



Evidence-based Practice Center Systematic Review Protocol

Project Title: *Treatments for Acute Pain: A Systematic Review*

I. Background and Objectives for the Systematic Review

Pain is nearly universal, contributing substantially to morbidity, mortality, disability, and health care 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 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.^{2,6,7}

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 is variable, and assessing treatment response is often not feasible. Additionally, access and care options may vary.^{1,8} 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.¹⁹⁻²⁵ In addition, some studies indicate that opioids may not be more effective than nonopioid therapies for some acute pain conditions,²⁶⁻³⁰ and use of opioids may negatively affect recovery and function.^{31,32} Opioids prescribed for surgery and other acute pain conditions often go unused, a potential source for diversion and misuse.³³⁻³⁵ 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 showing an association between use of opioids for acute pain and long-term use.²⁰ In the last several years, over 25 states have passed laws restricting prescribing of opioids for acute pain.^{21,36} Although data indicate some effects of policies in reducing opioid prescribing, studies on clinical outcomes are lacking. Concerns include the effectiveness of nonopioid treatment alternatives, potential undertreatment of acute pain, and other unintended consequences.^{37,38} A draft Agency for Healthcare Research and Quality (AHRQ) 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 of the 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 after discharge, dental pain, kidney stones, and sickle cell crisis). The intended audience includes the CDC, policy and decisionmakers, and clinicians who treat acute pain. A concurrent review addresses treatments for acute pain related to episodic migraines.

II. The 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 after discharge
- KQ6: Dental pain (surgical and nonsurgical after discharge)
- KQ7: Kidney stones
- KQ8: Sickle cell crisis (episodic pain)

For each condition above, we will address the following subquestions:

Opioid Therapy

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

- b. How does effectiveness of opioid therapy vary depending on: (1) patient demographics (e.g. age, race, ethnicity, gender); (2) patient medical or psychiatric comorbidities; (3) dose of opioids; (4) duration of opioid therapy, including number of opioid prescription refills and quantity of pills used; (5) opioid use history; (6) substance use history; (7) use of concomitant therapies?
- c. What are the harms of opioid therapy versus nonopioid pharmacologic therapy, or nonpharmacologic therapy with respect to: (1) misuse, opioid use disorder, and related outcomes; (2) overdose; (3) other harms including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?
- d. How do harms vary depending on: (1) patient demographics (e.g., age, gender); (2) patient medical or psychiatric comorbidities; (3) the dose of opioid used; (4) the duration of opioid therapy; (5) opioid use history; or (6) substance use history?
- e. What are the effects of prescribing opioid therapy versus not prescribing opioid therapy for acute pain on 1) short-term (<3 months) continued need for prescription pain relief, such as need for opioid refills, and 2) long-term opioid use (3 months or greater)?
- f. For patients with acute pain being considered for opioid therapy, what is the accuracy of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose?
- g. For patients with acute pain being considered for opioid therapy, what is the effectiveness of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose?
- h. For patients with acute pain being considered for opioid therapy, what is the effect of the following factors on the decision to prescribe opioids: (1) existing opioid management plans; (2) patient education; (3) clinician and patient values and preferences related to opioids; (4) urine drug screening; (5) use of prescription drug monitoring program data; (6) availability of close followup?

Nonopioid Pharmacologic Therapy

- i. What is the comparative effectiveness of nonopioid pharmacologic therapy (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [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: <1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to less than 4 weeks; 4 weeks or longer?
- j. How does effectiveness of nonopioid pharmacologic therapy vary depending on: (1) patient demographics (e.g. age, race, ethnicity, gender); (2) patient medical and psychiatric comorbidities; (3) the type of nonopioid medication; (4) dose of medication; (5) duration of treatment?
- k. What are the harms of nonopioid pharmacologic therapy versus other nonopioid pharmacologic therapy, or nonpharmacologic therapy with respect to: (1) misuse, (2) overdose; (3) other harms including gastrointestinal-related harms, cardiovascular-related

