



Evidence-based Practice Center Systematic Review Protocol

Project Title: *Opioid Treatments for Chronic Pain*

I. Background and Objectives for the Systematic Review

Chronic pain, often defined as pain lasting longer than 3 to 6 months, or past the time of normal tissue healing, is common.¹ The Centers for Disease Control and Prevention (CDC) estimates that 20.4 percent of U.S. adults in 2016 had chronic pain and 8.0 percent had high impact chronic pain.² Chronic pain is associated with an annual cost conservatively estimated at \$560 to \$635 billion, is associated with impaired physical and mental functioning and reduced quality of life, and is the leading cause of disability.¹ Chronic pain is associated with a variety of conditions and influenced by multiple biological, psychological, and social factors. Therefore, optimal approaches to the management of chronic pain should consider psychological and social factors as well as underlying biological mechanisms and physical manifestations of chronic pain (the “biopsychosocial” framework or perspective).³

Opioids and Chronic Pain

In the United States, prescription of opioid medications for chronic pain more than tripled from 1999 to 2015.⁴ This increase was accompanied by marked increases in rates of opioid use disorder and drug overdose mortality⁵⁻⁷ involving prescription opioids. From 1999 to 2014, over 165,000 people died from overdose related to prescription opioids in the United States,⁸ with an estimated 17,087 prescription opioid overdose deaths in 2016.⁷ In October 2017, the U.S. Department of Health and Human Services declared a nationwide public health emergency regarding the opioid crisis.⁹

Nationally, opioid prescribing trends began to plateau in 2010, likely due to implementation of opioid-related practice guidelines and other state-based initiatives. However, overdoses involving heroin, and more recently illicitly manufactured fentanyl,^{7,10} markedly increased since 2010. The majority of heroin users report their first opioid of abuse was a prescribed opioid, and concerns have been raised that efforts to reduce prescribing may result unintended consequence of increased illicit opioid use.¹¹

In 2013, the Agency for Healthcare Research and Quality (AHRQ) commissioned a comparative effectiveness review on the effectiveness and risks of opioid therapy for chronic pain, focusing on studies with long-term (≥ 1 year) followup.¹² The review addressed the risks and benefits of opioids for chronic pain, dosing strategies, and risk assessment and risk mitigation strategies. The AHRQ review found insufficient evidence to show benefits of long-term opioid therapy for chronic pain, due to the absence of trials with followup of at least 1 year. The review found that long-term opioid therapy was associated with increased risk of overdose, opioid abuse, and other harms; some harms (including overdose risk) were dose-dependent. Data on the effectiveness of risk mitigation strategies was limited.

The AHRQ comparative effectiveness review and a subsequent update⁸ commissioned by the CDC were used as the basis for developing the 2016 CDC guideline on opioids for chronic pain.^{8,13} The CDC guideline includes the following recommendations: use nonopioid therapy as the preferred therapy for chronic pain; perform risk assessment and initiate long-term opioid therapy only when benefits are likely to exceed risks; use risk mitigation strategies; and apply dose thresholds (“caution” with doses >50 morphine equivalent dose [MED] per day, “avoid” doses >90 MED/day).⁸ Of the 12 recommendations in the CDC guideline, all except for one (treatment for opioid use disorder) were deemed to be supported by low quality evidence.

Rational for Evidence Review Update

The purpose of this report is to update the prior AHRQ review and update^{8,12} on opioids for chronic pain. Given the ongoing magnitude of the opioid crisis, the low quality of evidence in the prior AHRQ review to support most of the recommendations in the 2016 CDC guideline, the availability of new evidence, and concerns regarding potential unintended consequences of implementing the guideline (e.g., increased use of illicit opioids, increased suicidality, worsening quality of life or function¹⁴), an update is warranted.

This update addresses the questions covered in the prior review, including efficacy and harms, comparisons with nonopioid therapies, dosing strategies, dose-response relationships, risk mitigation strategies, discontinuation and tapering of opioid therapy, and population differences.

What This Review Adds

In addition to incorporating new evidence for questions addressed in the prior AHRQ review, this update expands upon it by addressing shorter-term (1 to 12 month) as well as long-term (≥ 12 month) outcomes, opioid plus nonopioid combination therapy, strategies for treating acute exacerbations of chronic pain, effects of naloxone co-prescription, risks of co-prescribed benzodiazepines, effects of co-prescribed marijuana, tramadol (a dual action analgesic with weak opioid mu-agonist properties), and management of opioid use disorder related to prescription drug use. This update also includes contextual questions on clinician and patient values and preferences; the prior AHRQ review¹² did not include these contextual questions, though the CDC update⁸ addressed similar questions.

