Evidence Report/Technology Assessment

Number 218

The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain

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Evidence-Based Practice

Evidence Report/Technology Assessment

Number 218

The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This report may periodically be assessed for the urgency to update. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at: www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

This topic was nominated to AHRQ from the National Institutes of Health. Therefore, in place of Key Informants, a National Institutes of Health Working Group Planning Meeting was conducted to provide input into the key questions and the scope of the report.

Technical Expert Panel

In designing the review questions and methodology at the outset of this report, the EPC consulted several technical and content experts, reflecting a variety of viewpoints relevant to this topic. Technical experts consulted are expected to have divergent and possibly conflicting opinions. This diversity is helpful in achieving a well-rounded report. The study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain

Structured Abstract

Objectives. Chronic pain is common and use of long-term opioid therapy for chronic pain has increased dramatically. This report reviews the current evidence on effectiveness and harms of opioid therapy for chronic pain, focusing on long-term (≥1 year) outcomes.

Data sources. A prior systematic review (searches through October 2008), electronic databases (Ovid MEDLINE, Scopus, and the Cochrane Libraries January 2008 to August 2014), reference lists, and clinical trials registries.

Review methods. Using predefined criteria, we selected randomized trials and comparative observational studies of patients with cancer or noncancer chronic pain being considered for or prescribed long-term opioid therapy that addressed effectiveness or harms versus placebo, no opioid use, or nonopioid therapies; different opioid dosing methods; or risk mitigation strategies. We also included uncontrolled studies ≥1 year that reported rates of abuse, addiction, or misuse, and studies on the accuracy of risk prediction instruments for predicting subsequent opioid abuse or misuse. The quality of included studies was assessed, data were extracted, and results were summarized qualitatively.

Results. Of the 4,209 citations identified at the title and abstract level, a total of 39 studies were included. For a number of Key Questions, we identified no studies meeting inclusion criteria. Where studies were available, the strength of evidence was rated no higher than low, due to imprecision and methodological shortcomings, with the exception of buccal or intranasal fentanyl for pain relief outcomes within 2 hours after dosing (strength of evidence: moderate). No study evaluated effects of long-term opioid therapy versus no opioid therapy. In 10 uncontrolled studies, rates of opioid abuse were 0.6 percent to 8 percent and rates of dependence were 3.1 percent to 26 percent in primary care settings, but studies varied in methods used to define and ascertain outcomes. Rates of aberrant drug-related behaviors ranged from 5.7 percent to 37.1 percent. Compared with nonuse, long-term opioid therapy was associated with increased risk of abuse (one cohort study), overdose (one cohort study), fracture (two observational studies), myocardial infarction (two observational studies), and markers of sexual dysfunction (one cross-sectional study), with several studies showing a dose-dependent association. One randomized trial found no difference between a more liberal opioid dose escalation strategy and maintenance of current dose in pain or function, but differences between groups in daily opioid doses at the end of the trial were small. One cohort study found methadone associated with lower risk of mortality than long-acting morphine in a Veterans Affairs population in a propensity adjusted analysis (adjusted HR 0.56, 95 percent CI 0.51 to 0.62). Estimates of diagnostic accuracy for the Opioid Risk Tool were extremely inconsistent and other risk assessment instruments were evaluated in only one or two studies. No study evaluated the effectiveness of risk mitigation strategies on outcomes related to overdose, addiction, abuse, or misuse. Evidence was insufficient to evaluate benefits and harms of long-term opioid therapy in high-risk patients or in other subgroups.

Conclusions. Evidence on long-term opioid therapy for chronic pain is very limited but suggests an increased risk of serious harms that appears to be dose-dependent. More research is needed to understand long-term benefits, risk of abuse and related outcomes, and effectiveness of different opioid prescribing methods and risk mitigation strategies.

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Executive Summary

Introduction

Background

Chronic pain, often defined as pain lasting longer than 3 months or past the time of normal tissue healing,[1] is extremely common. According to a recent Institute of Medicine report, up to one-third of U.S. adults report chronic pain.[2] Chronic pain is a major cause of decreased quality of life and disability and is often refractory to treatment.[3,4] There has been a dramatic increase over the past 10 to 20 years in the prescription of opioid medications for chronic pain,[5-7] despite limited evidence showing long-term beneficial effects.[8,9] In addition, accumulating evidence indicates that prescription opioids may be associated with important harms, including accidental overdose, abuse, addiction, diversion, and accidents involving injuries (such as falls and motor vehicle accidents).[10-20] Perhaps of most concern is the dramatic increase in overdose deaths associated with opioids. In 2011, there were 16,917 fatal overdoses involving prescription opioids.[21] Prescription opioid misuse and abuse resulted in almost 660,000 emergency department visits in 2010, over twice as many as in 2004.[13] Substance abuse treatment admissions for opiates other than heroin increased more than six-fold from 1999 to 2009.[12] Opioids are also associated with adverse effects such as constipation, nausea, and sedation.[22] Finally, data indicate potential associations between long-term opioid therapy and other harms, such as adverse endocrinological effects and hyperalgesia.[23-25]

These data underscore the complexity of clinical decisionmaking around long-term opioid therapy, which requires individualized assessments of the balance between benefits and harms; appropriate opioid selection, dose initiation, and titration strategies; integration of risk assessment and mitigation strategies; and consideration of the use of alternative, nonopioid therapies.[9] Risk mitigation strategies that have been suggested for patients prescribed long-term opioids include use of opioid medication agreements, application of dose thresholds that warrant increased caution, regular clinical followup and monitoring, urine drug screens, use of abuse-deterrent opioid formulations, and use of data from prescription drug monitoring programs.[9]

Understanding benefits and harms of long-term opioid therapy for chronic pain is a challenge because effects may vary depending on patient characteristics (e.g., age, sex, pain condition, psychosocial factors, comorbidities), opioid characteristics (e.g., specific opioid, short- versus long-acting opioid, mode of administration, dose), dosing strategies (e.g., round-the-clock versus as-needed dosing, application of dose thresholds), concomitant therapies (e.g., use of benzodiazepines or other drugs that may interact with opioids), and characteristics of the clinical setting. Other challenges in interpreting the literature include potential limitations in generalizability due to study design and other methodological shortcomings (e.g., duration of followup, exclusion of patients at higher risk for harms, under-representation of certain sociodemographic groups, and high dropout rates), and gaps in research on important scientific questions.[26] Although guidelines on use of opioids for chronic pain are available, most recommendations are based on weak or limited evidence.[9,27] The increase in use of long-term opioid therapy for chronic pain, new information concerning harms associated with long-term opioid therapy, continued wide variations in practice related to long-term opioid therapy, and the availability of new evidence underscore the need for a current systematic review in this area.

The purpose of this report is to systematically review the current evidence on long-term opioid therapy for chronic pain, which will be used by the National Institutes of Health (NIH) to inform a Pathways to Prevention Workshop on the role of opioids in the treatment of chronic pain. Although guidelines have been published from the American Pain Society (APS)/ American Academy of Pain Medicine,[9] the Veterans Affairs (VA)/Department of Defense,[28] and other groups, the availability of new evidence warrants a new systematic review that could be used to inform updated or new guidelines, guide quality improvement efforts, and define and update priorities for further research in this area.[26] This review updates a prior systematic review on opioid therapy for chronic pain funded by the APS.[29] Differences between this review and the 2009 APS review are that it focuses specifically on benefits and harms associated with long-term use of opioid therapy and evaluates an additional Key Question on dose escalation versus maintenance of doses in patients on long-term opioid therapy, additional outcomes (e.g., cardiovascular events, infection, and psychological outcomes), and additional risk mitigation strategies (e.g., abuse-deterrent formulations and use of data from prescription drug monitoring programs).

Scope of Review and Key Questions

The Key Questions and analytic framework (Figure A) used to guide this report are shown below. The analytic framework shows the target populations, interventions, and outcomes that we examined.

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 (≥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); (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 nonopioid therapies (pharmacological or nonpharmacological) on outcomes related to pain, function, and quality of life?
d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacological or nonpharmacological) versus opioids or nonopioid 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 accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?

b. How do harms vary depending on: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including back pain], 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); (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 for 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 short- versus long-acting 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 long-acting 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 short- plus long-acting opioids versus long-acting 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?

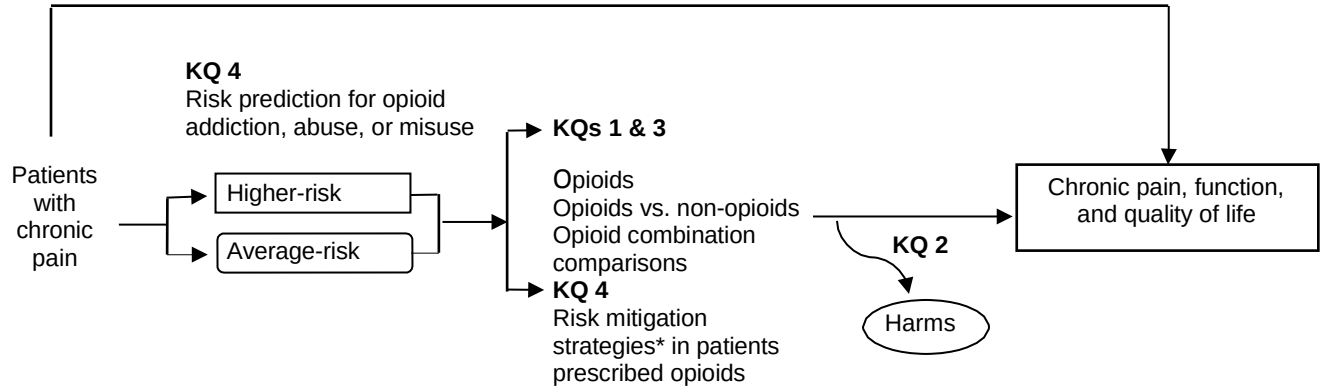
Key Question 4. Risk Assessment and Risk Mitigation Strategies

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?

