Opioid Treatments for Chronic Pain

Evidence Summary

Introduction

Chronic pain is common and is associated with an annual cost conservatively estimated at $560 to $635 billion, can result in impaired physical and mental functioning and reduced quality of life, and is the leading cause of disability in the United States.[1] Chronic pain is caused by a variety of conditions and is influenced by multiple biological, psychological, and social factors.

Opioids are often prescribed for chronic pain. In the United States, prescription of opioid medications for chronic pain more than tripled from 1999 to 2015.[2] This increase was accompanied by marked increases in rates of opioid use disorder and drug overdose mortality[2-4] involving prescription opioids. From 1999 to 2014, over 165,000 people died from overdose related to prescription opioids in the United States,[5] with an estimated 17,087 prescription opioid overdose deaths in 2016.[2] In October 2017, the U.S. Department of Health and Human Services declared a nationwide public health emergency regarding the opioid crisis.[6]

In 2013, the Agency for Healthcare Research and Quality (AHRQ) commissioned a comparative effectiveness

Purpose of Review

To assess the effectiveness and harms of opioid therapy for chronic noncancer pain, alternative opioid dosing strategies, and risk mitigation strategies

Key Messages

- Opioids are associated with small improvements versus placebo in pain and function, and increased risk of harms at short-term (1 to <6 months) followup; evidence on long-term effectiveness is very limited, and there is evidence of increased risk of serious harms that appear to be dose dependent.

- At short-term followup, evidence showed no differences between opioids versus nonopioid medications in improvement in pain, function, mental health status, sleep, or depression.

- Evidence on the effectiveness and harms of alternative opioid dosing strategies and the effects of risk mitigation strategies is lacking, although provision of naloxone to patients might reduce the likelihood of opioid-related emergency department visits, a taper support intervention might improve functional outcomes compared to no taper support, and co-prescription of benzodiazepines and gabapentinoids might increase risk of overdose.

- No instrument has been shown to be associated with high accuracy for predicting opioid overdose, addiction, abuse, or misuse.

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review on the effectiveness and risks of opioid therapy for chronic pain, focusing on studies with long-term (≥12 months) followup.[7] The review addressed the risks and benefits of opioids for chronic pain, dosing strategies, and risk assessment and risk mitigation strategies. The 2014 AHRQ report 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. Information on the effectiveness of opioid dosing strategies and risk mitigation strategies was limited.

The 2014 AHRQ report and a subsequent update[5] commissioned by the Centers for Disease Control and Prevention (CDC) were used as the basis for developing the 2016 CDC guideline on opioids for chronic pain.[5,8] 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 increasing doses >50 morphine equivalent dose [MED] per day, "avoid" increasing doses >90 MED/day).[5] Of the 12 recommendations in the CDC guideline, all except for one (treatment for opioid use disorder) were assessed as being supported by low quality evidence. Although a number of opioid prescribing practices were declining at the time that the CDC guideline was published, the rate of decline increased following its release.[9]

Rationale for This Review

The purpose of this review is to update the 2014 AHRQ report[7] on opioids for chronic pain. This update includes new evidence for questions covered in the 2014 AHRQ report, 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. This review is one of three concurrent AHRQ systematic reviews on treating chronic pain; the other reviews address nonpharmacologic treatments[10] and nonopioid pharmacological treatments.[11]

Scope and Key Questions

This Comparative Effectiveness Review focused on opioid treatments with short-term (1 to <6 months), intermediate-term (6 to <12 months), and long-term followup (≥12 months); with Key Questions on effectiveness and comparative effectiveness, harms and adverse events, dosing strategies, and risk assessment and risk mitigation strategies.

Key Question 1. Effectiveness and Comparative Effectiveness

a. In patients with chronic pain, what is the effectiveness of opioids versus placebo or no opioid for outcomes related to pain, function, and quality of life after short-term followup (1 to <6 months), intermediate-term followup (6 to <12 months), and long-term followup (≥12 months)?

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 cannabis) on outcomes related to pain, function, and quality of life after short-term followup (1 to <6 months), intermediate-term followup (6 to <12 months), and long-term followup (≥12 months)?

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

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) opioid use disorder, abuse, or misuse; (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 low 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 opioid 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., pure opioid agonists, 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 cannabis?

c. In patients with chronic pain, what are the comparative risks of opioids versus nonopioid therapies on: (1) opioid use disorder, abuse, or misuse; (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 mental health harms (e.g., depression)?

d. In patients with chronic pain, what are the comparative risks of opioids plus nonopioid interventions (pharmacologic or nonpharmacologic, including cannabis) versus opioids or nonopioid interventions alone on: (1) opioid use disorder, abuse, or misuse; (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 mental health harms (e.g., depression)?

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 opioid use disorder, abuse, or misuse; 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 opioid use disorder, abuse, or misuse; 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; risk of opioid use disorder, abuse, or misuse; 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 opioid use disorder, abuse, or misuse; 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 opioid use disorder, abuse, or misuse; 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 opiate withdrawal symptoms?

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, opiate 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?