II. The Key Questions

Key Question 1. Effectiveness and Comparative Effectiveness

- a. In patients with chronic pain, what is the effectiveness of opioid therapy versus placebo or no opioid therapy for outcomes related to pain, function, and quality of life, after short-term follow-up (up to 6 months), intermediate-term follow-up (6 to 12 months), and long-term follow-up (at least 1 year)?
- b. How does effectiveness vary depending on: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], visceral pain, fibromyalgia, sickle cell disease, inflammatory pain, headache disorders, and degree

of nociplasticity); (2) patient demographics (e.g., age, race, ethnicity, gender, socioeconomic status); (3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for opioid use disorder); (4) the mechanism of action of opioids used (e.g., pure opioid agonists, partial opioid agonists such as buprenorphine or drugs with mixed opioid and nonopioid mechanisms of action such as tramadol or tapentadol)?

c. In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacologic or nonpharmacologic, including marijuana) on outcomes related to pain, function, and quality of life, after short-term follow-up (up to 6 months), intermediate-term follow-up (6 to 12 months), and long-term follow-up (at least 1 year)?

d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacologic or nonpharmacologic, including marijuana) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used, after short-term follow-up (up to 6 months), intermediate-term follow-up (6 to 12 months), and long-term follow-up (at least 1 year)?

Key Question 2. Harms and Adverse Events

a. In patients with chronic pain, what are the risks of opioids versus placebo or no opioid on: (1) substance misuse, substance use disorder, and related outcomes; (2) overdose (intentional and unintentional); and (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)?

b. How do harms vary depending on: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including back pain], visceral pain, fibromyalgia, sickle cell disease, inflammatory pain, headache disorders, and degree of nociplasticity); (2) patient demographics; (3) patient comorbidities (including past or current substance use disorder or at high risk for opioid use disorder); (4) the dose of opioids used and duration of therapy; (5) the mechanism of action of opioids used (e.g., are there differences between pure opioid agonists and partial opioid agonists such as buprenorphine or drugs with opioid and nonopioid mechanisms of action such as tramadol and tapentadol); (6) use of sedative hypnotics; (7) use of gabapentinoids; (8) use of marijuana?

Key Question 3. Dosing Strategies

a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids for outcomes related to pain, function, and quality of life; risk of misuse, opioid use disorder, and overdose; and doses of opioids used?

b. In patients with chronic pain, what is the comparative effectiveness of short-acting versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of misuse, opioid use disorder, and overdose; and doses of opioids used?

- c. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; and risk of misuse, opioid use disorder, and overdose?
- d. In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids versus long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of misuse, opioid use disorder, and overdose; and doses of opioids used?
- e. In patients with chronic pain, what is the comparative effectiveness of scheduled, continuous versus as-needed dosing of opioids on outcomes related to pain, function, and quality of life; risk of misuse, opioid use disorder, and overdose; and doses of opioids used?
- f. In patients with chronic pain, what is the comparative effectiveness of opioid dose escalation versus dose maintenance or use of dose thresholds on outcomes related to pain, function, and quality of life?
- g. In patients with chronic pain, what is the comparative effectiveness of opioid rotation versus maintenance of current opioid therapy on outcomes related to pain, function, and quality of life; and doses of opioids used?
- h. In patients with chronic pain, what is the comparative effectiveness of different strategies for treating acute exacerbations of chronic pain on outcomes related to pain, function, and quality of life?
- i. In patients with chronic pain, what are the effects of decreasing opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and withdrawal?
- j. In patients with chronic pain, what is the comparative effectiveness of different tapering protocols and strategies on measures related to pain, function, quality of life, withdrawal symptoms, and likelihood of opioid cessation?
- k. In patients with chronic pain, what is the comparative effectiveness of different opioid dosages and durations of therapy for outcomes related to pain, function, and quality of life; risk of misuse, opioid use disorder, and overdose?