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

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

Nonpharmacologic Therapy

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

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

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

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

Table 1. PICOTS

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 4. Peripheral neuropathic pain (related to herpes zoster and trigeminal neuralgia) 5. Postoperative pain after discharge 6. Dental pain 7. Kidney stones 8. Sickle cell crisis (episodic pain) <p>*Special populations:</p> <ul style="list-style-type: none"> ▪ General adult ▪ Older populations >65 years ▪ Patients with history of substance use disorder ▪ Patients currently under treatment for opioid use disorder with opioid agonist therapy or naltrexone ▪ Patients with a history of psychiatric illness ▪ Patients with history of overdose ▪ Pregnant/breastfeeding women ▪ Patients with comorbidities (e.g., kidney disease, sleep disordered breathing)

Picots Element	Inclusion Criteria
Interventions	<p>Opioid therapy: a-e. Any systemic opioid, including agonists, partial agonists, and mixed mechanism opioids. f. Instruments, genetic/metabolic tests for predicting risk of misuse, opioid use disorder, and overdose g. Use of risk prediction instruments, genetic/metabolic tests h. The following factors: (1) existing opioid management plans; (2) patient education; (3) clinician and patient values and preferences related to opioids; (4) urine drug screening; (5) use of prescription drug monitoring program data; (6) availability of close followup</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>
Comparators	<p>Opioid therapy: a-d. Usual care, another opioid, nonopioid drug, or noninvasive, nonpharmacological therapy e. Usual care, another opioid, nonopioid drug, or noninvasive, nonpharmacological therapy, no opioid/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> <p>Nonopioid pharmacological therapy: Other nonopioid pharmacological therapy or noninvasive nonpharmacological therapy</p> <p>Noninvasive nonpharmacological therapy: Sham treatment, waitlist, usual care, attention control, and no treatment; or other noninvasive nonpharmacological therapy</p>
Outcomes	<p>Opioid therapy: a-d, g, i. Pain, function, pain relief satisfaction, and quality of life, harms, adverse events (including withdrawal, risk of misuse, opioid, opioid use disorder, overdose). e. Persistent opioid use f. Measures of diagnostic accuracy h. Opioid prescribing rates</p> <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	All KQs: RCTs; in addition: e. cohort studies (for long-term opioid use) f. studies assessing diagnostic accuracy h. cohort studies and before-after studies assessing effects on prescribing rates

Abbreviations: RCT = randomized controlled trial

III. Methods

Criteria for Inclusion/Exclusion of Studies in the Review

The criteria for inclusion and exclusion of studies will be based on the Key Questions and are described in the previous PICOTS section. Key Questions on opioid and nonopioid therapy focus on comparative effectiveness because the effectiveness of analgesics for treating acute pain are well established. Key Questions on nonopioid therapies include comparisons against sham, waitlist, usual care, attention control, and no therapy due to greater uncertainty regarding their role in management of acute pain.

Below are additional details on the scope of this project:

Study Design: For all Key Questions, we will include randomized controlled trials (RCTs). For subquestion E, we will also include cohort studies that control for potential confounders and evaluate effects on long-term opioid use. For subquestion F, we will include studies that evaluate the performance of a risk prediction instrument against a reference standard for opioid misuse, opioid use disorder, or overdose. For subquestion G, we will include RCTs, cohort studies, or before-after studies that evaluate effects on prescribing rates. For all KQs, we will exclude uncontrolled observational studies, case series, and case reports. Systematic reviews will be included as evidence if they are a strong match to a Key Question, PICOTS, and methods, and are assessed as being at low risk of bias, based on assessment using the AMSTAR-2 quality tool, on factors such as the methods used to conduct searches, select studies, abstract data, assess risk of bias, and synthesize data.^{40,41} If systematic reviews are included, we will update findings with new primary studies identified in our searches. Meta-analyses will be updated if the new evidence is of sufficient quality and quantity to impact conclusions, or if there is inconsistency between the findings of the new studies and the prior meta-analyses. If multiple systematic reviews are relevant and low risk of bias, we will select the most relevant, recent, and highest-quality review or reviews; if more than one is included for a particular topic we will evaluate areas of consistency and inconsistency across the reviews.⁴²

Non-English Language Studies: We will restrict to English-language articles, but will review English-language abstracts of non-English language articles to identify studies that would otherwise meet inclusion criteria, in order to help assess for the likelihood of language bias.

