Clinical Evidence Review for the CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016

Primary Clinical Questions

The following primary clinical questions regarding the effectiveness, benefits, and harms of long-term opioid therapy for chronic pain were addressed through reviews of the scientific evidence. Long-term opioid therapy is defined as use of opioids on most days for >3 months. The first four clinical questions were comprehensively addressed in the Agency for Healthcare Research and Quality (AHRQ)-sponsored systematic review (*1,2*), and updated literature searches were conducted to identify new studies. The fifth clinical question was added for the purpose of this guideline, and a new systematic review of the scientific evidence was conducted to address it.

Key Question 1. Effectiveness and Comparative Effectiveness

a. In patients with chronic pain, what is the effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term ($\geq$ 1 year) outcomes related to pain, function, and quality of life?
b. How does effectiveness vary depending on: (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); and (3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for addiction)?
c. In patients with chronic pain, what is the comparative effectiveness of opioids versus non-opioid therapies (pharmacologic or non-pharmacologic) on outcomes related to pain, function, and quality of life?
d. In patients with chronic pain, what is the comparative effectiveness of opioids plus non-opioid interventions (pharmacologic or non-pharmacologic) versus opioids or non-opioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?

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 abuse, addiction, and related outcomes; (2) overdose; and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle crashes, endocrinologic 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], 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 addiction); and (4) the dose of opioids used?

Key Question 3. Dosing Strategies

a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
b. In patients with chronic pain, what is the comparative effectiveness of immediate-release versus extended-release/long-acting (ER/LA) opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
c. In patients with chronic pain, what is the comparative effectiveness of different ER/LA opioids on outcomes related to pain, function, and quality of life and risk of overdose, addiction, abuse, or misuse?
d. In patients with chronic pain, what is the comparative effectiveness of immediate-release plus ER/LA opioids versus ER/LA opioids alone on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; 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 overdose, addiction, abuse, or misuse; and doses of opioids used?
f. In patients with chronic pain on long-term opioid therapy, what is the comparative effectiveness of dose escalation versus dose maintenance or use of dose thresholds on outcomes related to pain, function, and quality of life?
g. In patients on long-term opioid therapy, 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 on long-term opioid therapy, 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 on long-term opioid therapy, 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 on long-term opioid therapy, 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?

Key Question 4. Risk Assessment and Risk Mitigation Strategies

a. In patients with chronic pain being considered for long-term opioid therapy, what is the accuracy of instruments for predicting risk of opioid overdose, addiction, abuse, or misuse?
b. In patients with chronic pain, what is the effectiveness of use of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse?
c. In patients with chronic pain prescribed long-term 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, and (8) use of abuse-deterrent formulations on outcomes related to overdose, addiction, abuse, or misuse?
d. What is the comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids on outcomes related to overdose, abuse, misuse, pain, function, and quality of life?

Key Question 5. Effect of Opioid Therapy for Acute Pain on Long Term Use

a. In patients with acute pain, what are the effects of prescribing opioid therapy versus not prescribing opioid therapy for acute pain on long-term opioid use?

The review was focused on the effectiveness of long-term opioid therapy on long-term (≥1 year) outcomes related to pain, function, and quality of life to ensure that findings are relevant to patients with chronic pain and long-term opioid prescribing. The effectiveness of short-term opioid therapy has already been established (*3*). However, opioids have unique effects such as tolerance and physical dependence that might influence assessments of benefit over time. These effects raise questions about whether findings on short-term effectiveness of opioid therapy can be extrapolated to estimate benefits of long-term therapy for chronic pain. Thus, it is important to consider studies that provide data on long-term benefit. For certain opioid-related harms (overdose, fractures, falls, motor vehicle crashes), observational studies were included with outcomes measured at shorter intervals because such outcomes can occur early during opioid therapy, and such harms are not captured well in short-term clinical trials.

Systematic Review Methods

Detailed methods and data for the 2014 AHRQ report upon which this updated systematic review is based have been published (*1*,*2*). The protocol was developed using a standardized process (*4*) with input from experts and the public and was registered in the PROSPERO database (*5*).

Data Sources and Searches

For the 2014 AHRQ report, a research librarian searched MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, PsychINFO, and CINAHL for English-language articles published January 2008 through August 2014, using search terms for opioid therapy, specific opioids, chronic pain, and comparative study designs. Also included were relevant studies from an earlier review in which searches were conducted without a start date restriction (*3*), reference lists were reviewed, and ClinicalTrials.gov was searched. An update search to identify new evidence for the four clinical questions that were addressed in the 2014 AHRQ report and to identify studies for the additional question on the association between use of opioids for acute pain and long-term opioid use was performed in April 2015, using the same search strategies as in the 2014 AHRQ report.

Study Selection

Two investigators independently reviewed abstracts and full-text articles against pre-specified eligibility criteria. Included were randomized trials and observational studies (cohort studies, case-control studies, cross-sectional studies) that controlled for potential confounders of adults (age ≥18 years) with chronic (>3 months) pain prescribed long-term opioid therapy (defined as opioid use on most days for >3 months) that evaluated opioid therapy versus placebo, no opioid, or non-opioid therapy, different opioid dosing strategies; or risk mitigation strategies. Studies that did not report pain duration were included if the average duration of opioid therapy was >3 months and studies that did not report therapy duration were included if patients were prescribed ER/LA opioids, which are not recommended for short-term use. For overdose and injuries (fractures, falls, motor vehicle crashes), dose initiation and titration, and opioid therapy discontinuation, studies were included regardless of duration of follow-up. The focus was otherwise on outcomes reported after ≥1 year of opioid therapy. The review was focused on the effectiveness of long-term opioid therapy on long-term (≥1 year) outcomes related to pain, function, and quality of life to ensure that findings are relevant to patients with chronic pain and long-term prescribing. For opioid-related harms (overdose, fractures, falls, motor vehicle crashes) studies were included with outcomes measured at shorter intervals because such outcomes can occur early during opioid therapy.

Observational studies of chronic pain patients without a non-opioid control group that assessed abuse, misuse, or addiction as a primary outcome using predefined methods were included, as were studies on the accuracy of risk prediction instruments administered prior to opioid therapy initiation for predicting future misuse, abuse, or addiction.

Studies of tramadol, a dual-mechanism medication with weak opioid mu-receptor affinity were excluded. Studies of patients at the end of life were excluded, but studies of cancer pain were included if not focused on the end of life.

Data Extraction and Quality Assessment

One investigator extracted details about the study design, patient sample, setting, opioid therapy characteristics, and results and another investigator verified extractions for accuracy. Two investigators independently assessed risk of bias for each study using methods previously described (*2*). Discrepancies were resolved through a consensus process.

Data Synthesis

For the 2014 AHRQ report, the overall strength of each body of evidence was assessed as high, moderate, low, or insufficient using the approach described in the AHRQ Methods Guide (*4*). For the current report, ratings were updated with new evidence using methods developed by the GRADE Working Group (*6*). For consistency with other CDC recommendations, the overall body of evidence for each question was reviewed and categorized as type 1, 2, 3, or 4 using the GRADE approach outlined in the Advisory Committee for Immunization Practices (ACIP) Handbook for Developing Evidence-Based Recommendations (*7*). Within the ACIP GRADE framework, the body of evidence is categorized in a hierarchy. This hierarchy reflects the degree of confidence in the effect of

a clinical action on health outcomes. The categories include type 1 evidence (randomized clinical trials or overwhelming evidence from observational studies; considered "high" by the GRADE working group), type 2 evidence (randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies; considered "moderate" by the GRADE working group), type 3 evidence (observational studies, or randomized clinical trials with notable limitations; considered "low" by the GRADE working group), and type 4 evidence (clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations; considered "very low" by the GRADE working group). When no studies are present, evidence is considered to be insufficient. Consistent with the GRADE approach, type of evidence was categorized by study design as well as a function of limitations in study design or implementation, imprecision of estimates, variability in findings, indirectness of evidence, publication bias, magnitude of treatment effects, dose-response gradient, and constellation of plausible biases that could change effects. Results were synthesized qualitatively, highlighting new evidence identified during the update process. Meta-analysis was not attempted due to the small numbers of studies, variability in study designs and clinical heterogeneity, and methodological shortcomings of the studies.