Key Question 4. Risk Assessment and Risk Mitigation Strategie

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 opioid use disorder, abuse, or misuse, 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 opioid use disorder, abuse, or misuse, 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 opioid use disorder, abuse, or misuse, 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 pain, function, quality of life, opioid use disorder, abuse, misuse, and overdose?

Contextual Questions

1. What are clinician and patient values and preferences related to opioids and medication risks, benefits, and use?

2. What are the costs and cost-effectiveness of opioid therapy and risk mitigation strategies?

Contextual questions are not addressed using systematic methods, but provide a summary of the most relevant and high quality evidence.

Methods

The methods for this systematic review follow the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[12] See the review protocol (https://effectivehealthcare.ahrq.gov/topics/opioids-chronic-pain/protocol) and the full report for additional details.

Review Protocol

A multidisciplinary Technical Expert Panel was convened for this update review and provided input into the draft protocol as did the AHRQ Task Order Officer and representatives from the CDC. The final version of the protocol for this review was posted on the AHRQ Effective Health Care Program website (https://effectivehealthcare.ahrq.gov/topics/opioids-chronic-pain/protocol) and registered in the PROSPERO international database of prospectively registered systematic reviews (CRD42019127423).

Literature Search Strategy

We conducted electronic searches in Ovid® MEDLINE®, Embase®, PsycINFO®, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews in August 2019. Searches were conducted from January 2014 for Key Questions addressed in the 2014 AHRQ report (searches conducted through August 2014). For questions or areas not covered by the 2014 AHRQ publication, searches were conducted from database inception. Reference lists of included systematic reviews were screened for additional studies and relevant references from the 2014 AHRQ report were carried forward. A Federal Register notification for a Supplemental Evidence And Data for Systematic review (SEADS) portal was posted for submission of unpublished studies.

Inclusion and Exclusion Criteria, Study Selection, and Data Abstraction

Inclusion and exclusion criteria were developed a priori based on the Key Questions and PICOTS (Population, Interventions, Comparators, Outcomes, Timing, and Setting) and are detailed in Table 1 of the report and the published protocol. Randomized controlled trials (RCTs) reporting outcomes at least 1 month following completion of treatment. Trials comparing opioids with placebo or no intervention, nonopioids, or different opioids were included, as well as trials comparing opioids plus nonopioids with opioids and nonopioids. Outcomes of interest were pain, function, health status/quality of life, mental health outcomes, sleep, doses of opioid used (for comparisons involving opioids and nonopioid therapy) and harms.

For Key Question 4a, studies on the predictive utility of risk prediction instruments and other risk assessment methods compared against a reference standard were included. Details regarding process and inclusion/exclusion of studies are provided in the full report and Appendix B. We abstracted data on study characteristics, funding source, populations, interventions, comparators, and results.

Quality Assessment of Individual Studies

Study quality was independently assess by two investigators using predefined criteria, randomized trials were evaluated using criteria and methods developed by the Cochrane Back and Neck Group,[13] cohort and other observational studies of interventions were evaluated using criteria developed by the U.S. Preventive Services Task Force,[6] and studies of diagnostic accuracy were assessed using Quality Assessment of Diagnostic Accuracy Studies – Version 2 (QUADAS-2).[14] These criteria were used in conjunction with the approach recommended in the AHRQ Methods Guide.[15] Studies were rated as "good," "fair," or "poor". The quality ratings of studies included in the 2014 AHRQ report were reviewed to insure consistency in quality assessment.

Data Analysis and Synthesis

A random effects meta-analysis using the profile likelihood method was performed on short-term randomized trials of opioids versus placebo, opioids versus nonopioids, opioids plus nonopioids versus nonopioids alone, and opioids plus nonopioids versus opioids alone at short-term followup.[16] Pooled relative risks were calculated for pain, function, and harms (discontinuation due to adverse events, serious adverse events, somnolence, nausea, vomiting, constipation, dizziness, headache, and pruritus).

Different opioid arms within the same study were combined so each study was represented once in a meta-analysis, in order to avoid overweighting and the issue of correlation within the same study. For pooling mean difference or standard mean difference (SMD), adjusted mean difference from the analysis of covariance model or other appropriate regression model was used if reported by the study, followed by difference in change score and followup score. Missing standard deviations for followup and change scores were imputed.

For meta-analyses of opioids versus placebo, the main analysis was stratified by opioid type. For meta-analyses involving nonopioids (opioids versus nonopioids, opioids plus nonopioids vs. opioids, and opioids plus nonopioids versus nonopioids), the main analysis was stratified by the nonopioid. Additional stratified analyses were performed on pain type (neuropathic, fibromyalgia, or musculoskeletal/mixed), duration of followup (1 to <3 months or 3 to 6 months), trial quality (good, fair, or poor), use of a crossover design, opioid status (opioid-naïve, opioid-experienced, mixed, or not reported), publication date (prior to 2007 or in or after 2007), geographic region (United States or Canada, Europe or Australia, Asia, or multiple/mixed), and receipt of industry funding. Opioid dose was analyzed in categories based on the thresholds in the 2016 CDC guideline: less than 50, 50 to less than 90, or 90 or more mg MED/day.[5] For opioids versus placebo, opioid dose was also analyzed as a continuous variable in a meta-regression for the outcomes mean improvement in pain and function. For opioids versus placebo, analyses were also stratified according to whether the trial used an enriched enrollment randomized withdrawal (EERW) design. In the EERW design, patients are randomized to continuation of the opioids or discontinuation (placebo) following a run-in period to determine responsiveness to opioids and tolerability. Because the EERW design was seldom used before 2007, another stratified analysis on this factor was restricted to trials published in or after 2007.