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

Publication Date Range: Electronic searches for evidence were conducted in August 2019, and were conducted back to the inception of each database. Electronic searches will be updated while the draft report is out for public review to identify new publications. Literature identified during the updated search will be assessed by following the same process of dual review as all other studies considered for inclusion in the report. If any pertinent new literature is identified for inclusion in the report, it will be incorporated before the final submission of the report.

Literature Databases: Ovid[®] MEDLINE[®], PsycINFO[®], Embase[®], Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews will be searched to capture published literature. Search strategies for MEDLINE are available in **Appendix 1**.

Supplementing Searches: A Supplemental Evidence And Data for Systematic review (SEADS) portal will be available, and a Federal Register Notice will be posted for this review.

Hand Searching: Reference lists of included articles will also be reviewed for includable literature.

Contacting Authors: In the event that information regarding methods or results appears to be omitted from the published results of a study, or if we are aware of unpublished data, we will contact authors to obtain this information.

Process for Selecting Studies: Pre-established criteria will be used to determine eligibility for inclusion and exclusion of abstracts in accordance with the AHRQ Methods Guide, based on the Key Questions and PICOTS.⁴⁰ To ensure accuracy, all excluded abstracts will be dual reviewed to confirm exclusion. All citations deemed appropriate for inclusion by at least one of the reviewers will be retrieved. Each full-text article will be independently reviewed for eligibility by two team members, including any articles suggested by peer reviewers or that arise from the public posting process. Any disagreements will be resolved by consensus.

Data Abstraction and Data Management

After studies are selected for inclusion, data will be abstracted into categories that include but are not limited to: study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics, intervention characteristics, and results relevant to each Key Question as outlined in the previous PICOTS section. Information that will be abstracted that is relevant for assessing applicability will include the number of patients randomized relative to the number of patients enrolled, use of run-in or wash-out periods, and characteristics of the population, intervention, and care settings. All study data will be verified for accuracy and completeness by a second team member. A record of studies excluded at the full-text level with reasons for exclusion will be maintained.

Assessment of Methodological Risk of Bias of Individual Studies

Predefined criteria will be used to assess the quality of individual controlled trials, systematic reviews, and observational studies. Randomized and nonrandomized trials will be evaluated using criteria and methods developed by the Cochrane Back Review Group,⁴³ cohort studies will be evaluated using criteria developed by the U.S. Preventive Services Task Force,⁴⁴ and studies of diagnostic accuracy will be assessed using QUADAS-2.⁴⁵ Systematic reviews will be assessed using the AMSTAR-2 quality rating instrument on factors such as the methods used to conduct searches, select studies, abstract data, assess risk of bias, and synthesize data.⁴¹ These criteria and methods will be 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.⁴⁰ Studies will be given 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. Good-quality diagnostic accuracy studies use unbiased methods to select patients; report interpretation of the index test without knowledge of the reference standard; report a predefined threshold for a positive index test; report use of an appropriate reference standard; apply the reference standard to all patients; report interpretation of the reference standard blinded to the results of the index test; and report low attrition.⁴⁵

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 will not exclude studies rated poor quality a priori, but poor-quality studies will be considered less reliable than higher-quality studies when synthesizing the evidence, particularly if discrepancies between studies are present.

Two team members will independently assess quality. Any disagreements will be resolved by consensus.

Data Synthesis

We will construct evidence tables showing study characteristics (as discussed above), results, and quality ratings for all included studies, and summary tables to highlight the main findings.