While GRADE specifies the quality of a full body of evidence on a given topic representing multiple studies (types 1-4), it is beneficial to indicate the quality of individual studies when describing findings in a narrative format. Thus, in the summary of findings, we describe individual studies as being of "good," "fair," "moderate," or "poor" quality. Good quality studies are considered to have the least risk of bias and their results are likely to be valid; "fair quality" studies have some methodological shortcomings, but no flaw or combination of flaws are judged likely to cause major bias; "moderate" quality studies vary in their strengths and weaknesses, with the results of some studies likely to be valid and results of others only possibly valid; and "poor quality" studies have significant flaws that may invalidate the results (*1*).

Update Search Yield and New Evidence

From 257 articles identified in the update search, 16 articles were selected for full-text review based on titles and abstracts. Seven studies met inclusion criteria after full-text review (Tables 1 and 2; quality ratings shown in Tables 3 and 4) (*8-14*). One study addressed the association between opioid use and endocrinologic harms (*13*), one study compared mortality risk of methadone versus sustained-release morphine (*12*), one study evaluated the risk of unintentional overdose with initiation of opioid therapy with ER/LA versus immediate-release opioids (*11*), two studies addressed the predictive accuracy of risk assessment instruments (*9,10*), and two studies evaluated the association between use of opioid therapy for acute pain and long-term use (*8,14*). A list of studies excluded after full-text review with reasons for exclusion are shown in Table 5. Some of the excluded studies were included in a concurrently conducted review of contextual evidence commissioned to further inform the guideline. Table 6 shows the GRADE evidence table with type of evidence ratings for the four original clinical questions and the new clinical question, based on studies included in the AHRQ 2014 review plus additional studies identified in the update search. Additional details on findings from the original review are available in the full 2014 AHRQ report (*1*,*2*).

Findings

Main findings of this updated review are consistent with the findings of the 2014 AHRQ report (*1*). In summary, evidence on long-term opioid therapy for chronic pain outside of end-of-life care remains limited, with insufficient evidence to determine long-term benefits versus no opioid therapy, though evidence suggests risk of serious harms that appears to be dose-dependent. These findings supplement findings from a previous review of the effectiveness of opioids in adults with chronic non-cancer pain. In this previous review, based on randomized studies predominantly $\leq$12 weeks in duration, opioids were moderately effective for pain relief, with small benefits for functional outcomes; although estimates vary, based on uncontrolled studies, a high percentage of patients discontinued opioids in the long-term because of lack of effectiveness and adverse events (*3*).

Key Question 1. Effectiveness of Opioid Therapy

No study of opioid therapy versus placebo, no opioid therapy, or non-opioid therapy for chronic pain evaluated long-term (≥1 year) outcomes related to pain, function, or quality of life. As detailed in the 2014 AHRQ report, most placebo-controlled randomized clinical trials were ≤6 weeks in duration, and no cohort study of long-term opioid therapy versus no opioid therapy evaluated outcomes related to pain, function, or quality of life (*1*).

Key Question 2. Risks of Abuse, Addiction, Overdose, and Other Harms

Opioid Abuse, Addiction, and Related Outcomes

No randomized trial evaluated opioid abuse, addiction, or related outcomes with long-term opioid therapy versus placebo or no opioid therapy. The 2014 AHRQ report included one fair-quality cohort study that found long-term opioid therapy associated with increased risk of an opioid abuse or dependence diagnosis (based on ICD-9 codes) versus no opioid prescription (*15*). Rates of opioid abuse or dependence diagnosis ranged from 0.7% with lower-dose chronic therapy (1-36 morphine milligram equivalents [MME]/day) to 6.1% with higher-dose (≥120 MME/day) chronic therapy, versus 0.004% with no opioids; adjusted odds ratios [ORs] ranged from 14.9 (95% confidence interval [CI] = 10.4 - 21.5) for lower-dose to 122.5 (95% CI = 72.8 - 206.0) for higher-dose therapy.

Ten fair-quality uncontrolled studies included in the 2014 AHRQ report reported estimates of opioid abuse, addiction, and related outcomes (*16-26*). In primary care settings, prevalence of opioid abuse ranged from 0.6% to 8% and prevalence of dependence (using DSM-IV criteria) from 3% to 26% (*16,17,20*). In pain clinic settings, prevalence of misuse ranged from 8% to 16% and addiction ranged from 2% to 14% (*18,19,21,22,24-26*). Prevalence of aberrant drug-related behaviors (e.g., aberrant urine drug tests, medication agreement violations, or other behaviors indicative of misuse) ranged from 6% to 37%. Factors associated with increased risk of misuse included history of substance use disorder, younger age, major depression, and use of psychotropic medications (*17,23*).

Definitions for opioid abuse, addiction, and related outcomes and methods used to identify these events varied. All studies included in the AHRQ 2014 report were conducted before the introduction of the Diagnostic and Statistical Manual-5 (DSM-5) (*27*) diagnostic criteria for opioid use disorder. One new study identified during the update process evaluated the proportion of patients prescribed long-term opioids for chronic pain who met DSM-5, DSM-IV, ICD-10, and draft ICD-11 criteria for problematic opioid use (*28*), but did not meet inclusion criteria because it only reported lifetime (rather than current) rates. It found a similar proportion of patients met DSM-5 criteria for moderate or severe lifetime opioid use disorder or lifetime opioid dependence based on DSM-IV, ICD-10, or proposed ICD-11 criteria (8.5% to 9.9%), with good agreement. However, agreement was lower when mild DSM-5 opioid use disorder was also included.

Overdose

The 2014 AHRQ report included two studies on the association between opioid use and risk of overdose (*29,30*). One large fair-quality retrospective cohort study (n=9,940) found recent opioid use associated with increased risk of any overdose events (adjusted hazard ratio [HR] 5.2; 95% CI = 2.1 - 12.5) and serious overdose events (adjusted HR 8.4; 95% CI = 2.5 - 28) versus non-use (*29*). It also found higher doses associated with increased risk. Relative to 1 to <20 MME/day, the adjusted HR for an overdose was 1.44 (95% CE = 0.57 - 3.62) for 20 to <50 MME/day, 3.73 (95% CI = 1.47 - 9.50 for 50 to <100 MME/day, and 8.87 (95% CI = 3.99 - 19.72) for ≥100 MME/day. A similar pattern was observed for serious overdose.

A good-quality, population-based, nested case-control study (498 cases) also found a dose-dependent association with risk of overdose (*30*). Relative to 1 to <20 MME/day, the adjusted OR was 1.32 (95% CI = 0.94 to 1.84) for 20 to 49 MME/day, 1.92 (95% CI = 1.30 - 2.85) for 50 to 99 MME/day, 2.04 (95% CI = 1.28 - 3.24) for 100 to 199 MME/day, and 2.88 (95% CI = 1.79 - 4.63) for ≥200 MME/day.

Fractures

The 2014 AHRQ report included two studies on the association between opioid use and risk of fractures (*31,32*). A fair-quality cohort study (n=2,341 adults aged ≥60 years) found a higher fracture rate among current opioid users (6%) than among current non-users (4%) after a mean follow-up of 33 months, but the difference was not quite statistically significant (adjusted HR 1.28; 95% CI = 0.99 - 1.64) (*31*). A test for dose response was also of borderline statistical significance.

A good-quality case-control study (21,739 cases) found current opioid use, versus non-use, to be associated with increased risk of hip, humerus, or wrist fracture (adjusted OR 1.27; 95% CI = 1.21 - 1.33) (*32*). The risk was highest with one prescription (OR 2.70; 95% CI = 2.34 - 3.13) and decreased with higher numbers of prescriptions, with no increased risk for more than 20 cumulative prescriptions.