Figure A. Analytic framework



KQ, Key Question.

*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.

Methods

The methods for this Comparative Effectiveness Review (CER) follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[30] All methods were determined a priori.

Topic Refinement and Review Protocol

This topic was selected for review based on a nomination from NIH. The initial Key Questions for this CER were developed with input from an NIH working group. The Key Questions and scope were further developed with input from a Technical Expert Panel (TEP) convened for this report. The TEP provided high-level content and methodological guidance to the review process and consisted of experts in health services research, internal medicine, psychology, pain medicine, pharmacology, neurology, occupational medicine, pediatrics, and epidemiology. TEP members disclosed all financial or other conflicts of interest prior to participation. The AHRQ Task Order Officer and the investigators reviewed the disclosures and determined that the TEP members had no conflicts of interest that precluded participation.

The protocol for this CER was developed prior to initiation of the review, and was posted on the AHRQ Web site on December 19, 2013 at: http://effectivehealthcare.ahrq.gov/ehc/products/557/1837/chronic-pain-opioid-treatment-protocol-131219.pdf. The protocol was also registered in the PROSPERO international database of prospectively registered systematic reviews.[31]

Literature Search Strategy

A research librarian conducted searches in Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, PsychINFO, and CINAHL from 2008 to August 2014 (see Appendix A for full search strategies). We restricted search start dates to January 2008 because the searches in the prior APS review, which we used to identify potentially relevant studies, went through October 2008.[29] For outcomes (cardiovascular, infections, and psychological harms) and interventions (abuse-deterrent formulations, and use of prescription monitoring program data) not addressed in the APS review, we searched the same databases and did not apply any search date start restrictions.

We also hand-searched the reference lists of relevant studies and searched for unpublished studies in ClinicalTrials.gov. Scientific information packets (SIPs) with relevant published and unpublished studies were requested from 19 current application holders from the U.S. Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy (REMS) Extended-Release and Long-Acting (ER/LA) Opioid Analgesics List.[32] We received five SIP submissions.

Study Selection

We developed criteria for inclusion and exclusion of articles based on the Key Questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) approach (Appendix B). Articles were selected for full-text review if they were about long-term opioid therapy for chronic pain, were relevant to a Key Question, and met the predefined inclusion criteria as shown below. We excluded studies published only as conference abstracts, restricted inclusion to English-language articles, and excluded studies of nonhuman subjects. Studies had to report original data to be included.

Each abstract was independently reviewed for potential inclusion and full-text review by two investigators. Two investigators independently reviewed all full-text articles for final inclusion. Discrepancies were resolved through discussion and consensus. A list of the included articles is available in Appendix C; excluded articles are shown Appendix D with primary reasons for exclusion.

We selected studies of adults (age ≥18 years) with chronic pain (defined as pain lasting >3 months) being considered for long-term opioid therapy (Key Questions 4a and 4b) or prescribed long-term opioid therapy (all other Key Questions). We defined long-term opioid therapy as use of opioids on most days for >3 months; this threshold was selected to differentiate ongoing opioid therapy (as often used for chronic pain) from short-term therapy. We included studies that did not explicitly report the duration of pain if the average duration of opioid therapy was >3 months. We included studies that did not explicitly report the duration of opioid therapy if patients were prescribed long-acting opioids, as these are not typically prescribed for short-term use. We included studies with patients with chronic pain related to current or previously treated cancer, but excluded studies with patients with pain at end of life (e.g., patients with cancer in hospice care). We excluded studies with patients with acute pain, pregnant or breastfeeding women, and patients treated with opioids for addiction.

We included studies of patients prescribed any long- or short-acting opioid used as long-term therapy, either alone or in combination with another agent (Key Question 1d). We included tapentadol, a dual mechanism medication with strong opioid mu-receptor affinity, but excluded tramadol, which is also a dual mechanism medication but with weak opioid mu-receptor affinity that has not been identified as a cause of unintentional prescription drug overdose deaths.[33] We also excluded studies of parenteral opioids.

We included studies that compared long-term opioid therapy versus placebo, no therapy, or another drug or nondrug therapy; studies that evaluated different dose initiation, titration, or rotation strategies; studies of different methods for tapering or discontinuing opioids; studies on methods for treating acute exacerbations of pain in people with chronic pain; and studies on various risk mitigation strategies for reducing harms associated with opioids. Risk mitigation strategies included 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. We also included studies that compared the predictive accuracy of risk prediction instruments in people with chronic pain prior to initiation of opioids for predicting outcomes related to future misuse, abuse, or addiction, and studies on the effects of risk prediction instruments on clinical outcomes.

Outcomes were pain (intensity, severity, bothersomeness), function (physical disability, activity limitations, activity interference, work function), quality of life (including depression), and doses of opioids used. Evaluated harms included overdose, opioid use disorder, addiction, abuse, and misuse, as well as other opioid-related harms (including gastrointestinal harms, fractures, falls, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms [e.g., depression]). We focused on outcomes reported after at least 1 year of opioid therapy, with the exception of outcomes related to overdose and injuries (fractures, falls, and motor vehicle accidents), studies on treatment of acute exacerbations of chronic pain, studies on dose initiation and titration, and studies on discontinuation of opioid therapy, for which we included studies of any duration.

For all Key Questions, we included randomized trials and controlled observational studies (cohort studies, cross-sectional studies, and case-control studies) that performed adjustment on

potential confounders. We included uncontrolled observational studies of patients with chronic pain prescribed opioid therapy for at least 1 year that reported abuse, misuse, or addiction as a primary outcome and described predefined methods to assess these outcomes. Otherwise, we excluded uncontrolled observational studies, case series, and case reports. We reviewed systematic reviews for potentially relevant references.

Data Extraction

We extracted the following information from included studies into evidence tables using Excel spreadsheets: study design, year, setting, inclusion and exclusion criteria, population characteristics (including sex, age, race, pain condition, and duration of pain), sample size, duration of followup, attrition, intervention characteristics (including specific opioid and formulation, dose, and duration of therapy), results, and funding sources.

For studies on the predictive accuracy of risk prediction instruments, we attempted to create two-by-two tables from information provided (sample size, prevalence, sensitivity, and specificity) and compared calculated measures of diagnostic accuracy based on the two-by-two tables with reported results. We noted discrepancies between calculated and reported results when present. When reported, we also recorded the area under the receiver operating characteristic curve (AUROC).[34,35]

For studies of interventions, we calculated relative risks (RR) and associated 95 percent confidence intervals (CI) based on the information provided (sample sizes and incidence of outcomes of interest in each intervention group). We noted discrepancies between calculated and reported results when present.

Data extraction for each study was performed by two investigators. The first investigator extracted the data, and the second investigator independently reviewed the extracted data for accuracy and completeness.

Assessing Methodological Risk of Bias of Individual Studies

We assessed risk of bias (quality) for each study using predefined criteria. We used the term "quality" rather than the alternate term "risk of bias;" both refer to internal validity. Randomized trials were evaluated with criteria and methods developed by the Cochrane Back Review Group.[36] Cohort studies, case-control studies, and cross-sectional studies were rated using criteria from the U.S. Preventive Services Task Force.[37] Risk prediction instrument studies were rated using criteria from various sources.[38-40] These criteria were applied in conjunction with the approach recommended in the chapter, Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions,[41] in the AHRQ Methods Guide. Studies of predictive accuracy of risk prediction instruments were assessed using an approach adapted from the AHRQ Methods Guide for Medical Test Reviews,[38] which is based on methods developed by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) group.[39] We reassessed the quality of studies included in the prior APS review to ensure consistency in quality assessment. Two investigators independently assessed the quality of each study. Discrepancies were resolved through discussion and consensus.

Individual studies were rated as having "poor," "fair," or "good" quality. We rated the quality of each randomized trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; whether attrition was adequately reported and acceptable; similarity in use of cointerventions; compliance to allocated treatments; the use of intent-to-treat analysis; and avoidance of selective outcomes reporting.[36,37]

We rated the quality of each cohort study based on whether it enrolled a consecutive or random sample of patients meeting inclusion criteria; whether it evaluated comparable groups; whether rates of loss to followup were reported and acceptable; whether it used accurate methods for ascertaining exposures, potential confounders, and outcomes; and whether it performed adjustment for important potential confounders.[37] For cross-sectional studies, we used criteria for cohort studies, but did not rate criteria related to loss to followup. For uncontrolled studies on risk of abuse or related outcomes, we evaluated whether it enrolled a consecutive or random sample, whether outcome assessors were blinded to patient characteristics, whether rates of loss to followup were reported (for longitudinal studies) and acceptable, and whether pre-specified outcomes were assessed in all patients.

