.²⁰⁰ However, the trial was rated poor quality, and the statistical significance of the difference was not reported. There was no difference in rescue medication use (mean 17.6 vs. 21.4 tablet, $p>0.05$).

Cold Therapy Versus No Cold Therapy

Five trials evaluated cold therapy versus no cold therapy following third molar extraction (Table 34). The sample sizes ranged from 18 to 128 (N=331).^{183,196,199,214,217} Cold therapy consisted of cold compresses applied to the cheek overlying the surgical site. All trials compared a cold compress to no compress; one trial¹⁹⁶ also included a non-cold compress comparison. The duration of cold therapy was 45 minutes in one trial¹⁹⁶ and 24 to 48 hours in the others. Due to the nature of the intervention, patients could not be blinded. Two trials were rated fair quality^{196,214} and three trials poor quality.^{183,199,217} Methodological limitations included failure to report randomization and allocation concealment methods and no intention to treat analysis.

At one to three days following third molar extraction, differences in pain intensity ranged from -0.9 points on a 0 to 10 scale in favor of a cold compress to 0.3 points in favor of no compress, based on four trials.^{183,196,214,217} One of the trials found little difference in pain intensity between a cold compress versus a non-cold compress (1.9 vs. 2.2, $p=0.64$).¹⁹⁶ At 6 to 7 days, two trials^{183,196} found inconsistent effects of a cold compress versus no compress or a non-cold compress; in one other trial,²¹⁷ pain had resolved in all patients. One other trial reported that a cold compress was associated with decreased pain throughout the 7 day followup period, but did not provide data.¹⁹⁹

One trial found a cold compress associated with better quality of life versus no compress through postoperative day 7, but differences were small (1.2 to 2.4 points on the 14 to 56 Oral Health Impact Profile-14 score).¹⁹⁹ One trial¹⁹⁶ reported no adverse events, and one trial reported

nausea but the number of events was small and findings imprecise.²¹⁴ The other trials did not report adverse events.

Table 34. Cold therapy versus no cold therapy for dental pain

Author, Year Quality	Interventions	Procedure; Followup Duration Sample Size	Pain Intensity	Other Results
Altiparmak, 2018 ¹⁸³ Poor	A: Cold compress for 24 hours except during sleep B: No cold compress	Third molar extraction; 3 and 7 days n=18	Pain intensity (mean [SD], 0 to 10 VAS) 1.9 (3.3) vs. 2.2 (3.8) at day 3, p=0.64; 1.2 (0.2) vs. 1.4 (0.3) at day 7, p=0.06	NR
Forouzanfar, 2008 ¹⁹⁶ Fair	A: Cold compress for 45 minutes immediately following extraction B: Compress without ice for 45 minutes immediately following extraction C: No compress	Third molar extraction; Daily for 6 days n=95	Pain intensity (mean [SD], 0 to 100 VAS converted to 0 to 10 scale): 2.2 (1.6) vs. 2.5 (1.9) vs. 3.1 (2.2) at day 1, p=NS; 1.3 (1.8) vs. 1.1 (1.2) vs. 2.4 (2.5) at day 6, p<0.05 for A vs. C, p=NS for A vs. B	Patient reported treatment success (not defined): 64.7% (22/34) vs. 71.0% (22/31) vs. 43.3% (13/30); p>0.05 for A vs. B and A vs. C Ibuprofen use mean, mg/24 hour (SD): 1038.2 (702.4) vs. 1148.4 (732.1) vs. 1140.0 (882.2) at day 1, p=NS; 432.4 (787.3) vs. 464.5 (629.1) vs. 780.0 (802.3) at day 6, p=NS
Ibikunle, 2016 ¹⁹⁹ Poor	A: Cold compress intermittent application for 30 minutes every 90 minutes for 24 hours except during sleep B: No cold compress	Third molar extraction; 1, 3, and 7 days N=128	Pain significantly lower in A vs. B throughout postoperative evaluation period, p<0.05 (data not provided)	Oral Health Impact Profile-14 score (mean [SD NR], 14 to 56 scale): 20.4 vs. 21.6 at day 1, p=0.01; 37.5 vs. 39.9 at day 4, p=0.002; 26.9 vs. 28.9 at day 7, p=0.003 Quality of life affected (not defined): 93.9% vs. 96.8% at day 1, p=0.40; 18.8% vs. 59.4% at day 7, p=0.001
van der Westhuijzen, 2005 ²¹⁴ Fair	A: Cold compress for first 24 hours including during sleep B: No cold compress	Third molar extraction; 4 hours, evening of surgery, morning after surgery n=60	Pain intensity (mean [SD NR], 0 to 10 VAS): 3.1 vs. 3.3 at 4 hours, p>0.05; 3.1 vs. 2.8 at morning after surgery, p>0.05	Symptom control excellent or good: 97% (28/29) vs. 90% (27/30), p>0.05
Zandi, 2016 ²¹⁷ Poor	A: Cold compress, alternating on and off every 20 minutes for 24 hours except during sleep B: No cold compress	Third molar extraction; 2 and 7 days n=30	Pain (mean [SD], 0 to 100 VAS converted to 0 to 10 scale): 3.83 (2.33) vs. 4.43 (2.09) at day 2, p=0.29; 0 vs. 0 at day 7	Satisfaction (mean [SD], 0 to 10): 7.27 (1.48) vs. 7.00 (1.66), p=0.46

Abbreviations: NR = not reported; NS = not significant; SD = standard deviation; VAS = visual analog scale

KQs 6o and 6p ask how the comparative effectiveness and harms of nonpharmacologic therapy 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.

No evidence was found for KQ 6o or 6p.

KQ 7. Kidney Stone Pain

Key Points

- Opioid vs. NSAID, single dose
 - Morphine was associated with increased likelihood of persistent pain versus an NSAID (38% vs. 24%, RR 1.57, 95% CI 1.31 to 1.89), reduced likelihood of $\geq 50\%$ pain relief (93% vs. 97%, RR 0.95, 95% CI 0.93 to 0.98), and increased likelihood of rescue medication use (23% vs. 12%, RR 1.99, 95% CI 1.51 to 2.63) at 60 to 90 minutes, based on one trial (SOE: moderate).
 - Morphine associated with increased likelihood of any adverse event versus an NSAID, though the frequency of adverse events was low (3% vs. 1%, RR 2.70, 95% CI 1.15 to 6.38) (SOE: moderate).
 - Meperidine was associated with moderate to large increase in pain intensity at 1 hour compared with an NSAID (4 trials), inconsistent effects on likelihood of pain relief (3 trials), and increased likelihood of rescue medication use (6 trials, RR 1.48, 95% CI 1.02 to 2.14) (SOE: moderate for pain intensity and likelihood of rescue medication use, insufficient for likelihood of pain relief).
 - Meperidine was associated with increased likelihood of any adverse event (5 trials, RR 1.71, 95% CI 0.99 to 2.96), somnolence (4 trials, RR 1.98, 95% CI 0.82 to 4.79), and nausea (5 trials, N=573, RR 1.84, 95% CI 1.02 to 3.31) (SOE: low).
- Opioid vs. acetaminophen, single dose
 - Morphine was associated with increased likelihood of persistent pain (pain > 2 on a 0 to 10 scale) at 60 minutes (38% vs. 30%, RR 1.28, 95% CI 1.08 to 1.51), similar likelihood of $\geq 50\%$ pain relief at 90 minutes (93% vs. 92%, RR 1.01, 95% CI 0.97 to 1.04), and similar likelihood of rescue medication use (23% vs. 20%, RR 1.13, 95% CI 0.90 to 1.42), based on one trial (SOE: moderate).
 - Morphine was associated with increased likelihood of any adverse event versus acetaminophen, though the frequency of adverse events was low (3% vs. 1%, RR 2.71, 95% CI 1.15 to 6.39) (SOE: moderate).
- Opioid agonist vs. partial agonist
 - Insufficient evidence from one small trial (SOE: insufficient).
- NSAID vs. acetaminophen, single dose
 - Inconsistent effects of NSAIDs versus acetaminophen on pain intensity (3 trials) and likelihood of pain relief (2 trials); NSAIDs associated with decreased likelihood of rescue medication use (2 trials) (SOE: low for rescue medication use; insufficient for pain intensity and likelihood of pain relief).
 - The frequency of adverse events was low with NSAIDs and acetaminophen, based on 3 trials (SOE: moderate).
- Acupuncture vs. NSAID or acetaminophen
 - Acupuncture (single session) associated with moderately increased pain intensity versus a single dose of an NSAID or acetaminophen at 2 hours, based on 1 trial (SOE: low).

- There were few adverse events in one trial (SOE: low).

Summary of Findings

Twelve trials (N=2,762) evaluated interventions for acute renal colic (Appendix E, Table E-10).²²³⁻²³⁴ Nine trials evaluated opioid therapy (KQ 7a and 7c),^{223-226,229,230,232-234} Three trials evaluated nonopioid pharmacologic therapy (KQ 7i and 7j),^{227,228,231} and one trial evaluated nonpharmacologic therapy (KQ 7m and 7n).²²⁸ The mean age of patients ranged from 32 to 44 years, and the proportion female ranged from 15 to 59 percent. Three trials of opioid therapy excluded patients with alcohol or drug abuse history within the last 5 years.^{229,232,234} Otherwise the trials did not describe psychiatric or medical comorbidities. Pain duration was <7 days in one trial²³⁰ and not described in the others. One trial was rated good quality,²³³ nine trials fair quality,^{224-229,231,232,234} and two trials poor quality (Appendix F, Table F-1).^{223,230} Methodological limitations in the fair and poor quality trials included open label design, failure to report adequate randomization and allocation concealment methods, high or unclear attrition, and no intention to treat analysis.

Detailed Synthesis

Opioid Therapy

KQs 7a and 7c address the comparative effectiveness and harms of opioid therapy versus: (1) nonopioid pharmacologic therapy (e.g., acetaminophen, NSAIDs, antidepressants, anticonvulsants) or (2) nonpharmacologic therapy (e.g., exercise, cognitive behavioral therapy, acupuncture).

Nine trials (N=2,491) evaluated opioids for acute renal colic (Appendix E, Table E-10).^{223-226,229,230,232-234} Eight trials compared an opioid versus an NSAID,^{223,224,226,229,230,232-234} one trial compared an opioid versus acetaminophen,²³³ and one trial compared an opioid agonist versus a partial agonist.²²⁵ All trials evaluated single dose of parenteral therapy and were not designed to assess subsequent pain management. In five trials the duration of followup was 1 to 2 hours, and in four trials the duration of followup was up to 6 to 24 hours. Outcomes assessed at less than one hour were not abstracted. One trial was rated good quality,²³³ six trials fair quality,^{224-226,229,232,234} and two trials poor quality (Appendix F, Table F-1).^{223,230} Methodological limitations in the fair and poor quality trial included failure to report adequate randomization or allocation concealment methods, unblinded design, high or unclear attrition, and no or unclear use of intention treat analysis.

Opioid Versus NSAID

Eight trials compared an opioid versus an NSAID for acute renal colic (Table 35).^{223,224,226,229,230,232-234} Sample sizes ranged from 50 to 1,097 (N=1,918). The trials were conducted in the United States,^{224,229} Europe,^{226,234} and other countries.^{223,230,232,233} All of the trials evaluated a single parenteral dose of medication. In one trial²³³ the opioid was morphine, and in the other trials the opioid was meperidine (pethidine), a drug which has become less widely used in the United States due to risk of adverse events including seizures, anticholinergic effects, and drug-drug interactions, including serotonin syndrome.²³⁵ The NSAID was indomethacin in one trial (100 mg),²²³ ketorolac in four trials (10 to 90 mg),^{224,229,232,234} and diclofenac in three trials (75 mg).^{226,230,233} One trial was rated good quality,²³³ five trials fair quality,^{224,226,229,232,234} and two trials poor quality (Appendix F, Table F-1).^{223,230}

The trial of morphine versus an NSAID was the largest (n=1,097 for this comparison) and only good quality trial. It compared morphine 15 mg intravenous (IV) versus diclofenac 75 mg intramuscular injection (IM) (Table 35).²³³ Morphine was associated with increased likelihood of persistent pain (pain >2 on a 0 to 10 scale) at 60 minutes (38% vs. 24%, RR 1.57, 95% CI 1.31 to 1.89), slightly decreased likelihood of ≥50% pain relief at 90 minutes (93% vs. 97%, RR 0.95, 95% CI 0.93 to 0.98), and increased likelihood of rescue medication use (23% vs. 12%, RR 1.99, 95% CI 1.51 to 2.63). At 90 minutes, median pain intensity was 0 in both groups. Morphine was associated with increased likelihood of any adverse event, though the frequency of adverse events was low (3% vs. 1%, RR 2.70, 95% CI 1.15 to 6.38). No serious adverse events were reported. The likelihood of serum creatinine elevations was low in both groups; in those with creatinine elevations, normalization occurred within one week.

Seven trials evaluated meperidine versus an NSAID (Table 35). Sample sizes ranged from 50 to 234 (N=821). Meperidine was associated with increased pain intensity at 1 hour compared with an NSAID in four trials (difference 0.3 to 3.2 points on a 0 to 10 scale),^{226,229,230,232} and one other trial²³⁴ found meperidine associated with a smaller sum of pain intensity differences at 1 hour. At 1 to 1.5 hours, one trial found meperidine associated with decreased likelihood of ≥50 percent pain relief,²²⁷ but two other trials found high rates of pain relief for both meperidine and NSAIDs.^{223,232} One trial found meperidine associated with a smaller SPID versus NSAIDs at 6 hours.²²⁴ Meperidine was associated with increased likelihood of rescue medication use (5 trials, N=671, RR 1.48, 95% CI 1.02 to 2.14, I²=71%; Figure D-21).^{223,224,226,229,232,234} Meperidine was associated with increased likelihood of any adverse event (5 trials, N=471, RR 1.71, 95% CI 0.99 to 2.96, I²=62%; Figure D-22), somnolence (4 trials, N=555, RR 1.98, 95% 0.82 to 4.79, I²=65%; Figure D-23), and nausea (5 trials, N=573, RR 1.84, 95% CI 1.02 to 3.31, I²=42%; Figure D-24), though only the estimate for nausea was statistically significant.

Table 35. Opioid versus NSAIDs for acute renal colic

Author, Year Quality	Interventions	Followup Duration Sample Size	Pain Intensity	Other Results
al-Sahlawi, 1996 ²²³ Poor	A: Meperidine 100 mg IV x 1 B: Indomethacin 100 mg IV x 1	60 minutes n=100	NR	Percent with complete pain relief at 60 minutes 100% (50/50) vs. 100% (50/50) Rescue medication use at 30 minutes: 0% (0/50) vs. 4% (2/50), RR 0.20 (95% CI 0.01 to 4.06)
Cordell, 1996 ²²⁴ Fair	A: Meperidine 50 mg IV x 1 B: Meperidine 50 mg + Ketorolac 60 mg IV x 1 C: Ketorolac 60 mg IV x 1	6 hours N=106	Sum of pain intensity difference (mean [SD], sum of differences on 0 to 100 VAS from 15 minutes to 6 hours): 267.8 (26.0) vs. 319.3 (26.2) vs. 409.1 (24.7), p<0.001 for A vs. C, p=0.124 for A vs. B, p=0.009 for B vs. C	Rescue medication use: 89% (31/35) vs. 66% (23/35) vs. 64% (23/36); RR 1.35 (95% CI 1.03 to 1.76) for A vs. B, RR 1.39 (95% CI 1.06 to 1.82) for A vs. C, RR 1.03 (95% CI 0.73 to 1.45) for B vs. C Functional impairment at 6 hours (mean [SD NR], 0 to 4 scale, 4=severe impairment) 1.2 vs. 1.5 vs. 1.8, p=0.003 for A vs. C, other comparisons NS
García-Alonso, 1991 ²²⁶ Fair	A: Meperidine 100 mg IM x 1 B: Diclofenac 75 mg IM x 1	60 minutes n=234	Pain intensity (mean [SD NR], 0 to 10 VAS, in patients not requiring rescue treatment: 2.0 vs. 1.0 at 1 hour (p=NR)	Rescue medication use at 30 minutes: 20% (23/118) vs. 16% (19/116), RR 1.19 (95% CI 0.69 to 2.06)

Author, Year Quality	Interventions	Followup Duration Sample Size	Pain Intensity	Other Results
Larkin, 1999 ²²⁹ Fair	A: Meperidine 100 to 150 mg IM x 1 B: Ketorolac 60 mg IM x 1	90 minutes n=70	Pain intensity (mean [SD NR], 0 to 10 VAS): 4.0 vs. 1.8 at 90 minutes, p<0.05	Rescue medication use: 43% (16/37) vs. 33% (11/33), RR 1.30 (95% CI 0.71 to 2.38)
Marthak, 1991 ²³⁰ Poor	A: Meperidine 75 mg IM x 1 B: Diclofenac 75 mg IM x 1	60 minutes n=50	Pain intensity difference (mean improvement from baseline [SD NR], 0 to 100 VAS converted to 0 to 10 scale): 7.9 vs. 8.2 at 60 minutes, p=NS	Physician rated treatment as good to excellent: 88% (22/25) vs. 100% (25/25), RR 0.88 (95% CI 0.76 to 1.02)
Oosterlinck, 1990 ²³²	A. Meperidine 100 mg IM, single treatment B: Ketorolac 10 mg IM, single treatment C: Ketorolac 90 mg IM, single treatment	1 and 10 hours n=121	Pain intensity difference (mean improvement from baseline [SD], 0 to 100 VAS converted to 0 to 10 scale): 5.7 (2.6) vs. 5.4 (2.6) vs. 6.5 (1.8) at 1 hour, p=0.4 for A vs. B; p=0.12 for A vs. C; p=0.02 for B vs. C Pain none or mild at 60 minutes: 84% (31/37) vs. 82% (32/39) vs. 86% (30/35); RR 1.02 (95% CI 0.83 to 1.25) for A vs. B, RR 0.98 (95% CI 0.80 to 1.19) for A vs. C, RR 0.96 (95% CI 0.78 to 1.17) for B vs. C	Rescue medication use within 10 hours: 47% (18/38) vs. 39% (17/44) vs. 17% (6/36); RR 1.23 (95% CI 0.74 to 2.02) for A vs. B, RR 2.84 (95% CI 1.27 to 6.35) for A vs. C, and RR 2.31 (95% CI 1.02 to 5.26) for B vs. C
Pathan, 2016 ²³³ Good	A: Morphine 15 mg IV x 1 B: Diclofenac 75 mg IM x 1	60 and 90 minutes n=1,097	Pain intensity (median [IQR], 0 to 10 scale): 0 (0 to 2) vs. 0 (0 to 1) at 90 minutes Pain >2 on 0 to 10 scale at 60 minutes: 38% (207/549) vs. 24% (131/547), RR 1.57 (95% CI 1.31 to 1.89)	Rescue medication use: 23% (126/549) vs. 12% (63/547), RR 1.99 (95% CI 1.51 to 2.63) Pain intensity decreased ≥50% at 90 minutes: 93% (511/549) vs. 97.4% (533/547), RR 0.96 (95% CI 0.93 to 0.98)
Sandhu, 1994 ²³⁴	A: Meperidine 100 mg IM x 1 B: Ketorolac 30 mg IM x 1	60 minutes n=140	Sum of pain intensity differences (mean [SD NR], 0 to 10 VAS from 15 to 60 minutes): 32.7 vs. 39.0, p=NS	Rescue medication use: 74% (53/72) vs. 65% (44/68), RR 1.14 (95% CI 0.91 to 1.42)

Abbreviations: CI = confidence interval; IM = intramuscular; IQR = interquartile range; IV = intravenous; NR = not reported; RR = relative risk; SD = standard deviation; VAS = visual analog scale

Opioid Versus Acetaminophen

One good quality trial compared a single dose of morphine 15 mg IV versus acetaminophen 1000 mg IV was the largest (n=1,096 for this comparison) (Table 36).²³³ Morphine was associated with increased likelihood of persistent pain (pain >2 on a 0 to 10 scale) at 60 minutes (38% vs. 30%, RR 1.28, 95% CI 1.08 to 1.51), similar likelihood of ≥50% pain relief at 90 minutes (93% vs. 92%, RR 1.01, 95% CI 0.97 to 1.04), and similar likelihood of rescue medication use (23% vs. 20%, RR 1.13, 95% CI 0.90 to 1.42). At 90 minutes, median pain intensity was 0 in both groups. Morphine was associated with increased likelihood of any adverse event, though the frequency of adverse events was low (3% vs. 1%, RR 2.71, 95% CI 1.15 to 6.39). No serious adverse events were reported. The likelihood of serum creatinine

elevations was low in both groups; in those with creatinine elevations, normalization occurred within 1 week.

Opioid Agonist Versus Partial Agonist

One small (n=26), fair quality trial compared a single dose of meperidine 100 mg (an opioid agonist) versus the partial agonist buprenorphine 0.3 mg.²²⁵ Meperidine was associated with increased pain intensity at 12 hours (mean 4.2 vs. 1.2 on a 0 to 10 scale, mean difference 3.0, 95% CI 2.8 to 3.2) and less time pain free (mean 4.5 vs. 9.0 hours, p<0.01). Meperidine was also associated with increased likelihood of rescue medication use (92% vs. 46%, RR 2.00, 95% CI 1.09 to 3.67). There was no difference in the likelihood of nausea and vomiting.

Table 36. Opioid versus acetaminophen and opioid agonist versus partial agonist for acute renal colic

Author, Year Quality	Interventions	Followup Duration Sample Size	Pain Intensity	Other Results
Pathan, 2016 ²³³ Good	A: Morphine 15 mg IV x 1 B: Acetaminophen 1000 mg IV x 1	60 and 90 minutes n=1,096	Pain intensity (median [IQR], 0 to 10 scale): 0 (0 to 2) vs. 0 (0 to 2) at 90 minutes Pain >2 on 0 to 10 scale at 60 minutes: 38% (207/549) vs. 30% (162/548), RR 1.28 (95% CI 1.08 to 1.51)	Rescue medication use: 23% (126/549) vs. 20% (111/548), RR 1.13 (95% CI 0.90 to 1.42) Pain intensity decreased ≥50% at 90 minutes: 93% (511/549) vs. 92.5% (507/548), RR 1.01 (95% CI 0.97 to 1.04)
Finlay, 1982 ²²⁵ Fair	A: Meperidine 100 mg IM x 1 B: Buprenorphine 0.3 mg IM x 1	12 hours n=26	Pain intensity (mean [SD], 0 to 10 VAS): 4.16 (0.28) vs. 1.16 (0.12) at 12 hours, MD 3.0 (95% CI 2.8 to 3.2)	Rescue medication use: 92% (12/13) vs. 46% (6/13), RR 2.00 (95% CI 1.09 to 3.67) Period pain free in first 12 hours (mean [SD], hours) 4.47 (1.0) vs. 9.02 (0.9), p<0.01

Abbreviations: CI = confidence interval; IM = intramuscular; IV = intravenous; MD = mean difference; RR = relative risk; SD = standard deviation; VAS = visual analog scale

KQs 7b and 7d ask how the comparative effectiveness and harms 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.

Evidence on how comparative effectiveness and harms of opioid therapy for kidney stone pain vary according to patient and prescribing factors was lacking. Three trials excluded patients with a history of substance use disorder,^{229,232,234} and substance use disorder was not described in the others. Information on medical and psychiatric comorbidities was lacking. No study conducted within-study analyses of subgroup effects, with the exception of two trials that reported that results in the patients with ureteric calculi on imaging were similar compared with all patients presenting clinically with renal colic.^{233,234} Evidence was too limited to determine effects of different dose of meperidine on comparative effectiveness and harms. All trials evaluated single dose of opioids and did not address opioid use as an outpatient.

KQ 7e concerns 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).

No study compared the association between prescribing of opioids for acute renal colic versus not prescribing and continued use of opioids. Two studies found a history of kidney stones associated with increased likelihood of opioid use, but did not meet inclusion criteria because they were cross-sectional and did not evaluate prescribing for acute episodes as a risk factor.^{236,237}

KQs 7f and 7g address the accuracy and effectiveness of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose for patients with acute pain being considered for opioid therapy.

No evidence was found for KQs 7f and 7g.

KQ 7h addresses the effect of the following factors on the decision to prescribe opioids for patients with acute pain being considered for opioid therapy, what is: (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.

No evidence was found for KQ 7h.

Nonopioid Pharmacologic Therapy

KQ 7i and 7k address the comparative effectiveness and harms of nonopioid pharmacologic therapy versus: (1) nonopioid pharmacologic therapy or (2) nonpharmacologic therapy.

NSAID Versus Acetaminophen

Four trials (n=1, 325) compared a single dose of an NSAID versus acetaminophen for acute renal colic (Table 37).^{227,228,231,233} In all of the trials, the NSAID and acetaminophen were administered parenterally, except for one trial²³¹ in which acetaminophen was administered by mouth. The NSAID was diclofenac in three trials (75 mg) and piroxicam in one trial (20 mg). The dose of acetaminophen was 1000 mg. Outcomes were assessed at 1 to 2 hours. One trial was rated good quality,²³³ and three trials were rated fair quality.