For trials that reported likelihood of a pain or function response, the main analysis was based (in descending order of priority) on the proportion of patients experiencing 30 percent or more improvement in pain or function, improvement in pain or function at an alternative threshold closest to 30 percent or more, or "moderate" or "good" improvement in pain or function or pain relief using a categorical scale. The analysis was also performed on the likelihood of experiencing 50 percent or more improvement in pain. Trials that reported likelihood of a pain response varied with regard to whether patients lost to followup were excluded or considered nonresponders. In the primary analysis we used the data as reported in the trials; as a sensitivity analysis, all patients lost to followup were considered nonresponders.

Statistical heterogeneity was assessed using the I^2 statistic[17] and the Cochran χ^2 test. All meta-analyses were conducted using Stata/SE 14.0 (StataCorp, College Station, TX).

For long-term data and other comparisons and outcomes, there were insufficient data to perform meta-analysis. Evidence was synthesized qualitatively using the methods described in the AHRQ Methods Guide (see Grading the Strength of Evidence, below).[15] For analyses with more than 10 trials that were sufficiently homogeneous with regard to populations, interventions, and

outcomes, funnel plots and the Egger test were conducted for small sample effects.

The magnitude of effects for pain and function were classified using the same system as in the 2018 AHRQ noninvasive treatment for chronic pain review[18] and an earlier AHRQ comparative effectiveness review on treatments for low back pain.[19] A small effect was defined for pain as a mean between-group difference following treatment of 0.5 to 1.0 points on a 0- to 10-point numeric rating scale or visual analog scale and for function as a SMD of 0.2 to 0.5 or a mean difference of 5 to 10 points on the 0 to 100-point Oswestry Disability Index (ODI), 1 to 2 points on the 0 to 24-point Roland-Morris Disability Questionnaire (RDQ), or equivalent. A moderate effect was defined for pain as a mean difference of 10 to 20 points on a 0- to 100-point visual analog scale (VAS) and for function as an SMD of 0.5 to 0.8, or a mean difference of 10 to 20 points on the ODI, 2 to 5 points on the RDQ, or equivalent. Large/substantial effects were defined as greater than moderate. We applied similar thresholds to other outcomes measures.[20]

Grading the Strength of Evidence

The overall strength of evidence for each KQ and primary outcome (pain, function) was graded high, moderate, low, or insufficient based on study limitations; consistency of results across studies; the directness of the evidence linking the interventions with health outcomes; effect estimate precision; and reporting bias.[15] Summary strength of evidence tables were updated based on all the evidence, from the 2014 AHRQ report and this updated review.

Peer Review and Public Commentary

Experts were invited to provide external peer review of this systematic review; AHRQ and an associate editor also provided comments. In addition, the draft report was posted on the AHRQ website for 4 weeks to for public comment. Comments were reviewed and used to inform revisions to the final report.

Results

We included 115 randomized controlled trials, 40 observational studies, and seven studies of diagnostic accuracy of opioid risk prediction instruments to address four Key Questions and two Contextual Questions (Table A). The population of interest is adults with various types of chronic pain. The full report outlines the populations, interventions, comparators, and outcomes considered in our review, along with more detailed analysis of the findings (and reporting of insufficient evidence).