Cardiovascular Events

The 2014 AHRQ report included two studies on the association between opioid use and cardiovascular events (*33, 34*). One fair-quality cohort study (n=297,314) found cumulative opioid days' supply of ≥180 days over a 3.5-year period associated with increased risk of myocardial infarction versus no long-term opioid therapy (adjusted incidence rate ratio [IRR] 2.66; 95% CI = 2.30 - 3.08) (*33*). Relative to a cumulative dose of 0 to 1,350 MME over 90 days, the adjusted IRR for myocardial infarction was 1.21 (95% CI = 1.02 - 1.45) for 1,350 to <2,700 MME and ranged from 1.42 to 1.89 for doses ≥2,700 MME. A good-quality case-control study (11,693 cases) found current opioid therapy associated with increased odds of myocardial infarction versus non-use (adjusted OR 1.28; 95% CI = 1.19 - 1.37) (*34*). No study evaluated associations between long-term opioid therapy and risk of arrhythmia or sudden death.

Endocrinologic Harms

The 2014 AHRQ report included one fair-quality cross-sectional study of men with back pain (n=11,327) that found long-term opioid use associated with increased use of medications for erectile dysfunction or testosterone replacement versus non-use (adjusted OR 1.45; 95% CI = 1.12 - 1.87) (*35*). Compared with 0 to <20 MME/day, a dose of ≥20 MME/day was associated with increased risk (OR 1.58; 95 % CI = 1.03 - 2.43), but there was no increased risk at doses of 20 to <120 MME/day. Sexual dysfunction was not measured directly; other study limitations included unknown pain duration and inability to determine whether medication use preceded receipt of opioids.

One new fair-quality cross-sectional study (n=1,585) found higher dose long-term opioid therapy associated with increased risk of androgen deficiency among men receiving immediate-release opioids (adjusted OR per 10 MME/day 1.16, 95% CI = 1.09 - 1.23), but the dose response was very weak among men receiving ER/LA opioids (adjusted OR per 10 MME/day 1.01, 95% CI = 1.01 - 1.02) (*13*). The study did not examine the association between low testosterone levels and clinical symptoms.

Motor Vehicle Crash Injuries

The 2014 AHRQ report included one good-quality case-control study (5,300 cases) that found opioid doses ≥20 MME/day associated with increased odds of road trauma among drivers (*36*). Relative to 1 to <20 MME/day, the adjusted ORs ranged from 1.21 to 1.42 at doses ≥20 MME/day.

Other Harms

No study evaluated risks of falls, infections, or psychological, cognitive, or gastrointestinal harms among patients with chronic pain on long-term opioid therapy versus placebo or no opioid therapy.

Key Question 3. Comparative Effectiveness of Dosing Strategies

Initiation and Titration of Opioids

The 2014 AHRQ report found insufficient evidence from three fair-quality, open-label trials to determine comparative effectiveness of ER/LA versus immediate-release opioids for titrating patients to stable pain control because of inconsistent results and differences within trials in dosing protocols (titrated versus fixed dosing) and opioid doses (*37*,*38*).

One new fair-quality cohort study (*11*) of Veterans Affairs patients (n=840,606) found initiation of therapy with an ER/LA opioid associated with greater risk of overdose injury than initiation with an immediate-release opioid (adjusted HR 2.33, 95% CI = 1.26 - 4.32) (*11*). The risk was greatest in the first 2 weeks after initiation of treatment (adjusted HR 5.25, 95% CI = 1.88 - 14.72).

Comparative Effectiveness and Harms of ER/LA Opioids

The 2014 AHRQ report included three randomized, head-to-head trials of various ER/LA opioids that found no clear differences in 1-year outcomes related to pain or function (*39-41*), though findings were limited by methodological shortcomings and the use of study designs in which doses were titrated to effect or determined during a run-in period.

The 2014 AHRQ report included two cohort studies on the comparative risk of harms with various ER/LA opioids (*42*,*43*). A fair-quality retrospective cohort study based on national Veterans Affairs system pharmacy data (n=108,492) found methadone associated with lower overall risk of all-cause mortality versus morphine in a propensity stratified analysis (adjusted HR 0.56; 95% CI = 0.51 - 0.62); a similar pattern was seen in all propensity quintiles except the highest (*42*).

A fair-quality retrospective cohort study based on Oregon Medicaid data (n=5,684) found sustained-release oxycodone associated with lower risk of an emergency department visit or hospitalization involving an opioid-related adverse event versus sustained-release morphine (adjusted HR 0.45; 95% CI = 0.26 - 0.77) or death (adjusted HR 0.71; 95% CI = 0.54 - 0.94) (*43*). There were no statistically significant differences between methadone versus long-acting morphine in risk of death or overdose symptoms. Overdose symptoms (alteration of consciousness, malaise, fatigue, lethargy, or respiratory failure) were nonspecific for opioid-related adverse events.

One new fair-quality retrospective cohort study (n=38,756) also compared risk of mortality with methadone versus morphine (*12*). Unlike the Veterans Affairs study, among Tennessee Medicaid patients it found methadone associated with increased hazards of death (adjusted HR 1.46, 95% CI = 1.17 - 1.73). Findings were similar in the subgroup of patients that received methadone doses of 20 mg/day and comparable doses of morphine (<60 mg/day) (adjusted HR 1.59, 95% CI = 1.01 - 2.51).

Dose Escalation

The 2014 AHRQ report included one fair-quality randomized trial (n=140) that found no differences between more liberal dose escalation (doses increased for inadequate pain relief using preset dosing guidelines) versus maintenance of current doses (doses increased only if medically necessary because of clear dosage tolerance or acute injury) after 12 months in pain, function, all-cause withdrawals, or withdrawals due to opioid misuse (*44*). However, the difference in opioid doses prescribed at the end of the trial was relatively small (mean 52 MME/day with more liberal dosing versus 40 MME/day).

ER/LA Versus Immediate-release Opioids

The 2014 AHRQ report did not find evidence that ER/LA opioids are associated with reduced risk of overdose, addiction, abuse, or misuse compared with immediate-release opioids (*1*), as no study evaluated long-term effects of ER/LA versus immediate-release opioids. One fair-quality cross-sectional study identified for the update found ER/LA opioids associated with increased risk of androgen deficiency (morning serum testosterone <250 ng/dL) versus immediate-release opioids (adjusted OR 3.39, 95% CI = 2.39 - 4.77) (*13*). Another study identified for the

update focused on risk of ER/LA versus immediate-release opioids for initiation of therapy and was previously discussed (*11*).

Other Opioid Dosing Strategies

No study compared immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled, continuous dosing versus as-needed dosing; or opioid rotation versus maintenance of current therapy. Evidence on the comparative effectiveness of opioid tapering or discontinuation versus maintenance, and of different opioid tapering strategies, was limited to small, poor-quality studies (*45-47*). No study evaluated long-term benefits or harms associated with different strategies for treating acute exacerbations of chronic pain.

Key Question 4. Effectiveness of Risk Prediction and Mitigation Strategies

Risk Assessment Instruments

The 2014 AHRQ report included four studies (*48-51*) on the accuracy of risk assessment instruments, administered prior to opioid therapy initiation, for predicting opioid abuse or misuse. Results for the Opioid Risk Tool (ORT) (*49-51*) were extremely inconsistent, evidence for other risk assessment instruments was very sparse, and studies had serious methodological shortcomings, precluding reliable conclusions regarding predictive accuracy. For the ORT, sensitivity ranged from 0.20 to 0.99 in three studies and specificity was 0.16 and 0.88 in two studies (*49-51*). For the Screener and Opioid Assessment for Patients with Pain (SOAPP) Version 1, sensitivity was 0.68 and 0.73 in two studies and specificity was 0.38 in one study (*48,50*). No study evaluated the effectiveness of risk prediction instruments for improving outcomes related to overdose, addiction, abuse, or misuse.