We rated the quality of each case-control study based on whether it enrolled a consecutive or random sample of cases meeting predefined criteria; whether controls were derived from the same population as cases; whether cases and controls were comparable on key prognostic factors; whether it used accurate methods to ascertain outcomes, exposures, and potential confounders; and whether it performed adjustment for important potential confounders.[37]

We rated the quality of each study on the predictive value of risk prediction instruments based on whether it evaluated a consecutive or random sample of patients meeting pre-defined criteria, whether the patient population evaluated in the study was adequately described, whether the screening instrument included appropriate criteria, and whether outcomes were assessed in all patients independent of the results of the risk assessment instrument using adequately described methods.[38,39] We also evaluated whether the study was to develop a risk prediction instrument or to validate a previously developed instrument.[40]

Studies rated "good quality" were considered to have the least risk of bias and their results are likely to be valid. Studies rated "fair quality" have some methodological shortcomings, but no flaw or combination of flaws judged likely to cause major bias. In some cases, the article did not report important information, making it difficult to assess its methods or potential limitations. The moderate risk of bias category is broad and studies with this rating vary in their strengths and weaknesses; the results of some studies assessed to have moderate risk of bias are likely to be valid, while others may be only possibly valid. Studies rated "poor quality" have significant flaws that may invalidate the results. They have a serious or "fatal" flaw or combination of flaws in design, analysis, or reporting; large amounts of missing information; or serious discrepancies in reporting. The results of these studies are at least as likely to reflect flaws in the study design as the differences between the compared interventions. We did not exclude studies rated as having high risk of bias a priori, but they were considered the least reliable when synthesizing the evidence, particularly when discrepancies between studies were present.

Assessing Research Applicability

We recorded factors important for understanding the applicability of studies, such as whether the publication adequately described the study sample, the country in which the study was conducted, the characteristics of the patient sample (e.g., age, sex, race, pain condition, duration or severity of pain, medical comorbidities, and psychosocial factors), the characteristics of the interventions used (e.g., specific opioid, dose, mode of administration, or dosing strategy), the clinical setting (e.g., primary care or specialty setting), and the magnitude of effects on clinical outcomes.[42] We also recorded the funding source and role of the sponsor. We did not assign a rating of applicability (such as high or low) because applicability may differ based on the user of the report.

Evidence Synthesis and Rating the Body of Evidence

We constructed evidence tables summarizing study characteristics, results, and quality ratings for all included studies. We summarized evidence for each Key Question qualitatively used a hierarchy-of-evidence approach, where the best evidence was the focus of our synthesis for each Key Question. In the evidence tables, we included relevant studies from the prior APS review as well as new studies meeting inclusion criteria. Results were organized by Key Question. We did not attempt meta-analyses because of the small number of studies available for each Key Question; variability in study designs, patient samples, interventions, and measures; and methodological shortcomings in the available studies.

We assessed the overall strength of evidence (SOE) for each Key Question and outcome using the approach described in the AHRQ Methods Guide.[30] We synthesized the quality of the studies; the consistency of results within and between study designs; the directness of the evidence linking the intervention and health outcomes; and the precision of the estimate of effect (based on the number and size of studies and CIs for the estimates). We were not able to formally assess for publication bias due to small number of studies, methodological shortcomings, or differences across studies in designs, measured outcomes, and other factors. Rather, as described above, we searched for unpublished studies through searches of clinical trials registries and regulatory documents and by soliciting SIPs.

The SOE was based on the overall quality of each body of evidence, based on the risk of bias (graded low, moderate, or high); the consistency of results across studies (graded consistent, inconsistent, or unable to determine when only one study was available); the directness of the evidence linking the intervention and health outcomes (graded direct or indirect); and the precision of the estimate of effect, based on the number and size of studies and CIs for the estimates (graded precise or imprecise). We did not grade supplemental domains for cohort studies evaluating intermediate and clinical outcomes because too few studies were available for these factors to impact the SOE grades.

We graded the SOE for each Key Question using the four key categories recommended in the AHRQ Methods Guide.[30] A "high" grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect. A "moderate" grade indicates moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate. A "low" grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. An "insufficient" grade indicates evidence either is unavailable or is too limited to permit any conclusion, due to the availability of only poor-quality studies, extreme inconsistency, or extreme imprecision.

Peer Review and Public Commentary

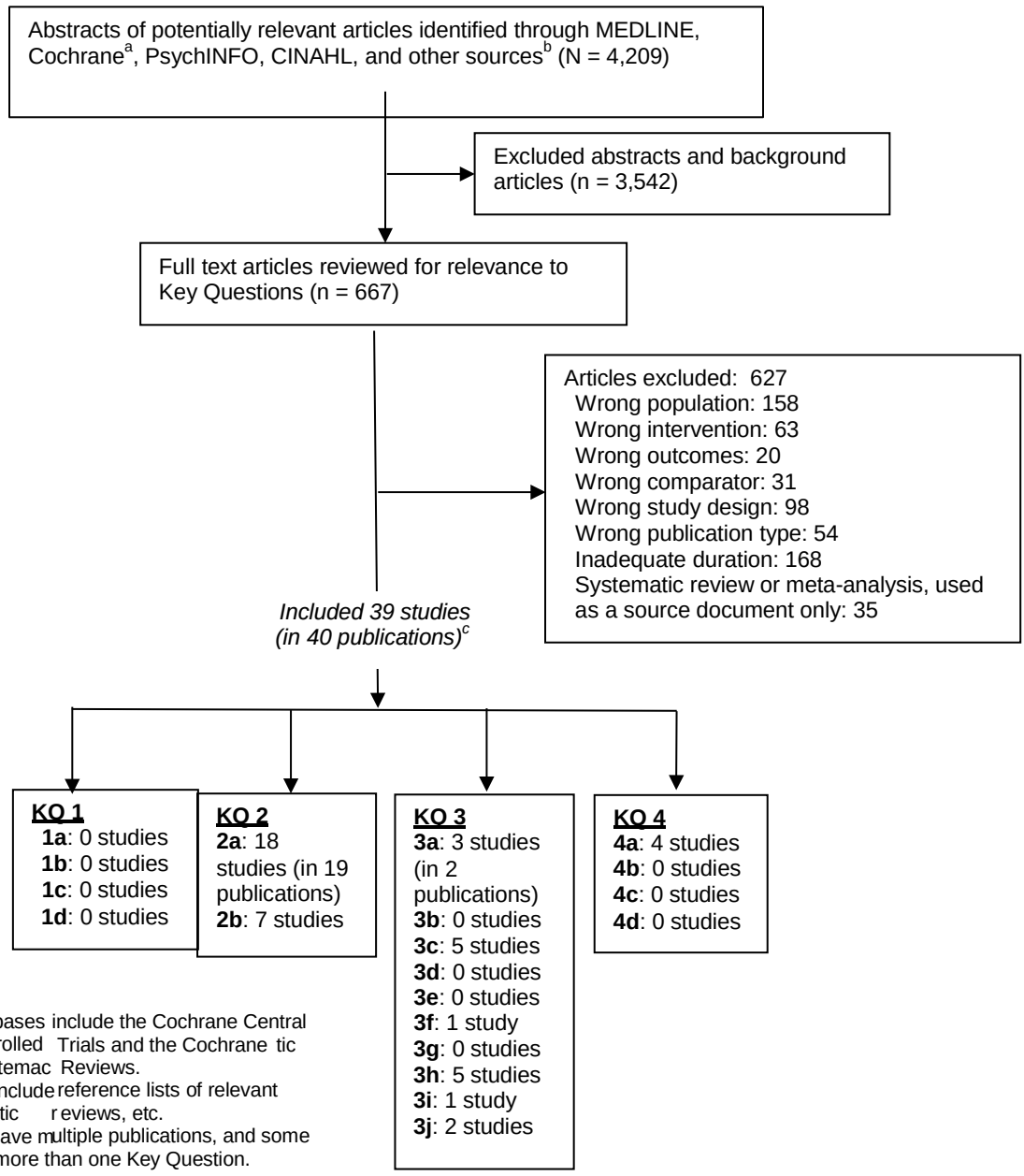
Experts in chronic pain and opioid therapy, as well as individuals representing important stakeholder groups, were invited to provide external peer review of this CER. The AHRQ Task Order Officer and a designated EPC Associate Editor also provided comments and editorial review. To obtain public comment, the draft report was posted on the AHRQ Web site for 4 weeks. A disposition of comments report detailing the authors' responses to the peer and public review comments will be made available after AHRQ posts the final CER on the public Web site.

Results

Overview

The search and selection of articles are summarized in the study flow diagram (Figure B). Database searches resulted in 4,209 potentially relevant articles. After dual review of abstracts and titles, 667 articles were selected for full-text review, and 39 studies (in 40 publications) were determined by dual review at the full-text level to meet inclusion criteria and were included in this review. Data extraction and quality assessment tables for all included studies per Key Question are available in Appendixes E and F.

Figure B. Literature flow diagram



[a] Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane tic Database of Systemac Reviews.
[b] Other sources include reference lists of relevant articles, systematic reviews, etc.
[c] Some studies have multiple publications, and some are included for more than one Key Question.

Key Question 1. Effectiveness and Comparative Effectiveness

No study evaluated the effectiveness or comparative effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (≥1 year) outcomes related to pain, function, or quality of life in patients with chronic pain (SOE: insufficient).

Key Question 2. Harms and Adverse Events

In patients with chronic pain, 10 uncontrolled studies of patients on opioid therapy for at least 1 year that used predefined methods for ascertaining rates of abuse and related outcomes, rates of opioid abuse were 0.6 percent to 8 percent and rates of dependence were 3.1 percent to 26 percent in primary care settings, and rates of abuse were 14.4 percent, misuse 8 percent, and addiction 1.9 percent in pain clinic settings, but studies varied in methods used to define and ascertain outcomes. Rates of aberrant drug-related behaviors (e.g., positive urine drug tests, medication agreement violations) ranged from 5.7 percent to 37.1 percent (SOE: insufficient). In controlled observational studies, opioids were associated with increased risk of abuse (one study), overdose (one study), fracture (two studies), myocardial infarction (two studies), and use of testosterone replacement or medications for erectile dysfunction (one study) versus no opioid use (strength of evidence: low). No study evaluated effects of opioids versus placebo or no opioid on gastrointestinal harms, motor vehicle accidents, infections, and psychological or cognitive harms. In patients with chronic pain prescribed long-term opioid therapy, observational studies reported an association between higher doses of opioids and risk of abuse (one study), overdose (two studies), fracture (one study), myocardial infarction (one study), motor vehicle accidents (one study), and use or testosterone replacement or medications for erectile dysfunction (one study) (SOE: low). No study examined how harms vary depending on the specific type or cause of pain, patient demographics, or patient comorbidities (including past or current substance abuse disorder or being at high risk for addiction).