Table A. Summary of findings

Key Question[a]	Summary of Findings
1a. Opioids vs. placebo or no opioid	• Opioids were associated with a small mean improvement vs. placebo in pain intensity at short-term followup (71 trials, N=19,616, SOE: high). • Opioids were associated with increased likelihood vs. placebo of experiencing a pain response at short-term followup (44 trials, N=12,481, SOE: high). • Opioids were associated with a small mean improvement vs. placebo in function at short-term followup (44 trials, N=12,427, SOE: high). • Opioids were associated with a mean improvement below the threshold for small vs. placebo in SF-36 measures of physical health status at short-term followup (23 trials, N=8005, SOE: high). • No difference between opioids vs. placebo in mean improvement on SF-36 measures of mental health status at short-term followup (21 trials, N=7586, SOE: high) • Opioids were associated with a small mean improvement vs. placebo in sleep quality at short-term followup (25 trials, N=6720, SOE: moderate).
1b. How does effectiveness vary depending on: the specific type or cause of pain; patient demographics; patient comorbidities; or opioid type?	• Effects of opioids vs. placebo on mean improvement in pain were greater at short-term followup in trials of patients with neuropathic pain (20 trials, N=2568) than musculoskeletal pain (50 trials, N=16,979) (SOE: low). • Limited evidence found similar effects of opioids vs. placebo when analyses were stratified by age (4 trials), sex (2 trials), and race (1 trial) (SOE: low). • Analyses of 70 placebo-controlled trials found no interactions between type of opioid on short-term pain, function, SF-36 health status, sleep, depression, or adverse effects; 5 trials directly comparing different types of opioids found a mixed mechanism agent associated with greater pain relief vs. a pure opioid agonist with fewer side effects and 3 trials that directly compared a partial vs. pure opioid agonist found no differences between a partial vs. pure opioid agonist (SOE: moderate).
1c. Opioids vs. nonopioid therapies	• No differences between opioids vs. nonopioids in mean improvement in pain (14 trials, N=2195) or likelihood of a pain response at short-term followup (12 trials, N=2886) at short-term followup (SOE: moderate). • There were no differences between opioids vs. nonopioids in mean improvement in function at short-term followup (11 trials, N=2010, SOE: high). • Opioids were associated with a greater improvement than nonopioids in SF-36 measures of physical health status at short-term followup that was below the threshold for small (6 trials, N=1423, SOE: moderate). • There were no differences between opioids vs. nonopioids in SF-36 mental health status (6 trials, N=1427), sleep (7 trials, N=1694), anxiety (3 trials, N=414) or depression (7 trials, N=748) at short-term followup (SOE: low for anxiety, moderate for other outcomes). • There were no interactions between nonopioid type and effects on any short-term outcome.

Table A. Summary of findings (continued)

Key Question[a]	Summary of Findings
1d. Opioids plus nonopioid interventions vs. opioids or nonopioid interventions alone	Opioid plus nonopioid vs. nonopioid • No differences between an opioid plus nonopioid vs. a nonopioid alone in mean improvement in pain at short-term followup (6 trials, N=628), likelihood of a pain response (6 trials, N=765), function (4 trials, N=549), or other outcomes (SOE: low for all outcomes). Opioid plus nonopioid vs. opioid • An opioid plus nonopioid was associated with greater improvement in pain at short-term followup vs. an opioid alone that was below the threshold for small (5 trials, N=623, SOE: low). • No statistically significant differences between an opioid plus nonopioid vs. an opioid alone in likelihood of a pain response (5 trials, N=831) or mean improvement in function (4 trials, N=521) though estimates favored combination therapy (SOE: low). • No differences between an opioid plus nonopioid vs. an opioid alone in mean improvement in SF-36 measures of physical or mental health status, sleep, anxiety, or depression, though analyses were limited by small numbers of trials (SOE: low). • Four trials of patients with neuropathic pain found an opioid plus nonopioid associated with lower doses of opioid used vs. an opioid alone, with pain relief better with combination therapy (SOE: low). • One cohort study of patients with chronic pain prescribed opioids found no association between degree of self-reported cannabis use and pain, function, likelihood of opioid discontinuation, or opioid dose through up to 4 years of followup; cannabis use was associated with increased anxiety (SOE: low).

Table A. Summary of findings (continued)

Key Question[a]	Summary of Findings
2a. Harms of opioids vs. placebo or no opioid	• Opioids were associated with increased risk of discontinuation due to adverse events vs. placebo at short-term followup (61 trials, N=19,994, SOE: high). • There was no difference between opioids vs. placebo in risk of serious adverse events at short-term followup (38 trials, N=13,160, SOE: moderate) • Opioids were associated with increased risk of nausea (60 trials, N=19,718), vomiting (49 trials, N=17,388), and constipation (58 trials, N=19,351) vs. placebo at short-term followup (SOE: high) • .Opioids were associated with increased risk of somnolence vs. placebo at short-term followup (52 trials, N=17,458, SOE: high). • Opioids were associated with increased risk of dizziness vs. placebo at short-term followup (53 trials, N=18,396, SOE: high). • Opioids were associated with increased risk of pruritus vs. placebo at short-term followup (30 trials, N=11,454, SOE: high). • Opioids were not associated with increased risk of headaches versus placebo at short-term followup (48 trials, N=17,405, SOE: high). • Two cohort studies found an association between opioid use and increased risk of abuse, dependence, or addiction (SOE: low). • Two cohort studies found an association between opioid use and increased risk of overdose events (SOE: low). • One cohort study found prescription of long-acting opioids associated with increased risk of all-cause mortality vs. nonopioid medications (SOE: low). • Six observational studies found an association between opioid use and risk of fracture and three observational studies found an association between opioid use and risk of falls, though differences were not statistically significant in all studies and estimates decreased with longer duration of opioid use in some studies (SOE: low). • Two observational studies found an association between opioid use and increased risk of myocardial infarction (SOE: low). • One cross-sectional study of men with back pain found long-term opioid use associated with increased risk for use of medications for erectile dysfunction or testosterone replacement vs. nonuse (SOE: low). • One cohort study found no association between any long-term opioid use and increased risk of attempted suicide/self-harm (SOE: low).