Key Question 4. Risk Assessment and Risk Mitigation Strategies

- a. In patients with chronic pain being considered for opioid therapy, what is the accuracy of instruments and tests (including metabolic and/or genetic testing) for predicting risk of misuse, opioid use disorder, and overdose?
- b. In patients with chronic pain, what is the effectiveness of use of risk prediction instruments and tests (including metabolic and/or genetic testing) on outcomes related to misuse, opioid use disorder, and overdose?
- c. In patients with chronic pain who are prescribed opioid therapy, what is the effectiveness of risk mitigation strategies, including (1) opioid management plans, (2) patient education, (3) urine drug screening, (4) use of prescription drug monitoring program data, (5) use of monitoring instruments, (6) more frequent monitoring intervals, (7) pill counts, (8) use of abuse-deterrent formulations, (9) consultation with mental health providers when mental health conditions are present, (10) avoidance of co-prescribing of sedative hypnotics, and (11) co-prescribing of naloxone on outcomes related to misuse, opioid use disorder, and overdose?

d. In patients with chronic pain, what is the comparative effectiveness of treatment strategies for managing patients with opioid use disorder related to prescription opioids on outcomes related to misuse, opioid use disorder, overdose, pain, function, and quality of life?

Contextual Questions

- a. What are clinician and patient values and preferences related to opioids and medication risks, benefits, and use?
- b. What are the costs and cost-effectiveness of opioid therapy and risk mitigation strategies?

Note: Contextual questions are not addressed using systematic methods, but target the most relevant and high-quality evidence.

The **population** of interest is adults (≥ 18 years of age) with various types of chronic pain (defined as pain lasting >3 months), including (for specific questions or subquestions) persons with acute exacerbations of chronic pain, pregnant or breastfeeding women, and persons with opioid use disorder related to use of prescription opioids. Details regarding the populations, interventions, comparators, and outcomes are shown in **Table 1**. For this review, opioids includes opioid agonists, partial agonists, and dual mechanism agents. **Outcomes** of interest include pain (intensity, severity, bothersomeness), function (physical disability, activity limitations, activity interference, work function), and quality of life (including depression); doses of opioid used and harms (including overdose, substance use disorder and misuse; other harms (including gastrointestinal harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms, including depression and suicidality). Intermediate outcomes such as pharmacokinetic and pharmacodynamic measures, drug-drug interaction markers, and dose conversions will be excluded.

For all questions, studies with at least 1 month of follow-up will be included. Results will be stratified according to short-term (1 to 6 months), intermediate term (6 to 12 months), and long-term (at least 1 year) follow-up.

Table 1. PICOTS

Key Question	Population	Intervention	Comparator	Outcome
1a, b	Adults (age ≥ 18 years) with various types of chronic pain including pregnant/breast-feeding women and patients treated with opioids for opioid use disorder Key Question 1b: Subgroups: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], fibromyalgia, sickle cell disease, inflammatory pain, and headache disorders); (2) patient demographics (e.g., age, race, ethnicity, gender); (3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for opioid use disorder)	Long- or short-acting opioids (including partial agonists and dual mechanism agents) Exclude: Intravenous or intramuscular administration of opioids	Placebo or no opioid therapy	Pain, function, and quality of life)

Key Question	Population	Intervention	Comparator	Outcome
1c	Adults (age ≥ 18 years) with various types of chronic pain	Long- or short-acting opioids (including partial agonists and dual action medications) Exclude: Intravenous or intramuscular administration of opioids	Nonopioid therapies (pharmacologic [antiepileptic drugs, benzodiazepines, nonsteroidal antiinflammatory drugs, skeletal muscle relaxants, serotonin norepinephrine reuptake inhibitors, topical lidocaine, topical capsaicin, topical diclofenac, tricyclic antidepressants, acetaminophen, memantine, and marijuana/cannabis] or nonpharmacologic [noninvasive])	Pain, function, and quality of life; doses of opioids used
1d	Adults (age ≥ 18 years) with various types of chronic pain	Opioids plus nonopioid interventions (pharmacologic or nonpharmacologic) Exclude: Intravenous or intramuscular administration of opioids	Opioids or nonopioid interventions alone, including marijuana	Pain, function, and quality of life, doses of opioids used