Key Question 3. Dosing Strategies

Three randomized, head-to-head trials of various long-acting opioids found no differences in long-term outcomes related to pain or function (SOE: low). One retrospective cohort study conducted in a Veterans Affairs setting that used a propensity-adjusted analysis found methadone associated with lower mortality risk than sustained-release morphine (SOE: low). One randomized trial found no difference between more liberal dose escalation versus maintenance of current doses on outcomes related to pain, function, or withdrawal due to opioid use, but doses of opioids at the end of the trial in the two groups were similar (52 versus 40 mg MED/day) (SOE: low). Five randomized trials found buccal or nasal fentanyl more effective than placebo or oral opioids for acute exacerbations of pain in patients with chronic pain, but focused on immediate (within 2 hours) outcomes (SOE: moderate). Studies on different methods for initiating and titrating opioids (three studies), decreasing doses or tapering off versus continuation (one study), and different tapering protocols and strategies (two studies), were limited in number, had methodological shortcomings, and showed no clear differences on outcomes related to pain and function (SOE: insufficient). No study examined effects of short- versus long-acting opioids, short- plus long-acting opioids versus long-acting opioids alone, scheduled, continuous versus as-needed dosing, or opioid rotation versus maintenance of current therapy in patients with chronic pain on long-term opioid therapy.

Key Question 4. Risk Assessment and Risk Mitigation Strategies

Four studies examined the accuracy of instruments for predicting risk of opioid overdose, addiction, abuse, or misuse in patients with chronic pain being considered for long-term opioid therapy. Three studies reported sensitivities for the Opioid Risk Tool that ranged from 0.20 to 0.99 (three studies) and specificities of 0.88 and 0.16 (two studies) (SOE: insufficient). Two studies found no clear differences between different risk assessment instruments in diagnostic accuracy. No study evaluated the effectiveness of the use of risk prediction instruments or other risk mitigation strategies, or the comparative effectiveness of treatment strategies for managing patients with a history of addiction on overdose, addiction, abuse, misuse, and related outcomes.

Key findings and SOE grades are summarized in the summary of evidence table (Table A). The factors used to determine the overall SOE grades are available in Appendix G.

Table A. Summary of evidence

Key Question Outcome	Strength of Evidence Grade	Conclusion
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 (≥1 year) outcomes related to pain, function, and quality of life?		
Pain, function, quality of life	Insufficient	No study of opioid therapy versus placebo or no opioid therapy evaluated long-term (≥1 year) outcomes related to pain, function, or 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); 3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for addiction)?		
Pain, function, quality of life	Insufficient	No studies
c. In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacological or nonpharmacological) on outcomes related to pain, function, and quality of life?		
Pain, function, quality of life	Insufficient	No studies
d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacological or nonpharmacological) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?		

Table A. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
Pain, function, quality of life	Insufficient	No Studies
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 accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?		
Abuse, addiction	Low	No randomized trial evaluated risk of opioid abuse, addiction, and related outcomes in patients with chronic pain prescribed opioid therapy. One retrospective cohort study found prescribed long-term opioid use associated with significantly increased risk of abuse or dependence versus no opioid use.
Abuse, addiction	Insufficient	In 10 uncontrolled studies, estimates of opioid abuse, addiction, and related outcomes varied substantially even after stratification by clinic setting
Overdose	Low	Current opioid use was associated with increased risk of any overdose events (adjusted HR 5.2, 95% CI 2.1 to 12) and serious overdose events (adjusted HR 8.4, 95% CI 2.5 to 28) versus current nonuse
Fractures	Low	Opioid use associated with increased risk of fracture in 1 cohort study (adjusted HR 1.28, 95% CI 0.99 to 1.64) and 1 case-control study (adjusted OR 1.27, 95% CI 1.21 to 1.33)
Myocardial infarction	Low	Current opioid use associated with increased risk of myocardial infarction versus nonuse (adjusted OR 1.28, 95% CI 1.19 to 1.37 and incidence rate ratio 2.66, 95% CI 2.30 to 3.08)
Endocrine	Low	Long-term opioid use associated with increased risk of use of medications for erectile dysfunction or testosterone replacement versus nonuse (adjusted OR 1.5, 95% CI 1.1 to 1.9)
Gastrointestinal harms, motor vehicle accidents, infections, psychological harms, cognitive harms	Insufficient	No studies
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)?		

Table A. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
Various harms	Insufficient	No studies
b. How do harms vary depending on the dose of opioids used?		
Abuse, addiction	Low	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 to 21) for 1-36 MED/day, 29 (95 percent CI 20 to 41) for 36-120 MED/day, and 122 (95 percent CI 73 to 205) for ≥120 MED/day.
Overdose	Low	Versus 1 to 19 mg MED/day, 1 cohort study found an adjusted HR for an overdose event of 1.44 (95% CI 0.57 to 3.62) for 20 to 49 mg MED/day that increased to 11.18 (95% CI 4.80 to 26.03) at >100 mg MED/day; 1 case-control study found an adjusted OR for an opioid-related death of 1.32 (95% CI 0.94 to 1.84) for 20 to 49 mg MED/day that increased to 2.88 (95% CI 1.79 to 4.63) at ≥200 mg MED/day
Fracture	Low	Risk of fracture increased from an adjusted HR of 1.20 (95% CI 0.92 to 1.56) at 1 to <20 mg MED/day to 2.00 (95% CI 1.24 to 3.24) at ≥50 mg MED/day; the trend was of borderline statistical significance
Myocardial infarction	Low	Relative to a cumulative dose of 0 to 1350 mg MED over 90 days, the incidence rate ratio for myocardial infarction for 1350 to <2700 mg was 1.21 (95% CI 1.02 to 1.45), for 2700 to <8100 mg was 1.42 (95% CI 1.21 to 1.67), for 8100 to <18,000 mg was 1.89 (95% CI 1.54 to 2.33), and for >18,000 mg was 1.73 (95% CI 1.32 to 2.26)
Motor vehicle accidents	Low	No association between opioid dose and risk of motor vehicle accidents.
Endocrine	Low	Relative to 0 to <20 mg MED/day, the adjusted OR for daily opioid dose of ≥120 mg MED/day for use of medications for erectile dysfunction or testosterone replacement was 1.6 (95% CI 1.0 to 2.4)

Table A. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
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; risks of overdose, addiction, abuse, or misuse; and doses of opioids used?		
Pain	Insufficient	Evidence from three trials on effects of titration with immediate-release versus sustained-release opioids reported inconsistent results on outcomes related to pain and are difficult to interpret due to additional differences between treatment arms in dosing protocols (titrated vs. fixed dosing) and doses of opioids used
Function, quality of life, outcomes related to abuse	Insufficient	No studies
b. In patients with chronic pain, what is the comparative effectiveness of short- versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?		

Table A. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
Pain, function, quality of life, outcomes related to abuse	Insufficient	No studies
c. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; and risk of overdose, addiction, abuse, or misuse?		
Pain and function	Low	No difference between various long-acting opioids
Assessment of risk of overdose, addiction, abuse, or misuse	Insufficient	No studies were designed to assess risk of overdose, addiction, abuse, or misuse
Overdose (as indicated by all-cause mortality)	Low	One cohort study found methadone to be associated with lower all-cause mortality risk than sustained-release morphine in a propensity adjusted analysis
Abuse and related outcomes	Insufficient	Another cohort study found some differences between long-acting opioids in rates of adverse outcomes related to abuse, but outcomes were nonspecific for opioid-related adverse events, precluding reliable conclusions
d. In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids vs. long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?		
Pain, function, quality of life, outcomes related to abuse	Insufficient	No studies
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?		
Pain, function, quality of life, outcomes related to abuse	Insufficient	No studies
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?		
Pain, function, withdrawal due to opioid misuse	Low	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 vs. 40 mg MED/day at the end of the trial)
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?		
Pain, function, quality of life, outcomes related to abuse	Insufficient	No studies

Table A. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
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?		
Pain	Moderate	Two randomized trials found buccal fentanyl more effective than placebo for treating acute exacerbations of pain and three randomized trials found buccal fentanyl or intranasal fentanyl more effective than oral opioids for treating acute exacerbations of pain in patients on long-term opioid therapy, based on outcomes measured up to 2 hours after dosing
Abuse and related outcomes	Insufficient	No studies
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?		
Pain, function	Insufficient	Abrupt cessation of morphine was associated with increased pain and decreased function compared to continuation of morphine
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?		
Opioid abstinence	Insufficient	No clear differences between different methods for opioid discontinuation or tapering in likelihood of opioid abstinence after 3 to 6 months
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?		
Diagnostic accuracy: Opioid Risk Tool	Insufficient	Based on a cutoff of >4, three studies (one poor-quality, two poor-quality) reported very inconsistent estimates of diagnostic accuracy, precluding reliable conclusions
Diagnostic accuracy: Screening and Opioid Assessment for Patients with Pain (SOAPP) version 1	Low	Based on a cutoff score of ≥8, sensitivity was 0.68 and specificity of 0.38 in 1 study, for a PLR of 1.11 and NLR of 0.83. Based on a cutoff score of >6, sensitivity was 0.73 in 1 study
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?		
Outcomes related to abuse	Insufficient	No study evaluated the effectiveness of risk prediction instruments for reducing outcomes related to overdose, addiction, abuse, or misuse

Table A. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
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?		
Outcomes related to abuse	Insufficient	No studies
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?		
Outcomes related to abuse	Insufficient	No studies

Abbreviations: CI=confidence interval, HR=hazard ratio, MED= morphine equivalent dose, mg=milligrams, NLR=negative likelihood ratio, OR=odds ratio, PLR=positive likelihood ratio, SOAPP= Screening and Opioid Assessment for Patients with Pain.