The trials reported inconsistent effects of NSAIDs versus acetaminophen on pain intensity (three trials)^{228,231,233} and likelihood of pain relief (two trials).^{227,233} Two trials found NSAIDs associated with decreased likelihood of rescue medication use (8% vs. 24%, RR 0.33, 95% CI 0.07 to 1.50 and 12% vs. 20%, RR 0.57, 95% CI 0.43 to 0.76).^{231,233} Few adverse events were reported in three trials.^{227,228,233} One trial found similar likelihood of serum creatinine elevations that normalized within 1 week.²³³

Table 37. NSAIDs versus acetaminophen for acute renal colic

Author, Year Quality	Interventions	Followup Duration Sample Size	Pain Intensity	Other Results
Grissa, 2011 ²²⁷ Fair	A: Piroxicam 20 mg IM x 1 B: Acetaminophen 1 g/100 mL IV x 1	90 minutes n=100	NR	≥50% pain relief: 48% (24/50) vs. 80% (40/50) at 90 minutes, RR 0.60 (95% CI 0.44 to 0.83)
Narci, 2008 ²³¹ Fair	A: Diclofenac 75 mg IM, x 1 + oral placebo B: Acetaminophen 1000 mg oral x 1 + IM placebo	60 minutes n=50	Pain intensity (mean [SD], 0 to 100 VAS converted to 0 to 10 scale): 1.41 (2.0) vs. 2.71 (1.69), MD -1.30 (95% CI -2.35 to -0.25)	Rescue medication use: 8% (2/25) vs. 24% (6/25), RR 0.33 (95% CI 0.07 to 1.50)

Author, Year Quality	Interventions	Followup Duration Sample Size	Pain Intensity	Other Results
Kaynar, 2015 ²²⁸ Fair	A: Diclofenac 75 mg IM x 1 B: Acetaminophen 1 g/100 mL IV x 1	2 hours n=80	Pain intensity (mean [SD NR], 0 to 10 VAS): 2.75 vs. 2.10, p=0.49	NR
Pathan, 2016 ²³³ Good	A: Diclofenac 75 mg IM x 1 C: Acetaminophen 1000 mg IV x 1	60 and 90 minutes n=1,095	Pain intensity (median [IQR], 0 to 10 scale): 0 (0 to 1) vs. 0 (0 to 2) at 90 minutes Pain >2 on 0 to 10 scale at 60 minutes: 24% (131/547) vs. 30% (162/548), RR 0.81 (95% CI 0.66 to 0.99)	Rescue medication use: 12% (63/547) vs. 20% (111/548), RR 0.57 (95% CI 0.43 to 0.76) Pain intensity decreased ≥50% at 90 minutes: 97.4% (533/547) vs. 92.5% (507/548), RR 1.05 (95% CI 1.02 to 1.08)

Abbreviations: CI = confidence interval; IM = intramuscular; IQR = interquartile range; IV = intravenous; NR = not reported; RR = relative risk; SD = standard deviation; VAS = visual analog scale

KQs 7j and 7l ask how the comparative effectiveness and harms 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.

Evidence was too limited to evaluate how comparative effectiveness and harms of nonopioid therapy varied in subgroups, due to the small number of trials. One trial reported that results were similar in the patients with ureteric calculi on imaging compared with all patients presenting clinically with renal colic.^{233,234}

Nonpharmacologic Therapy

KQs 7m and 7n address the comparative effectiveness of nonopioid pharmacologic therapy versus: (1) inactive controls or (2) other nonpharmacologic therapies.

Acupuncture Versus NSAID or Acetaminophen

One fair quality trial (n=121) compared a single acupuncture session versus a single dose of intramuscular diclofenac (75 mg) or intravenous acetaminophen (1000 mg) for acute renal colic (Appendixes E and F, Tables E-10 and F-1; Table 38).²²⁸ Outcomes were assessed at 2 hours. Details of the acupuncture treatment were not provided. Acupuncture was associated with higher pain intensity than either medication at 2 hours (mean 4.52 vs. 2.75 and 2.10 on a 0 to 10 scale, p<0.005 for acupuncture versus NSAID and for acupuncture versus acetaminophen). Few adverse events were reported.

Table 38. Acupuncture versus NSAID or acetaminophen for acute renal colic

Author, Year Quality	Interventions	Followup Duration Sample Size	Pain Intensity
Kaynar, 2015 ²²⁸ Fair	A: Acupuncture, appears to be a single session B: Diclofenac 75 mg IM x 1 C: Acetaminophen 1 g/100 mL IV x 1	2 hours n=160	Pain intensity (mean [SD NR], 0 to 10 VAS): 4.52 vs. 2.75 vs. 2.10, p<0.005 for A vs. B and C

Abbreviations: NR = not reported; SD = standard deviation; VAS = visual analog scale

KQs 7o and 7p address how the comparative effectiveness and harms of nonpharmacologic therapy 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.

No evidence was found for KQs 7o or 7p.

KQ 8. Sickle Cell Crisis

Key Points

- Opioid agonist or partial agonist vs. mixed agent
 - Evidence insufficient from two poor quality trials (SOE: insufficient).
- Relaxation vs. attention control
 - Insufficient evidence from one small trial (SOE: insufficient).

Summary of Findings

Evidence on the comparative effectiveness of interventions for acute sickle cell pain was limited to three small (n=18, 24, and 68) trials (Appendix E, Table E-11).²³⁸⁻²⁴⁰ Two trials evaluated opioid therapy (KQ 8a and 8c), and one trial evaluated nonpharmacologic therapy (KQ 8i and 8j). The mean age of patients ranged from 25 to 32 years, and the proportion of females was 28 percent to 70 percent. Baseline pain scores ranged from 6.2 to 7.6, and duration of pain was <7 days in one trial²⁴⁰ and not described in the other two trials.^{238,239} One trial of opioid therapy excluded patients with a history of substance use disorder; otherwise, the trials did not describe psychiatric or medical comorbidities. One trial²³⁸ was rated fair quality and two trials were rated poor quality (Appendix F, Table F-1).^{239,240} Methodological limitations in the trials included unclear blinding of patients and caregivers, failure to report adequate randomization and allocation concealment methods, and unclear use of intention to treat analysis. In one of the poor quality trials, some patients were randomized to interventions multiple times, and it was unclear how many patients received each intervention.²³⁹

Detailed Synthesis

Opioid Therapy

KQs 8a and 8c address the comparative effectiveness and harms of opioid therapy versus: (1) nonopioid pharmacologic therapy (e.g., acetaminophen, NSAIDs, antidepressants, anticonvulsants) or (2) nonpharmacologic therapy (e.g., exercise, cognitive behavioral therapy, acupuncture).

Opioid Agonist or Partial Agonist Versus Mixed Agent

Two poor quality trials compared different opioid types for acute sickle cell pain in ED settings (Table 39).^{239,240} One trial (n=68) found a single intravenous infusion of the pure opioid agonist meperidine 1 mg/kg associated with decreased pain intensity versus the mixed agent tramadol 1.5 mg/kg at 120 minutes (mean difference -2.9 on a 0 to 10 scale; 95% CI, -4.3 to -1.5).²⁴⁰ Adverse events were not reported. Parenteral tramadol is not available in the United States, though it is available in other parts of the world. The dose of meperidine mg in morphine

equivalent dose was 0.4 mg/kg. A published conversion ratio for parenteral tramadol was not available; based on the conversion ratio for oral tramadol the dose was 0.3 mg/kg.

The other trial (n=18 with 45 acute pain episodes) compared intramuscular butorphanol 2 mg (a partial agonist) versus morphine 6 mg (a pure agonist).²³⁹ After initial administration, the dose could be repeated in 30 to 60 minutes if needed for pain relief and then every 2 to 4 hours until pain relief or discharge. Pain was assessed at 60 and 120 minutes following each dose and at discharge. There was no difference between butorphanol versus morphine in pain intensity (adjusted mean scores 3.8 vs. 4.2 on a 0 to 10 scale, p=0.70) or pain relief (adjusted mean scores 4.9 vs. 4.2 on a 0 to 10 scale, p=0.80). Results were similar when the analysis was restricted to the first acute pain episode for each patient. There was also no difference in the likelihood of ED discharge (68% vs. 70%, p=0.92) or in global assessments of treatment (likelihood of a “good” or “excellent” global assessment of treatment 52% vs. 71%; p value for difference across all categories=0.75). There was no difference in adverse events, but few events (primarily nausea and vomiting) were reported (23% vs. 13%, p=0.46).

Table 39. Opioid agonist or partial agonist versus mixed agent for sickle cell pain

Author, Year Quality	Interventions	Followup Duration Sample Size	Pain Intensity	Other Pain Results
Gonzalez, 1988 ²³⁹ Poor	A. Butorphanol, 2 mg IM B. Morphine, 6 mg IM	60 and 120 minutes and at discharge n=18 with 45 randomized episodes	Pain (adjusted mean [SD NR], 0 to 100 VAS converted to 0 to 10 scale): 3.8 vs. 4.2, p=0.698	Pain relief (adjusted mean [SD NR], 0 to 100 VAS converted to 0 to 10 scale) 4.9 vs. 5.2, p=0.8005
Uzun, 2010 ²⁴⁰ Poor	A. Meperidine, 1 mg/kg IV (n=34) B. Tramadol, 1.5 mg/kg slow infusion (n=34)	120 minutes n=68	Pain (mean [SD] 0 to 10 VAS score): 3.5 (2.9) vs. 6.4 (3.0), MD, -2.9 (95% CI -4.3 to -1.5)	NR

Abbreviations: CI = confidence interval; IM = intramuscular; IV = intravenous; MD = mean difference; NR = not reported; SD = standard deviation; VAS = visual analog scale

No evidence was found for other subquestions (KQs 8b and 8d to 8h) related to opioid therapy for acute sickle cell pain.

Nonopioid Pharmacologic Therapy

KQs 8i and 8k address the comparative effectiveness and harms of nonopioid pharmacologic therapy versus: (1) nonopioid pharmacologic therapy or (2) nonpharmacologic therapy.

No studies of nonopioid pharmacologic therapy for sickle cell pain met inclusion criteria.

Nonpharmacologic Therapy

KQs 8m and 8n address the comparative effectiveness of nonopioid pharmacologic therapy versus: (1) inactive controls or (2) other nonpharmacologic therapy.

Relaxation Versus Attention Control

One small (n=24), fair quality, open-label trial compared a guided audio-visual relaxation intervention versus an attention control in patients with sickle cell disease in a clinic or prior to discharge from an acute care center or hospital (Table 40).²³⁸ The relaxation intervention was administered via six 2 to 20 minute video clips; participants were instructed to practice guided relaxation at least once a day for two weeks. The attention control was a 12 minute computer-

based discussion about sickle cell disease experiences and daily tracking of stress and pain. At two weeks, there was no statistically significant difference between relaxation versus attention control in pain intensity, though the estimate was imprecise and favored relaxation (mean difference -0.70 on a 0 to 10 scale; 95% CI, -1.72 to 0.32). Adverse events were not reported.

Table 40. Nonpharmacologic interventions for sickle cell pain

Author, Year Quality	Interventions	Followup Duration Sample Size	Pain Results
Ezenwa, 2016 ²³⁸ Fair	A: Tablet-based guided audio-visual relaxation--Video clips for guided relaxation lasting 2 to 20 minutes; patients told to practice guided relaxation at least once per day for two weeks B: Control	14 days n=24	Pain intensity, (mean [SD], 0 to 100 Composite Pain Index score converted to 0 to 10 scale): 3.5 (1.2) vs. 4.2 (1.2), MD -0.70 (95% CI -1.72 to 0.32)

Abbreviations: CI = confidence interval; MD = mean difference; SD = standard deviation

KQs 8o and 8p address how the comparative effectiveness and harms of nonpharmacologic therapy 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.

No evidence was found for KQs 8o and 8p.

Discussion

Key Findings and Strength of Evidence

This review synthesized the evidence on the comparative effectiveness of opioid and nonopioid pharmacologic therapy and the effectiveness and comparative effectiveness of nonpharmacologic therapy for eight acute pain conditions. It also synthesized the evidence on the accuracy and effectiveness of risk assessment instruments in persons with acute pain being considered for opioid therapy, the association between opioid prescribing versus not prescribing for acute pain and subsequent (including long-term) opioid use, and factors associated with opioid prescribing, for each of these conditions. The key findings for effectiveness and comparative effectiveness are summarized in Table 41 (focusing on pain intensity, stratified by followup duration) and the strength of evidence table (Appendix G), which also includes findings for function and adverse events.

Evidence was available from 183 randomized controlled trials on the comparative effectiveness of interventions for acute pain or effectiveness of nonpharmacologic therapy. The conditions with the most robust evidence were low back pain, postoperative pain and dental pain; evidence was particularly sparse for neck pain, neuropathic pain, and sickle cell pain. Pain was the main outcome addressed in the trials, though methods for measuring pain varied (e.g., differences in mean pain intensity, the likelihood of clinically significant improvement in pain, summed or average measures of pain, or the likelihood of rescue or repeat medication use). For postoperative pain, dental pain, and kidney stone pain, most comparative effectiveness trials of pharmacologic therapy (opioid or nonopioid) evaluated effects of a single dose on pain at <1 day (usually 8 hours or less) followup. Across conditions, most trials of pharmacologic therapy focused on outcomes at <1 week followup. The emphasis on short-term outcomes in the trials may reflect the natural history of acute pain, which tends to rapidly improve in the first days to week. Effects on function and quality of life were more commonly measured in trials that evaluated nonpharmacologic therapy and those that evaluated outcomes at longer followup.

Table 41. Summary of evidence of treatments for acute pain: pain

Key Question	Intervention and Comparison	Pain (Effect Size/SOE) ^a <1 Day	Pain (Effect Size/SOE) ^a 1 Day to <1 Week	Pain (Effect Size/SOE) ^a 1 Week to <2 Weeks	Pain (Effect Size/SOE) ^a 2 Weeks to 4 Weeks	Pain (Effect Size/SOE) ^a ≥4 Weeks
KQ1: Back pain	Opioid vs. NSAID	None +	None +	No evidence	No evidence	No evidence
	Opioid vs. muscle relaxant	No evidence	None +	No evidence	No evidence	None +
	Muscle relaxant vs. benzodiazepine	No evidence	Small to moderate +	No evidence	No evidence	No evidence
	NSAID or muscle relaxant vs. manipulation	No evidence	No evidence	None +	None +	None +
	Acupuncture vs. NSAID	No evidence	Insufficient	No evidence	Moderate +	Moderate +
	Exercise vs. usual care	No evidence	No evidence	None +	None +	None +
	Exercise vs. bed rest	No evidence	No evidence	None ++	None ++	None ++
	Traditional Chinese acupuncture vs. sham	No evidence	No evidence	No evidence	Moderate vs. nonpenetrating sham or usual care; None vs. needle sham +	None +
	Brace vs. no brace, osteoporotic compression fracture	No evidence	No evidence	No evidence	None +	None +
	Heat therapy vs. usual care or placebo	No evidence	Moderate ++	Moderate +	Moderate +	No evidence
	Manipulation vs. inactive controls	No evidence	None +	None +	None ++	None +
	Manipulation vs. sham, radiculopathy	No evidence	No evidence	Moderate +	No evidence	Moderate +
KQ2: Neck pain	Collar vs. usual activity, radiculopathy	No evidence	No evidence	No evidence	Moderate to large +	Moderate to large +
	Collar vs. exercise, radiculopathy	No evidence	No evidence	No evidence	None +	None +
	Exercise vs. usual activity, radiculopathy	No evidence	No evidence	No evidence	Moderate +	Moderate +
	Collar vs. usual activity, whiplash neck sprain	No evidence	No evidence	No evidence	No evidence	No difference +

Key Question	Intervention and Comparison	Pain (Effect Size/SOE) ^a <1 Day	Pain (Effect Size/SOE) ^a 1 Day to <1 Week	Pain (Effect Size/SOE) ^a 1 Week to <2 Weeks	Pain (Effect Size/SOE) ^a 2 Weeks to 4 Weeks	Pain (Effect Size/SOE) ^a ≥4 Weeks
	Collar vs. exercise, whiplash neck sprain	No evidence	No evidence	No evidence	No evidence	No difference +
	Exercise vs. usual activity, whiplash neck sprain	No evidence	No evidence	No evidence	No evidence	No difference +
	Ultrasound vs. sham whiplash neck sprain	No evidence	No evidence	None +	Small increase +	No evidence
KQ 3: Other musculoskeletal pain	NSAID vs. acetaminophen	None ++	None ++	No evidence	No evidence	No evidence
	Ultrasound vs. sham ultrasound	No evidence	None +	No evidence	No evidence	None +
	Acupressure vs. sham acupressure or usual care	No evidence	Moderate +	No evidence	No evidence	Moderate +
KQ4: Acute neuropathic pain	Opioid vs. gabapentin	No evidence	No evidence	Moderate +	No evidence	Moderate +
KQ 5: Postoperative pain	Opioid vs. NSAID, single dose, various surgeries	None +	No evidence	No evidence	No evidence	No evidence
	Opioid vs. NSAID, multidose course, various surgeries	Insufficient ^b	No evidence	No evidence	No evidence	No evidence
	Opioid vs. acetaminophen, single dose, cesarean section	None +	No evidence	No evidence	No evidence	No evidence
	NSAID vs. acetaminophen, various surgeries	Insufficient	No evidence	No evidence	No evidence	No evidence
	Acupuncture vs. sham, various surgeries	No evidence	Insufficient	No evidence	No evidence	No evidence
	Acupressure vs. sham, knee surgeries ^c	Insufficient	Insufficient	No evidence	No evidence	No evidence
	Cold therapy vs. sham, knee surgeries	No evidence	None +	No evidence	None +	None +
	Massage vs. no massage, various surgeries	Moderate to large +	No evidence	No evidence	No evidence	No evidence

Key Question	Intervention and Comparison	Pain (Effect Size/SOE) ^a <1 Day	Pain (Effect Size/SOE) ^a 1 Day to <1 Week	Pain (Effect Size/SOE) ^a 1 Week to <2 Weeks	Pain (Effect Size/SOE) ^a 2 Weeks to 4 Weeks	Pain (Effect Size/SOE) ^a ≥4 Weeks
	Music therapy vs. no music therapy, various surgeries	Moderate +	Small to moderate +	No evidence	No evidence	No evidence
	Exercise vs. no exercise, thyroid surgery	No evidence	No evidence	Large +	No evidence	None +
	TENS vs. sham TENS, liposuction	Moderate to large +	Moderate to large +	No evidence	No evidence	No evidence
KQ 6: Dental pain	Opioid plus acetaminophen vs. acetaminophen, single dose-surgical pain	Small ++	No evidence	No evidence	No evidence	No evidence
	Opioid vs. acetaminophen, single dose-surgical pain	None +	No evidence	No evidence	No evidence	No evidence
	Opioid plus acetaminophen or NSAID vs. NSAID, single dose surgical pain	Small to moderate increase +	No evidence	No evidence	No evidence	No evidence
	Opioid plus acetaminophen or NSAID vs. NSAID, multidose course-surgical pain	None +	No evidence	No evidence	No evidence	No evidence
	Opioid vs. NSAID (surgical and nonsurgical pain)	Insufficient	No evidence	No evidence	No evidence	No evidence
	NSAID vs. acetaminophen, single dose	Moderate to large ++	No evidence	No evidence	No evidence	No evidence
KQ7: Kidney stone pain	Morphine vs. NSAID, single dose	Small increase ++	No evidence	No evidence	No evidence	No evidence
	Meperidine vs. NSAID, single dose	Moderate to large increase ++	No evidence	No evidence	No evidence	No evidence
	Morphine vs. acetaminophen	Small increase ++	No evidence	No evidence	No evidence	No evidence

Key Question	Intervention and Comparison	Pain (Effect Size/SOE) ^a <1 Day	Pain (Effect Size/SOE) ^a 1 Day to <1 Week	Pain (Effect Size/SOE) ^a 1 Week to <2 Weeks	Pain (Effect Size/SOE) ^a 2 Weeks to 4 Weeks	Pain (Effect Size/SOE) ^a ≥4 Weeks
	NSAID vs. acetaminophen	Insufficient	No evidence	No evidence	No evidence	No evidence
	Acupuncture vs. NSAID or acetaminophen	Moderate increase +	No evidence	No evidence	No evidence	No evidence
KQ8: Sickle cell pain	Insufficient evidence	No evidence	No evidence	No evidence	No evidence	No evidence

^a Effect size: None or small, moderate, or large decrease in pain for intervention A vs. B, unless indicated as an increase in pain; SOE: + = low, ++ = moderate, +++ = high, or insufficient

^b Opioid was associated with increased likelihood of repeat or rescue medication use (SOE: moderate)

^c Acupressure associated with decreased pain medication use versus sham acupressure at <1 day and 1 day to <1 week (SOE: low)

Abbreviations: ACL = anterior cruciate ligament; KQ = Key Question; NSAID = nonsteroidal anti-inflammatory drug; SOE = strength of evidence; TENS = transcutaneous electrical nerve stimulation

There were no high strength of evidence ratings, due to small numbers of trials, methodological limitations, imprecision, and inconsistency. Most strength of evidence ratings were low or insufficient, reflecting the limitations in the evidence and high uncertainty in findings. For surgical dental pain and kidney stone pain, moderate strength of evidence indicated that opioids were associated with greater pain or need for rescue medication use versus nonsteroidal anti-inflammatory drugs (NSAIDs). Findings for postoperative pain were somewhat inconsistent. Although there was moderate strength of evidence that opioids are associated with increased likelihood of repeat or rescue medication use at 1 day to 1 week, evidence on pain intensity was insufficient due to inconsistency. In addition, results were based on a small number of trials and pain after a limited set of surgical procedures, most commonly cesarean section, anterior cruciate ligament (ACL) reconstruction, knee arthroplasty, and cholecystectomy. Due to variability in the severity and duration of pain following surgical procedures, findings cannot be broadly generalized to all postoperative pain. There was moderate strength of evidence that opioids were associated with increased risk of adverse events such as nausea, dizziness, and sedation versus nonopioid pharmacologic therapies, though the trials were not designed to assess serious adverse events, and few such events were reported. Evidence comparing opioids versus acetaminophen was less robust than for opioids versus NSAIDs, and somewhat mixed: for dental pain, moderate evidence indicated that opioids were associated with better pain outcomes on some measures, but for kidney stone pain, opioids were associated with worse pain. Evidence on NSAIDs versus acetaminophen was also somewhat mixed: for dental pain, evidence indicated that NSAIDs were associated with better pain outcomes, but for kidney stone pain, results were inconsistent. Evidence on nonopioid pharmacologic therapies other than opioids, NSAIDs, or acetaminophen was very limited. Determinations regarding the effectiveness of nonpharmacologic therapies for acute pain were also constrained by the available evidence. For low back pain, heat therapy was associated with a moderate decrease in pain versus usual care or placebo at 1 day to <1 week and at 2 to <4 weeks. There was likely no difference between manipulation versus inactive controls for non-radicular low back pain, though one trial of patients with radiculopathy found manipulation associated with increased likelihood of improvement in pain at 2 to <4 weeks, and at ≥ 4 weeks.⁷⁶ There was low strength of evidence supporting acupuncture over an NSAID for low back pain, but findings were based on one trial that evaluated one session of acupuncture and a single dose of an NSAID.⁴⁸ There was low strength of evidence supporting effectiveness of massage for postoperative pain, with likely no difference between cold therapy versus no cold therapy for this condition, with the possible exception of decreased pain medication use at <1 week. There was also low strength of evidence supporting effectiveness of acupressure for acute musculoskeletal pain. Reporting of harms for nonpharmacologic therapies was suboptimal, making it difficult to compare harms of pharmacologic and nonpharmacologic therapies. However, the noninvasive nonpharmacologic therapies evaluated in this report are generally not thought to be associated with serious harms, and harms were few when reported.

Trials of opioid therapy were not designed to evaluate effects on long-term use of opioids or associated outcomes such as misuse or substance use disorder. Adverse events associated with use of these and other medications for chronic pain were recently summarized in reports funded by the Agency for Healthcare Research and Quality on opioids and nonopioid pharmacologic therapy.^{43,44} Limited evidence from observational studies found being prescribed an opioid for acute low back pain or after minor or elective surgical procedures was associated with increased likelihood of opioid use at longer term (e.g., 6 months or 1 year) followup. Evidence on factors

associated with opioid prescribing in patients with the acute pain conditions addressed in this report was very limited, but suggested that legislation mandating use of prescription drug monitoring program data prior to prescribing was not associated with decreases in opioid prescribing for low back pain or postoperative pain. No study evaluated the accuracy or effectiveness of risk assessment instruments to inform use of opioids for acute pain; risk assessment instruments have focused on patients with chronic pain.⁴³

Findings in Relationship to What Is Already Known

Our review differs from most previously published reviews by focusing on head-to-head trials of pharmacologic therapy. Therefore, our findings complement the findings of reviews that evaluated the effectiveness of pharmacologic interventions based on placebo-controlled trials, but are generally consistent with them. For low back pain, such reviews found insufficient evidence to determine the effectiveness of opioid therapy for acute low back pain,²⁴¹ moderate evidence of small short-term effects of NSAIDs versus placebo on pain,²⁴² ineffectiveness of acetaminophen,²⁴³ and high-quality evidence of short-term benefits for pain relief with muscle relaxants.²⁴⁴ For dental pain, a review of systematic reviews of placebo-controlled and head-to-head trials of pharmacologic therapy found that a number of NSAIDs, alone or in combination with acetaminophen, were associated with similar or increased likelihood of achieving clinically significant pain relief versus various opioids, alone or in combination with an NSAID or acetaminophen.²⁴⁵ For acute pain due to kidney stones, our findings are consistent with a recent systematic review of placebo-controlled trials that found NSAIDs were more effective than opioids or acetaminophen for pain, though it focused on outcomes at 30 minutes after administration.²⁹ Like our review, a recent guideline on management of sickle cell pain found little evidence on pharmacologic therapy.²⁴⁶ Recent reviews of pharmacologic therapy for neuropathic pain focused on effectiveness in patients with chronic symptoms.²⁴⁷⁻²⁴⁹ Reviews have also found limited evidence suggesting effectiveness of NSAIDs relative to placebo²⁵⁰ for acute neck pain and strong evidence suggesting effectiveness of NSAIDs for acute ankle sprain.²⁵¹

For nonpharmacologic therapy, our review differs from previously published reviews by focusing on management of pain in outpatients or in patients soon to be discharged, and restricting inclusion to patients with symptom duration of <4 weeks. For low back pain, one prior review that included patients with pain for up to 6 weeks also found low to very low quality evidence suggesting no difference in effects of manipulation versus inert interventions, sham manipulation, or when added to another intervention, and evidence that manipulation was no better than active therapies.²⁵² Another review that included studies of patients with low back pain for up to 12 weeks found inconsistent evidence that acupuncture was more effective than NSAIDs for pain and limited evidence that acupuncture was more effective than sham.²⁵³ For postoperative pain, a prior review found evidence of effectiveness for transcutaneous electrical nerve stimulation (TENS) and cognitive behavioral therapy, but included trials of inpatient management following major surgical procedures and trials in which the intervention was initiated pre- or perioperatively.²⁵⁴ For acute ankle sprain, systematic reviews found evidence to support bracing and neuromuscular training to prevent recurrence of ankle sprain and early mobilization, exercise, and manual therapy for treatment of acute pain.²⁵¹ However, the purpose of these treatments was primarily to manage the underlying condition rather than treatment of pain, the focus of our review.