One additional fair-quality (n=124) (*9*) and one poor-quality (n=196) (*10*) study identified for this update compared the predictive accuracy of the ORT, the SOAPP-Revised, and the Brief Risk Interview. For the ORT, sensitivity was 0.58 and 0.75 and specificity 0.54 and 0.86; for the SOAPP-R, sensitivity was 0.53 and 0.25 and specificity 0.62 and 0.73, and for the Brief Risk Interview, sensitivity was 0.73 and 0.83 and specificity 0.43 and 0.88. For the ORT, positive likelihood ratios ranged from non-informative (positive likelihood ratio close to 1) to moderately useful (positive likelihood ratio >5). The SOAPP-Revised was associated with weak likelihood ratios (estimates close to 1) in both studies.

Risk Mitigation Strategies

No study evaluated the effectiveness of risk mitigation strategies (opioid management plans, patient education, urine drug testing, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, or use of abuse-deterrent formulations) for improving outcomes related to overdose, addiction, abuse, or misuse.

Key Question 5. Effects of Opioid Therapy for Acute Pain on Long-Term Use

The 2014 AHRQ report did not address effects of use of opioid therapy for acute pain on long-term use. Two fair-quality retrospective cohort studies identified for this update found opioid therapy prescribed for acute pain associated with greater likelihood of long-term use. One study (n=391,139) evaluated opioid-naïve patients who had undergone low-risk surgery (defined as cataract surgery, laparoscopic cholecystectomy, transurethral resection of the prostate, or varicose vein stripping) (*8*). Use of opioids within 7 days of surgery was associated with increased risk of use at 1 year (adjusted OR 1.44, 95% CI 1.39 to 1.50). Estimates were similar when findings were stratified by the specific surgical procedure (adjusted OR's ranged from 1.33 to 1.62). The other study found early opioid use (defined as within 15 days following onset) among 8,443 patients with a workers' compensation claim for acute low back pain associated with an increased likelihood of receiving five or more opioid prescriptions from 30 to 730 days following onset versus non-use that increased with greater early

exposure (*14*). Versus no early opioid use, the adjusted OR was 2.08 (95% CI 1.55 to 2.78) for 1-140 MME/day and increased to 6.14 (95% CI = 4.92 - 7.66) for ≥450 MME/day.

Summary

Main findings of this updated review are consistent with the findings of the 2014 AHRQ report (*1*). Evidence on long-term opioid therapy for chronic pain remains very limited, with insufficient evidence to determine long-term benefits, but suggests an increased risk of serious harms that appears to be dose-dependent. New studies added to the AHRQ report revealed additional harms of long-term opioid therapy, including increased risk of androgen deficiency among men receiving immediate-release opioids (*13*); increased risk of overdose among patients receiving methadone (*12*); increased risk of overdose with initiation of opioid therapy with ER/LA opioids compared with initiation with immediate-release opioids (*11*); and increased risk of long-term use of opioids when opioids are used for acute pain (*8,14*). New studies also revealed new information about the sensitivity and specificity of the ORT, the SOAPP-Revised, and the Brief Risk Interview, illustrating insufficient accuracy for classification of patients as at low risk for overdose, addiction, abuse, or misuse (*9,10*). More research is needed to understand long-term benefits, risk of abuse and related outcomes, effectiveness of different opioid prescribing methods and risk mitigation strategies, and accuracy of risk prediction instruments.

TABLE 1. New observational studies for the update review.

Author, year	Clinical question	Type of study, setting	Eligibility criteria	Comparison groups	Population characteristics	Method for Assessing Outcomes and Confounders	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Alam, 2012	Effects of opioid therapy for acute pain on long-term use	Retrospective cohort Canada	Patients aged ≥ 66 years who underwent cataract surgery, laparoscopic cholecystectomy, transurethral resection of the prostate, or varicose vein stripping surgery; excludes persons with opioids or non-steroidal anti-inflammatory drugs (NSAIDs) in prior year, died within 425 days, admitted for >3 days, hospitalized within 100 days, emergency operations, palliative care	A: Opioid prescription within 7 days of hospital discharge B: No opioid prescription within 7 days of hospital discharge	Early opioid users versus non-early opioid users Age (mean): 75 versus 77 years Race: Not reported Female: 61% versus 62% Prior opioids: Not reported Prior chronic pain: Not reported Charlson* comorbidity index ≥3: 3.0% versus 3.5%	Canadian Institute for Health Information Discharge Abstract Database, Ontario Health Insurance Plan database, Registered Persons Database, Ontario Cancer Registry	Screened: Unclear Eligible: Unclear Enrolled: 391,139 (27,636 received opioid within 7 days) Analyzed: 391,139 Loss to follow up: Not reported	Age, sex, Charlson comorbidity index, socioeconomic status, residence in long-term care facility, hospital type	Early opioid use versus no early opioid use, risk estimates reported as adjusted OR Using opioid 1 year after surgery: 1.44 (95% CI = 1.39 - 1.50) OR's 1.33 to 1.62 for different surgical procedures	Institute for Clinical Evaluative Services (funded by Ontario Ministry of Health and Long-term Care)	Fair
Miller, 2015	Dosing strategies	Cohort study USA (Veterans Administration; VA)	Patients who filled an opioid analgesic prescription, new users (no opioids in past 6 months), chronic pain; excluded hospice patients	A: ER/LA opioid B: Immediate-release opioid	ER/LA versus immediate-release opioid Age (median): 59 versus 60 years White: 76% versus 71% Female: 6% versus 6% Back/neck pain: 58% versus 38% Osteoarthritis: 19% versus 21% Depression: 32% versus 21% Alcohol-use disorder: 10% versus 8.6% Drug-related disorders: 9.1% versus 5.0%	VA database, including National Patient Care Database and Pharmacy Benefits Management Database	Screened: 2,476,671 new opioid users Eligible: 820,616 (18,887 ER/LA, 801,729 immediate-release) Enrolled: 820,616 Analyzed: 820,616 Loss to follow up: Not reported	Propensity score adjusted (based on concomitant medications, healthcare utilization, and interactions), age, sex, index dose	ER/LA versus immediate-release opioid, risk estimate reported as adjusted HR Unintentional overdose: 2.56 (95% CI = 1.67-3.93) Initial 14 days: 5.25 (95% CI = 2.61-10.54) 15-60 days: 2.19 (95% CI = 0.92-5.19) >60 days: 2.14 (95% CI = 1.25-3.65)	CDC	Fair