Discussion

Key Findings and Strength of Evidence

The key findings of this review are summarized in the summary of evidence table (Table A below) and the factors used to determine the overall SOE grades are summarized in Appendix G. For a number of Key Questions, we identified no studies meeting inclusion criteria. For Key Questions where studies were available, the SOE was rated no higher than low, due to small numbers of studies and methodological shortcomings, with the exception of buccal or intranasal fentanyl for pain relief outcomes within 2 hours after dosing, for which the SOE was rated moderate.

For effectiveness and comparative effectiveness, we identified no studies of long-term opioid therapy in patients with chronic pain versus no opioid therapy or nonopioid alternative therapies that evaluated outcomes at 1 year or longer. No studies examined how effectiveness varies based on various factors, including type of pain and patient characteristics. Most placebo-controlled randomized trials were shorter than 6 weeks in duration[43] and no cohort studies on the effects of long-term opioid therapy versus no opioid therapy on outcomes related to pain, function, or quality of life were found. Although uncontrolled studies of patients prescribed opioids are available,[8] findings are difficult to interpret due to the lack of a nonopioid comparison group.

Regarding harms, new evidence (published since the APS review) from observational studies suggests that being prescribed long-term opioids for chronic pain is associated with increased risk of abuse,[44] overdose,[45] fractures,[18,46] and myocardial infarction,[47] versus not currently being prescribed opioids. In addition, several recent studies suggest that the risk is dose-dependent, with higher opioid doses associated with increased risk.[11,18,44,45,48,49] Although two studies found an association between opioid dose and increased risk of overdose starting at relatively low doses (20 to 49 mg MED/day), estimates at higher doses were variable (adjusted HR 11.18 at >100 mg MED/day versus adjusted OR 2.88 for $\geq$200 mg MED/day).[45,49] However, few studies evaluated each outcome and the population evaluated and duration of opioid therapy were not always well characterized. In addition, as in all observational studies, findings are susceptible to residual confounding despite use of statistical adjustment and other techniques such as matching. A study also found long-term opioid therapy associated with increased likelihood of receiving prescriptions for erectile dysfunction or testosterone, which may be markers for sexual dysfunction due to presumed endocrinological effects of opioids.[11] However, it did not directly measure sexual dysfunction, and patients may seek or receive these medications for other reasons.

No study assessed the risk of abuse, addiction, or related outcomes associated with long-term opioid therapy use versus placebo or no opioid therapy. In uncontrolled studies, rates of abuse and related outcomes varied substantially, even after restricting inclusion to studies that evaluated patients on opioid therapy for at least one year and used pre-defined methods for ascertaining these outcomes, and stratifying studies according to whether they evaluated primary care populations or patients evaluated in pain clinic settings.[50-60] An important reason for the variability in estimates is differences in patient samples and in how terms such as addiction, abuse, misuse, and dependence were defined in the studies, and in methods used to identify these outcomes (e.g., formal diagnostic interview with patients versus chart review or informal assessment). In one study, estimates of opioid misuse were lower based on independent review than based on assessments by the treating physician.[59] No study evaluated patients with "opioid use disorder" as recently defined in the new DSM-V.[61]

Evidence on the effectiveness of different opioid dosing strategies is also extremely limited. One new trial of a more liberal dose escalation strategy versus maintenance of current doses found no differences in outcomes related to pain, function, or risk of withdrawal from the study due to opioid misuse, but the difference in opioid doses between groups at the end of the trial was small (52 versus 40 mg MED/day).[62] One study from Washington State reported a decrease in the number of opioid-associated overdose deaths after implementing a dose threshold,[63] but did not meet inclusion criteria for this review because it was an ecological, before-after study, and it is not possible to reliably determine whether changes in the number of opioid overdose deaths were related to other factors that could have impacted opioid prescribing practices. Evidence on benefits and harms of different methods for initiating and titrating opioids, short- versus long-acting opioids, scheduled and continuous versus as-needed dosing of opioids, use of opioid rotation, and methods for titrating or discontinuing patients off opioids was not available or too limited to reach reliable conclusions.

We also found limited evidence on the comparative benefits and harms of specific opioids. Three head-to-head trials found few differences in pain relief between various long-acting opioids at 1 year followup,[64-66] but the usefulness of these studies for evaluating comparative effectiveness may be limited because patients in each arm had doses titrated to achieve adequate pain control. None of the trials was designed to evaluate abuse, addiction, or related outcomes.

Methadone has been an opioid of particular interest because it is disproportionately represented in case series and epidemiological studies of opioid-associated deaths.[67] Characteristics of methadone that may be associated with increased risk of serious harms are its long and variable half-life, which could increase the risk for accidental overdose, and its association with electrocardiographic QTc interval prolongation, which could increase the risk of potentially life-threatening ventricular arrhythmia.[68] However, the highest-quality observational study, which was conducted in VA patients with chronic pain and controlled well for confounders using a propensity-adjusted analysis, found methadone to be associated with lower risk of mortality as compared with sustained-release morphine.[69] These results suggest that in some settings, methadone may not be associated with increased mortality risk, though research is needed to understand the factors that contribute to safer prescribing in different clinical settings.

Although five randomized trials found buccal or intranasal fentanyl more effective than placebo or oral opioids for treating acute exacerbations of chronic pain, all focused on short-term treatment and immediate outcomes in the minutes or hours after administration.[70-74] No study was designed to assess long-term benefits or harms, including accidental overdose, abuse, or addiction. In 2007, the U.S. FDA released a public health advisory due to case reports of deaths and other life-threatening adverse effects in patients prescribed buccal fentanyl.[75]

Evidence also remains limited on the utility of opioid risk assessment instruments, used prior to initiation of opioid therapy, for predicting likelihood of subsequent opioid abuse or misuse. In three studies of the ORT, estimates were extremely inconsistent (sensitivity ranged from 0.20 to 0.99).[76-78] A study that directly compared the accuracy of the ORT and two other risk assessment instruments reported weak likelihood ratios for predicting future abuse or misuse (PLR 1.27 to 1.65 and NLR 0.86 to 0.91).[76] Risk prediction instruments other than the ORT (such as the SOAPP version 1, revised SOAPP, or DIRE) were only evaluated in one or two studies, and require further validation. Studies on the accuracy of risk instruments for identifying aberrant behavior in patients already prescribed opioids are available,[53,56,76,79-85] but were outside the scope of this review.

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, monitoring instruments, more frequent monitoring intervals, pill counts, or abuse-deterrent formulations on outcomes related to overdose, addiction, abuse or misuse. Studies on effects of risk mitigation strategies were primarily focused on ability to detect misuse (e.g., urine drug testing and prescription monitoring program data) or on effects on markers of risky prescribing practices or medication-taking behaviors,[86] and did not meet inclusion criteria for this review, which focused on effects on clinical outcomes. One study found that rates of poison center treatment incidents and opioid-related treatment admissions increased at a lower rate in States with a prescription drug monitoring program than in States without one, but used an ecological design, did not evaluate a cohort of patients prescribed opioids for chronic pain, and was not designed to account for other factors that could have impacted opioid prescribing practices.[86]

Although evidence indicates that patients with a history of substance abuse or at higher risk for abuse or misuse due to other risk factors are more likely to be prescribed opioids than patients without these risk factors,[87-90] we identified no study on the effectiveness of methods for mitigating potential harms associated with long-term opioid therapy in high-risk patients.

Findings in Relationship to What is Already Known

Our findings are generally consistent with prior systematic reviews of opioid therapy for chronic pain that also found no long-term, placebo-controlled randomized trials.[8,43] One systematic review of outcomes associated with long-term opioid therapy concluded that many patients discontinue treatment due to adverse events or insufficient pain relief, though patients who continue opioid therapy experience clinically significant pain relief.[8] However, results of the studies included in this review are difficult to interpret because the studies had no nonopioid therapy control group, reported substantial between-study heterogeneity, and were susceptible to potential attrition and selection bias. Our findings are also consistent with a systematic review on comparative benefits and harms of various long-acting opioids and short- versus long-acting opioids, which found no clear differences, primarily based on short-term randomized trials.[91]

Our review reported rates of abuse and related outcomes that are higher than a previously published systematic review of long-term opioid therapy that reported a very low rate of opioid addiction (0.27 percent).[8] Factors that may explain this discrepancy are that the prior review included studies that did not report predefined methods for ascertaining opioid addiction, potentially resulting in underreporting, and primarily included studies that excluded high-risk patients. Like a previous systematic review, we found variability in estimates of abuse and related outcomes, with some potential differences in estimates based on clinical setting (primary care versus pain clinic) and patient characteristics (e.g., exclusion of high-risk patients).[92]

Regarding risk mitigation strategies, our findings were similar to a previously published systematic review that found weak evidence with which to evaluate risk prediction instruments.[93] Unlike our review, which found no evidence on effects of risk mitigation strategies on risk of abuse, addiction, or related outcomes, a previously published review found use of opioid management plans and urine drug screens to be associated with decreased risk of misuse behaviors.[14] However, this conclusion was based on four studies that did not meet inclusion criteria for our review because effects of opioid management plans and urine drug screens could not be separated from other concurrent opioid prescribing interventions,[94,95] use of a historical control group,[96,97] or before-after study design.[94]

Applicability

A number of issues could impact the applicability of our findings. One challenge was difficulty in determining whether studies focused on patients with chronic pain. Although a number of large observational studies reported harms based on analyses of administrative databases, they were frequently limited in their ability to assess important clinical factors such as the duration or severity of pain. For some of these studies, we inferred the presence of chronic pain from prescribing data, such as the number of prescriptions over a defined period or the use of long-acting opioid preparations. Some potentially relevant studies were excluded because it was not possible to determine whether the sample evaluated had chronic pain or received long-term therapy.[16,98-103]

Another issue that could impact applicability is the type of opioid used in the studies. Both long-acting and short-acting opioids are often prescribed for chronic pain. In some studies, use of short-acting opioids predominated.[11,18,49] Results of studies of short-acting opioids may not generalize to patients prescribed long-acting opioids.