Applicability

A number of issues could impact the applicability of our findings. Most randomized trials were conducted in emergency department or postoperative care unit settings, which might reduce applicability to outpatient management of acute pain. Further, trials of pharmacologic therapy frequently evaluated a single dose and some trials of nonpharmacologic therapy evaluated a single treatment session, potentially limiting the applicability of findings to a multidose course of treatment. Trials excluded important patient subgroups, such as persons with a history of substance use disorder, prior opioid use, and psychological or medical comorbidities, or did not report information regarding these factors. In addition, trials were not designed to evaluate how benefits or harms varied in subgroups defined by these factors or others, such as age, sex, and race/ethnicity. Another limitation to applicability is that most trials—particularly trials of pharmacologic therapy—were designed to assess short-term (<1 week, and often <1 day) effects on pain, with few trials evaluating effects on non-pain outcomes or at longer term followup. Finally, the applicability of findings for one pain condition (including pain due to specific surgical procedures) addressed in this review to another pain condition in this review, or to acute pain conditions not addressed in this review, is uncertain. For example, opioids were associated with decreased pain versus acetaminophen for dental pain, but increased pain versus acetaminophen for kidney stone pain. The applicability of findings from one acute pain condition to others may vary depending on the type and nature of the pain. For example, evidence on pharmacologic therapy for low back pain may have high applicability to neck pain, another musculoskeletal condition in the spine, but less applicable to sickle cell pain, neuropathic pain, or abdominal pain.

Implications for Clinical and Policy Decision Making

Our review has potential implications for clinical and policy decision making. A number of policies on management of acute pain have focused on limiting the amount or duration of opioids prescribed. Although such policies are associated with decreases in the rate and amount of opioid prescribing,²⁵⁵⁻²⁵⁸ effects of such policies on pain and other patient outcomes are not well studied.²⁵⁹ The findings of our review that opioids are not superior to NSAIDs for some commonly encountered acute pain conditions, and in some cases may be inferior, may provide indirect evidence that such policies may not adversely affect outcomes among patients with those conditions, provided that NSAIDs or other effective alternatives are utilized. Evidence of an increased risk of adverse events with opioids compared with other pharmacologic therapies and indicating an association between acute opioid prescribing for low back pain and postoperative pain and long-term use also may provide indirect support for policies aimed at reducing overprescribing of opioids for acute pain, though such findings are susceptible to residual confounding.

There was a lack of evidence to guide clinical and policy decision making around most nonpharmacologic therapies. In addition to considerations regarding effectiveness, use of nonpharmacologic therapies as an alternate or in addition to pharmacologic therapy should account for issues related to timely access, burdens (e.g., time off work to attend treatment sessions), costs, availability, and reimbursement. Heat therapy has been incorporated into low back pain guidelines as a potential self-care option that does not require a visit with a healthcare provider and relatively low costs.²⁶⁰ Although guidelines on low back pain and postoperative pain suggest use of nonpharmacologic therapies (massage, acupuncture, and spinal manipulation

for low back pain and transcutaneous electrical nerve stimulation and cognitive-behavioral therapies for postoperative pain) these recommendations were based in part on evidence not eligible for this review (e.g., subacute pain, pre- or perioperative interventions, and inpatient management of major surgical procedures).^{254,260}

The lack of evidence about how benefits and harms of therapies vary in subgroups (such as older adults, pregnant persons, or those with comorbidities, including history of substance use disorder or prior opioid use) is an important limitation on clinical and policy decision making. Evidence on the association between enactment of legislation requiring use of prescription drug management program data prior to prescribing an opioid for acute pain has shown little effect on opioid prescribing rates. Research is needed to identify risk mitigation, education, and other medication management factors associated with prescribing practices (ideally, overprescribing), in order to better inform policy decision.

Limitations of the Review Process

We excluded non-English language articles and did not search for studies published only as abstracts. We did not conduct statistical and graphical methods for assessing small sample effects (a potential marker for publication bias) due to small numbers of trials and heterogeneity in study design methods, patient populations, and outcomes. Searches on clinical trial registries and public solicitation did not identify unpublished studies suggesting publication bias. We did not have access to individual patient data, which limited our ability to evaluate subgroup effects. Meta-analyses could not be conducted for most questions due to small numbers of studies, methodological limitations, and heterogeneity across studies in interventions, study designs, and outcomes. There was also variability within the predefined acute pain categories (e.g., presence of absence of radiculopathy, type of musculoskeletal pain, surgical or nonsurgical dental pain, and specific surgical procedure), which could obscure potential differential effects by specific condition or procedure, though results were reported by specific condition when possible. Because of anticipated statistical heterogeneity, we utilized a random effects model when meta-analysis was performed. We defined acute pain as lasting <4 weeks, though other definitions have utilized longer thresholds (e.g., <6 or <12 weeks), which decreased the evidence included in this review. However, pain improves rapidly in the first few days and the trajectory for improvement slows and responsiveness to treatments tends to decrease the longer that pain is present. Therefore, the 4 week threshold potentially reduced heterogeneity due to variability among patients related to duration of pain. Within the prespecified 4 week threshold, variability in duration (e.g., 1 or 2 days versus 3 to 4 weeks) could also potentially impact effects of treatment, but evidence was insufficient to determine the impact of acute pain duration. We excluded trials that combined multiple therapies (e.g., manipulation, massage, and physical modalities) because it was not possible to disentangle the effects of the individual components. The exception was an opioid plus acetaminophen or an NSAID, because this combination is commonly used in clinical practice and excluding such studies would have substantially reduced the available evidence on opioids. When sufficient data were available, we analyzed effects of an opioid plus acetaminophen or an NSAID separately from an opioid alone. We analyzed NSAIDs as a class, which might obscure potential within-class differences. However, a previous systematic review found that analgesic effects of different NSAIDs were similar.²⁶¹ We also excluded trials in which the outcomes were only assessed at <1 hour; therefore, our review does not address the immediate effects of interventions. The report did not address acute headache,

which is being addressed in a separate AHRQ-funded review, and other types of acute pain (e.g., abdominal pain, chest pain, gynecological or urological pain, and others).

Limitations of the Evidence Base

The evidence base had important limitations. Importantly, there was very little evidence for sickle cell pain, acute neuropathic pain, and neck pain. Evidence was also limited for musculoskeletal pain other than low back pain and kidney stone pain. Evidence on the effectiveness of nonpharmacologic therapy for acute pain was generally more limited than evidence on the effectiveness of pharmacologic therapy, despite broader inclusion criteria (i.e., effectiveness and comparative effectiveness studies, rather than just comparative effectiveness studies) for nonpharmacologic therapy. Most trials had important methodological limitations, reducing certainty in findings. The trials primarily focused on outcomes related to pain, usually at <1 week and often at <1 day, with relatively limited measurement of function and quality of life. In addition, trials were not designed to evaluate the likelihood of long-term opioid use or harms related to the addiction and overdose potential of opioids. Most trials of pharmacologic therapy and some trials of nonpharmacologic therapy evaluated a single dose or session of treatment, which may not indicate benefits and harms of multiple doses or sessions. In addition, therapy was usually initiated in emergency department or postoperative care settings, with few trials focusing on outpatient management of acute pain. The trials were not designed to evaluate how benefits and harms varied in subgroups defined by demographics (including age, sex, and race/ethnicity) or clinical factors (including history of substance use disorder, prior opioid use, and history of cancer). Patients with a history of substance use disorder or prior opioid use represent an important clinical challenge, but were excluded or trials did not describe these characteristics. The trials were also not designed to evaluate how benefits and harms varied according to opioid dose or amount prescribed. Evidence on effects of interventions on long-term opioid use was primarily available from observational studies, based on claims data on dispensing, which may not accurately measure actual use of prescribed opioids and does not capture use of unprescribed opioids. Evidence on the accuracy and effectiveness of risk assessment instruments was unavailable and evidence on how risk mitigation strategies, patient education, and other factors impact prescribing of opioids was very limited.

Research Gaps

Many research gaps limit the full understanding of the effectiveness, comparative effectiveness, and harms of treatments for acute pain, as well as aspects of opioid prescribing (risk assessment instruments, long-term use, and factors impacting prescribing). Among the acute pain conditions addressed in this review, evidence is particularly lacking for sickle cell pain, neuropathic pain, and neck pain. Research on management of acute sickle cell pain is an important priority, given the disparities in care associated with this condition.²⁶² Neuropathic pain is more commonly managed as a chronic condition and evidence from management of low back pain may have applicability to neck pain. Research is needed to identify effective nonpharmacologic therapies. Cannabis has become legal in many states for medical as well as recreational use, though evidence on acute pain is lacking. Research is needed to determine the effectiveness of cannabis for acute pain.

Patients at higher risk for or with a history of or current opioid use disorder or misuse or with mental health and medical comorbidities are commonly encountered in clinical practice, but evidence on management of acute pain in these populations is very limited. Studies that enroll

such patients and evaluate how benefits and harms vary compared with patients without such factors would be very helpful for informing treatment and policy approaches. Research is also needed to better understand the degree to which acute pain treatments can be individualized based on demographic, clinical, or genetic factors. Studies should measure multiple important outcomes, including pain, function, and quality of life, such as sleep, and mental health outcomes. Studies are also needed to better understand the association between use of opioid and nonopioid therapies and risk of misuse and opioid use disorder using standardized methods. Research is also needed to better understand how patients value different outcomes (beneficial and harmful) associated with interventions for acute pain, and effects of strategies that consider such preferences in decision making. Studies should address how policies aimed at reducing the duration or dose of opioid prescribing impact patient outcomes such as pain and quality of life and the effectiveness of interventions to mitigate such effects (e.g., identification and followup of patients with persistent pain and timely refills or referrals for treatment), in addition to effects on prescribing. Research is also needed to develop and validate instruments for accurately predicting risk of opioid use disorder or misuse in persons with acute pain, and to determine how using risk prediction instruments impacts treatment decisions and, ultimately, patient outcomes.

It is important for future studies on opioids to evaluate longer-term outcomes, including long-term use and potentially associated harms (e.g., opioid use disorder, overdose, impaired social and emotional cognition, and workforce nonparticipation). Well-designed clinical registries that prospectively enroll patients with acute pain prescribed and not prescribed opioids could complement randomized trials evaluating long-term outcomes.

Conclusions

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. Evidence on nonpharmacological therapies was limited, but heat therapy, spinal manipulation, massage, acupuncture, acupressure, a cervical collar, and exercise were effective for specific acute pain conditions. Research is needed to determine 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.

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260. Qaseem A, Wilt TJ, McLean RM, et al. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med*. 2017 Apr 04;166(7):514-30. doi: <https://dx.doi.org/10.7326/M16-2367>. PMID: 28192789.
261. Chou R, McDonagh MS, Nakamoto E, et al. AHRQ Comparative Effectiveness Reviews. Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011.
262. Lee L, Smith-Whitley K, Banks S, et al. Reducing Health Care Disparities in Sickle Cell Disease: A Review. *Public Health Rep*. 2019 Nov/Dec;134(6):599-607. doi: 10.1177/0033354919881438. PMID: 31600481.

Abbreviations and Acronyms

ACL	anterior cruciate ligament
AHRQ	Agency for Healthcare Research and Quality
ARD	absolute risk difference
CDC	Centers for Disease Control and Prevention
CI	confidence interval
DASH	Disabilities of the Arm, Shoulder, and Hand
ED	emergency department
EPC	Evidence-based Practice Center
HVLA	high-velocity low amplitude
IM	intramuscular
IV	intravenous
IQR	interquartile range
KQ	Key Question
MD	mean difference
MPQ	McGill Pain Questionnaire
NMES	neuromuscular electrical stimulation
NR	not reported
NRS	numerical rating scale
NSAID	nonsteroidal anti-inflammatory drug
NS	not significant
ODI	Oswestry Disability Index
PCA	patient-controlled analgesia
PICOTS	population, intervention, comparator, outcome, timing, setting
PID	pain intensity difference
RCT	randomized controlled trial
RMDQ	Roland-Morris Disability Questionnaire
RR	relative risk
SD	standard deviation
SEADS	Supplemental Evidence and Data for Systematic Review
SF-36	36-Item Short-Form Survey
SMD	standardized mean difference
SOE	strength of evidence
SPADI	Shoulder Pain and Disability Index
SPID	sum of pain intensity difference
SOE	strength of evidence
TENS	transcutaneous electrical nerve stimulation

VAS	visual analog scale
VRS	verbal rating scale
WOMAC	Western Ontario and McMaster Universitie

Appendix A. Literature Search Strategies

Treatment Effectiveness and Harms

Ovid MEDLINE(R) 1946 to July Week 4 2020

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. 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

**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to August 5, 2020,
Ovid MEDLINE(R) Epub Ahead of Print August 5, 2020**

1. (acute adj3 pain).ti,kf.
2. (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,kf.
3. (treatment or therap* or intervention*).ti,kf.
4. (1 or 2) and 3
5. (random* or control* or placebo or sham or trial).ti,kw.
6. (systematic or "meta analysis" or metanalysis or medline).ti,kf.
7. 4 and (5 or 6)
8. 7 not (animal or mouse or mice or rat* or dog* or canine).ti.
9. 8 not chronic.ti.
10. "PubMed-not-MEDLINE".st.
11. 9 not 10

Ovid MEDLINE(R) ALL 1946 to August 5, 2020

Postoperative 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. 14 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

Ovid MEDLINE(R) ALL 1946 to August 5, 2020

Musculoskeletal supplemental search

- 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 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 (psyclit 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 63 not 50
 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

Cochrane Central Register of Controlled Trials July 2020

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
14. conference abstract.pt.
15. "journal: conference abstract".pt.
16. "journal: conference review".pt.
17. or/14-16
18. 13 not 17

PsycINFO 1806 to August Week 1 2020

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 ondotogenic 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 or adolescence <13 to 17 years>)
22. 20 not 21
23. 22 not chronic.ti.

Cochrane Database of Systematic Reviews 2005 to August 5, 2020

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

Elsevier Embase August 5, 2020

('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)

Opioid Use Risk Assessment and Mitigation

Ovid MEDLINE(R) 1946 to July Week 4 2020

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

Cochrane Central Register of Controlled Trials July 2020

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, Sick 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 medline records
44. 42 not 43

Appendix B. Methods

Details of Study Selection

Inclusion and Exclusion Criteria

Studies were selected for inclusion using pre-established criteria based on the Key Questions and PICOTs (Table B-1). The focus of the report was on outpatient management of acute pain. Therefore, it excluded studies on the inpatient management of acute pain, including inpatient management of pain following major surgical procedures. However, acute pain is often initially managed in emergency department and acute care settings. Therefore, studies in which therapy was initiated in such studies were included, even if therapy was not continued following discharge (e.g. single dose studies of pharmacologic therapy or single session of pharmacologic therapy). Studies of therapies initiated in postoperative care settings were also included, if they were conducted in patients who had undergone outpatient surgical procedures, procedures in which the expected postoperative stay was no more than 1 day, or major surgical procedures shortly before discharge. Because few studies on outpatient management of sickle cell pain were expected, studies were not restricted by inpatient versus outpatient setting.

The population was restricted to patients with acute (<4 weeks pain). Studies with mixed populations of acute and nonacute pain were included if the duration of pain was 4 weeks or longer in <10% of patients or if the average duration of pain was <2 weeks.

The interventions evaluated in this report were opioid therapy, nonopioid pharmacologic therapy (NSAIDs, acetaminophen, skeletal muscle relaxants, benzodiazepines, antidepressants, anticonvulsants, or cannabis), and noninvasive nonpharmacologic therapy used for 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]). Interventions that involved combinations of different therapy were excluded, with the exception of an opioid plus acetaminophen or NSAID, since these medications are commonly administered together; this combination was classified as an opioid and analyzed separately from an opioid alone if sufficient data were available. Studies in which all patients received background therapy (i.e., not involved in the analyzed comparison) were included, as long as the background therapy could reasonably be considered usual care (e.g., non-opioid analgesics, education, or home exercises).

The comparisons addressed in this report varied depending on the intervention type. For pharmacologic therapy, (opioid or nonopioid), this report focused on studies of comparative effectiveness, to address decisional dilemmas regarding the choice of pharmacologic therapy. The efficacy of pharmacologic therapy versus placebo has been addressed in other reviews. For nonpharmacologic therapy, there is more uncertainty about efficacy for acute pain. Therefore, studies comparing nonpharmacologic therapy versus inactive therapies (placebo, sham therapy, no therapy, attention control, or minimal intervention) were included, as well as head-to-head studies of comparative effectiveness. Questions also addressed the accuracy and effectiveness of risk prediction instruments and factors associated with opioid prescribing.

Outcomes were pain (including satisfaction with pain relief), function, quality of life (including mood and sleep), and harms. One question addressed the accuracy of risk assessment instruments and one question addressed effects of prescribing versus no prescribing on long-term

use. Outcomes were assessed at prespecified time periods: <1 day, 1 day to <1 week, 1 week to <2 weeks, 2 weeks to <4 weeks, and ≥ 4 weeks.

For Key Questions related to effectiveness and comparative effectiveness, inclusion was restricted to RCTs. Controlled observational studies (cohort, case-control, and before-after studies) were eligible to assess effects of opioid prescribing versus no prescribing on long-term use, accuracy and effectiveness of risk prediction instruments, and factors influencing prescribing.

Table B-1. Inclusion criteria by PICOTS element

PICOTS Element	Inclusion Criteria
Population	<p>Adults with acute pain related to the following conditions:</p> <ol style="list-style-type: none"> 1. Acute back pain (including back pain with radiculopathy) 2. Acute neck pain (including neck pain with radiculopathy) 3. Other musculoskeletal pain (not requiring surgery) 4. Peripheral neuropathic pain (related to herpes zoster and, trigeminal neuralgia) 5. Postoperative pain (excluding inpatient management of pain following major surgical procedures) 6. Dental pain 7. Kidney stones 8. Sickle cell crisis (episodic pain) <p>*Special populations:</p> <p>General adult</p> <p>Older populations >65 years</p> <p>Patients with history of substance use disorder</p> <p>Patients currently under treatment for opioid use disorder with opioid agonist therapy or naltrexone</p> <p>Patients with a history of psychiatric illness</p> <p>Patients with history of overdose</p> <p>Pregnant/breastfeeding women</p> <p>Patients with comorbidities (e.g., kidney disease, sleep disordered breathing)</p>
Interventions	<p>Opioid therapy:</p> <p>a-e. Any systemic opioid, including agonists, partial agonists, and mixed mechanism opioids (tapentadol or tramadol).</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>Nonopioid therapy: Oral, parenteral, or topical nonopioid pharmacological therapy used for acute pain (acetaminophen, nonsteroidal anti-inflammatory drugs, skeletal muscle relaxants, benzodiazepines, antidepressants, anticonvulsants, cannabis).</p> <p>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])</p>

PICOTS Element	Inclusion Criteria
Comparators	<p>Opioid therapy:</p> <ul style="list-style-type: none"> 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 <p>Nonopioid pharmacological therapy:</p> <p>Other nonopioid pharmacological therapy or noninvasive nonpharmacological therapy</p> <p>Noninvasive nonpharmacological therapy:</p> <p>Sham treatment, waitlist, usual care, attention control, and no treatment; or other noninvasive nonpharmacological therapy</p>
Outcomes	<p>Opioid therapy:</p> <ul style="list-style-type: none"> 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 <p>Nonopioid therapy: pain, function, pain relief satisfaction, quality of life and quality of life, harms, adverse events, opioid use</p> <p>Noninvasive nonpharmacological therapy: pain, function, pain relief satisfaction, quality of life and quality of life, harms, adverse events, opioid use</p>
Time of followup	<1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to <4 weeks; ≥4 weeks
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)
Study design	<p>All KQs: RCTs; in addition:</p> <ul style="list-style-type: none"> 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

Abbreviations: RCT = randomized controlled trial

Study Design. Controlled observational studies (cohort, case-control, and before-after studies) were eligible to assess effects of opioid prescribing versus no prescribing on long-term use, accuracy and effectiveness of risk prediction instruments, and factors influencing prescribing.

For all Key Questions, we included randomized controlled trials (RCTs). Controlled observational studies (cohort, case-control, and before-after studies) were eligible to assess effects of opioid prescribing versus no prescribing on long-term use, accuracy and effectiveness of risk prediction instruments, and factors influencing prescribing. For all KQs, we excluded uncontrolled observational studies, case series, and case reports. Systematic reviews were not included but references were reviewed for potentially relevant studies.

Non-English Language Studies: Inclusion was restricted to English-language articles, but did review English-language abstracts of non-English language articles to identify studies that would otherwise meet inclusion criteria, in order to inform assessments regarding the potential for language bias.

Data Extraction

Data were extracted from included studies into standardized Excel spreadsheets. Data abstracted were: study design, year, setting, country, sample size, eligibility criteria, population

and clinical characteristics, intervention characteristics, and results. All study data was verified for accuracy and completeness by a second team member. A record of studies excluded at the full-text level with reasons for exclusion was maintained (Appendix H).

Many studies reported summary data based on multiple pain measurements over a specified time period (e.g., average pain or sum of pain intensity differences). When available, we reported outcomes reported at a specific time point; when necessary, data were estimated from figures provided in the studies. We extracted continuous as well as dichotomous results. We prioritized results for pain intensity in the following order: (1) mean difference in pain intensity at follow-up; (2) mean difference in pain intensity change from baseline; (3) mean difference in pain relief at followup; (4) other outcome for pain intensity. Summary data were used to supplement outcomes measured at specific time points. Effects on pain intensity were converted when necessary to a 0 to 10 scale to facilitate interpretation across studies using different scales. Opioid doses were calculated in milligram morphine equivalents using published conversions.¹ Unadjusted relative risks and mean differences with 95 percent confidence intervals were calculated if necessary, using online calculators (MedCalc).

Risk of Bias Assessment of Individual Studies

Predefined criteria were used to assess the quality of individual controlled trials, systematic reviews, and observational studies. Randomized and nonrandomized trials were evaluated using criteria and methods developed by the Cochrane Back Review Group,² cohort studies were evaluated using criteria developed by the U.S. Preventive Services Task Force,³ and studies of diagnostic accuracy were assessed using QUADAS-2.⁴ These criteria were used in conjunction with 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.⁵ Studies were assigned an overall rating of “good,” “fair,” or “poor.”

Studies rated “good” are considered to have the least risk of bias, and their results are generally considered valid. Good-quality intervention studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocating patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes.

Studies rated “fair” are susceptible to some bias, though not enough to invalidate the results. These studies may not meet all the criteria for a rating of good quality, but no flaw or combination of flaws is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The fair-quality category is broad, and studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are likely to be valid, while others may be only possibly valid.

Studies rated “poor” have significant flaws that imply biases of various types that may invalidate the results. They have a serious or “fatal” flaw (or combination of flaws) in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies are at least as likely to reflect flaws in the study design as to show true difference between the compared interventions. We did not exclude studies rated poor quality a priori, but poor-quality studies were considered less reliable and given less weight than higher-quality studies when synthesizing the evidence, particularly when discrepancies between studies were present.

Two team members independently assessed quality. Disagreements were resolved by consensus.

Data Synthesis and Analysis

We constructed evidence tables showing study characteristics, results, and quality ratings for all included studies, and summary tables to highlight the main findings, organized by Key Question (acute pain condition).

Meta-analyses were limited by the small number of studies for each comparison and outcome, methodological limitations in the studies, and variability in the studies, including methods for measuring outcomes.⁶ Comparisons and outcomes for which there were sufficient studies to perform meta-analyses were limited to opioids versus NSAIDs or acetaminophen for dental pain and kidney stone pain, for the outcomes rescue or repeat medication use and selected harms. Meta-analyses were conducted using Review Manager 5.3 (The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). Otherwise, evidence synthesis was qualitative.

Key Questions addressed how the comparative effectiveness and harms varied according to patient demographics, medical and psychiatric comorbidities, pain types, treatment features and dosing strategies. Although planned techniques to assess these factors included sensitivity and stratified analyses, evidence was too limited to apply these techniques.