Table A. Summary of findings (continued)

Key Question[a]	Summary of Findings
2b. How do harms vary depending on: (1) the specific type or cause of pain; (2) patient demographics; (3) patient comorbidities; (4) the dose of opioids used and duration of therapy; (5) opioid type; (6) use of sedative hypnotics; (7) use of gabapentinoids; (8) use of marijuana?	• Analyses of placebo-controlled trials found no interactions between the pain type and risk of harms (SOE: low). • Three cohort studies found an association between concurrent use of benzodiazepines and opioids vs. opioids alone; in one study the risk of overdose decreased with longer duration of concurrent use (SOE: low). • Three observational studies found an association between concurrent use of gabapentinoids and opioids vs. opioids alone and increased risk of overdose; risks were higher at increased gabapentinoid doses (SOE: low). Dose/duration • Analyses of placebo-controlled trials indicated no interaction between higher opioid dose category and increased risk of short-term harms; trials directly comparing higher vs. lower dose were limited but reported similar findings (SOE: low). • Two cohort studies found higher doses of long-term opioid therapy associated with increased risk of opioid abuse, dependence, or addiction compared with lower doses (SOE: low). • Four observational studies consistently found an association between higher doses of long-term opioids and risk of overdose or overdose mortality (SOE: low). • One cohort study found higher dose of opioids associated with increased risk of all-cause mortality; longer duration was associated with decreased risk of all-cause mortality (SOE: low). • One cohort study found modest associations between higher dose of long-term opioid and increased risk of falls and major trauma (SOE: low). • One case-control study found opioid dose higher than 20 mg MED/day associated with increased odds of road trauma injury when the analysis was restricted to drivers, with no dose-dependent association at doses higher than 20 mg MED/day (SOE: low). • Three cohort studies found association between higher opioid dose and risk of various endocrinological adverse events (SOE: low). • One cohort study found an association between longer duration of therapy and increased risk of new-onset depression; there was no association between higher dose and increased risk. A smaller study by the same authors reported similar findings for treatment-resistant depression (SOE: low). Co-prescription of benzodiazepines or gabapentinoids • Three cohort studies found an association between concurrent use of benzodiazepines and opioids versus opioids alone and increased risk of overdose; in one study, the risk decreased with longer duration of concurrent use (SOE: low). • Three observational studies found an association between concurrent use of gabapentinoids and opioids versus opioids alone and increased risk of overdose; risks were higher at increased gabapentinoid doses (SOE: low).

Table A. Summary of findings (continued)

Key Question[a]	Summary of Findings
2c. Harms of opioids vs. nonopioid therapies	• Opioids were associated with increased risk of discontinuation due to adverse events (12 trials, N=3637), somnolence (12 trials, N=3377), nausea (11 trials, N=3137), constipation (12 trials, N=3377), vomiting (6 trials, N=2644), pruritus (5 trials, N=2577, and headache (8 trials, N=2759) vs. a nonopioid at short-term followup (SOE: moderate [discontinuation due to adverse events, constipation, somnolence] to high [nausea, vomiting, headache, pruritus]).
2d. Harms of opioids plus nonopioid interventions vs. opioids or nonopioid interventions alone	Opioid plus nonopioid vs. nonopioid • An opioid plus nonopioid was associated with increased risk of nausea (5 trials, N=330) and constipation (6 trials, N=633) vs. a nonopioid alone at short-term followup. Effects on risk of discontinuation due to adverse events were not statistically significant (6 trials, N=707). Effects on risk of somnolence (6 trials, N=663) and constipation (6 trials, N=663) were also no statistically significant, but there was an interaction with trial quality and effects were statistically significant when a poor-quality trial was excluded (SOE: low for discontinuation due to adverse events, moderate for nausea, constipation, and somnolence). Opioid plus nonopioid vs. opioid • No differences between an opioid plus nonopioid vs. an opioid alone in risk of discontinuation due to adverse events (5 trials, N=782), nausea (5 trials, N=585), constipation (6 trials, N=860), or somnolence (6 trials, N=860) vs. an opioid alone at short-term followup.
3b. Short-acting vs. long-acting opioids	• Two trials found no differences in effectiveness or harms between long- vs. short-acting formulations of the same opioid administered at similar doses (SOE: low). • A cohort study found long-acting opioid associated with increased risk of overdose vs. short-acting opioids; risk decreased with longer duration of exposure (SOE: low).
3c. Different long-acting opioids	• Four trials (N=2721) of long-acting oxycodone vs. tapentadol reported mean differences in pain, but the dose was lower in the oxycodone arms. Oxycodone was associated with increased risk of discontinuation due to adverse events and gastrointestinal adverse events, with no difference in risk of serious adverse events (SOE: low). • Three trials (N=1405) compared similar doses of long-acting oxycodone vs. morphine; effects on pain, SF-36 physical and mental health; adverse events were inconsistent, with some trials reporting no differences (SOE: low). • Three trials (N=957) compared transdermal fentanyl vs. long-acting morphine. Two trials reported no differences in pain or other outcomes. The third trial found a small difference in pain intensity favoring transdermal fentanyl. Two trials found a lower likelihood of constipation with transdermal fentanyl than long-acting morphine but discontinuations due to adverse events was higher with transdermal fentanyl (SOE: low). • Other long-acting opioid comparisons were evaluated in one or two trials, with no differences in effects (SOE: low) • Two cohort studies of Medicaid patients found methadone associated with increased risk of overdose or all-cause mortality vs. morphine and one cohort study of Veterans Affairs patients found methadone associated with decreased risk (SOE: low).