Meta-analyses will be conducted to summarize data and obtain more precise estimates on outcomes for which studies are homogeneous enough to provide a meaningful combined estimate.⁴⁶ The decision to conduct quantitative synthesis will depend on presence of at least two studies, completeness of reported outcomes and a lack of heterogeneity among the reported results. To determine whether meta-analyses are indicated, we will consider the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes, and may conduct sensitivity analyses. Meta-analyses will be conducted using a random effects model. The Key Questions are designed to assess the comparative effectiveness and harms by patient demographics, medical and psychiatric comorbidities, pain types, treatment features and dosing strategies, though techniques including sensitivity and stratified analyses. Stratified analyses will also be conducted on characteristics pertaining to study design and setting (e.g., quality, geographic setting, clinical setting, study design type, use of crossover design).⁴⁶

Results will be presented separately for each Key Question/condition for the prespecified outcomes.

The magnitude of effects for pain and function will be classified using the same system used in other recent AHRQ reviews conducted on pain.⁴⁷⁻⁵¹ Using the same classifications provides a consistent benchmark for comparing results of pain interventions across reviews. In these

reviews, 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 is 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 are defined as greater than moderate. We will apply 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 Evidence for Major Comparisons and Outcomes

Regardless of whether evidence is synthesized quantitatively or qualitatively, the strength of evidence for each Key Question/body of evidence will be initially assessed by one researcher for each clinical outcome (see PICOTS) by using the approach described in the AHRQ Methods Guide.⁴⁰ To ensure consistency and validity of the evaluation, the strength of evidence will be reviewed by the entire team of investigators prior to assigning a final grade 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)

The strength of evidence will be assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale by evaluating and weighing the combined results 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.

Assessing Applicability

Applicability will be assessed in accordance with the AHRQ Methods Guide,⁵² 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 chronic pain have such comorbidities, and may respond more poorly to treatment. Similarly, trials that use active run-in periods evaluate highly selected populations who tolerated and responded well to the study intervention, rather than the general population of acute pain patients being considered for the intervention. The following factors that may affect applicability have been identified and include eligibility criteria and patient factors (e.g., demographic characteristics [age, sex, race/ethnicity, socioeconomic status, prior use of opioids], duration or severity of pain, presence of medical and psychiatric comorbidities [including prior substance use history], 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 [e.g., placebo, waitlist, usual care, or no therapy; type of non-opioid pharmacological therapy; type of nonpharmacological therapy], 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 or crossover design). We will use this information 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.

IV. References

1. Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, D.C.: The National Academies Press; 2011.
2. Henschke N, Kamper SJ, Maher CG. The epidemiology and economic consequences of pain. *Mayo Clin Proc*. 2015 Jan;90(1):139-47. doi: 10.1016/j.mayocp.2014.09.010. PMID: 25572198.
3. Tighe P, Buckenmaier CC, 3rd, Boezaart AP, et al. Acute pain medicine in the United States: a status report. *Pain Med*. 2015 Sep;16(9):1806-26. doi: 10.1111/pme.12760. PMID: 26535424.
4. Kent ML, Tighe PJ, Belfer I, et al. The ACTION-APS-AAPM Pain Taxonomy (AAAPT) multidimensional approach to classifying acute pain conditions. *Pain Med*. 2017 May 1;18(5):947-58. doi: 10.1093/pm/pnx019. PMID: 28482098.
5. Buvanendran A, Fiala J, Patel KA, et al. The incidence and severity of postoperative pain following inpatient surgery. *Pain Med*. 2015 Dec;16(12):2277-83. doi: 10.1111/pme.12751. PMID: 25917518.
6. Dix P, Sandhar B, Murdoch J, et al. Pain on medical wards in a district general hospital. *Br J Anaesth*. 2004 Feb;92(2):235-7. doi: 10.1093/bja/aeh052. PMID: 14722175.
7. Cordell WH, Keene KK, Giles BK, et al. The high prevalence of pain in emergency medical care. *Am J Emerg Med*. 2002 May;20(3):165-9. PMID: 11992334.
8. The Interagency Pain Research Coordinating Committee. *National pain strategy: a comprehensive population health level strategy for pain*. Bethesda, MD: National Institutes of Health; 2016. https://iprcc.nih.gov/National_Pain_Strategy/NPS_Main.htm.
9. McGreevy K, Bottros MM, Raja SN. Preventing chronic pain following acute pain: risk factors, preventive strategies, and their efficacy. *Eur J Pain Suppl*. 2011;5(2):365-72. doi: 10.1016/j.eujps.2011.08.013. PMID: 22102847.