Ray, 2015	Dosing strategies	Retrospective cohort USA	Patients aged 30 - 74 years prescribed methadone or morphine; excluded patients with cancer or other life-threatening diseases, history of drug abuse, and nursing home residents	A: Methadone: Morphine SR	Methadone versus morphine SR Age (median): 47 versus 48 years White: 84% versus 84% Female: 58% versus 58% Back pain: 77% versus 78% Other musculoskeletal pain: 11% versus 12% Acute pain: 1.4% versus 1.5% Duration of pain: Not reported Mean pain score: Not reported	Tennessee Medicaid database, death certificates, hospital discharge database	Screened: Unclear Eligible: Unclear Enrolled: 38,756 (6,014 methadone and 32,742 morphine) Analyzed: 38,756 Loss to follow up: Not reported	196 covariates, analysis also stratified by deciles of a time-dependent propensity score or mortality risk score	Methadone versus morphine SR, risk estimates reported as adjusted HR All-cause mortality: 1.46 (95% CI = 1.17-1.83) Sudden unexpected death: 1.47 (95% CI = 1.13-1.90); 2.54 (1.33-4.84) meeting definition of opioid overdose, 1.12 (95% CI = 0.80-1.59) meeting definition of sudden cardiac death, 2.02 (95% CI = 1.21-3.37) for either. other respiratory/cardiovascular death: 1.78 (95% CI = 0.91-3.46). Findings for all-cause mortality similar in sensitivity analyses that controlled for nonproportional hazards, propensity-score matched, stratified by calendar year, restricted to first year of opioid use, censored on switching to another opioid, restricted to age <65 years, restricted to known opioid indication, restricted to new users of study opioid	National Heart, Lung, and Blood Institute; National Institute of Arthritis and Musculoskeletal and Skin Diseases; and Vanderbilt University	Fair
Rubinstein, 2014	Harms and adverse events and dosing strategies	Cross-sectional (retrospective) USA	Men aged 18 - 80 years with at least one total testosterone level and continuous opioid use (possession of 90 days supply during last 100 days)	A: ER/LA opioid B: Immediate-release opioid	ER/LA versus immediate-release opioid Age (median): 54 versus 54 years Race: Not reported Male: 100% Obese: 47% versus 43% Diabetes: 17% versus 18%	Kaiser Permanente Northern California databases	Screened: Unclear Eligible: Unclear Enrolled: 1.585 (616 ER/LA versus 919 immediate-release) Analyzed: 1.585 Loss to follow up: Not reported	Obesity, number of co-morbid conditions (diabetes, hyperlipidemia, and hypertension) stratified by age (less or greater than 50 years), dose in MME	ER/LA versus immediate-release opioid, risk estimates reported as adjusted OR Total morning testosterone <250 ng/dL: 3.39 (95% CI = 2.39-4.77) Dose-response per 10 MME, immediate-release opioids: 1.16 (95% CI = 1.09-1.23) Dose-response per 10 MME, ER/LA opioids: 1.01 (95% CI = 1.01-1.02)	Kaiser Permanente Northern California Community Benefit Program	Fair
Webster, 2007	Effects of opioid therapy for acute pain on long-term use	Retrospective cohort USA	Workers with low back pain and ≥ 1 days of compensated loss time, and 1 year of job tenure; excluded for prior compensated loss >10 days, medical services in first 15 days, fracture	A: No opioid use in first 15 days B: MME 0-140 in first 15 days C: MME 141-225 D: MME 226-450 E: MME >450	Early opioid users versus no early opioid use Age (mean): 40-41 versus 40 years Race: Not reported Male: 69-78% versus 62% Prior opioids: Not reported Prior low back pain: Not reported High severity low back pain: 22-37% versus 26%	Workers' compensation database	Screened: 21,212 Eligible: 8,443 Enrolled: 8,443 (1,792 early opioids versus 6,651 no opioids) Analyzed: 8,443 Loss to follow up: Not reported	Age, sex, job tenure, injury severity	Adjusted ORs for late opioid use (30 to 730 days after onset) A: 1 (reference) B: 2.08 (95% CI = 1.55 - 2.78) C: 2.89 (95% CI = 2.25 - 3.69) D: 3.69 (95% CI = 2.88 - 4.73) E: 6.14 (95% CI = 4.92 - 7.66)	No funding source reported	Fair

Abbreviations: OR = odds ratio; CI = confidence interval; HR = hazard ratio; MME = morphine milligram equivalents

* The Charlson Comorbidity Index is a method of categorizing patient comorbidity based on the ICD diagnosis codes; a score of zero indicates that no comorbidities were found

TABLE 2. New risk prediction studies for the update review.

Author, Year	Study Design	Eligibility Criteria	Population Characteristics	N	Instrument	Method of Administration	Reference Standard	True Positives (n)	False Positives (n)	True Negatives (n)	False Negatives (n)	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	AUROC	Quality
Jones, 2013	Cohort, unclear if prospective or retrospective	Patients being considered for opioids in pain clinic	Mean age 50 years 58% female Race: Not reported Pain: 60% low back, 18% neck	n=196	ORT SOAPP-R BRI	ORT and SOAPP-R: Self-report BRI: Clinician interview	Failed urine drug screen, failed pill count, or data that patient obtained opioid medication from another provider without approval, or exhibiting significant problem behaviors	Data not provided	Data not provided	Data not provided	Data not provided	ORT score ≥4: 0.58 SOAPP-R high risk: 0.53 BRI high risk: 0.73	ORT score ≥4: 0.54 SOAPP-R high risk: 0.62 BRI high risk: 0.43	ORT score ≥4: 1.26 SOAPP-R high risk: 1.39 BRI high risk: 1.28	ORT score ≥4: 0: 0.78 SOAPP-R high risk: 0.76 BRI high risk: 0.63	Not reported	Poor
Jones, 2014	Prospective cohort	Pain patients evaluated for possible use of opioids in pain treatment in a neurology clinic	Mean age: Not reported (range 19 - 85 years) 67% female White: 80% Pain: 44 % low back, 26% neck, 13% headache	n=124	ORT SOAPP-R BRI	ORT and SOAPP-R: Self-report BRI: Clinician interview	Failed urine drug screen, failed pill count, or data that patient obtained opioid medication from another provider without approval, or exhibiting significant problem behaviors	OR T score ≥4 (high risk): 9 SOAPP-R high risk: 3 BRI high risk (medium or higher assessed risk in any category): 10	OR T score ≥4 (high risk): 16 SOAPP-R high risk: 30 BRI high risk: 13	OR T score ≥4 (high risk): 96 SOAPP-R high risk: 82 BRI high risk: 99	OR T score ≥4 (high risk): 3 SOAPP-R high risk: 9 BRI high risk: 2	ORT score ≥4: 0.75 (95% CI = 0.43 - 0.94) SOAPP-R high risk: 0.25 (95% CI = 0.06 - 0.57) BRI high risk: 0,.83 (95% CI = 0.52 - 0.97)	ORT score ≥4: 0.86 (95% CI = 0.78 - 0.92) SOAPP-R high risk: 0.73 (95% CI = 0.64 - 0.81) BRI high risk: 0.88 (95% CI = 0.81 - 0.94)	ORT score ≥4: 5.25 (95% CI = 3.00 - 9.18) SOAPP-R high risk: 0.93 (95% CI = 0.33 - 2.61) BRI high risk: 7.18 (95% CI = 4.06 - 12.7)	ORT score ≥4: 0.29 (95% CI = 0.11 - 0.78) SOAPP-R high risk: 1.02 (95% CI = 0.73 - 1.45) BRI high risk: 0.19 (95% CI = 0.05 - 0.67)	ORT: 0.74 SOAPP-R: 0.52 BRI: 0.93	Fair

Abbreviations: AUROC = area under receiver operating characteristic, ORT = Opioid Risk Tool, SOAPP-R = Screener and Opioid Assessment for Patients with Pain–Revised, BRI = Brief Risk Interview

TABLE 3. Quality assessment for additional observational studies for the update review.

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Is there important differential loss to follow up or overall high loss to follow up?	Did the study perform appropriate statistical analyses on potential confounders?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality
Alam, 2012	Yes	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Fair
Miller, 2015	Yes	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Fair
Ray, 2015	Yes	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Fair
Rubinstein, 2014	Yes	No	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Fair
Webster, 2007	Yes	No	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Fair

TABLE 4. Quality assessment for additional risk prediction studies for the update review.

Author, year	Evaluates population other than the one used to derive the instrument	Avoided case-control design	Consecutive series of patients or a random subset	Describes severity of symptoms, opioid dose/duration and underlying conditions	Adequate description of screening instrument	Appropriate criteria included in screening instrument	Adequate description of methods for identifying aberrant drug-related behaviors	Appropriate criteria used to identify aberrant drug-related behaviors	Aberrant drug-related behaviors assessed in all enrollees	Blinded assess-ment of aberrant drug-related behaviors	Quality
Jones, 2013	No	Yes	Unclear	No (severity, dose)	Yes	Yes	No	Unclear	Unclear	No	Poor
Jones, 2014	Yes	Yes	Yes	No (severity, dose)	Yes	Yes	Yes	Unclear	Unclear	Unclear	Fair

TABLE 5. Studies excluded following full-text review.

Study, year	**Reason for exclusion**
Bartoli, 2015 (*52*)	Duration of follow-up too short for RCT; long-term study was uncontrolled
Cifuentes, 2010 (*53*)	Did not assess long-term opioid use
Daitch, 2014 (*54*)	Uncontrolled study, duration of follow-up too short
Degenhardt, 2015 (*28*)	Assessed wrong outcome (lifetime prevalence of opioid use disorders, current prevalence not reported)
Franklin, 2008 (*55*)	Did not assess long-term opioid use
Franklin, 2009 (*56*)	Did not compare use of opioids for acute pain versus non-use
Fredheim, 2014 (*57*)	Did not compare use of opioids versus non-use
Pedersen, 2014 (*58*)	Systematic review; used as reference source only
Rauck, 2014 (*59*)	Duration of follow-up too short
Turner, 2015 (*60*)	Not chronic pain

TABLE 6. GRADE Clinical Evidence Review Ratings.