Table A. Summary of findings (continued)

Key Question[a]	Summary of Findings
3f. Opioid dose escalation vs. dose maintenance or use of dose thresholds	• One trial of more liberal dose escalation vs. maintenance of current doses found no difference in outcomes related to pain, function, or risk of discontinuation due to opioid misuse, but opioid doses were similar (52 vs. 40 mg MED /day at the end of the trial) (SOE: low).
3h. Different strategies for treating acute exacerbations of chronic pain	• Two randomized trials found buccal fentanyl more effective than placebo for treating acute exacerbations of pain in patients prescribed long-term opioid therapy for chronic pain, based on pain relief measured up to 2 hours after dosing (SOE: moderate). • Two randomized trials found buccal fentanyl more effective than oral opioids for treating acute exacerbations of pain in patients prescribed long-term opioid therapy for chronic pain, based on pain relief measured up to 2 hours after dosing. (SOE: moderate).
3i. Decreasing opioid doses or tapering off opioids vs. continuation of opioids	• One trial found a taper support intervention associated with no difference vs. usual care at 22 weeks in BPI pain severity, but greater improvement in BPI pain interference; effects persisted at 34-week followup. Effects on opioid dose were not statistically significant (SOE: low).
3j. Different tapering protocols and strategies	• One trial of patients undergoing tapering in a 15-day intensive outpatient interdisciplinary pain program found no differences between varenicline vs. placebo as an adjunct to tapering in median time to tapering completion, opioid withdrawal symptoms, pain, or depression (SOE: low). • One cohort study of patients prescribed 120 mg MED/day or more of long-term opioid therapy found each additional week to discontinuation associated with a 7% reduction in risk of an opioid-related emergency department visit or hospitalization (SOE: low).
3k. Different opioid dosages and durations of therapy	• In head-to-head trials, opioid doses of 50 to 90 mg MED/day were associated with a minimally greater (below the threshold for small) improvement mean pain intensity versus doses less than 50 mg MED/day; there was no difference in mean improvement in function. Analyses of placebo-controlled trials also found an interaction (p=0.005) between higher opioid dose and greater improvement in mean pain intensity, with some evidence of a plateauing effect at 50 mg or greater MED/day (SOE: moderate). • In analyses of placebo-controlled trials, effects on mean improvement in pain were larger at 1 to 3 months than at 3 to 6 months; similar patterns were observed for likelihood of pain response and mean improvement in function (SOE: low).

Table A. Summary of findings (continued)

Key Question[a]	Summary of Findings
4a. Accuracy of instruments for predicting risk of opioid overdose, addiction, abuse, or misuse	• Two studies (N=203) evaluated the Screening and Opioid Assessment for Patients with Pain (SOAPP) Version 1 instrument. In one study, sensitivity was 0.68 and specificity was 0.38 at a cutoff score of at least 8, for a PLR of 1.11 and NLR of 0.83 for predicting positive urine drug tests. One study reported a sensitivity for predicting opioid discontinuation due to aberrant drug-related behavior of 0.73 at a cutoff score of greater than 6 (SOE: low). • Four studies (N=840) evaluated the Screening and Opioid Assessment for Patients with Pain-Revised (SOAPP-R). At a cutoff score of at least 18, sensitivity ranged from 0.25 to 0.53 and specificity ranged from 0.62 to 0.77 for predicting aberrant drug-related behaviors (4 studies). The AUROC ranged from 0.52 to 0.55 (3 studies) (SOE: low). • One study (n=263) found the Pain Medication Questionnaire associated with a sensitivity of 0.34, specificity of 0.77, and AUROC of 0.57 for predicting opioid discontinuation due to abuse (SOE: low). • Three new studies (N=577) evaluated the Brief Risk Interview (BRI). A BRI high-risk assessment was associated with sensitivities that ranged from 0.73 to 0.83 and specificities that ranged from 0.43 to 0.88 for predicting opioid misuse or abuse, with AUROCs of 0.65 and 0.93 in two studies (SOE: low). • One study (N=257) evaluated the Brief Risk Questionnaire. At a cutoff score of at least 3, sensitivity was 0.80, specificity 0.41, and the AUROC was 0.61 (SOE: low).
4c. Risk mitigation strategies	• One cohort study found co-prescription of naloxone in patients prescribed opioids for chronic pain associated with no difference between no naloxone in all-cause mortality or opioid poisoning deaths, though naloxone co-prescription was associated with decreased risk of ED visits at 1 year followup (SOE: low). • No study evaluated the effectiveness of other risk mitigation strategies vs. non-use of the risk mitigation strategy for improving outcomes related to misuse, opioid use disorder, and overdose.
4d. Treatment strategies for managing patients with opioid use disorder related to prescription opioids	• A trial of patients with prescription opioid dependence not requiring opioids for a pain diagnosis found buprenorphine taper associated with a lower percentage of negative urine samples, more days per week of illicit opioid use, and higher risk of relapse vs. buprenorphine maintenance (SOE: low). • A trial of patients with opioid dependence due to prescription opioids for chronic pain found no difference between methadone vs. buprenorphine/naloxone in likelihood of study retention, pain, or function; there were also no differences in likelihood of a positive urine for opioids, cocaine, or other drugs, though patients randomized to methadone were less likely to self-report opioid use (SOE: low).