Key Question	Population	Intervention	Comparator	Outcome
2a	Adults (age ≥ 18 years) with various types of chronic pain Key Question 2b: subgroups (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including back pain], fibromyalgia, sickle cell disease, inflammatory pain, headache disorders); (2) patient demographics; (3) patient comorbidities (including past or current substance use disorder or at high risk for opioid use disorder); (4) the dose of opioids used; (5) the mechanisms of actions of the opioids; and (6) use of sedative hypnotics	Long- or short-acting opioids (including tapentadol, buprenorphine, and tramadol) opioids Exclude: Intravenous or intramuscular administration of opioids	Placebo or no opioid	Substance misuse, substance use disorder and related outcomes, overdose, and other harms
3a	Adults (age ≥ 18 years) with various types of chronic pain	Long- or short-acting opioids (including tapentadol, buprenorphine, and tramadol)	Other opioids with different dose initiation and titration strategies	Pain, function, and quality of life; doses of opioids used

Key Question	Population	Intervention	Comparator	Outcome
3b	Adults (age ≥ 18 years) with various types of chronic pain	Short-acting opioid	Long-acting opioid	Pain, function, and quality of life; risk of misuse, opioid use disorder, overdose and other harms; doses of opioids used
3c	Adults (age ≥ 18 years) with various types of chronic pain	Long-acting opioid	Other long-acting opioid	Pain, function, and quality of life; risk of misuse, opioid use disorder, and overdose and other harms; doses of opioids used
3d	Adults (age ≥ 18 years) with various types of chronic pain	Short and long acting opioid	Long-acting opioid	Pain, function, and quality of life; risk of misuse, opioid use disorder, overdose and other harms; doses of opioids used
3e	Adults (age ≥ 18 years) with various types of chronic pain	Scheduled, continuous dosing	As-needed dosing	Pain, function, and quality of life; risk of misuse, opioid use disorder, overdose, and other harms; doses of opioids used
3f	Adults (age ≥ 18 years) with various types of chronic pain	Opioid dose escalation	Dose maintenance or use of dose thresholds	Pain, function, and quality of life
3g	Adults (age ≥ 18 years) with various types of chronic pain	Opioid rotation	Maintenance of current opioid therapy	Pain, function, and quality of life; doses of opioids used

Key Question	Population	Intervention	Comparator	Outcome
3h	Adults (age ≥ 18 years) with various types of chronic pain and an acute exacerbation	Treatments for acute exacerbations of chronic pain	Other treatments for acute exacerbations of chronic pain	Pain, function, and quality of life
3i	Adults (age ≥ 18 years) with various types of chronic pain	Decreasing opioid doses or of tapering off opioids	Continuation of opioids	Pain, function, and quality of life; withdrawal and other harms (including overdose, use of illicit opioids, suicidality, and anger/violence)
3j	Adults (age ≥ 18 years) with various types of chronic pain	Tapering protocols and strategies	Other tapering protocols or strategies	Pain, function, quality of life, likelihood of opioid cessation, withdrawal symptoms and other harms (including overdose, use of illicit opioids, suicidality, and anger/violence)
3k	Adults (age ≥ 18 years) with various types of chronic pain	Dosage of opioid	Other dose of same opioid	Pain, function, and quality of life; risk of misuse, opioid use disorder, overdose and other harms
4a	Adults (age ≥ 18 years) with various types of chronic pain	Instruments, genetic/metabolic tests for predicting risk of misuse, opioid use disorder, and overdose	Reference standard for misuse, opioid use disorder, or overdose; or other benchmarks	Measures of diagnostic accuracy

Key Question	Population	Intervention	Comparator	Outcome
4b	Adults (age ≥ 18 years) with various types of chronic pain	Use of risk prediction instruments, genetic/metabolic tests	Usual care or other control	Misuse, opioid use disorder, overdose and other harms
4c	Adults (age ≥ 18 years) with various types of chronic pain	Risk mitigation strategies, including (1) opioid management plans, (2) patient education, (3) urine drug screening, (4) use of prescription drug monitoring program data, (5) use of monitoring instruments, (6) more frequent monitoring intervals, (7) pill counts, (8) use of abuse-deterrent formulations, (9) consultation with mental health providers when mental health conditions are present, (10) avoidance of benzodiazepine co-prescribing and (11) co-prescribing of naloxone	Usual care	Pain, function, quality of life, misuse, opioid use disorder, overdose and other harms (including use of illicit opioids, suicidality, and anger/violence)
4d	Adults (age ≥ 18 years) with various types of chronic pain and opioid use disorder	Treatment strategies	Other treatment strategies	Pain, function, quality of life, misuse, opioid use disorder, overdose, other harms, pain, function, and quality of life