Selection of patients could also impact applicability. The few randomized trials that met inclusion criteria typically excluded patients at high risk of abuse or misuse and frequently used run-in periods prior to allocating treatments. The use of a run-in period preselects patients who respond to and tolerate initial exposure to the studied treatment. Therefore, benefits observed in the trials might be greater and harms lower than seen in actual clinical practice.[104]

Another factor impacting applicability is that most trials were not designed or powered to assess risk of abuse, addiction, or related outcomes. For example, trials of buccal fentanyl for acute exacerbations of chronic pain focused exclusively on immediate (episode-based) outcomes and were not designed to assess long-term outcomes, including outcomes related to the potential for abuse.[70-74] Long-term head-to-head trials of long-acting opioids excluded patients at high risk for these outcomes and reported no events.[64-66]

The setting in which studies were conducted could also impact applicability. As noted in other sections of this report, rates of overdose, abuse, addiction, and related outcomes are likely to vary based on the clinical setting. Therefore, we stratified studies reporting rates of abuse according to whether they were performed in primary care or pain clinic settings. The highest-quality comparative study of methadone versus another opioid (long-acting morphine) found decreased mortality risk but was conducted in a VA setting,[69] which could limit applicability to other settings, due to factors such as how clinicians were trained in methadone use, policies on opioid prescribing, availability of resources to manage opioid prescribing, or other factors.

Implications for Clinical and Policy Decisionmaking

Our review has important implications for clinical and policy decisionmaking. Based on our review, most clinical and policy decisions regarding use of long-term opioid therapy must necessarily still be made on the basis of weak or insufficient evidence. This is in accordance with findings from a 2009 U.S. guideline on use of opioids for chronic pain, which found 21 of 25 recommendations supported by only low-quality evidence,[105] and a 2010 Canadian guideline,[106] which classified 3 of 24 recommendations as based on (short-term) randomized trials and 19 recommendations as based solely or partially on consensus opinion. Although randomized trials show short-term, moderate improvements in pain in highly selected, low-risk populations with chronic pain, such efficacy-based evidence is of limited usefulness for informing long-term opioid prescribing decisions in clinical practice.

Given the marked increase in numbers of overdose deaths and other serious adverse events that have occurred following the marked increase in opioid prescribing for chronic pain, recent policy efforts have focused on safer prescribing of opioids. A recent review of opioid guidelines found broad agreement regarding a number of risk mitigation strategies despite weak evidence, such as risk-assessment guided patient assessment for opioid therapy, urine drug testing, use of prescription monitoring program data, abuse-deterrent formulations, and opioid management plans.[107] Based on low-quality evidence regarding harms associated with long-term opioid therapy, our review provides some limited support for clinical policy efforts aimed at reducing harms. One area in which there has been less agreement across guidelines is whether dose thresholds that warrant more intense monitoring or used to define maximum ceiling doses should be implemented, and if so, what is the appropriate threshold. Some evidence is now available on dose-dependent harms associated with opioids,[45,49] which could help inform policies related to dose thresholds. However, research on the effects of implementing dose thresholds on clinical outcomes is limited to a single ecological study.[63] In addition, although two observational studies were consistent in reporting a relationship between higher opioid dose and risk of overdose, estimates were highly variable at similar doses.[45,49] This makes it difficult to determine an optimal maximum dose threshold based on an objective parameter, such as a dose inflection point where risk rises markedly. Other studies have begun to characterize cardiovascular, endocrinological, and injury-related harms associated with long-term opioid therapy and could be used to inform clinical decisions, though using such information in balanced assessments to inform clinical and policy decisionmaking remains a challenge given the lack of evidence regarding long-term benefits.

Limitations of the Review Process

We excluded non-English language articles and did not search for studies published only as abstracts. We did not attempt meta-analysis or assess for publication bias using graphical or statistical methods to detect small sample effects due to the paucity of evidence. Although we found no evidence of unpublished studies through searches on clinical trial registries and regulatory documents and solicitation of unpublished studies through SIP requests, the usefulness of such methods for identifying unpublished observational studies may be limited, as such studies are often not registered. We identified no unpublished randomized trials meeting inclusion criteria. We focused on studies that reported outcomes after at least one year of opioid therapy, though applying a shorter duration threshold for inclusion could have provided additional evidence. However, we identified no placebo-controlled trials of opioid therapy for at least 6 months.

Limitations of the Evidence Base

As noted previously, the critical limitation of our review is the lack of evidence in the target population (patients with chronic pain) and intervention (long-term opioid therapy), despite broadening of inclusion criteria to incorporate studies in which we assumed that patients were being treated for chronic pain due to the type of opioid prescribed (long-acting opioid) or number of prescriptions. We were also unable to determine how benefits and harms vary in subgroups, such as those defined by demographic characteristics, characteristics of the pain condition, and other patient characteristics (e.g., medical or psychological comorbidities). Due to the lack of evidence and methodological shortcomings in the available studies, no body of evidence (with

the exception of buccal or intranasal fentanyl for immediate pain relief) was rated higher than low, meaning that conclusions are highly uncertain.

Research Gaps

Many research gaps limit the full understanding of the effectiveness, comparative effectiveness, and harms of long-term opioid therapy, as well as of the effectiveness of different dosing methods and risk mitigation strategies, and effectiveness in special populations. Longer-term studies of patients clearly with chronic pain comparing those who are prescribed long-term opioid therapy with those receiving other pharmacological and non-pharmacological therapies are needed. Studies that include higher-risk patients, commonly treated with opioids in clinical practice, and that measure multiple important outcomes, including pain, physical and psychological functioning, as well as misuse and abuse, would be more helpful than efficacy studies focused solely on pain intensity. Greater standardization of methods for defining and identifying abuse-related outcomes in studies that report these outcomes are needed. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group recently issued recommendations on measuring abuse liability in analgesic clinical trials.[108]

Additional research is also needed to develop and validate risk prediction instruments, and to determine how using them impacts treatment decisions and, ultimately, patient outcomes. More research is needed on the comparative benefits and harms of different opioids or formulations and different prescribing methods. Studies comparing effectiveness and harms of methadone versus other long-acting opioids, to determine if findings from a study[69] conducted in a VA setting are reproducible in other settings, and to better understand factors associated with safer methadone prescribing.

Research is also needed to understand the effects of risk mitigation strategies such as urine drug screening, use of prescription drug monitoring program data, and abuse-deterrent formulations on clinical outcomes such as rates of overdose, abuse, addiction, and misuse. In one before-after study, the introduction of an abuse-deterrent opioid was followed by patients switching to other prescription opioids or illicit opioids,[109] underscoring the need for research to understand both the positive and negative clinical effects of risk mitigation strategies.

Long-term randomized trials of opioid therapy are difficult to implement due to attrition, challenges in recruitment, or ethical factors (e.g., long-term allocation of patients with pain to placebo or allocation to non-use of risk mitigation strategies recommended in clinical practice guidelines). Nonetheless, pragmatic and other non-traditional randomized trial approaches could be used to address these challenges.[110] Observational studies could also help address a number of these research questions, but should be specifically designed to evaluate patients with chronic pain prescribed long-term opioid therapy and appropriately measure and address potential confounders. Well-designed clinical registries that enroll patients with chronic pain prescribed and not prescribed chronic opioids could help address the limitations of studies based solely or primarily on administrative databases, which are often unable to fully characterize the pain condition (e.g., duration, type, and severity) or other clinical characteristics and frequently do not have information regarding outcomes related to pain, function, and quality of life. Such registry studies could be designed to extend the observations from randomized trials of opioids versus placebo or other treatments, but would differ from currently available studies by following patients who discontinue or do not start opioids, in addition to those who continue on or start opioid therapy.

Conclusions

Evidence on long-term opioid therapy for chronic pain is very limited, but suggests an increased risk of serious harms that appears to be dose-dependent. Based on our review, most clinical and policy decisions regarding use of long-term opioid therapy must necessarily still be made on the basis of weak or insufficient evidence. More research is needed to understand long-term benefits, risk of abuse and related outcomes, and effectiveness of different opioid prescribing methods and risk mitigation strategies.