The magnitude of effects for pain and function was classified using the same system used in other recent AHRQ reviews on pain conducted at our Evidence-based Practice Center (EPC).⁷⁻¹¹ Using the same classifications provides a consistent benchmark for comparing results of pain interventions across acute and chronic pain conditions. Based on these criteria, a small/slight effect is defined for pain as a mean between-group difference following treatment of 5 to 10 points on a 0- to 100-point visual analog scale (VAS), 0.5 to 1.0 points on a 0- to 10-point numeric rating scale, or equivalent; for function as a mean difference of 5 to 10 points on the 0- to 100-point Oswestry Disability Index (ODI) or 1 to 2 points on the 0- to 24-point Roland-Morris Disability Questionnaire (RDQ), or equivalent; and for any outcome as a standardized mean difference (SMD) of 0.2 to 0.5. A moderate effect was defined for pain as a mean difference of 10 to 20 points on a 0- to 100-point VAS, for function as a mean difference of 10 to 20 points on the ODI or 2 to 5 points on the RDQ, and for any outcome as an SMD of 0.5 to 0.8. Large/substantial effects were defined as greater than moderate. We applied similar thresholds to other outcomes measures. Small effects using this system may be below published thresholds for clinically meaningful effects. However, there is variability across individual patients regarding what constitutes a clinically meaningful effect, which is influenced by a number of factors such as preferences, duration and type of chronic pain, baseline symptom severity, harms, and costs. For some patients a small improvement in pain or function using a treatment with low cost or no serious harms may be important.

Grading the Strength of the Body of Evidence

Regardless of whether evidence was synthesized quantitatively or qualitatively, the strength of evidence for each Key Question/body of evidence was initially assessed by one researcher for each clinical outcome (see PICOTS) by using the approach described in the AHRQ Methods Guide.⁵ To ensure consistency and validity of the assessment, the strength of evidence grade was reviewed by the entire team of investigators prior to assigning a final grade. The strength of evidence grades were based on the following factors:

- Study limitations (low, medium, or high level of study limitations)

- Consistency (consistent, inconsistent, or unknown/not applicable)
- Directness (direct or indirect)
- Precision (precise or imprecise)
- Reporting bias (suspected or undetected)

Each body of evidence was assigned an overall strength of evidence grade of high, moderate, low, or insufficient based on the assessment of the above domains:

- High—We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
- Moderate—We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- Low—We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient—We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Plain-language statements are used in the Main Points and the Evidence Summary to convey the strength of evidence (SOE). High SOE is described as "is associated with" or simply "reduces/increases;" moderate SOE is described as "probably;" and low SOE is described as "might be."

Peer Review and Public Commentary

Peer reviewers were invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC will consider all peer review comments prior to finalization of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

Assessing Applicability

Applicability was assessed in accordance with the AHRQ Methods Guide,¹² which is based on the PICOTS framework. Applicability addresses the extent to which outcomes associated with an intervention are likely to be similar across different patients and settings in clinical practice based on the populations, interventions, comparisons, and outcomes evaluated in the

studies. For example, exclusion of acute pain patients with psychiatric comorbidities reduces applicability to clinical practice since many patients with acute pain have such comorbidities, and may respond more poorly to treatment. Factors that may affect applicability which we have identified a priori include eligibility criteria and patient factors (e.g., demographic characteristics, duration or severity of pain, presence of medical and psychiatric comorbidities, event rates and symptom severity in treatment and control groups), intervention factors (e.g., dose and duration of therapy, intensity and frequency of monitoring, level of adherence support, use of co-interventions), comparisons (e.g., type of comparator, effectiveness and feasibility of active comparators), outcomes (e.g., use of unvalidated or nonstandardized outcomes, measurement of short-term or surrogate outcomes), settings (e.g., clinical setting, country), and study design features (e.g., use of run-in periods). We will use information regarding these factors to assess the situations in which the evidence is most relevant and to evaluate applicability to real-world clinical practice in typical U.S. settings, summarizing applicability assessments qualitatively.

Appendix B References

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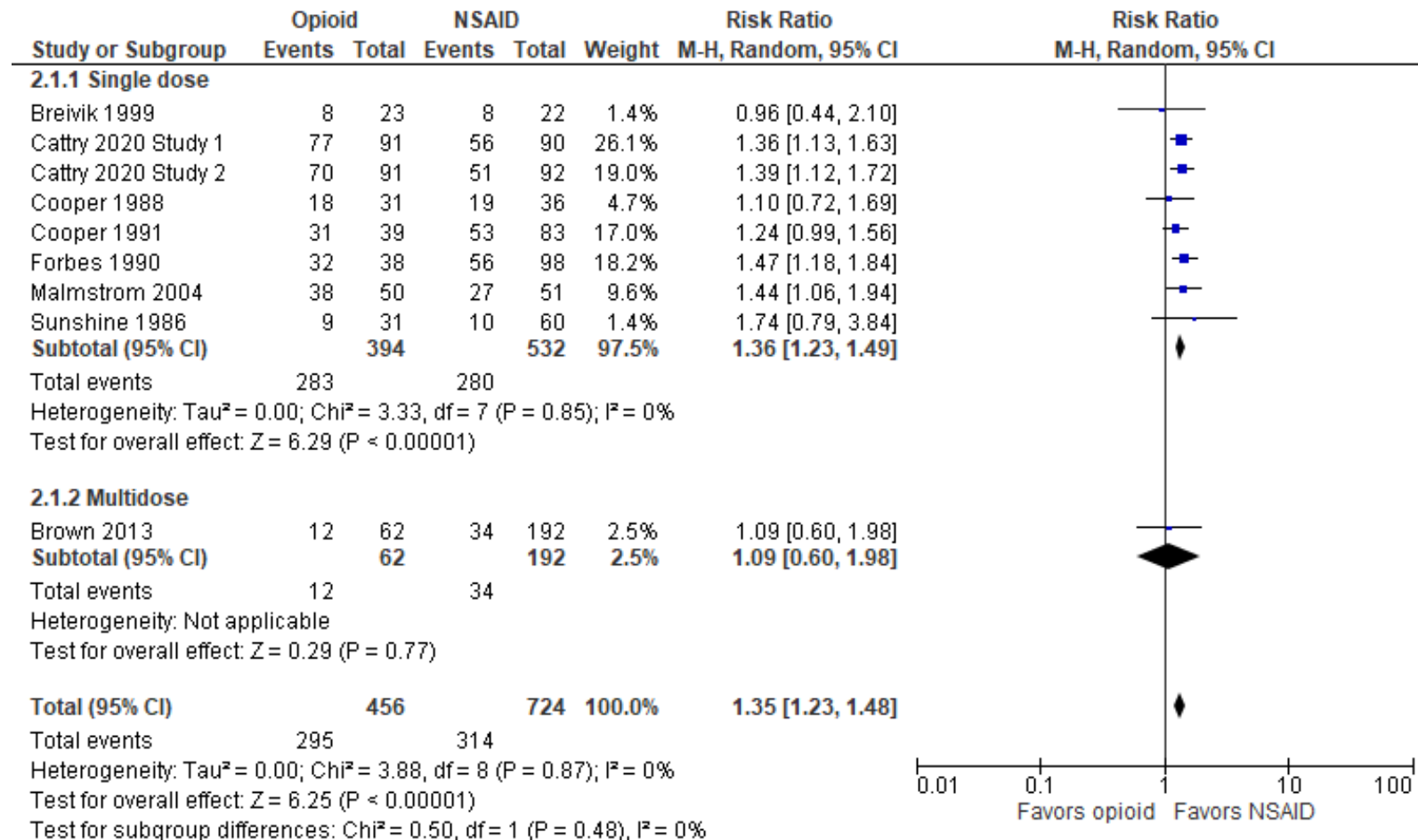
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Appendix D. Forest Plots

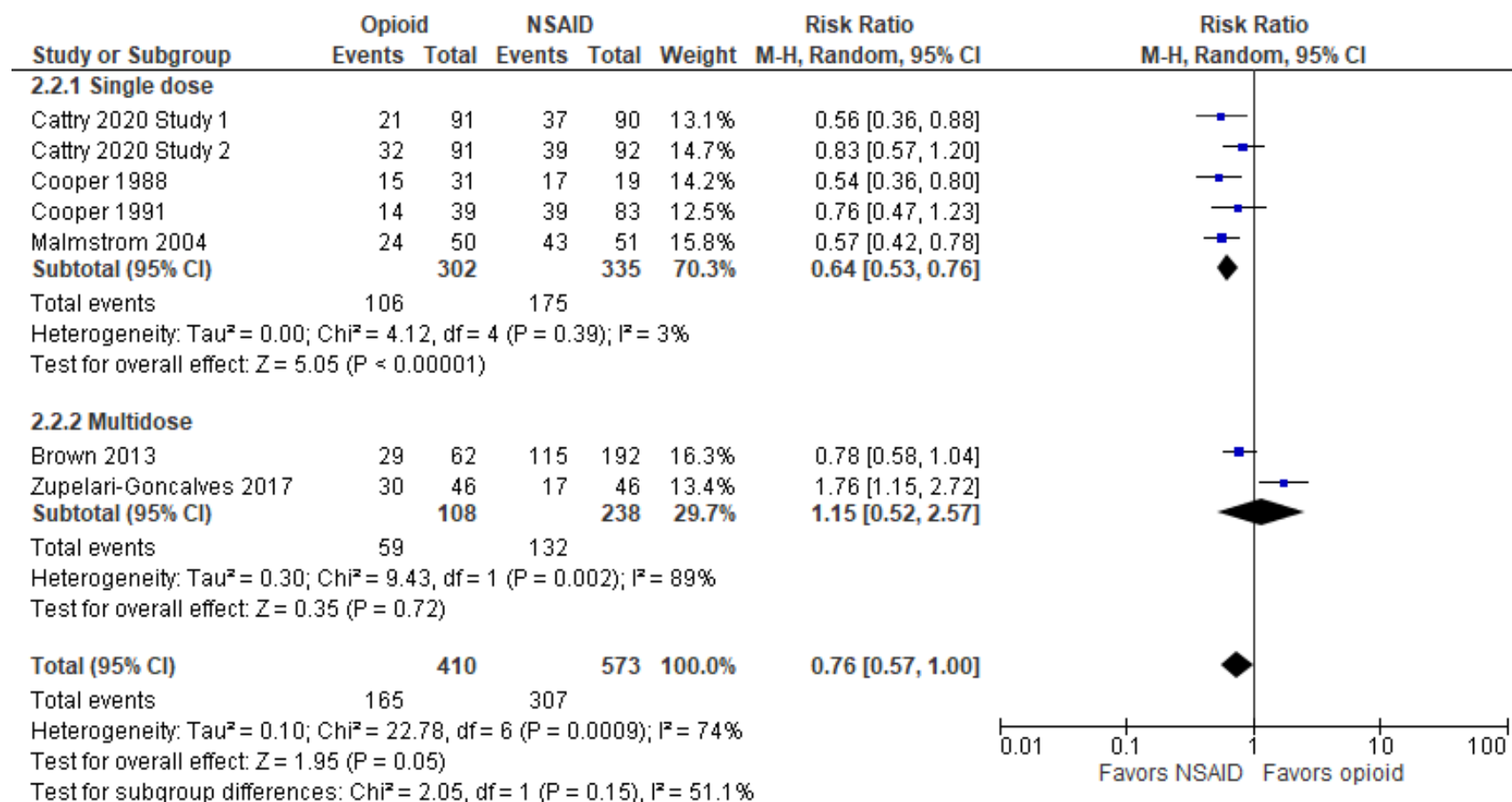
Key Question 6. Dental Pain

Figure D-1. Rescue or repeat medication use for opioid versus NSAID for dental pain



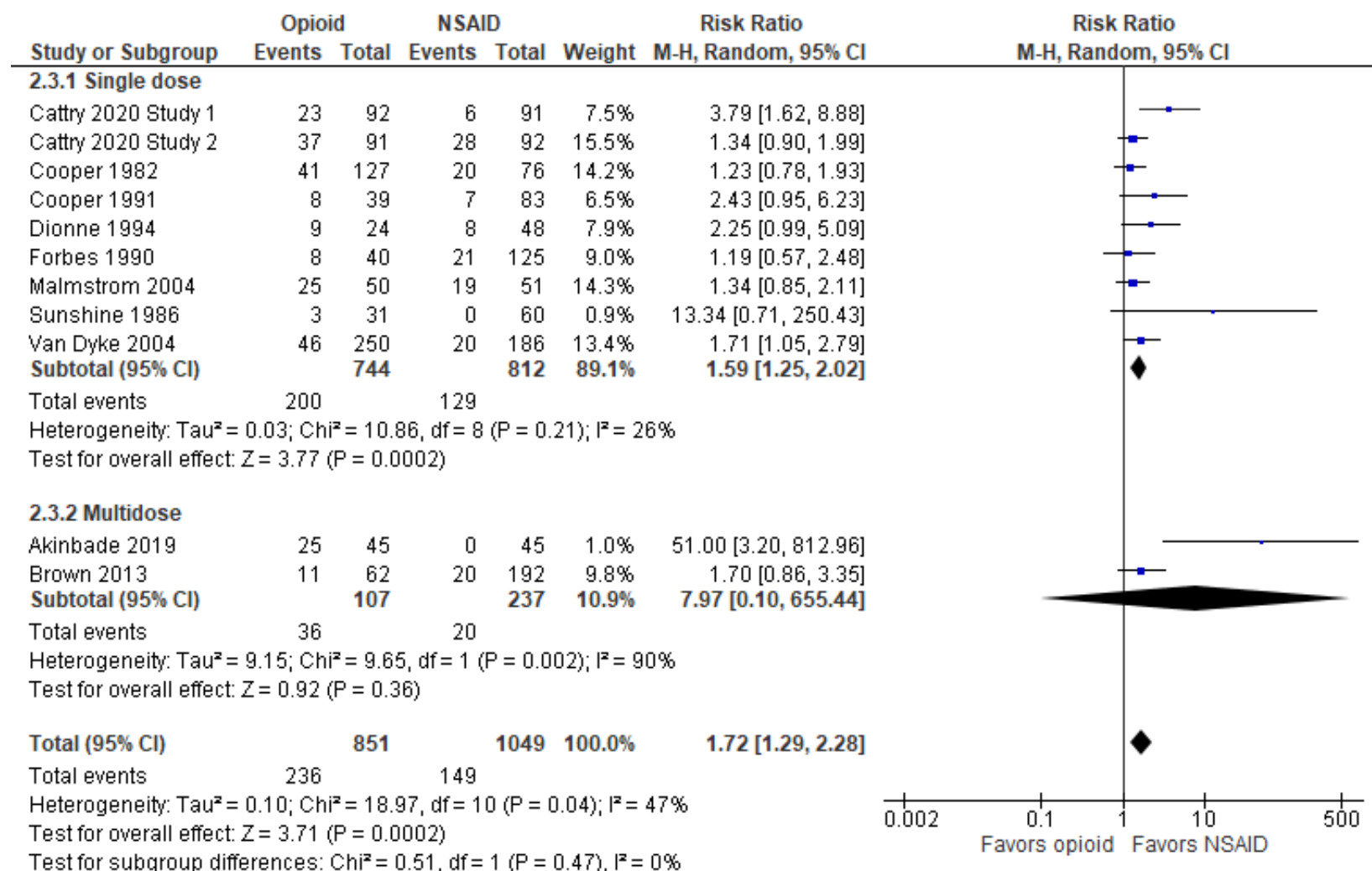
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

Figure D-2. Medication rated very good or excellent for opioid versus NSAID for dental pain



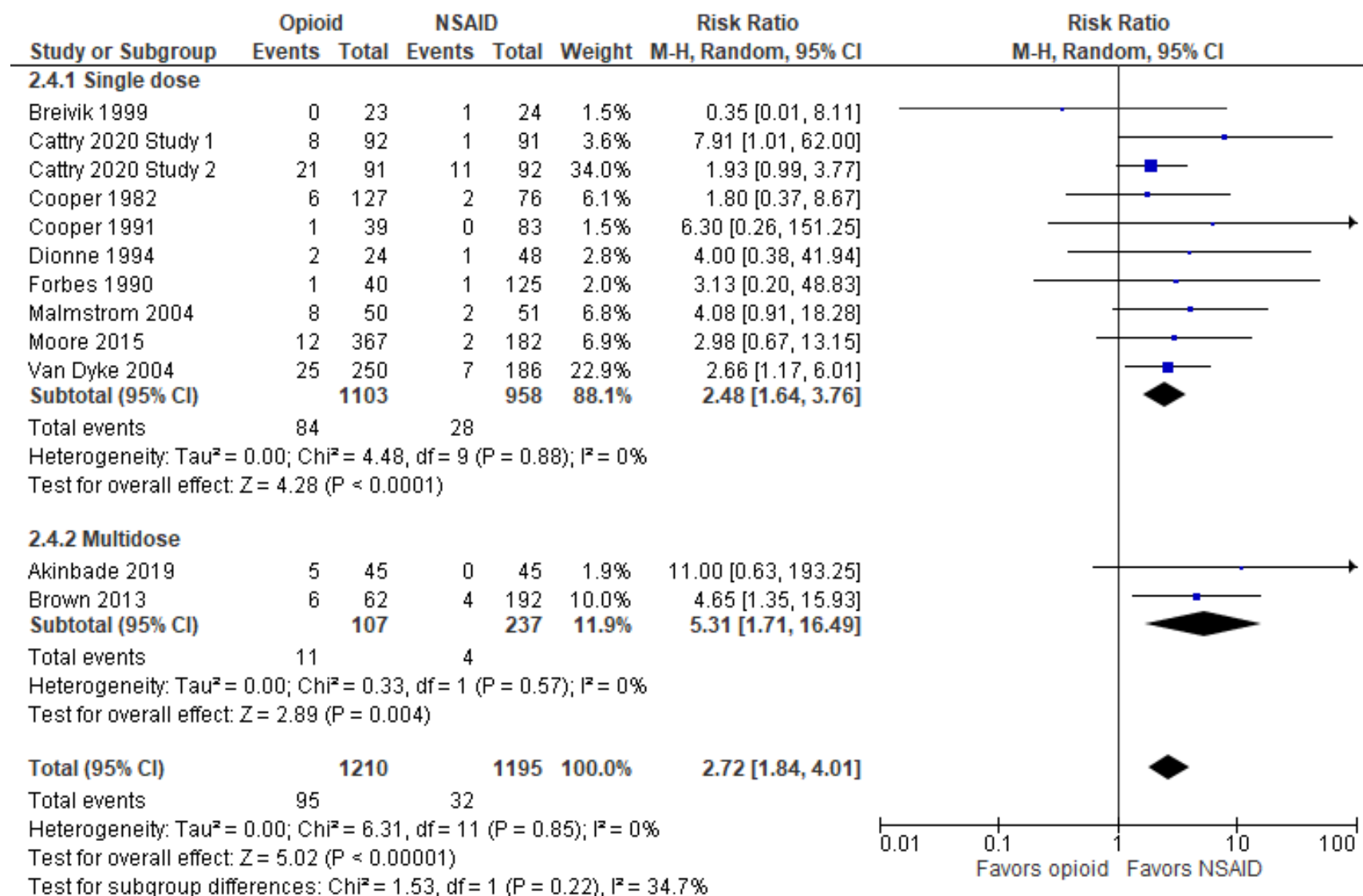
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

Figure D-3. Any adverse event for opioid versus NSAID for dental pain



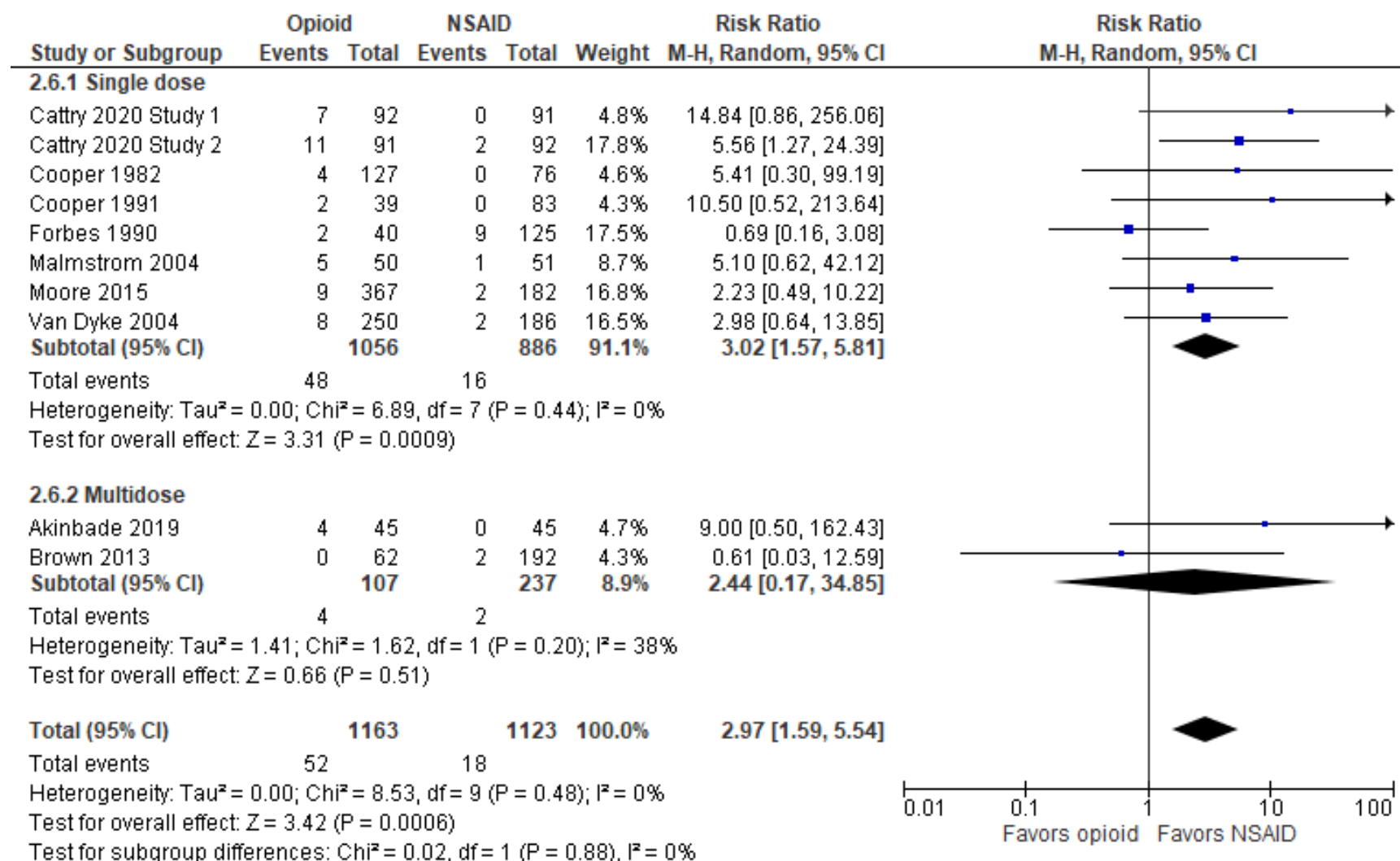
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

Figure D-4. Nausea for opioid versus NSAID for dental pain



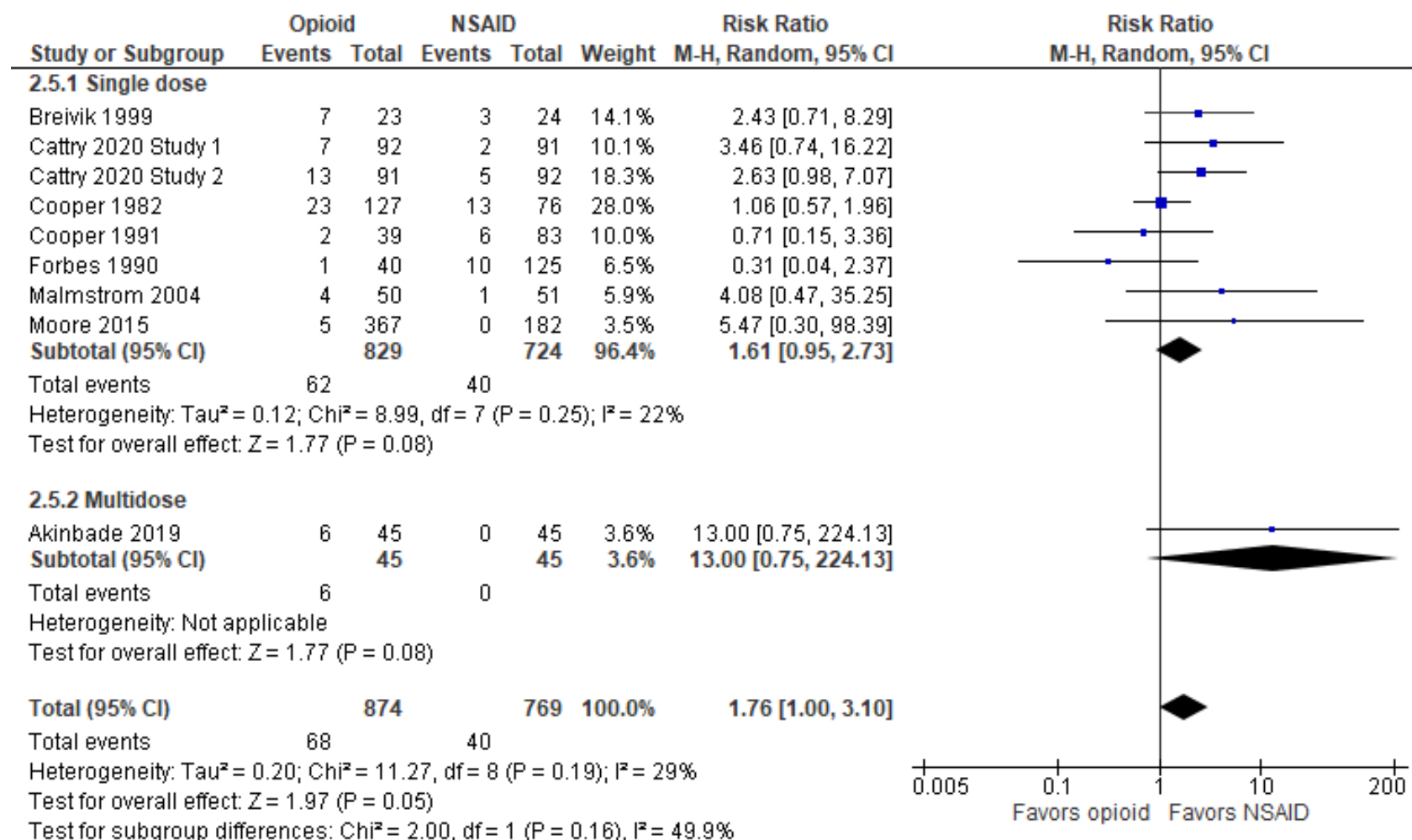
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