10. Glare P, Aubrey K, Myles P. Postoperative pain management and opioids 1 (series): Transition from acute to chronic pain after surgery. *Lancet*. 2019(393):1537–46 (epub ahead of print [https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736\(19\)30352-6.pdf](https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(19)30352-6.pdf)).
11. Apfelbaum JL, Chen C, Mehta SS, et al. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg*. 2003 Aug;97(2):534-40, table of contents. PMID: 12873949.
12. Moore RA, Wiffen PJ, Derry S, et al. Non-prescription (OTC) oral analgesics for acute pain - an overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2015 Nov 4(11):CD010794.
13. Darnall BD, Stacey BR, Chou R. Medical and psychological risks and consequences of long-term opioid therapy in women. *Pain Med*. 2012 Sep;13(9):1181-211. doi: 10.1111/j.1526-4637.2012.01467.x. PMID: 22905834.
14. Ezenwa MO, Fleming MF. Racial disparities in pain management in primary care. *J Health Dispar Res Pract*. 2012;5(3):12-26. PMID: 24244911.
15. Nafiu OO, Chimbira WT, Stewart M, et al. Racial differences in the pain management of children recovering from anesthesia. *Paediatr Anaesth*. 2017 Jul;27(7):760-7. doi: 10.1111/pan.13163. PMID: 28504322.
16. Goyal MK, Kuppermann N, Cleary SD, et al. Racial disparities in pain management of children with appendicitis in emergency departments. *JAMA Pediatr*. 2015 Nov;169(11):996-1002. doi: 10.1001/jamapediatrics.2015.1915. PMID: 26366984.
17. Dowell D, Kunins HV, Farley TA. Opioid analgesics—risky drugs, not risky patients. *JAMA*. 2013;309(21):2219-20. doi: 10.1001/jama.2013.5794.
18. National Institutes of Health National Institute on Drug Abuse. Overdose Death Rates. 2019. <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>. Accessed May 29, 2019.
19. Mundkur ML, Franklin JM, Abdia Y, et al. Days' supply of initial opioid analgesic prescriptions and additional fills for acute pain conditions treated in the primary care setting - United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2019 Feb 15;68(6):140-3. doi: 10.15585/mmwr.mm6806a3. PMID: 30763301.
20. Dowell D, Haegerich TM, Chou R. CDC Guideline for prescribing opioids for chronic pain--United States, 2016. *JAMA*. 2016 Apr 19;315(15):1624-45. doi: 10.1001/jama.2016.1464. PMID: 26977696.
21. National Conference of State Legislatures. Prescribing Policies: States Confront Opioid Overdose Epidemic. 2018. <http://www.ncsl.org/research/health/prescribing-policies-states-confront-opioid-overdose-epidemic.aspx>. Accessed May 29, 2019.
22. Reznikoff C. How acute pain leads to chronic opioid use. *Cleve Clin J Med*. 2018 Nov;85(11):837-41. doi: 10.3949/ccjm.85a.18038. PMID: 30395519.
23. Brummett CM, Waljee JF, Goesling J, et al. New persistent opioid use after minor and major surgical procedures in US adults. *JAMA Surg*. 2017 Jun 21;152(6):e170504. doi: 10.1001/jamasurg.2017.0504. PMID: 28403427.
24. Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. *BMJ*. 2018 Jan 17;360:j5790. doi: 10.1136/bmj.j5790. PMID: 29343479.
25. Shah A, Hayes CJ, Martin BC. Characteristics of Initial prescription episodes and likelihood of long-term opioid use - United States, 2006-2015. *MMWR Morb Mortal Wkly Rep*. 2017 Mar 17;66(10):265-9. doi: 10.15585/mmwr.mm6610a1. PMID: 28301454.
26. Lewis RA, Williams NH, Sutton AJ, et al. Comparative clinical effectiveness of management strategies for sciatica: systematic review and network meta-analyses. *Spine J*. 2015 Jun 1;15(6):1461-77. doi: 10.1016/j.spinee.2013.08.049. PMID: 24412033.
27. Moore PA, Hersh EV. Combining ibuprofen and acetaminophen for acute pain management after third-molar extractions: translating clinical research to dental practice. *J Am Dent Assoc*. 2013 Aug;144(8):898-908. PMID: 23904576.
28. Pathan SA, Mitra B, Cameron PA. A systematic review and meta-analysis comparing the efficacy of nonsteroidal anti-inflammatory drugs, opioids, and paracetamol in the treatment of acute renal colic. *Eur Urol*. 2018 Apr;73(4):583-95. doi: 10.1016/j.eururo.2017.11.001. PMID: 29174580.
29. Chang AK, Bijur PE, Esses D, et al. Effect of a single dose of oral opioid and nonopioid analgesics on acute extremity pain in the emergency department: a randomized clinical trial. *JAMA*. 2017 Nov 7;318(17):1661-7. doi: 10.1001/jama.2017.16190. PMID: 29114833.