Additional Inclusion Criteria:

Timing:

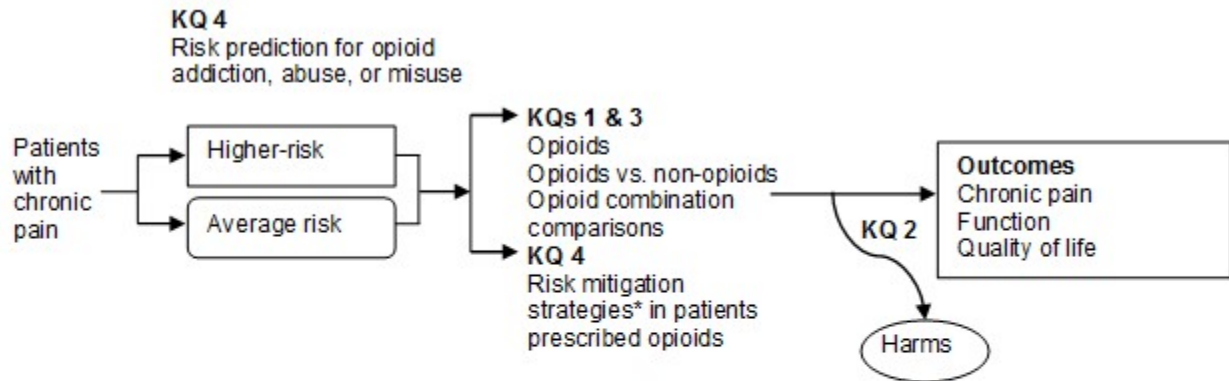
- For all questions, studies with at least 1 month of followup will be included. Results will be stratified according to short-term (1 to 6 months), intermediate term (6 to 12 months), and long-term (≥ 1 year) followup.

Setting:

- Include: Outpatient settings (e.g., primary care, pain clinics, other specialty clinics, emergency rooms, urgent care clinics)
- Exclude: Addiction treatment settings, inpatient settings

III. Analytic Framework

Analytic Framework



KQ, Key Question.

*Including opioid management plans, patient education, urine drug screen, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, use of abuse-deterrent formulations, consultation with mental health providers when mental health conditions are present, avoidance of benzodiazepine co-prescribing, and co-prescribing of naloxone.

IV. 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.

Below are additional details on the scope of this project:

Study Design: For Key Question 4a, we will include studies that evaluate the predictive utility of risk prediction instruments and other risk assessment methods. For all Key Questions, we will include randomized controlled trials (RCTs). We will also include cohort studies and case-control studies for studies on harms and long-

term (≥ 1 year) effectiveness.. For all key questions, we will exclude uncontrolled observational studies, case series, and case reports. For Key Question 4a, we will exclude studies that do not evaluate the performance of a risk prediction instrument against a reference standard. Systematic reviews will be used as primary sources of evidence if they are a strong match to a key question in our review, 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.^{15,16} If systematic reviews are included, we will update findings with any new primary studies identified in our searches. If multiple systematic reviews are relevant and low risk of bias, we will focus on the findings from the most recent and highest-quality reviews and evaluate areas of consistency and inconsistency across the reviews.¹⁷

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: Searches will begin in January 2014 for key questions addressed in the prior AHRQ review, which conducted, searches through August 2014. For questions or areas not covered by the prior review, no search date limitations will be imposed.

Library searches will be updated while the draft report is out for peer 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[®], PsychINFO[®], Embase[®], Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews will be searched to capture both published and grey 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.¹⁵ 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 by using clearly defined templates and criteria as appropriate. Randomized trials will be evaluated using criteria and methods developed by the Cochrane Back Review Group,¹⁸ cohort and other observational studies of interventions will be evaluated using criteria developed by the U.S. Preventive Services Task Force,⁹ and studies of diagnostic accuracy will be assessed using QUADAS-2.¹⁹ 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.¹⁶ 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.¹⁵ Studies will be rated as “good,” “fair,” or “poor,” or as specified by the particular criteria. We will re-review the quality ratings of studies included in the prior review to insure consistency in quality assessment.