Figure D-5. Dizziness for opioid versus NSAID for dental pain



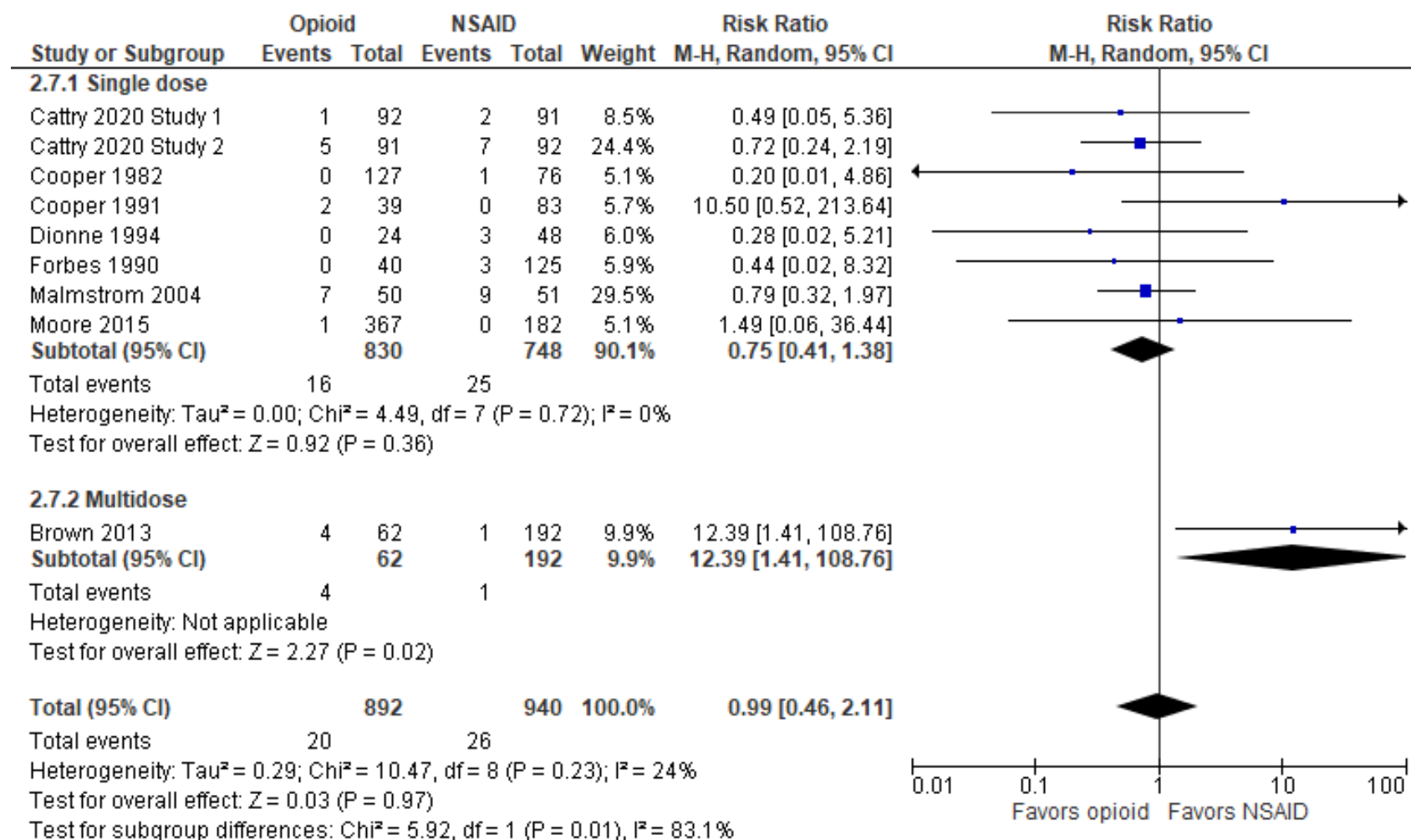
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

Figure D-6. Drowsiness for opioid versus NSAID for dental pain



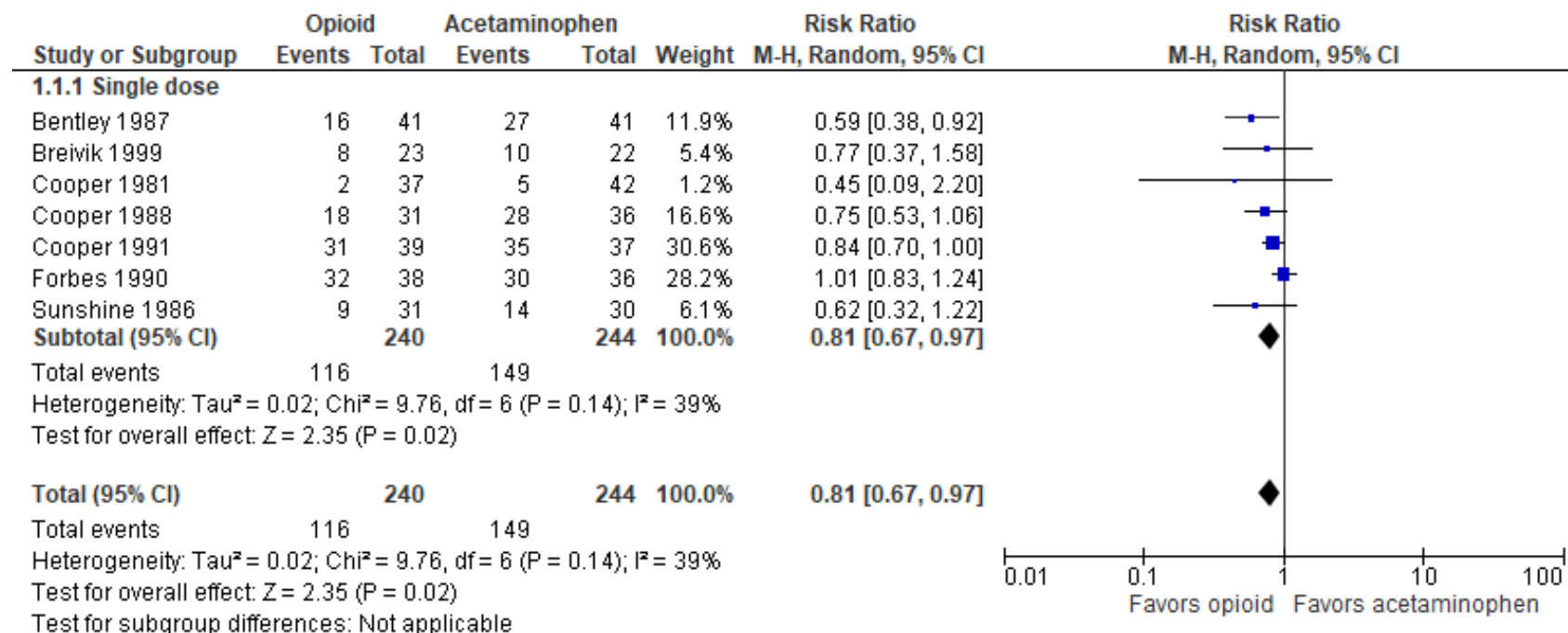
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

Figure D-7. Headache for opioid versus NSAID for dental pain



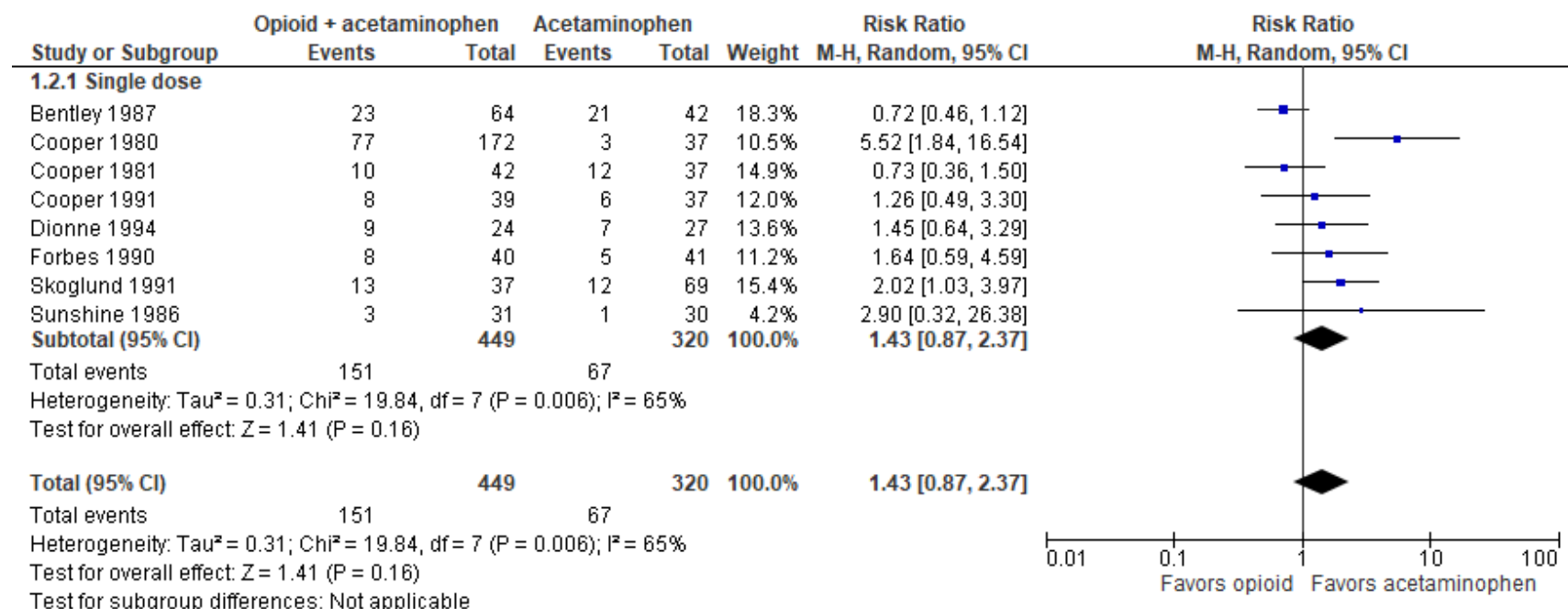
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

Figure D-8. Rescue or repeat medication use for opioid versus acetaminophen for dental pain



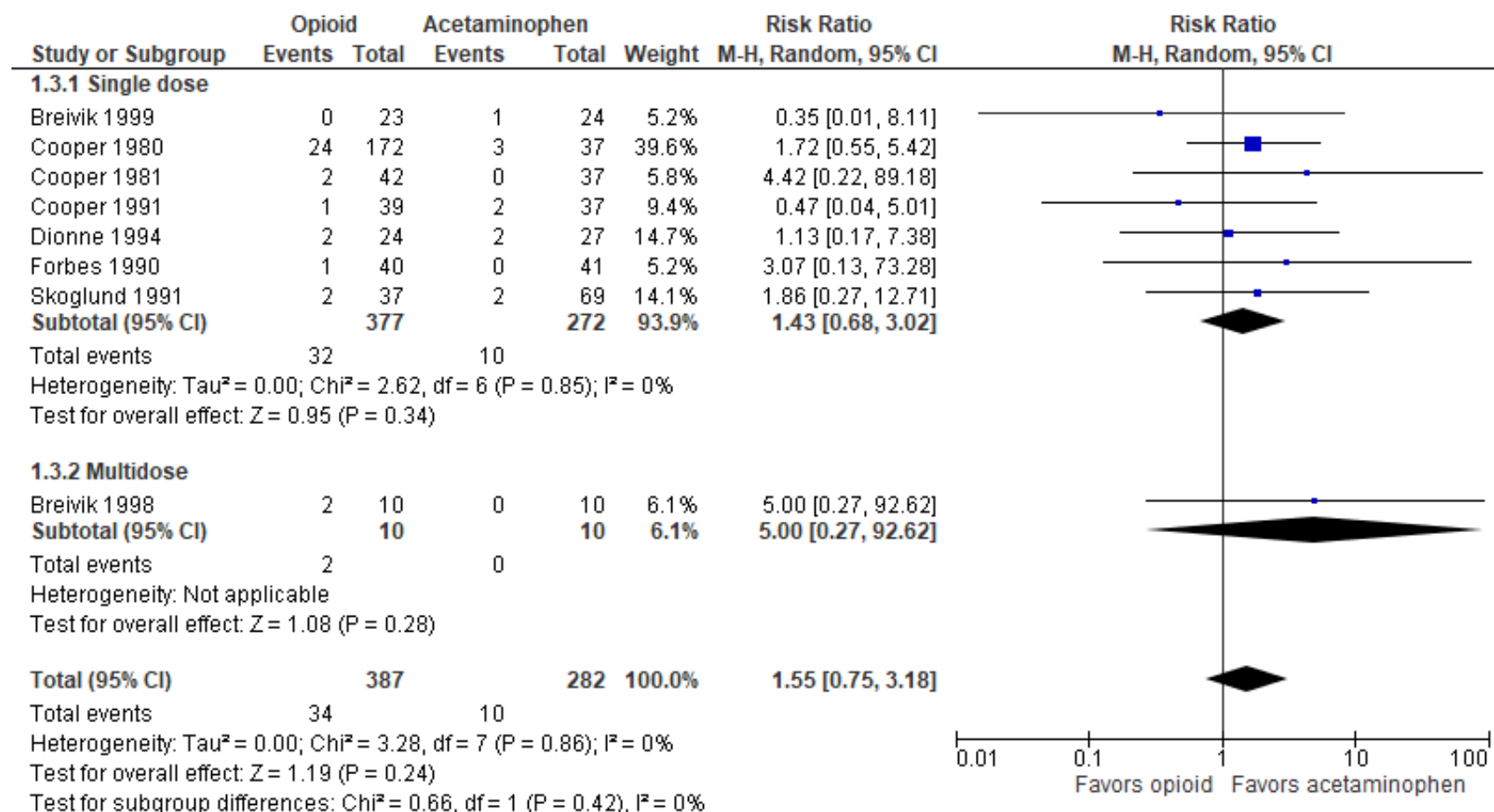
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel

Figure D-9. Any adverse event for opioid + acetaminophen versus acetaminophen for dental pain



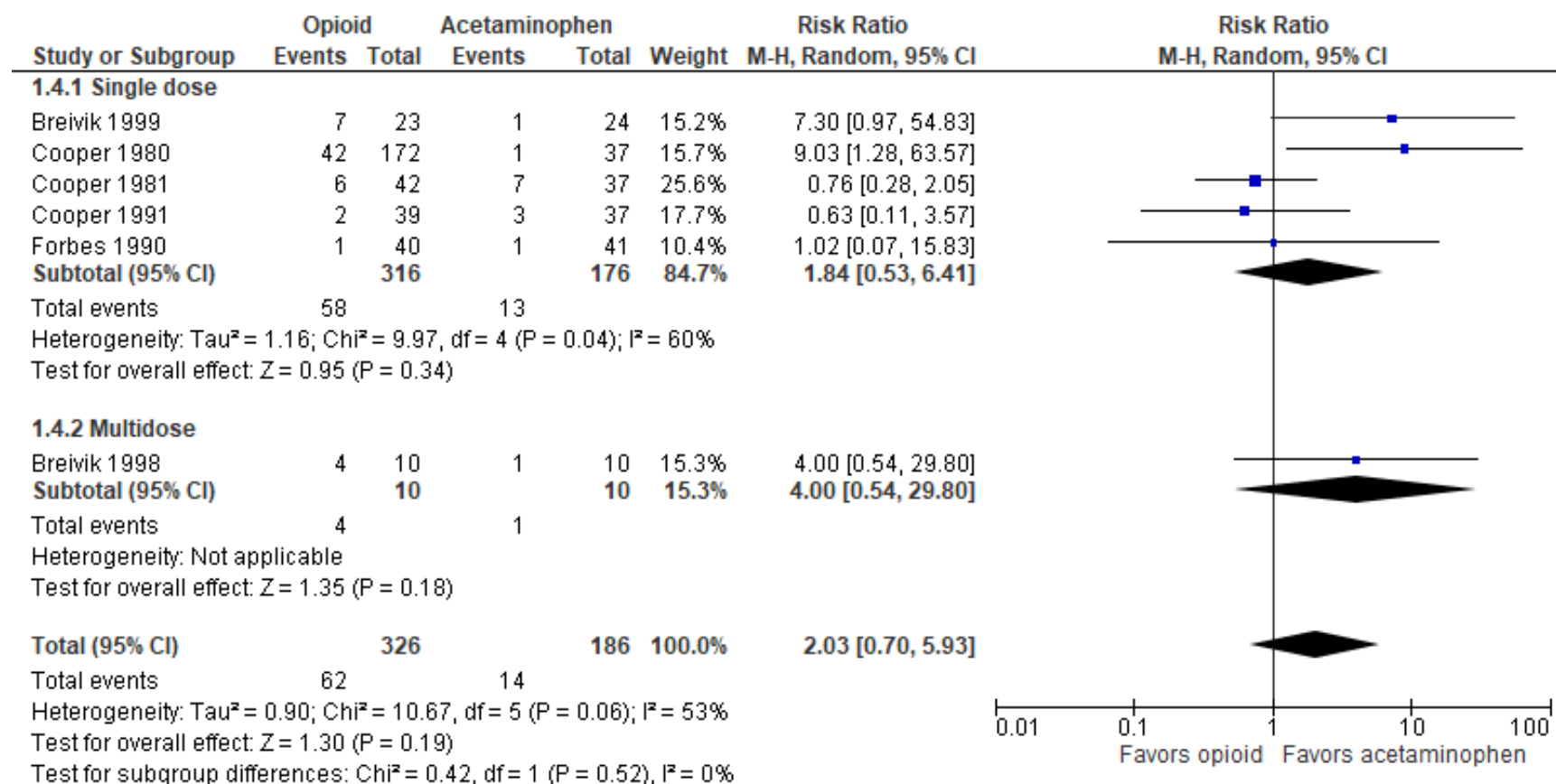
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel

Figure D-10. Nausea for opioid versus acetaminophen for dental pain



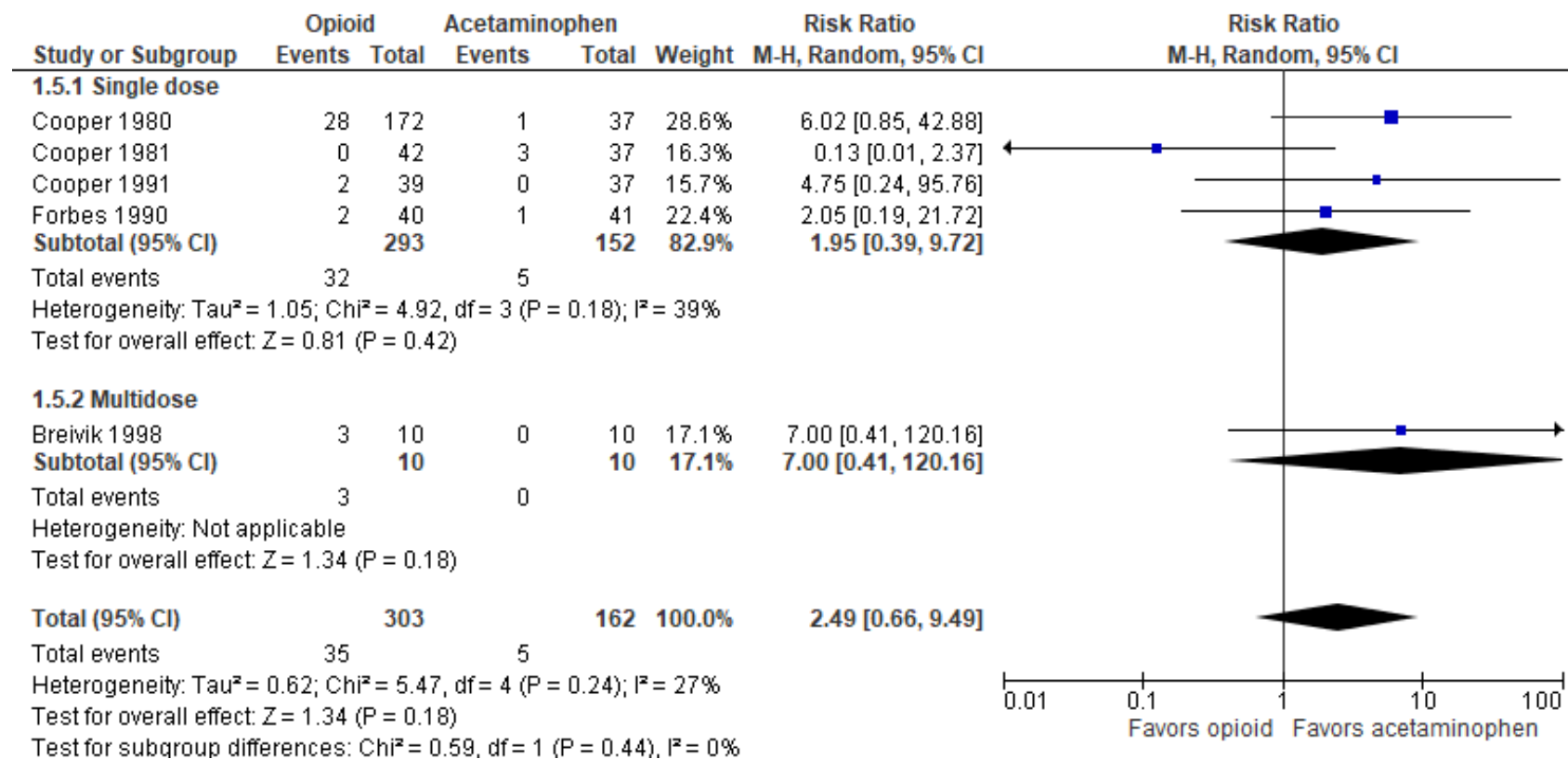
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel

Figure D-11. Drowsiness for opioid versus acetaminophen for dental pain



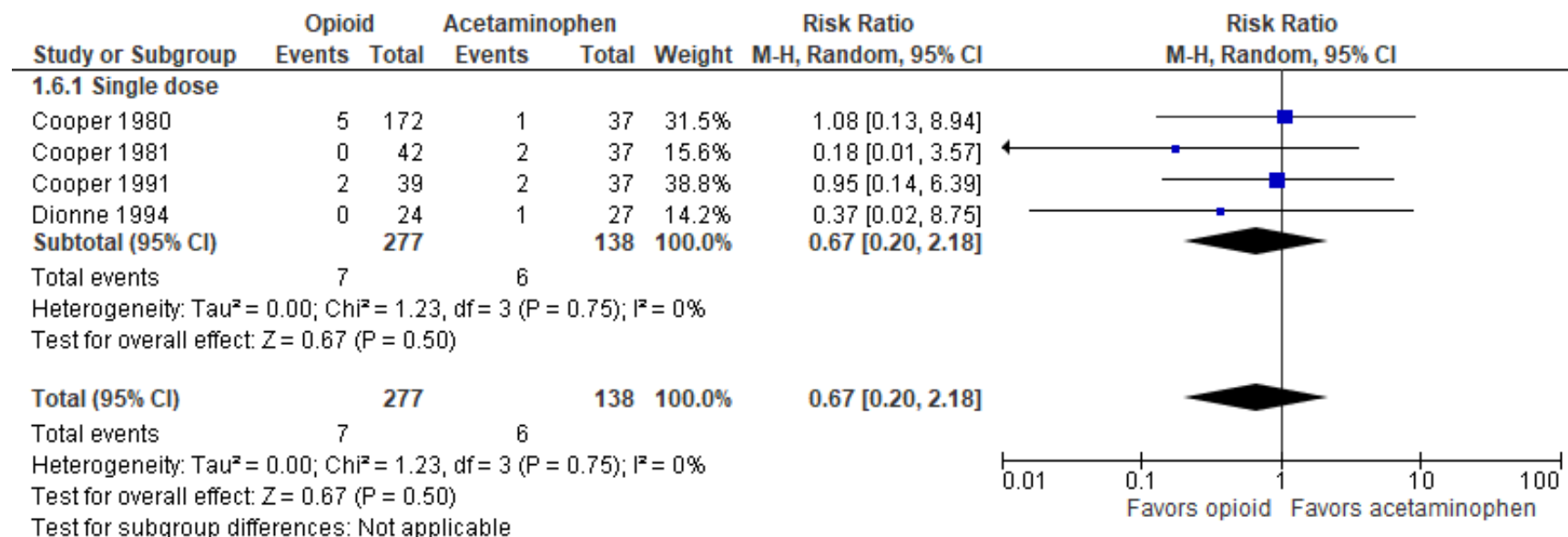
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel