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of evidence	Other factors	Estimates of effect/findings
Effectiveness and comparative effectiveness (KQ1)							
Effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (≥1 year) outcomes							
Pain, function, and quality of life	None	–	–	–	Insufficient	–	No evidence
Harms and adverse events (KQ2)							
Risks of opioids versus placebo or no opioids on opioid abuse, addiction, and related outcomes; overdose; and other harms							
Abuse or addiction	1 cohort study (*n* = 568,640)	Serious limitations	Unknown (1 study)	No imprecision	3	–	One retrospective cohort study found long-term use of prescribed opioids associated with an increased risk of abuse or dependence diagnosis versus no opioid use (adjusted OR ranged from 14.9 to 122.5, depending on dose).
Abuse or addiction	10 uncontrolled studies (*n* = 3,780)	Very serious limitations	Very serious inconsistency	No imprecision	4	–	In primary care settings, prevalence of opioid abuse ranged from 0.6% to 8% and prevalence of dependence from 3% to 26%. In pain clinic settings, prevalence of misuse ranged from 8% to 16% and addiction from 2% to 14%. Prevalence of aberrant drug-related behaviors ranged from 6% to 37%.
Overdose	1 cohort study (*n* = 9,940)	Serious limitations	Unknown (1 study)	Serious imprecision	3	–	Current opioid use associated with increased risk of any overdose events (adjusted HR 5.2, 95% CI = 2.1–12) and serious overdose events (adjusted HR 8.4, 95% CI = 2.5–28) versus current nonuse.

Fractures	1 cohort study (*n* = 2,341) and 1 case–control study (*n* = 21,739 case patients)	Serious limitations	No inconsistency	No imprecision	3	–	Opioid use associated with increased risk of fracture in 1 cohort study (adjusted HR 1.28, 95% CI = 0.99–1.64) and 1 case-control study (adjusted OR 1.27, 95% CI = 1.21–1.33).
Myocardial infarction	1 cohort study (*n* = 426,124) and 1 case–control study (*n* = 11,693 case patients)	No limitations	No inconsistency	No imprecision	3	–	Current opioid use associated with increased risk of myocardial infarction versus nonuse (adjusted OR 1.28, 95% CI = 1.19–1.37 and incidence rate ratio 2.66, 95% CI = 2.30–3.08).
Endocrinologic harms	1 cross-sectional study (*n* = 11,327)	Serious limitations	Unknown (1 study)	No imprecision	3	–	Long-term opioid use associated with increased risk for use of medications for erectile dysfunction or testosterone replacement versus nonuse (adjusted OR 1.5, 95% CI = 1.1–1.9).
How do harms vary depending on the opioid dose used?							
Abuse or addiction	1 cohort study (*n* = 568,640)	Serious limitations	Unknown (1 study)	No imprecision	3	–	One retrospective cohort study found higher doses of long-term opioid therapy associated with increased risk of opioid abuse or dependence than lower doses. Compared to no opioid prescription, the adjusted odds ratios were 15 (95 percent CI = 10–21) for 1 to 36 MME/day, 29 (95 % CI = 20–41) for 36 to120 MME/day, and 122 (95 % CI = 73–205) for ≥120 MME/day.
Overdose	1 cohort study (*n* = 9,940) and 1 case–control study (*n* = 593 case patients in primary analysis)	Serious limitations	No inconsistency	No imprecision	3	Magnitude of effect, dose response relationship	Versus 1 to <20 MME/day, one cohort study found an adjusted HR for an overdose event of 1.44 (95% CI = 0.57–3.62) for 20 to 49 MME/day that increased to 8.87 (95% CI = 3.99–19.72) at ≥100 MME/day; one case-control study found an adjusted OR for an opioid-related death of 1.32 (95% CI = 0.94–1.84) for 20 to 49 MME/day that increased to 2.88 (95% CI = 1.79–4.63) at ≥200 MME/day.

Fractures	1 cohort study (*n* = 2,341)	Serious limitations	Unknown (1 study)	Serious imprecision	3	–	Risk of fracture increased from an adjusted HR of 1.20 (95% CI = 0.92–1.56) at 1 to <20 MME/day to 2.00 (95% CI = 1.24–3.24) at ≥50 MME/day; the trend was of borderline statistical significance.
Myocardial infarction	1 cohort study (*n* = 426,124)	Serious limitations	Unknown (1 study)	No imprecision	3	–	Relative to a cumulative dose of 0 to 1350 MME during a 90-day period, the incidence rate ratio for myocardial infarction for 1350 to <2700 MME was 1.21 (95% CI = 1.02–1.45), for 2700 to <8100 MME was 1.42 (95% CI = 1.21–1.67), for 8100 to <18,000 MME was 1.89 (95% CI = 1.54–2.33), and for ≥18,000 MME was 1.73 (95% CI = 1.32–2.26).
Motor vehicle crash injuries	1 case–control study (*n* = 5,300 case patients)	No limitations	Unknown (1 study)	No imprecision	3	–	No association between opioid dose and risk of motor vehicle crash injuries even though opioid dosages ≥20 MME/day were associated with increased odds of road trauma among drivers.
Endocrinologic harms	1 cross-sectional study (*n* = 11,327) New for update: 1 additional cross-sectional study (*n*=1,585)	Serious limitations	Consistent	No imprecision	3	–	Relative to 0 to <20 MME/day, the adjusted OR for ≥120 MME/day for use of medications for erectile dysfunction or testosterone replacement was 1.6 (95% CI = 1.0–2.4). One new cross-sectional study found higher-dose long-term opioid therapy associated with increased risk of androgen deficiency among men receiving immediate-release opioids (adjusted OR per 10 MME/day 1.16, 95% CI = 1.09–1.23), but the dose response was very weak among men receiving ER/LA opioids.

Dosing strategies (KQ3)

Comparative effectiveness of different methods for initiating opioid therapy and titrating doses

Pain	3 randomized trials (*n* = 93)	Serious limitations	Serious inconsistency	Very serious imprecision	4	–	Trials on effects of titration with immediate-release versus ER/LA opioids reported inconsistent results and had additional differences between treatment arms in dosing protocols (titrated versus fixed dosing) and doses of opioids used.
Overdose	New for update: 1 cohort study (*n* = 840,606)	Serious limitations	Unknown (1 study)	No imprecision	4	–	One new cross-sectional study found initiation of therapy with an ER/LA opioid associated with increased risk of overdose versus initiation with a immediate-release opioid (adjusted HR 2.33, 95% CI = 1.26–4.32).

Comparative effectiveness of different ER/LA opioids

Pain and function	3 randomized trials (*n* = 1,850)	Serious limitations	No inconsistency	No imprecision	3	–	No differences
All-cause mortality	1 cohort study (*n* = 108,492) New for update: 1 cohort study (*n* = 38,756)	Serious limitations	Serious inconsistency	No imprecision	4	–	One cohort study found methadone to be associated with lower all-cause mortality risk than sustained-release morphine in a propensity-adjusted analysis (adjusted HR 0.56, 95% CI = 0.51–0.62) and one cohort study among Tennessee Medicaid patients found methadone to be associated with higher risk of all-cause mortality than sustained-release morphine (adjusted HR 1.46, 95% CI = 1.17–1.73).
Abuse and related outcomes	1 cohort study (*n* = 5,684)	Serious limitations	Unknown (1 study)	Serious imprecision	4	–	One cohort study found some differences between ER/LA opioids in rates of adverse outcomes related to abuse, but outcomes were nonspecific for opioid-related adverse events, precluding reliable conclusions.