Studies rated “good” are considered to have the least risk of bias, and their results are generally be considered valid. Good-quality 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 will not exclude studies rated poor-quality a priori, but poor-quality studies will be considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies are present.

Quality will be independently assessed by two team members. 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. In the evidence tables, we will include relevant studies from the prior AHRQ review and update^{12,13} as well as new studies identified in current searches.

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.²⁰ 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, comorbidities, pain types, treatment features and dosing strategies, though techniques including sensitivity and stratified analyses. Meta-regression may be conducted to explore statistical heterogeneity using additional variables on methodological or other characteristics (e.g., quality, randomization or blinding, outcome definition and ascertainment) given enough number of studies (≥ 6 to 10 for continuous outcomes, ≥ 4 for continuous outcomes).²⁰

Results will be presented as structured by the key questions, and prioritized outcomes will be presented first.

The magnitude of effects for pain and function will be classified using the same system as in the 2018 AHRQ noninvasive treatment for chronic pain review. A small/slight effect was 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 will apply similar methodology to other outcomes measures. Small effects using this system may not meet standard thresholds for clinically meaningful effects; however, the clinical relevance of effects classified as small/slight might vary for individual patients depending on preferences, baseline symptom severity, harms, cost, and other factors.

Grading the Strength of Evidence (SOE) 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.¹⁵ 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's Methods Guide,²¹ 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 chronic 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 chronic pain patients being considered for the intervention. 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, underlying pain condition, 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., primary care vs. specialty setting, country), and study design features (e.g., use of run-in periods or enriched enrollment randomized withdrawal 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.

V. References

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VI. Definition of Terms

Not applicable.

VII. 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.

VIII. 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 three 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.

IX. 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.

X. Role of the Funder

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XI. Registration

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

Appendix 1. MEDLINE Search Strategies

Key Questions 1-3

1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. 9 or 10 or 11
13. 8 and 12
14. limit 13 to english language
15. 14 not (intravenous or intramuscular or injection* or intrathecal or epidural or block or preoperative or perioperative or acute).ti.
16. limit 15 to yr="2014 -Current"

Key Questions 4a-b

1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Decision Support Techniques/

18. "Predictive Value of Tests"/
19. Prognosis/
20. Risk Assessment/
21. Risk Factors/
22. Proportional Hazards Models/
23. "Reproducibility of Results"/
24. "Sensitivity and Specificity"/
25. (sensitivity or specificity or accuracy).ti,ab,kf.
26. (risk and (predict\$ or assess\$)).ti,ab,kf.
27. or/17-26
28. 16 and 27
29. limit 28 to yr="2014 -Current"
30. limit 29 to english language

Key Question 4c

1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Patient Compliance/
18. Health Services Misuse/
19. Substance Abuse Detection/
20. Drug Monitoring/
21. (urine adj7 (screen\$ or test\$ or detect\$)).ti,ab,kf.
22. Contracts/
23. Patient Education as Topic/
24. Drug Overdose/
25. or/17-24
26. risk\$.ti,ab,kf.
27. ("risk evaluation and mitigation" or "rems").ti,ab,kf.

28. Risk Reduction Behavior/ or Risk/
29. or/26-28
30. 16 and 25 and 29
31. limit 30 to yr="2014 -Current"
32. Naloxone/
33. naloxone.ti,ab,kf.
34. 16 and 29 and (32 or 33)
35. 31 or 34
36. limit 35 to english language

Key Question 4d

1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Patient Compliance/
18. Health Services Misuse/
19. Substance Abuse Detection/
20. Drug Monitoring/
21. (urine adj7 (screen\$ or test\$ or detect\$)).ti,ab,kf.
22. (abus\$ or misus\$ or diversion\$ or divert\$).ti,ab,kf.
23. (opioid\$ adj7 (contract\$ or agree\$)).ti,ab,kf.
24. Contracts/
25. Patient Education as Topic/
26. Drug Overdose/
27. or/17-26
28. Substance Abuse Detection/
29. Opiate Substitution Treatment/
30. Risk Management/
31. or/28-30

- 32. 16 and 27 and 31
- 33. Treatment Outcome/
- 34. (treatment and (outcome or strateg\$ or plan\$)).ti,ab,kf.
- 35. 32 and (33 or 34)
- 36. limit 35 to yr="2014 -Current"
- 37. limit 36 to english language