Figure D-12. Dizziness for opioid versus acetaminophen for dental pain



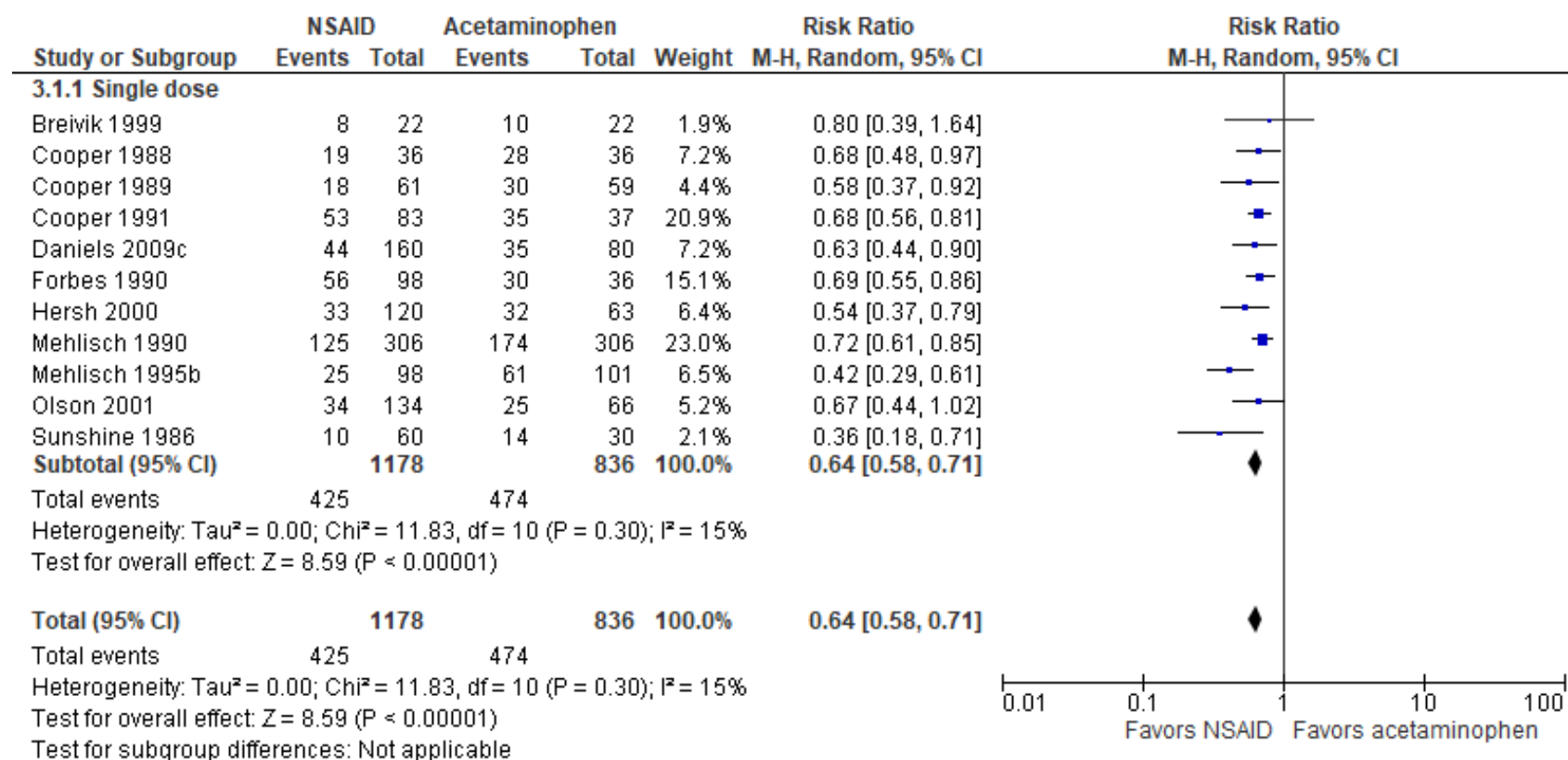
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel

Figure D-13. Headache for opioid versus acetaminophen for dental pain



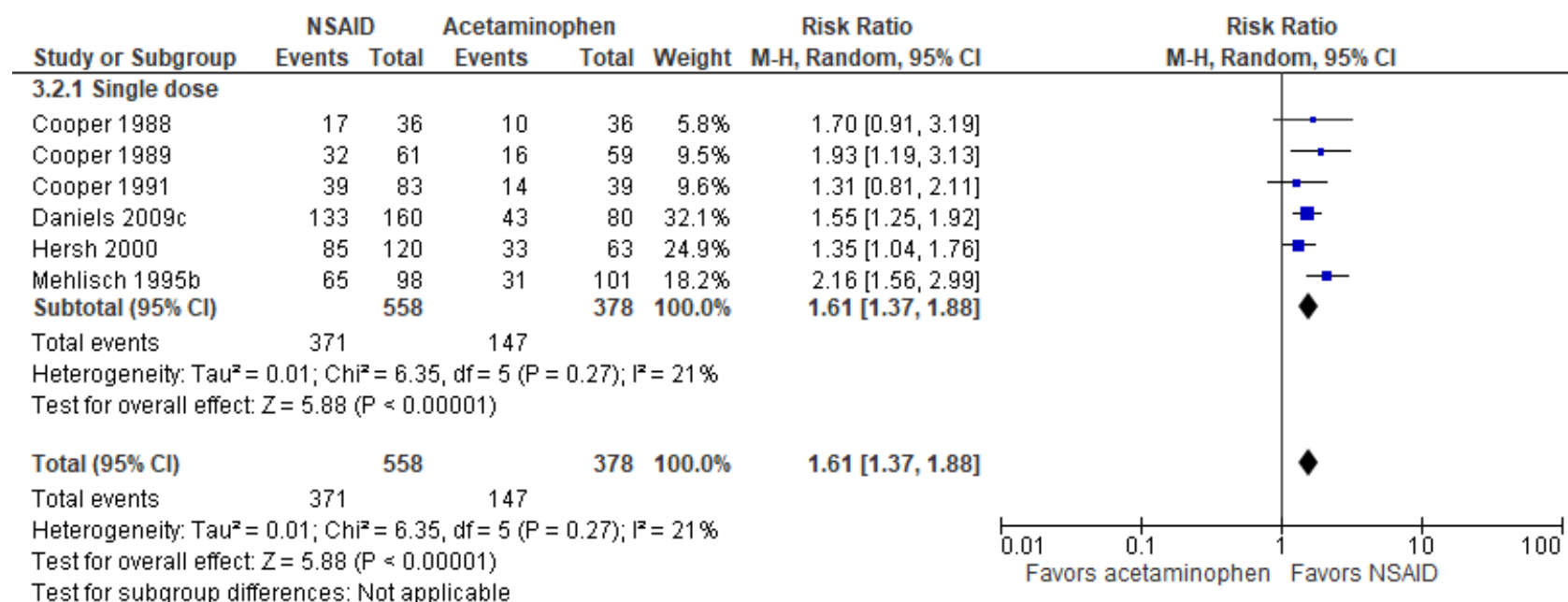
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel

Figure D-14. Rescue or repeat medication use for NSAID versus acetaminophen for dental pain



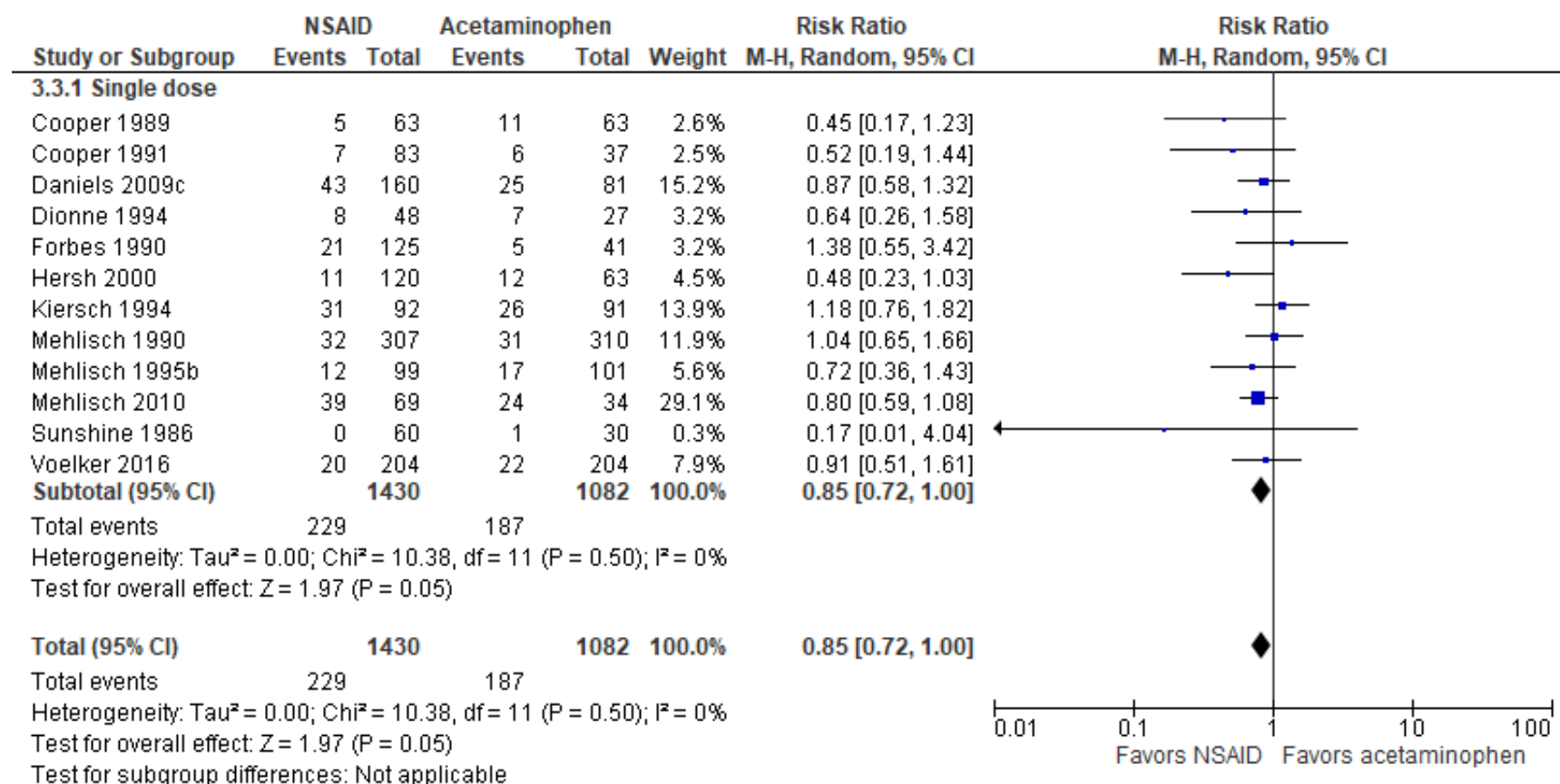
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

Figure D-15. Medication rated very good or excellent for NSAID versus acetaminophen for dental pain



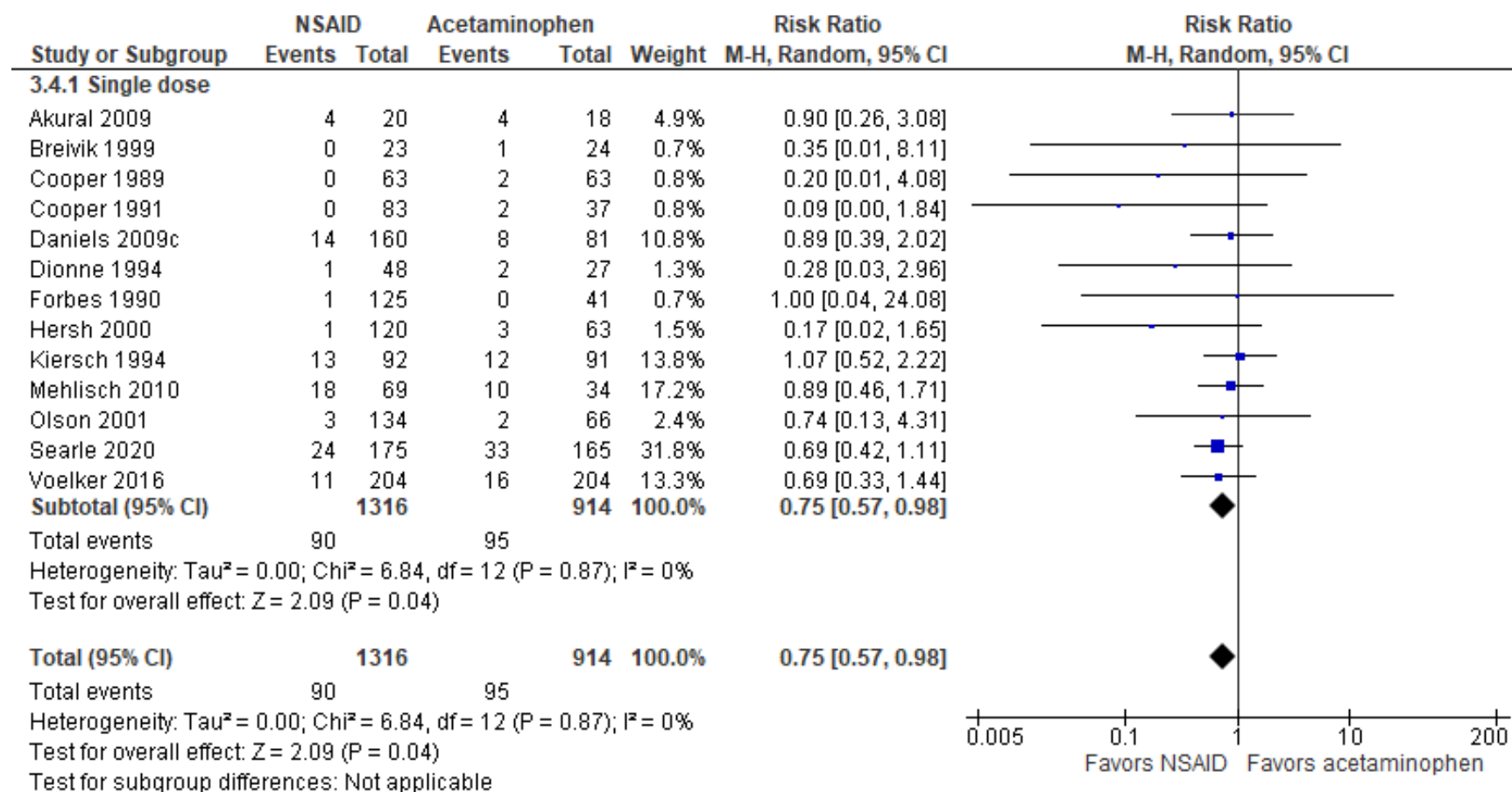
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

Figure D-16. Any adverse event for NSAID versus acetaminophen for dental pain



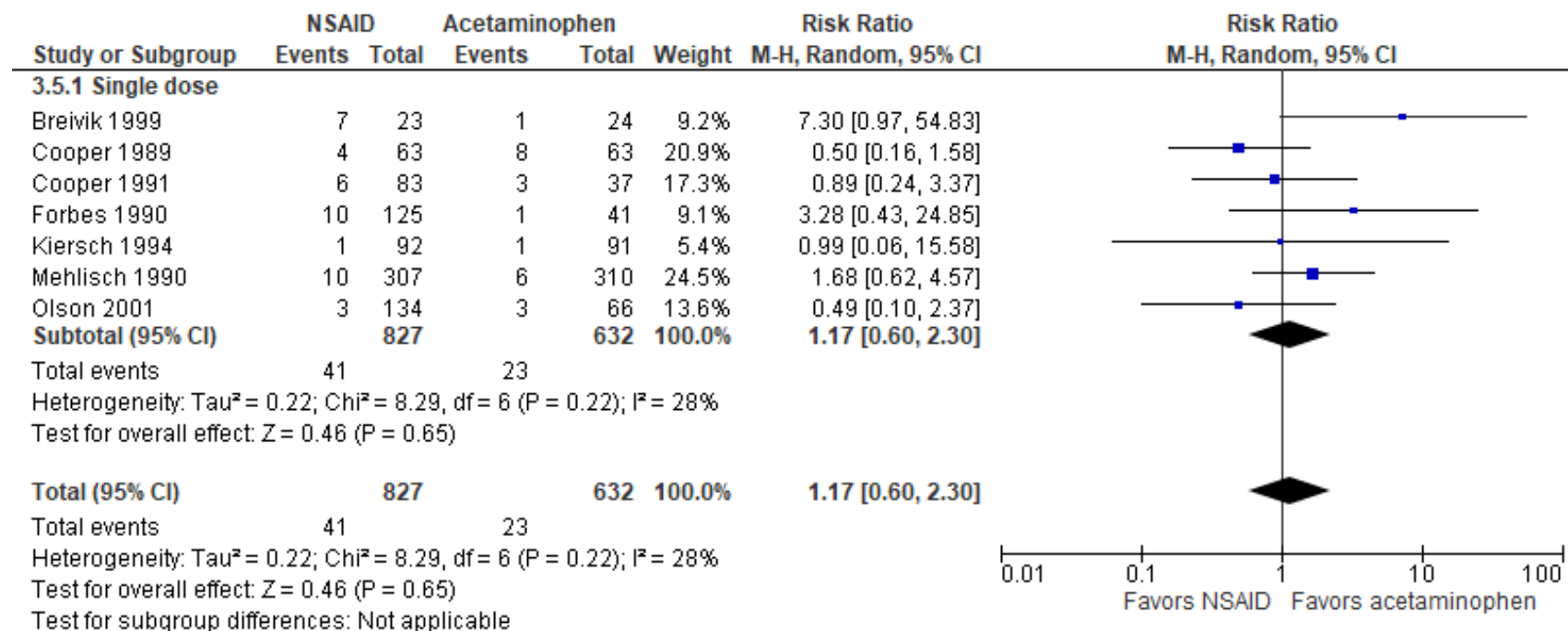
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

Figure D-17. Nausea for NSAID versus acetaminophen for dental pain



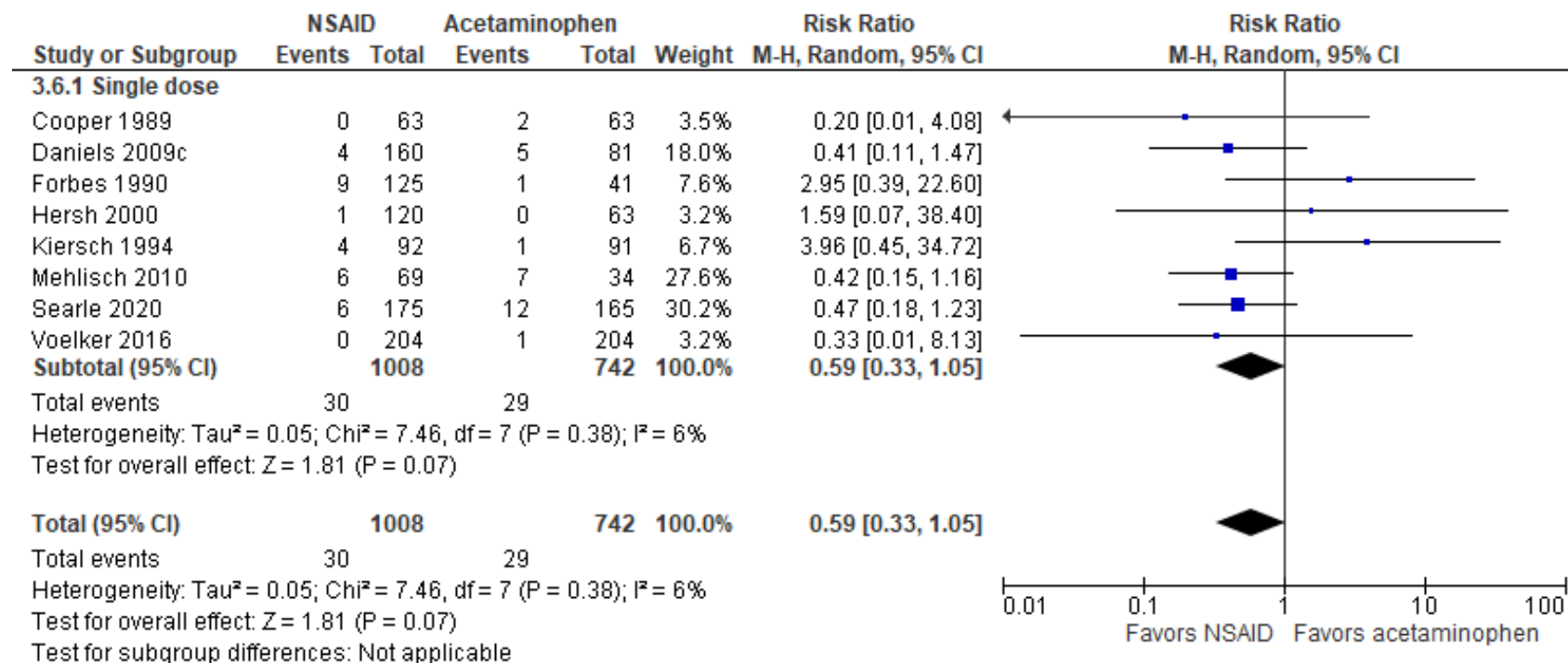
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

Figure D-18. Drowsiness for NSAID versus acetaminophen for dental pain



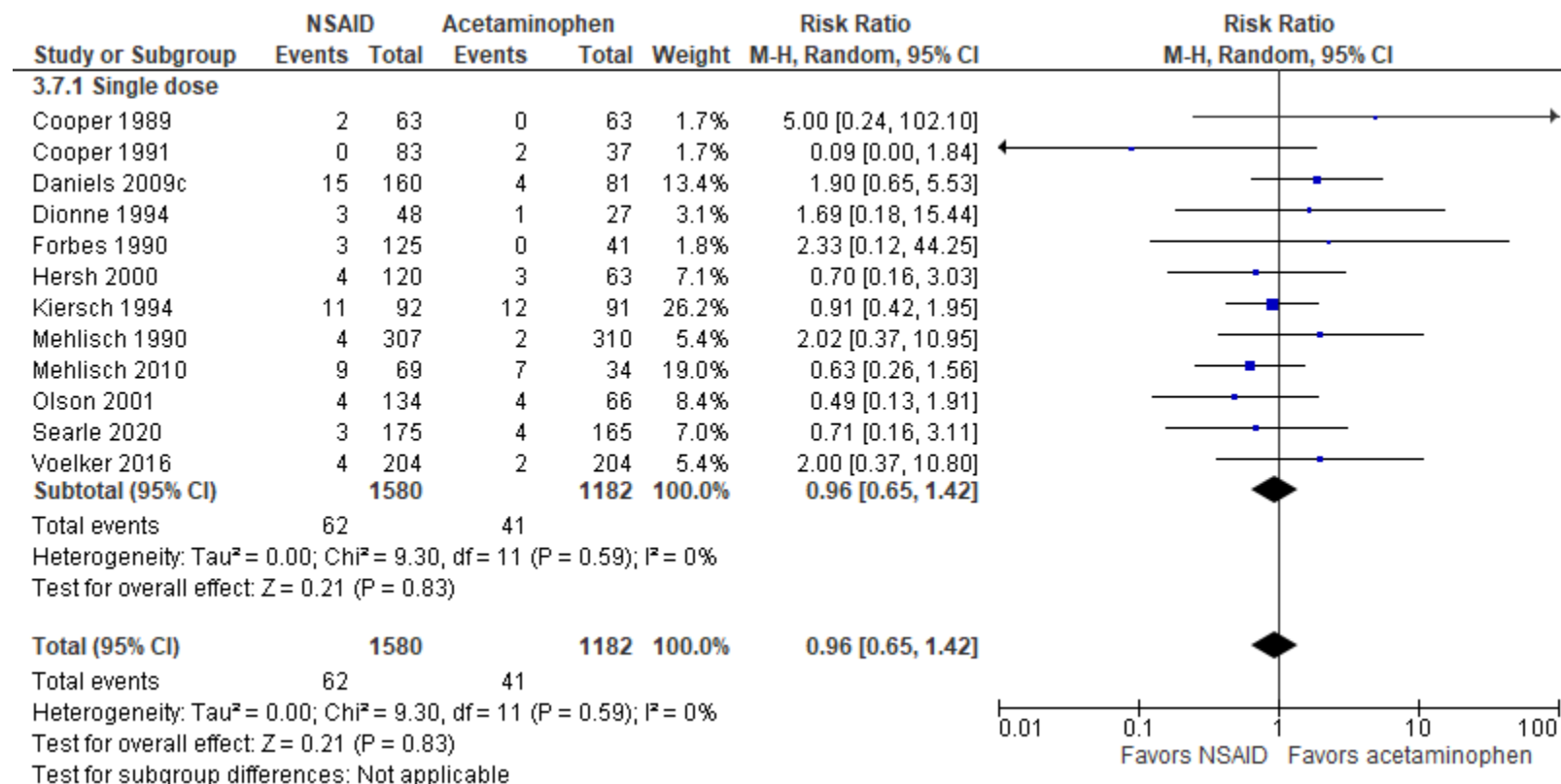
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