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Introduction

Background

Chronic pain, often defined as pain lasting longer than 3 months or past the time of normal tissue healing,[1] is extremely common. According to a recent Institute of Medicine report, up to one-third of U.S. adults report chronic pain.[2] Chronic pain is a major cause of decreased quality of life and disability and is often refractory to treatment.[3, 4] There has been a dramatic increase over the past 10 to 20 years in the prescription of opioid medications for chronic pain,[5-7] despite limited evidence showing long-term beneficial effects.[8, 9] In addition, accumulating evidence indicates that prescription opioids may be associated with important harms, including accidental overdose, abuse, addiction, diversion, and accidents involving injuries (such as falls and motor vehicle accidents).[10-20] Perhaps of most concern is the dramatic increase in overdose deaths associated with opioids. In 2011, there were 16,917 fatal overdoses involving prescription opioids.[21] Prescription opioid misuse and abuse resulted in almost 660,000 emergency department visits in 2010, over twice as many as in 2004.[13] Substance abuse treatment admissions for opiates other than heroin increased more than six-fold from 1999 to 2009.[12] Opioids are also associated with adverse effects such as constipation, nausea, and sedation.[22] Finally, data indicate potential associations between long-term opioid therapy and other harms, such as adverse endocrinological effects and hyperalgesia.[23-25]

These data underscore the complexity of clinical decisionmaking around long-term opioid therapy, which requires individualized assessments of the balance between benefits and harms; appropriate opioid selection, dose initiation, and titration strategies; integration of risk assessment and mitigation strategies; and consideration of the use of alternative, nonopioid therapies.[9] Risk mitigation strategies that have been suggested for patients prescribed long-term opioids include use of opioid medication agreements, application of dose thresholds that warrant increased caution, regular clinical followup and monitoring, urine drug screens, use of abuse-deterrent opioid formulations, and use of data from prescription drug monitoring programs.[9]

Understanding benefits and harms of long-term opioid therapy for chronic pain is a challenge because effects may vary depending on patient characteristics (e.g., age, sex, pain condition, psychosocial factors, comorbidities), opioid characteristics (e.g., specific opioid, short- versus long-acting opioid, mode of administration, dose), dosing strategies (e.g., round-the-clock versus as-needed dosing, application of dose thresholds), concomitant therapies (e.g., use of benzodiazepines or other drugs that may interact with opioids), and characteristics of the clinical setting. Other challenges in interpreting the literature include potential limitations in generalizability due to study design and other methodological shortcomings (e.g., duration of followup, exclusion of patients at higher risk for harms, under-representation of certain sociodemographic groups, and high dropout rates), and gaps in research on important scientific questions.[26] Although guidelines on use of opioids for chronic pain are available, most recommendations are based on weak or limited evidence.[9, 27] The increase in use of long-term opioid therapy for chronic pain, new information concerning harms associated with long-term opioid therapy, continued wide variations in practice related to long-term opioid therapy, and the availability of new evidence underscore the need for a current systematic review in this area.

The purpose of this report is to systematically review the current evidence on long-term opioid therapy for chronic pain, which will be used by the National Institutes of Health (NIH) to inform a Pathways to Prevention Workshop on the role of opioids in the treatment of chronic pain. Although guidelines have been published from the American Pain Society (APS)/

American Academy of Pain Medicine,[9] the Veterans Affairs (VA)/Department of Defense,[28] and other groups, the availability of new evidence warrants a new systematic review that could be used to inform updated or new guidelines, guide quality improvement efforts, and define and update priorities for further research in this area.[26] This review updates a prior systematic review on opioid therapy for chronic pain funded by the APS.[29] Differences between this review and the 2009 APS review are that it focuses specifically on benefits and harms associated with long-term use of opioid therapy and evaluates an additional Key Question on dose escalation versus maintenance of doses in patients on long-term opioid therapy, additional outcomes (e.g., cardiovascular events, infection, and psychological outcomes), and additional risk mitigation strategies (e.g., abuse-deterrent formulations and use of data from prescription drug monitoring programs).

Scope of Review and Key Questions

The Key Questions and analytic framework (Figure 1) used to guide this report are shown below. The analytic framework shows the target populations, interventions, and outcomes that we examined.

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 (≥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); (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 nonopioid therapies (pharmacological or nonpharmacological) on outcomes related to pain, function, and quality of life?
d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacological or nonpharmacological) versus opioids or nonopioid 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 accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?
b. How do harms vary depending on: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including back pain], 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); 4) the dose of opioids used?

Key Question 3. Dosing Strategies

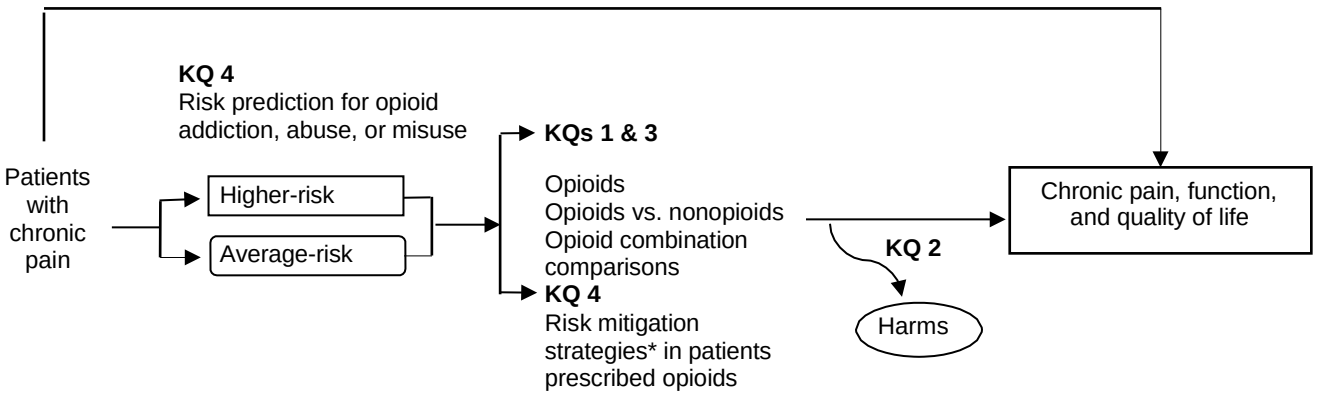
a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids for outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
b. In patients with chronic pain, what is the comparative effectiveness of short- versus long-acting 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 long-acting 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 short- plus long-acting opioids versus long-acting 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?

Figure 1. Analytic framework



KQ, Key Question.

*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.

Methods

The methods for this Comparative Effectiveness Review (CER) follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[30] All methods were determined a priori.

Topic Refinement and Review Protocol

This topic was selected for review based on a nomination from NIH. The initial Key Questions for this CER were developed with input from an NIH working group. The Key Questions and scope were further developed with input from a Technical Expert Panel (TEP) convened for this report. The TEP provided high-level content and methodological guidance to the review process and consisted of experts in health services research, internal medicine, psychology, pain medicine, pharmacology, neurology, occupational medicine, pediatrics, and epidemiology. TEP members disclosed all financial or other conflicts of interest prior to participation. The AHRQ Task Order Officer and the investigators reviewed the disclosures and determined that the TEP members had no conflicts of interest that precluded participation.

The protocol for this CER was developed prior to initiation of the review, and was posted on the AHRQ Web site on December 19, 2013 at: http://effectivehealthcare.ahrq.gov/ehc/products/557/1837/chronic-pain-opioid-treatment-protocol-131219.pdf. The protocol was also registered in the PROSPERO international database of prospectively registered systematic reviews.[31]

Literature Search Strategy

A research librarian conducted searches in Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, PsychINFO, and CINAHL from 2008 to August 2014 (see Appendix A for full search strategies). We restricted search start dates to January 2008 because the searches in the prior APS review, which we used to identify potentially relevant studies, went through October 2008.[29] For outcomes (cardiovascular, infections, and psychological harms) and interventions (abuse-deterrent formulations, and use of prescription monitoring program data) not addressed in the APS review, we searched the same databases and did not apply any search date start restrictions.

We also hand-searched the reference lists of relevant studies and searched for unpublished studies in ClinicalTrials.gov. Scientific information packets (SIPs) with relevant published and unpublished studies were requested from nineteen current application holders from the U.S. Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy (REMS) Extended-Release and Long-Acting (ER/LA) Opioid Analgesics List.[32] We received five SIP submissions.

Study Selection

We developed criteria for inclusion and exclusion of articles based on the Key Questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) approach (Appendix B). Articles were selected for full-text review if they were about long-term opioid therapy for chronic pain, were relevant to a Key Question, and met the predefined inclusion criteria as shown below. We excluded studies published only as conference abstracts, restricted

inclusion to English-language articles, and excluded studies of nonhuman subjects. Studies had to report original data to be included.

Each abstract was independently reviewed for potential inclusion and full-text review by two investigators. Two investigators independently reviewed all full-text articles for final inclusion. Discrepancies were resolved through discussion and consensus. A list of the included articles is available in Appendix C; excluded articles are shown Appendix D with primary reasons for exclusion.

We selected studies of adults (age ≥18 years) with chronic pain (defined as pain lasting >3 months) being considered for long-term opioid therapy (Key Questions 4a and 4b) or prescribed long-term opioid therapy (all other Key Questions). We defined long-term opioid therapy as use of opioids on most days for >3 months; this threshold was selected to differentiate ongoing opioid therapy (as often used for chronic pain) from short-term therapy. We included studies that did not explicitly report the duration of pain if the average duration of opioid therapy was >3 months. We included studies that did not explicitly report the duration of opioid therapy if patients were prescribed long-acting opioids, as these are not typically prescribed for short-term use. We included studies with patients with chronic pain related to current or previously treated cancer, but excluded studies with patients with pain at end of life (e.g., patients with cancer in hospice care). We excluded studies with patients with acute pain, pregnant or breastfeeding women, and patients treated with opioids for addiction.