[a]No studies addressed Key Questions 3d, 3e,3g, 4b. For Key Question 3a, evidence was insufficient.

AUROC = area under the receiver operating curve; BPI = Brief Pain Inventory; BRI = Brief Risk Interview; DIRE = Diagnosis, Intractability, Risk and Efficacy Inventory; ED = emergency department; MED = morphine equivalent dose; NLR=negative likelihood raio; ORT = Opioid Risk Tool; PLR=positive likelihood ratio; SOAPP = Screening and Opioid Assessment for Patients with Pain; SOAPP-R = Screening and Opioid Assessment for Patients with Pain (Revised); SOE = strength of evidence

The full report of our review presents additional detail on the findings for the Key Questions and in addition addresses the two Contextual Questions on (1) clinician and patient values and preferences, and (2) costs and cost-effectiveness or opioid therapy and risk mitigation strategies.

Discussion

Key Findings and Strength of Evidence

This report updates the 2014 AHRQ report. The key findings, including SOE ratings, are summarized in Table A and reflect the combined evidence from the 2014 AHRQ report and this update. For short-term outcomes, data were available from over 71 placebo-controlled trials of opioids. All trials were 6 months in duration or less, with most (87.5%) trials 3 months or less. Opioids were associated with beneficial effects versus placebo, but MDs were small: for pain, less than 1 point on a 0 to 10 scale and for function, an SMD of 0.22 (or <1 point on the 0 to 10 BPI interference scale and <1 point on the 0 to 24 RDQ. Some differences were statistically significant but below the pre-defined threshold for small (<0.5 on a 0 to 10 scale or an SMD <0.2); average effects in this range are unlikely to be clinically significant in most patients.

Effects of opioids versus placebo on short-term health status/quality of life, sleep quality, and mental health outcomes were reported less frequently than pain and function. Opioids were associated with a small mean improvement in short-term sleep quality versus placebo and might be associated with a small mean short-term improvement in SF-36 mental health status. Effects on SF-36 physical health status were below the threshold for small and there was no effect on mental health outcomes.

Effects of opioids on short-term outcomes were generally consistent across opioid types. For pain, effects were somewhat greater in trials of neuropathic than musculoskeletal pain, with an average difference of about 0.5 point on a 0 to 10 scale. Study methods also had some effect on findings, with use of a crossover design associated with larger effects for some outcomes.

Opioids were associated with increased risk of short-term, bothersome harms versus placebo, including discontinuation due to adverse events (number needed to harm [NNH 10], gastrointestinal events [NNH 7.1 for nausea, 14.3 for vomiting, and 7.1 for constipation], somnolence [NNH 11.1], dizziness [NNH 12.5], and pruritus [NNH 14.3]). There were few serious adverse events and no difference between opioids versus placebo in risk in the short-term trials, though serious adverse events were not well-defined by the trials

Evidence on short-term outcomes does not address the practice of long-term use of opioids and associated benefits and harms. As in the 2014 AHRQ report, we identified no long-term (>1 year) RCTs of opioid therapy versus placebo. One new cohort study found no association between long-term opioid therapy versus no opioids and pain, function or other outcomes.[21] New observational studies were consistent with the 2014 AHRQ report in finding an association between use of prescription opioids and risk of addiction,[22] overdose,[22] fractures,[23-25] falls[24,26] and cardiovascular events;[27] a new study also found an association between opioid use and risk of all-cause mortality.[27] New observational studies were also consistent with the 2014 AHRQ report in finding associations between higher doses of opioids and risks of overdose, addiction, and endocrinological adverse events;[22,23,26-29] new studies also found an association between higher dose and increased risk of incident or refractory depression.[30,31] Effects of longer duration of opioid exposure varied across outcomes, from increasing risk (all-cause mortality, depression) to decreasing risk. Limited evidence indicated an association between co-prescription of gabapentinoids[32-34] or benzodiazepines[35-37] and increased risk of overdose,

with most pronounced risk occurring soon after initiation of these medications.

This update also expanded upon the 2014 AHRQ report by including short-term randomized trials that directly compared opioids versus nonopioids and combination therapy with an opioid plus nonopioid versus an opioid or nonopioid alone. There were no differences between opioids versus nonopioids in short-term pain, function, health status/quality of life, sleep quality, or mental health outcomes, though opioids were associated with increased risk of short-term adverse effects. The most commonly evaluated nonopioids were NSAIDS, gabapentinoids, and nortriptyline. All trials of combination therapy evaluated patients with neuropathic pain and primarily evaluated gabapentinoids or nortriptyline, potentially limiting applicability of findings to other pain types and other nonopioids. Evidence on long-term effects of combination therapy versus an opioid or nonopioid alone, including effects on overdose risk and risks related to opioid use disorder, was lacking.