Figure D-19. Dizziness for NSAID versus acetaminophen for dental pain



Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

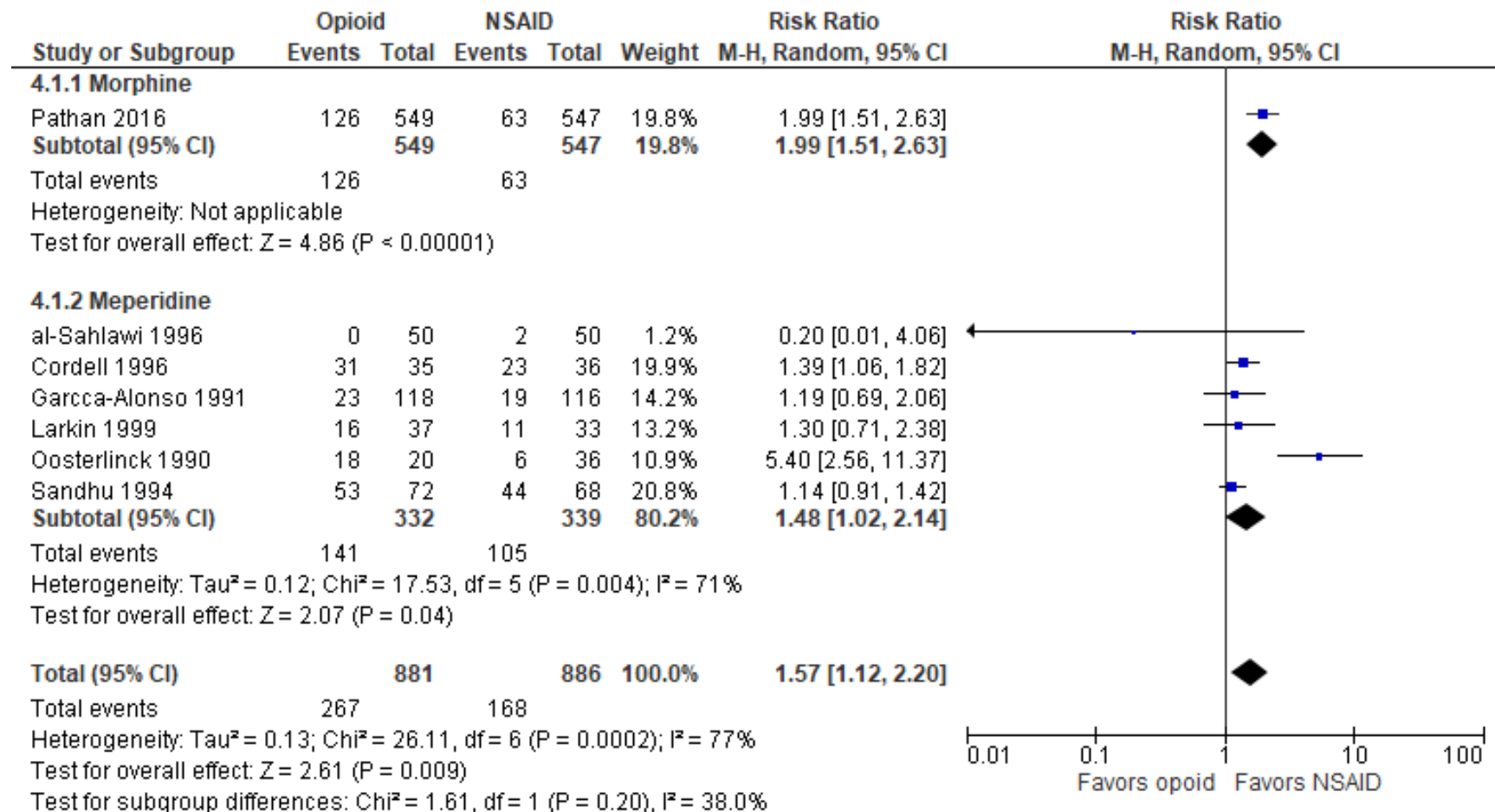
Figure D-20. Headache for NSAID versus acetaminophen for dental pain



Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

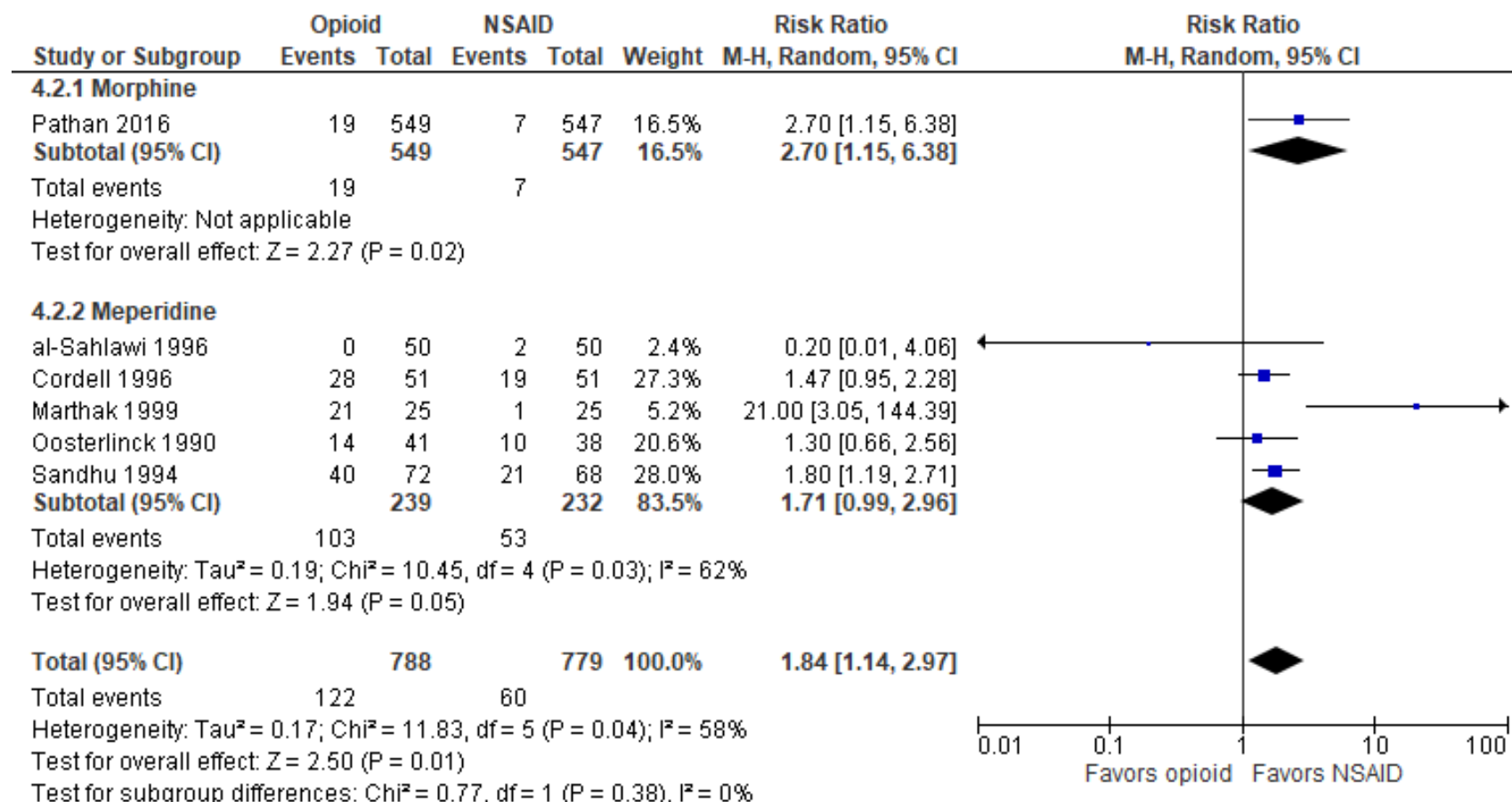
Key Question 7. Kidney Stone Pain

Figure D-21. Rescue or repeat medication use for opioid versus NSAID for acute renal colic



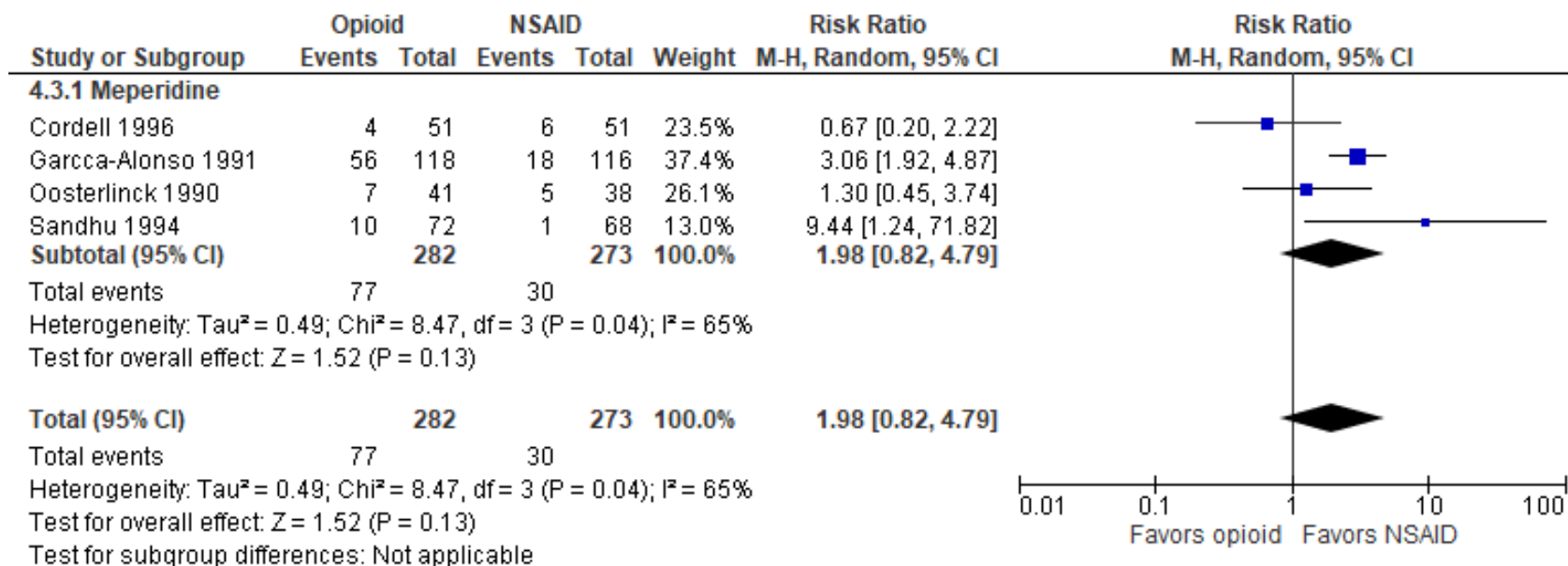
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

Figure D-22. Any adverse event for opioid versus NSAID for acute renal colic



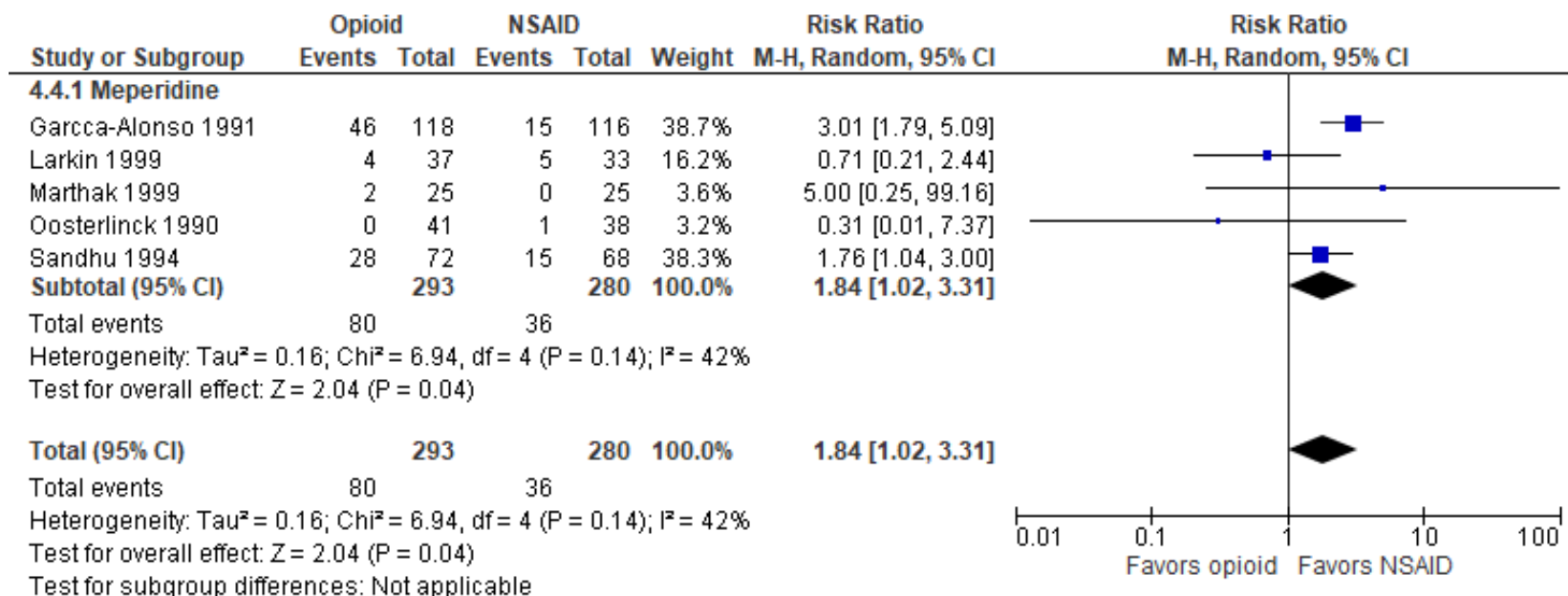
Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

Figure D-23. Somnolence for opioid versus NSAID for acute renal colic



Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

Figure D-24. Nausea for opioid versus NSAID for acute renal colic



Abbreviations: CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; NSAID = nonsteroidal anti-inflammatory drug

Appendix E. Evidence Tables

Shown in associated Excel files.

Appendix F. Risk of Bias Assessment

Shown in associated Excel files.

Appendix G. Details on Strength of Evidence

Table G-1. Treatments for acute pain: findings and strength of evidence for interventions

Intervention	Outcomes	Timing of Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Quality	Consistency	Findings	SOE
KQ 1: Acute low back pain Opioid vs. NSAID	Pain	<1 d; 1 d to <1 w	1	113	Direct	Precise	Fair	Unable to assess	No differences	Low
	Serious AEs, study withdrawal due to AEs, any AE	<1 d; 1 d to 1 w	1	113	Direct	Precise	Fair	Unable to assess	Higher risk with opioid	Low
KQ 1: Acute low back pain Opioid vs. muscle relaxant	Pain, function	1 to <2 w; ≥4 w	1	216	Direct	Imprecise	Good	Unable to assess	No differences	Low
	Dizziness, nausea or vomiting	1 to <2 w; ≥4 w	1	216	Direct	Precise	Good	Unable to assess	Higher risk with opioid	Moderate
KQ 1: Acute low back pain Muscle relaxant vs. benzodiazepine	Pain	1 d to <1 w	2	110	Direct	Imprecise	Fair	Consistent	Small to moderate decrease in pain with muscle relaxant	Low
	AEs	1 d to <1 w	2	110	Direct	Imprecise	Fair	Inconsistent	Unable to determine	Insufficient
KQ 1: Acute low back pain NSAID or muscle relaxant vs. manipulation	Pain, function	1 to <2, 2 to <4, and ≥4 w	3	320	Direct	Precise	Fair	Inconsistent	Likely no differences	Low
	AEs	1 to <2, 2 to <4, and ≥4 w	3	320	Direct	Imprecise	Fair	Inconsistent	Unable to determine	Insufficient
KQ 1: Acute low back pain Acupuncture vs. NSAID	Pain, function	2 to <4 w and ≥4 w	1	58	Direct	Imprecise	Fair	Unable to assess	Moderate improvement in pain and function with acupuncture	Low
KQ 1: Acute low back pain Exercise vs. usual care	Pain, function	1 to 52 w	2	194	Direct	Imprecise	Fair	Consistent	No differences	Low
	AEs	--	--	--	--	--	--	--	No evidence	Insufficient

Intervention	Outcomes	Timing of Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Quality	Consistency	Findings	SOE
KQ 1: Acute low back pain Exercise vs. bed rest	Pain, function	1 to 52 w	3	384	Direct	Precise	Fair	Consistent	No differences	Moderate
	Sick days	2 to 4 w and ≥ 4 w	1	100	Direct	Precise	Fair	Unable to assess	Fewer sick days with opioid	Low
	AEs	1 to 52 w	3	384	Direct	Imprecise	Fair	Unable to assess	Sparse data	Insufficient
KQ 1: Acute low back pain Traditional Chinese acupuncture vs. sham or usual care	Pain, function	2 to <4 w	1	261	Direct	Imprecise	Fair	Inconsistency based on type of sham	Acupuncture decreased persistent pain vs. non-penetrating sham or usual care, but not needle sham	Low
	Pain, function	≥ 4 w	1	261	Direct	Imprecise	Fair	Unable to assess	No differences	Low
	Serious AEs, study withdrawal due to AEs	2 to <4 w, ≥ 4 w	1	261	Direct	Imprecise	Fair	Unable to assess	No events reported	Low
KQ 1: Acute low back pain Brace vs. no brace, osteoporotic compression fracture	Pain, function, opioid use	2 to <4 w, ≥ 4 w	1	60	Direct	Precise	Fair	Unable to assess	No differences	Low
KQ 1: Acute low back pain Heat therapy vs. usual care or placebo	Pain, function	1 d to <1 w, 1 to <2 w, 2 to <4 w	6	425	Direct	Imprecise to precise	Fair	Consistent	Moderate improvement in pain and function with heat therapy	Low to moderate
	Adverse events	1 d to <1 w, 1 to <2 w, 2 to <4 w	6	425	Direct	Imprecise	Fair	Consistent	No serious AEs and few non-serious AEs	Low

Intervention	Outcomes	Timing of Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Quality	Consistency	Findings	SOE
KQ 1: Acute low back pain Manipulation vs. inactive controls, no radiculopathy	Pain, function	1 d to <1 w, 1 to <2 w, 2 to <4 w, or ≥4 w	6	555	Direct	Imprecise	Fair	Consistent	No differences	Low to moderate
	Adverse events	1 d to <1 w, 1 to <2 w, 2 to <4 w, or ≥4 w	6	555	Direct	Imprecise	Fair	Consistent	Limited reporting, few or no serious AEs	Low
KQ 1: Acute low back pain Manipulation vs. sham, radiculopathy	Pain	2 to <4 w, ≥4 w	1	102	Direct	Precise	Good	Unable to assess	Decreased likelihood of pain with manipulation	Low
	AEs	2 to <4 w, ≥4 w	1	102	Direct	Imprecise	Good	Unable to assess	No AEs reported in either group	Low
KQ 2: Acute neck pain Collar vs. usual activity, neck pain with radiculopathy	Pain, function	2 to <4 w, ≥4 w	1	135	Direct	Imprecise	Fair	Unable to assess	Moderate to large decrease in pain with collar, no difference in function	Low
KQ 2: Acute neck pain Brace vs. exercise, neck pain with radiculopathy	Pain, function	2 to <4 w, ≥4 w	1	139	Direct	Imprecise	Fair	Unable to assess	No differences	Low
KQ 2: Acute neck pain Exercise vs. usual activity, neck pain with radiculopathy	Pain, function	2 to <4 w, ≥4 w	1	136	Direct	Imprecise	Fair	Unable to assess	Moderate to large decrease in pain with exercise, no difference in function	Low

Intervention	Outcomes	Timing of Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Quality	Consistency	Findings	SOE
KQ 2: Acute neck pain Ultrasound vs. sham, neck pain with radiculopathy	Pain	1 to <2 w, 2 to <4 w	1	54	Direct	Imprecise	Fair	Unable to assess	No difference at 1 to <2 w, small decrease with ultrasound at 2 to <4 w	Low
KQ 2: Acute neck pain Collar vs. usual activity, whiplash neck strain	Pain, health status	≥4 weeks	1	303	Direct	Precise	Fair	Unable to assess	No difference at ≥4 weeks	Low
KQ 2: Acute neck pain Collar vs. exercise, whiplash neck strain	Pain, health status	≥4 weeks	1	297	Direct	Precise	Fair	Unable to assess	No difference at ≥4 weeks	Low
KQ 2: Acute neck pain Exercise vs. usual activity, whiplash neck strain	Pain, health status	≥4 weeks	1	296	Direct	Precise	Fair	Unable to assess	No difference at ≥4 weeks	Low
KQ 3: Other musculoskeletal pain NSAID vs. acetaminophen	Pain	<1 d, 1 d to <1 w, 1 to <2 w, ≥4 w	8	1,100	Direct	Imprecise	Good	Consistent	No differences	Moderate
KQ 3: Other musculoskeletal pain Ultrasound vs. sham	Pain	1 d to <1 w, ≥4 w	3	190	Direct	Imprecise	Fair	Consistent	No differences	Low

Intervention	Outcomes	Timing of Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Quality	Consistency	Findings	SOE
KQ 3: Other musculoskeletal pain Acupressure vs. sham acupressure or usual care	Pain, health status	1 d to <1 w, ≥4 w	1	62	Direct	Precise	Fair	Unable to assess	Moderate decrease in pain and small improvement in health status with acupressure	Low
KQ 4: Acute neuropathic pain Opioid vs. gabapentin, herpes zoster	Pain	1 to <2 w, ≥4 w	1	45	Direct	Imprecise	Fair	Unable to assess	Increased likelihood of improvement in pain	Low
	Constipation	1 to <2 w, ≥4 w	1	45	Direct	Imprecise	Fair	Unable to assess	Increased risk of constipation with opioid	Low
KQ 5: Postoperative pain Opioid vs. NSAID, single dose, various surgeries	Pain, rescue medication use	<1 d	2	421	Direct	Imprecise	Fair	Consistent	No differences	Low
KQ 5: Postoperative pain Opioid vs. NSAID, multidose course, various surgeries	Pain	1 d to <1 w	4	830	Direct	Imprecise	Fair	Inconsistent	Unable to determine	Insufficient
	Rescue medication use	1 d to <1 w	4	860	Direct	Imprecise	Fair	Consistent	RR 1.22 to 2.04	Moderate
KQ 5: Postoperative pain Opioid vs. acetaminophen, single dose, cesarean section	Pain, re-medication	<1 d	1	96	Direct	Imprecise	Fair	Unable to assess	No difference	Low

Intervention	Outcomes	Timing of Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Quality	Consistency	Findings	SOE
KQ 5: Postoperative pain Opioid vs. acetaminophen, multidose course, various surgeries	Study withdrawal due to AEs	<1 d, 1 d to <1 w	3	252	Direct	Imprecise	Fair	Consistent	Increased risk with opioid	Low
KQ 5: Postoperative pain NSAID vs. acetaminophen, single dose, various surgeries	Pain, rescue medication use	<1 d	2	113	Direct	Imprecise	Fair	Inconsistent	Unable to determine	Insufficient
KQ 5: Postoperative pain Acupuncture vs. sham, various surgeries	Pain	1 d to <1 w	2	106	Direct	Imprecise	Fair	Inconsistent	Unable to determine	Insufficient
KQ 5: Postoperative pain Acupressure vs. sham, knee surgeries	Pain	<1 d, 1 d to <1 w	2	130	Direct	Imprecise	Fair	Consistent	Unable to determine	Insufficient
	Pain medication use	<1 d, 1 d to <1 w	2	130	Direct	Imprecise	Fair	Consistent	Decreased with acupuncture	Low
	Pain intensity	<1 w	3	168	Direct	Imprecise	Fair	Consistent	No differences	Low

Intervention	Outcomes	Timing of Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Quality	Consistency	Findings	SOE
KQ 5: Postoperative pain	Pain intensity; function, QoL	2 to <4 w, ≥4 w	1	60	Direct	Imprecise	Good	Unable to assess	No differences	Low
Cold therapy vs. sham or usual care, knee surgeries	Pain medication use	<1 w	1	60	Direct	Imprecise	Good	Unable to assess	Decreased with cold therapy	Low
KQ 5: Postoperative pain Massage vs. no massage, various surgeries	Pain intensity, decreased pain medication use, anxiety	<1 d	2 to 5	733	Direct	Precise	Poor	Consistent	Moderate to large decrease with massage at <1 day, decreased pain medication use, and decreased anxiety	Low
KQ 5: Postoperative pain Music therapy vs. no music therapy, various surgeries	Pain	<1 d, 1 d to <1 w	2	148	Direct	Imprecise	Fair	Consistent	Small to moderate decrease in pain intensity	Low
KQ 5: Postoperative pain Exercise vs. no exercise, thyroid surgery	Function	1 to <2 w, ≥4 w	1	80	Direct	Imprecise	Fair	Unable to assess	Large decrease with exercise at 1 week, no difference at 1 month	Low
KQ 5: Postoperative pain TENS vs. sham TENS, liposuction	Pain intensity, analgesic use	<1 d, 1 d to <1 w	1	42	Direct	Imprecise	Fair	Unable to assess	Moderate to large decrease in pain intensity and decreased analgesic use with TENS	Low