30. Friedman BW, Dym AA, Davitt M, et al. Naproxen with cyclobenzaprine, oxycodone/acetaminophen, or placebo for treating acute low back pain: a randomized clinical trial. *JAMA*. 2015 Oct 20;314(15):1572-80. doi: 10.1001/jama.2015.13043. PMID: 26501533.
31. Franklin GM, Stover BD, Turner JA, et al. Early opioid prescription and subsequent disability among workers with back injuries: the Disability Risk Identification Study Cohort. *Spine (Phila Pa 1976)*. 2008 Jan 15;33(2):199-204. doi: 10.1097/BRS.0b013e318160455c. PMID: 18197107.
32. Webster BS, Verma SK, Gatchel RJ. Relationship between early opioid prescribing for acute occupational low back pain and disability duration, medical costs, subsequent surgery and late opioid use. *Spine (Phila Pa 1976)*. 2007 Sep 1;32(19):2127-32. doi: 10.1097/BRS.0b013e318145a731. PMID: 17762815.
33. Bartels K, Mayes LM, Dingmann C, et al. Opioid use and storage patterns by patients after hospital discharge following surgery. *PLoS One*. 2016;11(1):e0147972. PMID: Pmc4732746.
34. Bicket MC, Long JJ, Pronovost PJ, et al. Prescription opioid analgesics commonly unused after surgery: a systematic review. *JAMA Surg*. 2017 Nov 1;152(11):1066-71. PMID: Pmc5701659.
35. Neuman M, Bateman B, Wunsch H. Postoperative pain management and opioids 2 (series): Inappropriate opioid prescription after surgery. *Lancet*. 2019;393:1547–57 (epub ahead of print: [https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736\(19\)30428-3.pdf](https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(19)30428-3.pdf)).
36. Davis CS, Lieberman AJ, Hernandez-Delgado H, et al. Laws limiting the prescribing or dispensing of opioids for acute pain in the United States: A national systematic legal review. *Drug Alcohol Depend*. 2019 Jan 1;194:166-72. doi: 10.1016/j.drugalcdep.2018.09.022. PMID: 30445274.
37. Chua KP, Brummett CM, Waljee JF. Opioid prescribing limits for acute pain: potential problems with design and implementation. *JAMA*. 2019 Feb 19;321(7):643-4. doi: 10.1001/jama.2019.0010. PMID: 30703214.
38. US Department of Health and Human Services Office of the Assistant Secretary for Health. Draft Report on Pain Management Best Practices: Updates, Gaps, Inconsistencies, and Recommendations. 2019. <https://www.hhs.gov/ash/advisory-committees/pain/reports/2018-12-draft-report-on-updates-gaps-inconsistencies-recommendations/index.html#1-introduction>. Accessed May 29, 2019.
39. Agency for Healthcare Research and Quality: Effective Health Care Program. Treatment of Acute Pain: An Evidence Map. 2019. <https://effectivehealthcare.ahrq.gov/topics/acute-pain-treatment/protocol>. Accessed May 29, 2019.
40. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality; 2017. <https://effectivehealthcare.ahrq.gov/topics/ce-methods-guide/overview>. Accessed June 1, 2019.
41. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017 Sep 21;358:j4008. doi: 10.1136/bmj.j4008. PMID: 28935701.
42. White CM, Ip S, McPheeters M, et al. Using existing systematic reviews to replace de novo processes in conducting Comparative Effectiveness Reviews. In: Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews [posted September 2009]. Rockville (MD). Available at: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/methods-guidance-de-novo-processes_methods.pdf.
43. Furlan AD, Pennick V, Bombardier C, et al. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976)*. 2009 Aug 15;34(18):1929-41. doi: 10.1097/BRS.0b013e3181b1c99f. PMID: 19680101.
44. U.S. Preventive Services Task Force. Methods and processes. 2018. <https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes>. Accessed December 17, 2018.
45. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011 Oct 18;155(8):529-36. doi: 10.7326/0003-4819-155-8-201110180-00009. PMID: 22007046.
46. Morton SC, Murad MH, O'Connor E, et al. Quantitative Synthesis—An Update. Methods Guide for Comparative Effectiveness Reviews. (Prepared by the Scientific Resource Center under Contract No. 290-2012-0004-C). AHRQ Publication No. 18-EHC007-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2018. Posted final reports are located on the Effective Health Care Program search page (<https://effectivehealthcare.ahrq.gov/>). <https://doi.org/10.23970/AHRQEPCEMETHGUIDE3>.
47. Chou R, Deyo R, Friedly J, et al. Noninvasive Treatments for Low Back Pain. Comparative Effectiveness Review No. 169. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No.