ER/LA versus immediate-release opioids							
Endocrinologic harms	New for update: 1 cross-sectional study (*n* = 1,585)	Serious limitations	Unknown (1 study)	No imprecision	4	–	One cross-sectional study found ER/LA opioids associated with increased risk of androgen deficiency versus immediate-release opioids (adjusted OR 3.39, 95% CI = 2.39–4.77).
Dose escalation versus dose maintenance or use of dose thresholds							
Pain, function, or withdrawal due to opioid misuse	1 randomized trial (*n* = 140)	Serious limitations	Unknown (1 study)	Very serious imprecision	3	–	No difference between more liberal dose escalation versus maintenance of current doses in pain, function, or risk of withdrawal due to opioid misuse, but there was limited separation in opioid doses between groups (52 versus 40 MME/day at the end of the trial).
Immediate-release versus ER/LA opioids; immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled and continuous versus as-needed dosing of opioids; or opioid rotation versus maintenance of current therapy							
Pain, function, quality of life, and outcomes related to abuse	None	–	–	–	Insufficient	–	No evidence
Effects of decreasing or tapering opioid doses versus continuation of opioid therapy							
Pain and function	1 randomized trial (*n* = 10)	Very serious limitations	Unknown (1 study)	Very serious imprecision	4	–	Abrupt cessation of morphine was associated with increased pain and decreased function compared with continuation of morphine.
Comparative effectiveness of different tapering protocols and strategies							
Opioid abstinence	2 nonrandomized trials (*n* = 150)	Very serious limitations	No inconsistency	Very serious imprecision	4	–	No clear differences between different methods for opioid discontinuation or tapering in likelihood of opioid abstinence after 3–6 months

Risk assessment and risk mitigation strategies (KQ4)

Diagnostic accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or misuse among patients with chronic pain being considered for long-term opioid therapy

Opioid Risk Tool	3 studies of diagnostic accuracy (*n* = 496) New for update: 2 studies of diagnostic accuracy (*n* = 320)	Serious limitations	Very serious inconsistency	Serious imprecision	4	–	Based on a cutoff score of >4 (or unspecified), five studies (two fair-quality, three poor-quality) reported sensitivity that ranged from 0.20 to 0.99 and specificity that ranged from 0.16 to 0.88).
Screener and Opioid Assessment for Patients with Pain, Version 1	2 studies of diagnostic accuracy (*n* = 203)	Very serious limitations	No inconsistency	Serious imprecision	3	–	Based on a cutoff score of ≥8, sensitivity was 0.68 and specificity was 0.38 in one study, for a positive likelihood ratio of 1.11 and a negative likelihood ratio of 0.83. Based on a cutoff score of >6, sensitivity was 0.73 in one study.
Screener and Opioid Assessment for Patients with Pain-Revised	New for update: 2 studies of diagnostic accuracy (*n* = 320)	Very serious limitations	No inconsistency	Serious imprecision	3	–	Based on a cutoff score of >3 or unspecified, sensitivity was 0.25 and 0.53 and specificity was 0.62 and 0.73 in two studies, for likelihood ratios close to 1.
Brief Risk Interview	New for update: 2 studies of diagnostic accuracy (*n* = 320)	Very serious limitations	No inconsistency	Serious imprecision	3	–	Based on a "high risk" assessment, sensitivity was 0.73 and 0.83 and specificity was 0.43 and 0.88 in two studies, for positive likelihood ratios of 1.28 and 7.18 and negative likelihood ratios of 0.63 and 0.19.

Effectiveness of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse in patients with chronic pain

Outcomes related to abuse	None	–	–	–	Insufficient	–	No evidence

Effectiveness of risk mitigation strategies, including opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, and use of abuse-deterrent formulations, on outcomes related to overdose, addiction, abuse, or misuse

Outcomes related to abuse	None	–	–	–	Insufficient	–	No evidence

Outcomes related to abuse	None	–	–	–	Insufficient	–	No evidence
Effects of opioid therapy for acute pain on long-term use (KQ5)							
Long-term opioid use	New for update: 2 cohort studies (*n* = 399,852)	Serious limitations	No inconsistency	No imprecision	3	–	One study found use of opioids within 7 days of low-risk surgery associated with increased likelihood of opioid use at 1 year (adjusted OR 1.44, 95% CI = 1.39–1.50), and one study found use of opioids within 15 days of onset of low back pain among workers with a compensation claim associated with increased risk of late opioid use (adjusted OR 2.08, 95% CI = 1.55–2.78 for 1 to 140 MME/day and OR 6.14, 95% CI = 4.92–7.66 for ≥450 MME/day).

Note: Ratings were made per GRADE quality assessment criteria; thus "no limitations" indicates that limitations assessed through the GRADE method were not identified.

Abbreviations: OR = odds ratio, HR = hazard ratio, CI = confidence interval, MME = morphine milligram equivalents

References

1. Chou R, Deyo R, Devine B, et al. The effectiveness and risks of long-term opioid treatment of chronic pain. Evidence Report/Technology Assessment No. 218. (Prepared by the Pacific Northwest Evidene-based Practice Center under Contract No. 290-2012-00014-I). AHRQ Publication No. 14-E005-EF. Rockville, MD: Agency for Healthcare Research and Quality; September 2014. Available at: Available at: http://www.effectivehealthcare.ahrq.gov/ehc/products/557/1971/chronic-pain-opioid-treatment-report-141007.pdf2014.
2. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chonic pain: A systematic review for a National Institutes of Health Pathways To Prevention Workshop. Ann Intern Med. 2015;162:276-86.
3. American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Guideline for the use of chronic opioid therapy in chronic noncancer pain: Evidence review. 2009. Available at: http://www.americanpainsociety.org/uploads/pdfs/Opioid_Final_Evidence_Report.pdf2009.
4. Agency for Healthcare Research and Quality. Methods guide for effectiveness and comparative effectiveness reviews. Effective Health Care Program. AHRQ Publication No. 10(13)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2013. Chapters available at: www.effectivehealthcare.ahrq.gov.
5. Graham E. The effectiveness and risks of long-term opioid treatment of chronic pain. PROSPERO: International prospective register of systematic reviews. York, UK: University of York, 2014. Available at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014007016.
6. Guyatt GH, Oxman AD, Vist G, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924-6.
7. Ahmed F. U.S. Advisory Committee on Immunization Practices handbook for developing evidence-based recommendations. Version 1.2. Atlanta, GA: Centers for Disease Control and Prevention (CDC); 2013. Available from http://www.cdc.gov/vaccines/acip/recs/GRADE/about-grade.html#resources.
8. Alam A, Gomes T, Zheng H, Mamdani MM, Juurlink DN, Bell CM. Long-term analgesic use after low-risk surgery. Arch Intern Med. 2012;172:425-30.
9. Jones T, Lookatch S, Grant P, McIntyre J, Moore T. Further validation of an opioid risk assessment tool: the Brief Risk Interview. J Opioid Manag. 2014;10:353-64.
10. Jones T, Moore T. Preliminary data on a new opioid risk assessment measure: the Brief Risk Interview. J Opioid Manag. 2013;9:19-27.
11. Miller M, Barber CW, Leatherman S, et al. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. JAMA Intern Med. 2015;175:608-15.
12. Ray WA, Chung CP, Murray KT, Cooper WO, Hall K, Stein CM. Out-of-hospital mortality among patients receiving methadone for noncancer pain. JAMA Intern Med. 2015;175:420-7.
13. Rubinstein A, Carpenter DM. Elucidating risk factors for androgen deficiency associated with daily opioid use. Am J Med. 2014;127:1195-201.
14. Webster BS, Verma SK, Gatchel RJ. Relationship between early opioid prescribing for acute occupational low back pain and disability duration, medical costs, subsequent surgery and late opioid use. Spine. 2007;32:2127-32.
15. Edlund MJ, Martin BC, Russo JE, Devries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain. Clin J Pain. 2014;30:557-64.
16. Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors, mental health and pain--development of a typology of chronic pain patients. Drug Alcohol Depend. 2009;104:34-42.
17. Boscarino JA, Rukstalis M, Hoffman SN, et al. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. Addiction. 2010;105:1776-82.
18. Compton PA, Wu SM, Schieffer B, Pham Q, Naliboff BD. Introduction of a self-report version of the Prescription Drug Use Questionnaire and relationship to medication agreement noncompliance. J Pain Symptom Manage. 2008;36:383-95.
19. Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG. A survey of chronic noncancer pain patients prescribed opioid analgesics. Pain Med. 2003;4:340-51.

20. Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. J Pain. 2007;8:573-82.
21. Hojsted J, Nielsen PR, Guldstrand SK, Frich L, Sjogren P. Classification and identification of opioid addiction in chronic pain patients. European J Pain. 2010;14:1014-20.
22. Portenoy RK, Farrar JT, Backonja MM, et al. Long-term use of controlled-release oxycodone for noncancer pain: Results of a 3-year registry study. Clin J Pain. 2007;23:287-99.
23. Carrington Reid M, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, O'Connor PG. Use of opioid medications for chronic noncancer pain syndromes in primary care. J Gen Intern Med. 2002;17:173-9.
24. Saffier K, Colombo C, Brown D, Mundt MP, Fleming MF. Addiction Severity Index in a chronic pain sample receiving opioid therapy. J Subst Abuse Treat. 2007;33:303-11.
25. Schneider JP, Kirsh KL. Defining clinical issues around tolerance, hyperalgesia, and addiction: a quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. J Opioid Manage. 2010;6:385-95.
26. Wasan AD, Butler SF, Budman SH, et al. Does report of craving opioid medication predict aberrant drug behavior among chronic pain patients? Clin J Pain. 2009;25:193-8.
27. Association AP. Diagnostic and statistical manual of mental disorders, Fifth edition. Arlington, VA: American Psychiatric Association; 2013.
28. Degenhardt L, Bruno R, Lintzeris N, et al. Agreement between definitions of pharmaceutical opioid use disorders and dependence in people taking opioids for chronic non-cancer pain (POINT): A cohort study. Lancet Psychiatry. 2015;2:314-22.
29. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: A cohort study. Ann Intern Med. 2010;152:85-92.
30. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med. 2011;171:686-91.
31. Saunders KW, Dunn KM, Merrill JO, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. J Gen Intern Med. 2010;25:310-5.
32. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of fracture in adults: A nested case-control study using the general practice research database. Am J Epidemiol. 2013;178:559-69.
33. Carman WJ, Su S, Cook SF, Wurzelmann JI, McAfee A. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. Pharmacoepidemiol Drug Saf. 2011;20:754-62.
34. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. J Intern Med. 2013;273:511-26.
35. Deyo RA, Smith DH, Johnson ES, et al. Prescription opioids for back pain and use of medications for erectile dysfunction. Spine. 2013;38:909-15.
36. Gomes T, Redelmeier DA, Juurlink DN, Dhalla IA, Camacho X, Mamdani MM. Opioid dose and risk of road trauma in Canada: a population-based study. JAMA Intern Med. 2013;173:196-201.
37. Salzman RT, Roberts MS, Wild J, Fabian C, Reder RF, Goldenheim PD. Can a controlled-release oral dose form of oxycodone be used as readily as an immediate-release form for the purpose of titrating to stable pain control? J Pain Symptom Manage. 1999;18:271-9.
38. Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. A randomized prospective study. Spine. 1998;23:2591-600.
39. Allan L, Richarz U, Simpson K, Slappendel R. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naive patients with chronic low back pain. Spine. 2005;30:2484-90.
40. Wild JE, Grond S, Kuperwasser B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. Pain Pract. 2010;10:416-27.
41. Mitra F, Chowdhury S, Shelley M, Williams G. A feasibility study of transdermal buprenorphine versus transdermal fentanyl in the long-term management of persistent non-cancer pain. Pain Med. 2013;14:75-83.
42. Krebs EE, Becker WC, Zerzan J, Bair MJ, McCoy K, Hui S. Comparative mortality among Department of Veterans Affairs patients prescribed methadone or long-acting morphine for chronic pain. Pain. 2011;152:1789-95.
43. Hartung DM, Middleton L, Haxby DG, Koder M, Ketchum KL, Chou R. Rates of adverse events of long-acting opioids in a state Medicaid program. Ann Pharmacother. 2007;41:921-8.

44. Naliboff BD, Wu SM, Schieffer B, et al. A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. J Pain. 2011;12:288-96.
45. Cowan DT, Wilson-Barnett J, Griffiths P, Vaughan DJ, Gondhia A, Allan LG. A randomized, double-blind, placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine. Pain Med. 2005;6:113-21.
46. Ralphs JA, Williams AC, Richardson PH, Pither CE, Nicholas MK. Opiate reduction in chronic pain patients: a comparison of patient-controlled reduction and staff controlled cocktail methods. Pain. 1994;56:279-88.
47. Tennant FS, Jr., Rawson RA. Outpatient treatment of prescription opioid dependence: Comparison of two methods. Arch Intern Med. 1982;142:1845-7.
48. Akbik H, Butler SF, Budman SH, Fernandez K, Katz NP, Jamison RN. Validation and clinical application of the Screener and Opioid Assessment for Patients with Pain (SOAPP). J Pain Symptom Manage. 2006;32:287-93.
49. Jones T, Moore T, Levy JL, et al. A comparison of various risk screening methods in predicting discharge from opioid treatment. Clin J Pain. 2012;28:93-100.
50. Moore TM, Jones T, Browder JH, Daffron S, Passik SD. A comparison of common screening methods for predicting aberrant drug-related behavior among patients receiving opioids for chronic pain management. Pain Med. 2009;10:1426-33.
51. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: Preliminary validation of the Opioid Risk Tool. Pain Med. 2005;6:432-42.
52. Bartoli A, Michna E, He E, Wen W. Efficacy and safety of once-daily, extended-release hydrocodone in individuals previously receiving hydrocodone/acetaminophen combination therapy for chronic pain. Postgrad Med. 2015;127:5-12.
53. Cifuentes M, Webster B, Genevay S, Pransky G. The course of opioid prescribing for a new episode of disabling low back pain: Opioid features and dose escalation. Pain. 2010;151:22-9.
54. Daitch D, Daitch J, Novinson D, Frey M, Mitnick C, Pergolizzi J. Conversion from high-dose full-opioid agonists to sublingual buprenorphine reduces pain scores and improves quality of life for chronic pain patients. Pain Med. 2014;15:2087-94.
55. Franklin GM, Stover BD, Turner JA, Fulton-Kehoe D, Wickizer TM. Early opioid prescription and subsequent disability among workers with back injuries: the Disability Risk Identification Study Cohort. Spine. 2008;33:199-204.
56. Franklin GM, Rahman EA, Turner JA, Daniell WE, Fulton-Kehoe D. Opioid use for chronic low back pain: A prospective, population-based study among injured workers in Washington State, 2002-2005. Clin J Pain. 2009;25:743-51.
57. Fredheim OM, Mahic M, Skurtveit S, Dale O, Romundstad P, Borchgrevink PC. Chronic pain and use of opioids: a population-based pharmacoepidemiological study from the Norwegian prescription database and the Nord-Trondelag health study. Pain. 2014;155:1213-21.
58. Pedersen L, Borchgrevink PC, Riphagen, II, Fredheim OM. Long- or short-acting opioids for chronic non-malignant pain? A qualitative systematic review. Acta Anaesthesiol Scand. 2014;58:390-401.
59. Rauck RL, Nalamachu S, Wild JE, et al. Single-entity hydrocodone extended-release capsules in opioid-tolerant subjects with moderate-to-severe chronic low back pain: A randomized double-blind, placebo-controlled study. Pain Med. 2014;15:975-85.
60. Turner BJ, Liang Y. Drug overdose in a retrospective cohort with with non-cancer pain treated with opioids, antidepressants, and/or sedative-hypnotics: Interactions with mental health disorders. J Gen Intern Med. 2015. EPub Ahead of Print. doi: 10.1007/s11606-015-3199-4.