Intervention	Outcomes	Timing of Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Quality	Consistency	Findings	SOE
KQ 6: Dental pain Opioid + acetaminophen vs. acetaminophen, single dose	Pain	<1 d	11	828	Direct	Precise	Fair	Inconsistent	Inconsistent effects on pain intensity, but larger sum of pain intensity differences with opioid	Moderate (for sum of pain intensity differences)
	Rescue or repeat medication use	<1 d	7	484	Direct	Precise	Fair	Consistent	RR 0.81, 95% CI 0.56 to 0.97	Moderate
KQ 6: Dental pain Opioid vs. acetaminophen, single dose	Pain, rescue medication use	<1 d	2	149	Direct	Imprecise	Fair	Consistent	No differences	Low
KQ 6: Dental pain Opioid (with or without acetaminophen) vs. acetaminophen, single dose	Any AE, nausea, drowsiness, dizziness	<1 d	4 to 8	445 to 769	Direct	Imprecise	Fair	Consistent	Increased risk with opioid	Low
KQ 6: Dental pain Opioid plus acetaminophen or NSAID vs. NSAID, single dose	Pain, rescue or repeat medication use	<1 d	8 to 12	926 to 2,021	Direct	Precise	Fair	Inconsistent (pain intensity); consistent (rescue or repeat medication use)	Small to moderate increase in pain intensity with opioids, increased likelihood of rescue or repeat medication use (RR 1.35, 95% CI 1.23 to 1.48)	Low for pain; moderate for rescue or repeat medication use

Intervention	Outcomes	Timing of Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Quality	Consistency	Findings	SOE
KQ 6: Dental pain Opioid vs. acetaminophen, multidose course	Pain intensity	1 d to <1 w	1	20	Direct	Imprecise	Fair	Consistent	No difference	Low
KQ 6: Dental pain Opioid (with or without acetaminophen) vs. NSAID	Any AE, nausea, dizziness, drowsiness	<1 d, 1 d to <1 w	9 to 12	1,959 to 2,784	Direct	Precise	Fair	Consistent	RR 1.72 (95% CI 1.29 to 2.28) for any AE, 2.72 (95% CI 1.84 to 4.01) for nausea, 2.97 (95% CI 1.59 to 5.54) for dizziness, and 1.76 (95% CI 1.00 to 3.10) for drowsiness	Moderate
KQ 6: Dental pain NSAID vs. acetaminophen, single dose	Pain intensity, rescue or repeat medication use	<1 d	11 to 15	2,014 to 2,506	Direct	Precise	Fair	Consistent	Moderate to large decrease in pain with NSAID, decreased likelihood of rescue or repeat medication use (RR 0.64, 95% CI 0.58 to 0.71)	Moderate
	Any AE	<1 d	12	2,512	Direct	Precise	Fair	Consistent	RR 0.85 (95% CI 0.72 to 1.00)	Moderate

Intervention	Outcomes	Timing of Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Quality	Consistency	Findings	SOE
KQ 7: Kidney stone pain Morphine vs. NSAID, single dose	Pain, rescue medication use	<1 d	1	1,097	Direct	Precise	Good	Unable to assess	Increased likelihood of pain, and rescue medication use with morphine	Moderate
	Any AE	<1 d	1	1,097	Direct	Precise	Good	Unable to assess	3% vs. 1%, RR 2.70 (95% CI 1.15 to 6.38)	Moderate
KQ 7: Kidney stone pain Meperidine vs. NSAID, single dose	Pain, rescue medication use	<1 d	4 to 6	475 to 671	Direct	Precise	Fair	Inconsistent	Moderate to large increase in pain intensity with meperidine, increased likelihood of rescue medication use	Moderate
	Any AE, somnolence, nausea	<1 d	4 to 5	471 to 573	Direct	Imprecise	Fair	Inconsistent	RR 1.71 (95% CI 0.99 to 2.96) for any AE, RR 1.98 (95% CI 0.82 to 4.79) for somnolence, and RR 1.84 (95% CI 1.02 to 3.31) for nausea	Low
KQ 7: Kidney stone pain Morphine vs. acetaminophen, single dose	Pain, rescue medication use	<1 d	1	1,096	Direct	Precise	Good	Unable to assess	Increased likelihood of pain with morphine, similar rescue medication use	Moderate

Intervention	Outcomes	Timing of Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Quality	Consistency	Findings	SOE
	Any AE	<1 d	1	1,096	Direct	Precise	Good	Unable to assess	3% vs. 1%, RR 2.71 (95% CI 1.15 to 6.39)	Moderate
KQ 7: Kidney stone pain NSAID vs. acetaminophen, single dose	Pain, rescue medication use	<1 d	2 to 3	1,145 to 1,225	Direct	Imprecise (for pain)	Fair	Inconsistent (pain)	Inconsistent effects on pain; decreased likelihood of rescue medication use with NSAID	Low for rescue medication use, insufficient for pain
KQ 7: Kidney stone pain Acupuncture vs. NSAID or acetaminophen	Pain	<1 d	1	160	Direct	Imprecise	Fair	Unable to assess	Moderate increase in pain with acupuncture	Low
KQ8: Sickle cell pain Insufficient evidence	--	--	--	--	--	--	--	--	--	--

Abbreviations: AE = adverse event; CI = confidence interval; D = day; KQ = Key Question NSAID = nonsteroidal anti-inflammatory drug; QoL = quality of life; RR = relative risk; SOE = strength of evidence; TENS = transcutaneous electrical nerve stimulation; W = week

Appendix H. Excluded Studies List

1. Fingolimod (Gilenya): An oral sphingosine 1-phosphate receptor modulator. Formulary. 2010;45(12). **Exclusion reason:** Ineligible publication type
2. The effects of gabapentin and ibuprofen on pain and reduction of morphine consumption in patients suffering from orthopedic fractures admitted in hospital emergency room. International Journal of Pharmaceutical Research. 2019;11(4):191-6. **Exclusion reason:** Not in English
3. Abdallah FW, Halpern SH, Aoyama K, et al. Will the Real Benefits of Single-Shot Interscalene Block Please Stand Up? A Systematic Review and Meta-Analysis. Anesth Analg. 2015 May;120(5):1114-29. doi: <https://dx.doi.org/10.1213/ANE.0000000000000688>. PMID: 25822923. **Exclusion reason:** Publication used as source document
4. Abdel Shaheed C, Maher CG, Williams KA, et al. Efficacy, Tolerability, and Dose-Dependent Effects of Opioid Analgesics for Low Back Pain: A Systematic Review and Meta-analysis. JAMA Intern Med. 2016 Jul 01;176(7):958-68. doi: <https://dx.doi.org/10.1001/jamainternmed.2016.1251>. PMID: 27213267. **Exclusion reason:** Publication used as source document
5. Abdel Shaheed C, Maher CG, Williams KA, et al. Interventions available over the counter and advice for acute low back pain: systematic review and meta-analysis. J Pain. 2014 Jan;15(1):2-15. doi: 10.1016/j.jpain.2013.09.016. PMID: 24373568. **Exclusion reason:** Publication used as source document
6. Abdel Shaheed C, Maher CG, Williams KA, et al. Efficacy and tolerability of muscle relaxants for low back pain: Systematic review and meta-analysis. Eur J Pain. 2017 02;21(2):228-37. doi: 10.1002/ejp.907. PMID: 27329976. **Exclusion reason:** Publication used as source document
7. Abou-Karam M, Dube S, Kvann HS, et al. Parental Report of Morphine Use at Home after Pediatric Surgery. J Pediatr. 2015 Sep;167(3):599-604.e1-2. doi: <https://dx.doi.org/10.1016/j.jpeds.2015.06.035>. PMID: 26205183. **Exclusion reason:** Background information only
8. Aboursheid T, Albaroudi O, Alahdab F. Inhaled nitric oxide for treating pain crises in people with sickle cell disease. Cochrane Database Syst Rev. 2019(10) PMID: 31603241. **Exclusion reason:** Ineligible intervention
9. Abou-Setta AM, Beaupre LA, Rashid S, et al. Comparative effectiveness of pain management interventions for hip fracture: a systematic review. Ann Intern Med. 2011 Aug 16;155(4):234-45. doi: 10.7326/0003-4819-155-4-201108160-00346. PMID: 21844549. **Exclusion reason:** Publication used as source document
10. Acevedo JJ, Beskin JL. Complications of plantar fascia rupture associated with corticosteroid injection. Foot Ankle Int. 1998 Feb;19(2):91-7. doi: 10.1177/107110079801900207. PMID: 9498581. **Exclusion reason:** Ineligible population
11. Achterberg J, Kenner C, Casey D. Behavioral strategies for the reduction of pain and anxiety associated with orthopedic trauma. Biofeedback Self Regul. 1989 Jun;14(2):101-14. PMID: 2675983. **Exclusion reason:** Ineligible study design
12. Acosta-Olivo C, Siller-Adame A, Tamez-Mata Y, et al. Laser Treatment on Acupuncture Points Improves Pain and Wrist Functionality in Patients Undergoing Rehabilitation Therapy after Wrist Bone Fracture. A Randomized, Controlled, Blinded Study. Acupunct Electrother Res. 2017 Jan;42(1):11-25. doi: 10.3727/036012917x14908026365007. PMID: 29772132. **Exclusion reason:** Ineligible intervention

13. Adachi N, Munesada M, Yamada N, et al. Effects of aromatherapy massage on face-down posture-related pain after vitrectomy: a randomized controlled trial. *Pain Manag Nurs*. 2014 Jun;15(2):482-9. doi: 10.1016/j.pmn.2012.12.004. PMID: 23466193. **Exclusion reason:** Ineligible setting
14. Adamek S, Matouskova O, Polanecky O, et al. The effect of postoperative pain treatment on the incidence of anastomotic insufficiency after rectal and rectosigmoidal surgery. *Prague Med Rep*. 2013;114(4):214-21. doi: 10.14712/23362936.2014.10. PMID: 24485338. **Exclusion reason:** Ineligible study design
15. Adhikari S, Koirala P, Kafle D. Comparison of Scapular Manipulation With External Rotation Method of Reduction of Acute Anterior Shoulder Dislocation for Sedation Requirements and Success Rates. *J Spec Oper Med*. 2018 2018;18(3):34-7. PMID: 30222834. **Exclusion reason:** Ineligible intervention
16. Adib-Hajbaghery M, Etri M. Effect of acupressure of Ex-Le7 point on pain, nausea and vomiting after appendectomy: A randomized trial. *J Res Med Sci*. 2013;18(6):482. PMID: 24250696. **Exclusion reason:** Ineligible population
17. Afshar K, Jafari S, Marks AJ, et al. Nonsteroidal anti-inflammatory drugs (NSAIDs) and non-opioids for acute renal colic. *Cochrane Database Syst Rev*. 2015 Jun 29(6):CD006027. doi: 10.1002/14651858.CD006027.pub2. PMID: 26120804. **Exclusion reason:** Publication used as source document
18. Aghababian RV, Volturo GA, Heifetz IN. Comparison of diflunisal and naproxen in the management of acute low back strain. *Clin Ther*. 1986;9 Suppl C:47-51. PMID: 2951011. **Exclusion reason:** Ineligible comparator
19. Ahiskalioglu EO, Ahiskalioglu A, Aydin P, et al. Effects of a single-dose preemptive pregabalin on acute and chronic pain after inguinal hernia repair with mesh under spinal anaesthesia: A randomised controlled trial. *Eur J Anaesthesiol*. 2016 Aug;33(8):605-7. doi: 10.1097/EJA.0000000000000395. PMID: 27120252. **Exclusion reason:** Ineligible intervention
20. Ahmed HE, Craig WF, White PF, et al. Percutaneous electrical nerve stimulation: an alternative to antiviral drugs for acute herpes zoster. *Anesth Analg*. 1998 Oct;87(4):911-4. doi: 10.1097/00000539-199810000-00031. PMID: 9768793. **Exclusion reason:** Ineligible comparator
21. Ahn NY, Park HJ. Effects of Korean hand acupressure on opioid-related nausea and vomiting, and pain after caesarean delivery using spinal anaesthesia. *Complement Ther Clin Pract*. 2017 Aug;28:101-7. doi: 10.1016/j.ctcp.2017.05.014. PMID: 28779916. **Exclusion reason:** Ineligible study design
22. Aida N, Shibuya M, Yoshino K, et al. Respiratory muscle stretch gymnastics in patients with post coronary artery bypass grafting pain: impact on respiratory muscle function, activity, mood and exercise capacity. *J Med Dent Sci*. 2002 Dec;49(4):157-70. PMID: 12641387. **Exclusion reason:** Ineligible outcome
23. Airaksinen OV, Kyrklund N, Latvala K, et al. Efficacy of cold gel for soft tissue injuries: a prospective randomized double-blinded trial. *Am J Sports Med*. 2003 Sep-Oct;31(5):680-4. doi: 10.1177/03635465030310050801. PMID: 12975186. **Exclusion reason:** Ineligible comparator
24. Akarsu S, Sahin S, Kara C, et al. A comparison between parenteral paracetamol and diclofenac for acute postoperative pain treatment in patients after caesarean section. *Turk jinekoloji ve obstetrik dernegi dergisi*. 2010;7(4):262-6. **Exclusion reason:** Not in English

25. Akbari GA, Entezariasl M, Isazadehfah K. Comparison of the effects of indomethacin, diclofenac and acetaminophen suppositories on pain score and pethidine usage after cesarean section. *Journal of Isfahan Medical School*. 2012;30(179). **Exclusion reason:** Not in English
26. Akhter N, Zahid Siddiq M. Comparative efficacy of diclofenac sodium alone and in combination with thiocolchicoside in patients with low back pain. *Medical Forum Monthly*. 2017;28(11):93-6. **Exclusion reason:** Ineligible comparator
27. Akmese ZB, Oran NT. Effects of Progressive Muscle Relaxation Exercises Accompanied by Music on Low Back Pain and Quality of Life During Pregnancy. *J Midwifery Womens Health*. 2014 Sep-Oct;59(5):503-9. doi: 10.1111/jmwh.12176. PMID: 24965313. **Exclusion reason:** Ineligible population
28. Aksoy C, Karan A, Diraçoğlu D. Low back pain: Results of an open clinical trial comparing the standard treatment alone to the combination of standard treatment and thiocolchicoside. *J Orthop Traumatol*. 2002;3(2):103-8. doi: 10.1007/s101950200036. **Exclusion reason:** Ineligible comparator
29. Aksoy MK, Altan L, Guner A. The effectiveness of soft and semi-rigid cervical collars on acute cervical radiculopathy. *European Research Journal*. 2018;4(1):16-25. **Exclusion reason:** Ineligible population
30. Al Hajeri A, Fedorowicz Z. Piracetam for reducing the incidence of painful sickle cell disease crises. *Cochrane Database Syst Rev*. 2016 Feb 12;2:CD006111. doi: <https://dx.doi.org/10.1002/14651858.CD006111.pub3>. PMID: 26869149. **Exclusion reason:** Publication used as source document
31. Albin SR, Koppenhaver SL, Marcus R, et al. Short-term Effects of Manual Therapy in Patients After Surgical Fixation of Ankle and/or Hindfoot Fracture: A Randomized Clinical Trial. *J Orthop Sports Phys Ther*. 2019 May;49(5):310-9. doi: 10.2519/jospt.2019.8864. PMID: 30759357. **Exclusion reason:** Ineligible population
32. Alexander L, Hall E, Eriksson L, et al. The combination of non-selective NSAID 400 mg and paracetamol 1000 mg is more effective than each drug alone for treatment of acute pain. A systematic review. *Swed Dent J*. 2014;38(1):1-14. PMID: 26995806. **Exclusion reason:** Publication used as source document
33. Ali AA. Management of the first episode of acute low back pain: a comparison between two treatment protocols (PhD). Texas Woman's University. 2002. **Exclusion reason:** Ineligible publication type
34. Ali AA. Management of the first episode of acute low back pain: a comparison between two treatment protocols. Texas Woman's University. 2002. **Exclusion reason:** Ineligible publication type
35. Alijanipour P, Tan TL, Matthews CN, et al. Periarticular Injection of Liposomal Bupivacaine Offers No Benefit Over Standard Bupivacaine in Total Knee Arthroplasty: A Prospective, Randomized, Controlled Trial. *J Arthroplasty*. 2017 02;32(2):628-34. doi: 10.1016/j.arth.2016.07.023. PMID: 27667533. **Exclusion reason:** Ineligible intervention
36. Allred KD, Byers JF, Sole ML. The effect of music on postoperative pain and anxiety. *Pain Manag Nurs*. 2010 Mar;11(1):15-25. doi: 10.1016/j.pmn.2008.12.002. PMID: 20207324. **Exclusion reason:** Ineligible intervention
37. Almeida CC, Silva V, Junior GC, et al. Transcutaneous electrical nerve stimulation and interferential current demonstrate similar effects in relieving acute and chronic pain: a systematic review with meta-analysis. *Braz J Phys Ther*. 2018 Sep - Oct;22(5):347-54. doi: <https://dx.doi.org/10.1016/j.bjpt.2017.12.005>. PMID: 29426587. **Exclusion reason:** Publication used as source document
38. Alpaslan C, Kahraman S, Guner B, et al. Does the use of soft or hard splints affect the short-term outcome of temporomandibular joint arthrocentesis? *Int J Oral Maxillofac Surg*. 2008 May;37(5):424-7. doi: 10.1016/j.ijom.2008.01.022. PMID: 18356022. **Exclusion reason:** Ineligible study design

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40. Al-Sukhun J, Al-Sukhun S, Penttila H, et al. Preemptive analgesic effect of low doses of celecoxib is superior to low doses of traditional nonsteroidal anti-inflammatory drugs. *J Craniofac Surg*. 2012 Mar;23(2):526-9. doi: 10.1097/SCS.0b013e31824cd4fb. PMID: 22421863. **Exclusion reason:** Ineligible intervention
41. Altan L, Kasapoglu Aksoy M, Kosegil Ozturk E. Efficacy of diclofenac & thiocolchioside gel phonophoresis comparison with ultrasound therapy on acute low back pain; a prospective, double-blind, randomized clinical study. *Ultrasonics*. 2019 Jan;91:201-5. doi: 10.1016/j.ultras.2018.08.008. PMID: 30139568. **Exclusion reason:** Ineligible comparator
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43. Aluko A, DeSouza L, Peacock J. The effect of core stability exercises on variations in acceleration of trunk movement, pain, and disability during an episode of acute nonspecific low back pain: a pilot clinical trial. *J Manipulative Physiol Ther*. 2013 Oct;36(8):497-504.e1-3. doi: 10.1016/j.jmpt.2012.12.012. PMID: 23948426. **Exclusion reason:** Ineligible comparator
44. Alvarenga MB, de Oliveira SM, Francisco AA, et al. Effect of low-level laser therapy on pain and perineal healing after episiotomy: A triple-blind randomized controlled trial. *Lasers Surg Med*. 2017 02;49(2):181-8. doi: 10.1002/lsm.22559. PMID: 27426042. **Exclusion reason:** Ineligible intervention
45. Amato F, Morrone EG, Lacquaniti G. Efficacy, safety and tolerance of subcutaneous injection of high dosages of diclofenac in patients with neuropathic non-cancer pain and neuropathic cancer pain: Data from a clinical setting. *Eur J Inflamm*. 2015;13(1):32-9. doi: 10.1177/1721727X15576850. **Exclusion reason:** Ineligible population
46. Ameis A, Randhawa K, Yu H, et al. The Global Spine Care Initiative: a review of reviews and recommendations for the non-invasive management of acute osteoporotic vertebral compression fracture pain in low- and middle-income communities. *Eur Spine J*. 2018 09;27(Suppl 6):861-9. doi: https://dx.doi.org/10.1007/s00586-017-5273-6. PMID: 29038868. **Exclusion reason:** Publication used as source document
47. Amin-Hanjani S, Corcoran J, Chatwani A. Cold therapy in the management of postoperative cesarean section pain. *Am J Obstet Gynecol*. 1992 Jul;167(1):108-9. doi: 10.1016/s0002-9378(11)91638-x. PMID: 1442907. **Exclusion reason:** Ineligible outcome
48. Andersen LL, Jay K, Andersen CH, et al. Acute effects of massage or active exercise in relieving muscle soreness: randomized controlled trial. *J Strength Cond Res*. 2013 Dec;27(12):3352-9. doi: 10.1519/JSC.0b013e3182908610. PMID: 23524365. **Exclusion reason:** Ineligible population
49. Andersen LL, Kjaer M, Sogaard K, et al. Effect of two contrasting types of physical exercise on chronic neck muscle pain. *Arthritis Rheum*. 2008 Jan 15;59(1):84-91. doi: 10.1002/art.23256. PMID: 18163419. **Exclusion reason:** Ineligible population
50. Andersen T, Christensen FB, Ernst C, et al. The effect of electrical stimulation on lumbar spinal fusion in older patients: a randomized, controlled, multi-center trial: part 1: functional outcome. *Spine*. 2009 Oct 01;34(21):2241-7. doi: 10.1097/BRS.0b013e3181b02988. PMID: 19934802. **Exclusion reason:** Ineligible intervention

51. Andersson S, Fredin H, Lindberg H, et al. Ibuprofen and compression bandage in the treatment of ankle sprains. *Acta Orthop Scand*. 1983 Apr;54(2):322-5. doi: 10.3109/17453678308996578. PMID: 6342332. **Exclusion reason:** Ineligible comparator
52. Angelo JL, Wu J, Sirody J, et al. Reduction in Prescribed Opioids after General Surgery Procedures at a Public Hospital. *Am Surg*. 2019 Oct 01;85(10):1198-203. PMID: 31657324. **Exclusion reason:** Ineligible intervention
53. Anie KA, Green J. Psychological therapies for sickle cell disease and pain [Systematic Review]. *Cochrane Database Syst Rev*. 2015;5:5. PMID: 25966336 **Exclusion reason:** Publication used as source document
54. Anonymous. Pain Management in the Opioid-Dependent Pregnant Woman. *J Perinat Neonatal Nurs*. 2017 Apr/Jun;31(2):E1. doi: 10.1097/JPN.0000000000000261. PMID: 28437303. **Exclusion reason:** Ineligible publication type
55. Antall GF, Kresevic D. The use of guided imagery to manage pain in an elderly orthopaedic population. *Orthop Nurs*. 2004 Sep-Oct;23(5):335-40. doi: 10.1097/00006416-200409000-00012. PMID: 15554471. **Exclusion reason:** Ineligible setting
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57. Aoki T, Numajiri M, Yamamoto M. A well controlled comparative study of piroxicam gel, indomethacin gel and placebo gel in the treatment of trauma. *Japanese Pharmacology and Therapeutics*. 1984;12(12):101-17. **Exclusion reason:** Ineligible comparator
58. Aparna P, Geetha P, Shanmugasundaram P. Comparison of aceclofenac and combination (Aceclofenac + thiocolchicoside) therapy in acute low back pain patients. *Res J Pharm Technol*. 2017;9(11):1927-9. **Exclusion reason:** Ineligible study design
59. Aqua K, Gimbel JS, Singla N, et al. Efficacy and tolerability of oxymorphone immediate release for acute postoperative pain after abdominal surgery: a randomized, double-blind, active- and placebo-controlled, parallel-group trial. *Clin Ther*. 2007 Jun;29(6):1000-12. doi: 10.1016/j.clinthera.2007.06.001. PMID: 17692717. **Exclusion reason:** Ineligible setting
60. Araki S, Kawamura O, Mataka T. Randomized controlled trial comparing the effect of manual acupuncture with sham acupuncture for acute low back pain. *Journal of Japanese Society for Acupuncture*. 2001;51(382). **Exclusion reason:** Not in English
61. Araujo FX, Scholl Schell M, Ribeiro DC. Effectiveness of Physiotherapy interventions plus Extrinsic Feedback for neck disorders: A systematic review with meta-analysis. *Musculoskelet Sci Pract*. 2017 06;29:132-43. doi: 10.1016/j.msksp.2017.04.005. PMID: 28412631. **Exclusion reason:** Publication used as source document
62. Archer KR, Coronado RA, Haug CM, et al. A comparative effectiveness trial of postoperative management for lumbar spine surgery: changing behavior through physical therapy (CBPT) study protocol. *BMC Musculoskelet Disord*. 2014 Oct 01;15:325. doi: <https://dx.doi.org/10.1186/1471-2474-15-325>. PMID: 25273991. **Exclusion reason:** Background information only
63. Argoff C, McCarberg B, Gudín J, et al. SoluMatrix Diclofenac: Sustained Opioid-Sparing Effects in a Phase 3 Study in Patients with Postoperative Pain. *Pain Med*. 2016 10;17(10):1933-41. doi: 10.1093/pm/pnw012. PMID: 26995799. **Exclusion reason:** Ineligible comparator

64. Arias-Buria JL, Valero-Alcaide R, Cleland JA, et al. Inclusion of trigger point dry needling in a multimodal physical therapy program for postoperative shoulder pain: a randomized clinical trial. *J Manipulative Physiol Ther.* 2015 Mar-Apr;38(3):179-87. doi: 10.1016/j.jmpt.2014.11.007. PMID: 25666690. **Exclusion reason:** Ineligible comparator
65. Arici E, Tastan S, Can MF. The effect of using an abdominal binder on postoperative gastrointestinal function, mobilization, pulmonary function, and pain in patients undergoing major abdominal surgery: A randomized controlled trial. *Int J Nurs Stud.* 2016 Oct;62:108-17. doi: 10.1016/j.ijnurstu.2016.07.017. PMID: 27474943. **Exclusion reason:** Ineligible setting
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