Evidence on the effectiveness of different opioid dosing strategies remains very limited. One trial included in the 2014 AHRQ report found no differences between a more liberal dose escalation strategy versus maintenance of current doses in pain, function, or discontinuation due to opioid misuse, but the liberal escalation strategy was associated with only a small difference in opioid doses (52 vs. 40 mg MED/day).[38] There were no clear differences between short- and long-acting opioids or between different long-acting opioids in effects on pain or function, but in most trials doses were titrated to achieve adequate pain control. None of the head-to-head trials were designed to evaluate overdose, abuse, addiction, or related outcomes. Evidence on comparative risks of methadone versus other opioids remains limited and inconsistent in showing increased risk of outcomes related to overdose.[27,39,40] Evidence on benefits and harms of different methods for initiating and titrating opioids, scheduled and

continuous versus as-needed dosing of opioids, use of opioid rotation, and methods for titrating or discontinuing patients off opioids remains unavailable or too limited to reach reliable conclusions.

New evidence on the accuracy of risk prediction instruments was consistent with the 2014 AHRQ report, which found highly inconsistent estimates of diagnostic accuracy, methodological limitations and few studies of risk assessment instruments other than the Opioid Risk Tool (ORT) and Screening and Opioid Assessment for Patients with Pain-Revised (SOAPP-R). Studies on the accuracy of risk instruments for identifying aberrant behavior in patients already prescribed opioids were not addressed in this review.

Evidence on the effectiveness of risk mitigation strategies also remains very limited. One new observational study found provision of naloxone to patients prescribed opioids in primary care clinics associated with decreased likelihood of emergency department visits, but no difference in risk of overdose.[41] Evidence of opioid tapering versus usual care was largely limited to a trial that found a taper support intervention associated with better functional outcomes and a trend towards lower opioid doses versus usual opioid care.[42] Regarding alternative tapering methods, one small new trial found no difference between tapering with varenicline versus tapering with placebo in likelihood of opioid abstinence, pain, or depression.[43] A cohort study found discontinuation of opioid therapy associated with increased risk of overdose mortality versus continuation, but there was no statistically significant difference in risk of all-cause mortality.[44] It was not possible to determine a causal association between opioid discontinuation and overdose mortality because most patients had a safety reason for discontinuation, the study did not attempt to control for potential confounders other than age and race, most patients received opioids from another provider after discontinuation, and there was no information about time to discontinuation.

Rather, the findings may indicate that patients with indications for opioid discontinuation are at high risk for opioid-related adverse events.

No trial compared different rates of opioid tapering, though one observational study found an association between longer time to opioid discontinuation in patients on long-term, high-dose opioid therapy and decreased risk of opioid-related emergency department visit or hospitalization.[45] The Food and Drug Administration recently issued a warning on not discontinuing long-term opioid therapy abruptly.[46] No study evaluated the effectiveness of risk mitigation strategies, such as use of risk assessment instruments, opioid management plans, patient education, urine drug screening, prescription drug monitoring program data review, monitoring instruments, more frequent monitoring intervals, pill counts, abuse-deterrent formulations, or avoidance of co-prescribing of benzodiazepines on risk of overdose, addiction, abuse or misuse.

Evidence on the effectiveness of interventions for opioid use disorder in patients with prescription opioid dependence or opioid use disorder was also limited and might have limited applicability to patients currently prescribed opioids for chronic pain

Limitations

Meta-analyses could not be conducted for most questions due to small numbers of studies, methodological limitations, and heterogeneity across studies in interventions evaluated, study designs, and outcomes assessed. Although we restricted inclusion of observational studies to those that controlled for potential confounders, even well-conducted observational studies are susceptible to residual confounding and bias. Evidence from randomized trials was almost exclusively restricted to trials ≤6 months in duration, and most trials had methodological shortcomings. Few studies evaluated how benefits and harms vary in subgroups defined by demographic characteristics, characteristics of the pain condition, medical or psychological comorbidities, and substance use history.

Implications and Conclusions

Our review has implications for clinical and policy decision making. Findings support the recommendation in the 2016 CDC guideline[5] that opioids are not first-line therapy and to preferentially use nonopioid alternatives, based on small short-term benefits, increased risk of harms (including serious harms such as opioid use disorder and overdose) and similar benefits compared with nonopioid therapies. Evidence on long-term benefits remains very limited, and additional evidence confirms an association between opioids and increased risk of serious harms that appears to be dose-dependent. Most clinical and policy decisions regarding risk mitigation strategies and opioid dosing strategies for chronic noncancer pain must still be made on the basis of weak or insufficient evidence, and research on the effectiveness of different opioid prescribing methods and risk mitigation strategies remains a priority.

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