- 290-2012-00014-I.) AHRQ Publication No. 16-EHC004-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2016.
48. Skelly AC, Chou R, Dettori JR, et al. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review. Comparative Effectiveness Review No. 209. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No 18-EHC013-EF. Rockville, MD: Agency for Healthcare Research and Quality; June 2018. Posted final reports are located on the Effective Health Care Program search page (<https://effectivehealthcare.ahrq.gov/>). DOI: <https://doi.org/10.23970/AHRQEPCCER209>.
 49. Systematic Review Update: Noninvasive Nonpharmacologic Treatments for Chronic Pain. Agency for Healthcare Research and Quality. <https://effectivehealthcare.ahrq.gov/topics/noninvasive-nonpharm-pain-update/protocol>. Accessed August 8, 2019.
 50. Nonopioid Pharmacologic Treatments for Chronic Pain. Agency for Healthcare Research and Quality. <https://effectivehealthcare.ahrq.gov/topics/nonopioid-chronic-pain/protocol>. Accessed August 8, 2019.
 51. Opioid Treatments for Chronic Pain. Agency for Healthcare Research and Quality. <https://effectivehealthcare.ahrq.gov/topics/opioids-chronic-pain/protocol>. Accessed August 8, 2019.
 52. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol*. 2011 Nov;64(11):1198-207. doi: 10.1016/j.jclinepi.2010.11.021. PMID: 21463926.

V. Definition of Terms

Not applicable.

VI. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

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 are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

VII. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final 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.

VIII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

IX. Role of the Funder

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X. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix 1. MEDLINE Search Strategies

Treatment effectiveness and harms

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

Risk prediction and mitigation

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