We included studies of patients prescribed any long- or short-acting opioid used as long-term therapy, either alone or in combination with another agent (Key Question 1d). We included tapentadol, a dual mechanism medication with strong opioid mu-receptor affinity, but excluded tramadol, which is also a dual mechanism medication but with weak opioid mu-receptor affinity that has not been identified as a cause of unintentional prescription drug overdose deaths.[33] We also excluded studies of parenteral opioids.

We included studies that compared long-term opioid therapy versus placebo, no therapy, or another drug or nondrug therapy; studies that evaluated different dose initiation, titration, or rotation strategies; studies of different methods for tapering or discontinuing opioids; studies on methods for treating acute exacerbations of pain in people with chronic pain; and studies on various risk mitigation strategies for reducing harms associated with opioids. Risk mitigation strategies included 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. We also included studies that compared the predictive accuracy of risk prediction instruments in people with chronic pain prior to initiation of opioids for predicting outcomes related to future misuse, abuse, or addiction, and studies on the effects of risk prediction instruments on clinical outcomes.

Outcomes were pain (intensity, severity, bothersomeness), function (physical disability, activity limitations, activity interference, work function), quality of life (including depression), and doses of opioids used. Evaluated harms included overdose, opioid use disorder, addiction, abuse, and misuse, as well as other opioid-related harms (including gastrointestinal, fractures, falls, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms [e.g., depression]). We focused on outcomes reported after at least 1 year of opioid therapy, with the exception of outcomes related to overdose and injuries (fractures, falls, and motor vehicle accidents), studies on treatment of acute exacerbations of chronic pain, studies on dose initiation and titration, and studies on discontinuation of opioid therapy, for which we included studies of any duration.

For all Key Questions, we included randomized trials and controlled observational studies (cohort studies, cross-sectional studies, and case-control studies) that performed adjustment on potential confounders. We included uncontrolled observational studies of patients with chronic pain prescribed opioid therapy for at least 1 year that reported abuse, misuse, or addiction as a primary outcome and described predefined methods to assess these outcomes. Otherwise, we excluded uncontrolled observational studies, case series, and case reports. We reviewed systematic reviews for potentially relevant references.

Data Extraction

We extracted the following information from included studies into evidence tables using Excel spreadsheets: study design, year, setting, inclusion and exclusion criteria, population characteristics (including sex, age, race, pain condition, and duration of pain), sample size, duration of followup, attrition, intervention characteristics (including specific opioid and formulation, dose, and duration of therapy), results, and funding sources.

For studies on the predictive accuracy of risk prediction instruments, we attempted to create two-by-two tables from information provided (sample size, prevalence, sensitivity, and specificity) and compared calculated measures of diagnostic accuracy based on the two-by-two tables with reported results. We noted discrepancies between calculated and reported results when present. When reported, we also recorded the area under the receiver operating characteristic curve (AUROC).[34, 35]

For studies of interventions, we calculated relative risks (RR) and associated 95 percent confidence intervals (CI) based on the information provided (sample sizes and incidence of outcomes of interest in each intervention group). We noted discrepancies between calculated and reported results when present.

Data extraction for each study was performed by two investigators. The first investigator extracted the data, and the second investigator independently reviewed the extracted data for accuracy and completeness.

Assessing Methodological Risk of Bias of Individual Studies

We assessed risk of bias (quality) for each study using predefined criteria. We used the term "quality" rather than the alternate term "risk of bias;" both refer to internal validity. Randomized trials were evaluated with criteria and methods developed by the Cochrane Back Review Group.[36] Cohort studies, case-control studies, and cross-sectional studies were rated using criteria from the U.S. Preventive Services Task Force.[37] Risk prediction instrument studies were rated using criteria from various sources.[38-40] These criteria were applied in conjunction with the approach recommended in the chapter, Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions,[41] in the AHRQ Methods Guide. Studies of predictive accuracy of risk prediction instruments were assessed using an approach adapted from the AHRQ Methods Guide for Medical Test Reviews,[38] which is based on methods developed by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) group.[39] We reassessed the quality of studies included in the prior APS review to ensure consistency in quality assessment. Two investigators independently assessed the quality of each study. Discrepancies were resolved through discussion and consensus.

Individual studies were rated as having "poor," "fair," or "good" quality. We rated the quality of each randomized trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; whether attrition was

adequately reported and acceptable; similarity in use of cointerventions; compliance to allocated treatments; the use of intent-to-treat analysis; and avoidance of selective outcomes reporting.[36, 37]

We rated the quality of each cohort study based on whether it enrolled a consecutive or random sample of patients meeting inclusion criteria; whether it evaluated comparable groups; whether rates of loss to followup were reported and acceptable; whether it used accurate methods for ascertaining exposures, potential confounders, and outcomes; and whether it performed adjustment for important potential confounders.[37] For cross-sectional studies, we used criteria for cohort studies, but did not rate criteria related to loss to followup. For uncontrolled studies on risk of abuse or related outcomes, we evaluated whether it enrolled a consecutive or random sample, whether outcome assessors were blinded to patient characteristics, whether rates of loss to followup were reported (for longitudinal studies) and acceptable, and whether pre-specified outcomes were assessed in all patients.

We rated the quality of each case-control study based on whether it enrolled a consecutive or random sample of cases meeting predefined criteria; whether controls were derived from the same population as cases; whether cases and controls were comparable on key prognostic factors; whether it used accurate methods to ascertain outcomes, exposures, and potential confounders; and whether it performed adjustment for important potential confounders.[37]

We rated the quality of each study on the predictive value of risk prediction instruments based on whether it evaluated a consecutive or random sample of patients meeting pre-defined criteria, whether the patient population evaluated in the study was adequately described, whether the screening instrument included appropriate criteria, and whether outcomes were assessed in all patients independent of the results of the risk assessment instrument using adequately described methods.[38, 39] We also evaluated whether the study was to develop a risk prediction instrument or to validate a previously developed instrument.[40]

Studies rated "good quality" were considered to have the least risk of bias and their results are likely to be valid. Studies rated "fair quality" have some methodological shortcomings, but no flaw or combination of flaws judged likely to cause major bias. In some cases, the article did not report important information, making it difficult to assess its methods or potential limitations. The moderate risk of bias category is broad and studies with this rating vary in their strengths and weaknesses; the results of some studies assessed to have moderate risk of bias are likely to be valid, while others may be only possibly valid. Studies rated "poor quality" have significant flaws that may invalidate the results. They have a serious or "fatal" flaw or combination of flaws in design, analysis, or reporting; large amounts of missing information; or serious discrepancies in reporting. The results of these studies are at least as likely to reflect flaws in the study design as the differences between the compared interventions. We did not exclude studies rated as having high risk of bias a priori, but they were considered the least reliable when synthesizing the evidence, particularly when discrepancies between studies were present.

Assessing Research Applicability

We recorded factors important for understanding the applicability of studies, such as whether the publication adequately described the study sample, the country in which the study was conducted, the characteristics of the patient sample (e.g., age, sex, race, pain condition, duration or severity of pain, medical comorbidities, and psychosocial factors), the characteristics of the interventions used (e.g., specific opioid, dose, mode of administration, or dosing strategy), the clinical setting (e.g., primary care or specialty setting), and the magnitude of effects on clinical outcomes.[42] We also recorded the funding source and role of the sponsor. We did not assign a

rating of applicability (such as high or low) because applicability may differ based on the user of the report.

Evidence Synthesis and Rating the Body of Evidence

We constructed evidence tables summarizing study characteristics, results, and quality ratings for all included studies. We summarized evidence for each Key Question qualitatively used a hierarchy-of-evidence approach, where the best evidence was the focus of our synthesis for each Key Question. In the evidence tables, we included relevant studies from the prior APS review as well as new studies meeting inclusion criteria. Results were organized by Key Question. We did not attempt meta-analyses because of the small number of studies available for each Key Question; variability in study designs, patient samples, interventions, and measures; and methodological shortcomings in the available studies.

We assessed the overall strength of evidence (SOE) for each Key Question and outcome using the approach described in the AHRQ Methods Guide.[30] We synthesized the quality of the studies; the consistency of results within and between study designs; the directness of the evidence linking the intervention and health outcomes; and the precision of the estimate of effect (based on the number and size of studies and CIs for the estimates). We were not able to formally assess for publication bias due to small number of studies, methodological shortcomings, or differences across studies in designs, measured outcomes, and other factors. Rather, as described above, we searched for unpublished studies through searches of clinical trials registries and regulatory documents and by soliciting SIPs.

The SOE was based on the overall quality of each body of evidence, based on the risk of bias (graded low, moderate, or high); the consistency of results across studies (graded consistent, inconsistent, or unable to determine when only one study was available); the directness of the evidence linking the intervention and health outcomes (graded direct or indirect); and the precision of the estimate of effect, based on the number and size of studies and CIs for the estimates (graded precise or imprecise). We did not grade supplemental domains for cohort studies evaluating intermediate and clinical outcomes because too few studies were available for these factors to impact the SOE grades.

We graded the SOE for each Key Question using the four key categories recommended in the AHRQ Methods Guide.[30] A “high” grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect. A “moderate” grade indicates moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate. A “low” grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. An “insufficient” grade indicates evidence either is unavailable or is too limited to permit any conclusion, due to the availability of only poor-quality studies, extreme inconsistency, or extreme imprecision.

Peer Review and Public Commentary

Experts in chronic pain and opioid therapy, as well as individuals representing important stakeholder groups, were invited to provide external peer review of this CER. The AHRQ Task Order Officer and a designated EPC Associate Editor also provided comments and editorial review. To obtain public comment, the draft report was posted on the AHRQ Web site for 4 weeks. A disposition of comments report detailing the authors' responses to the peer and public

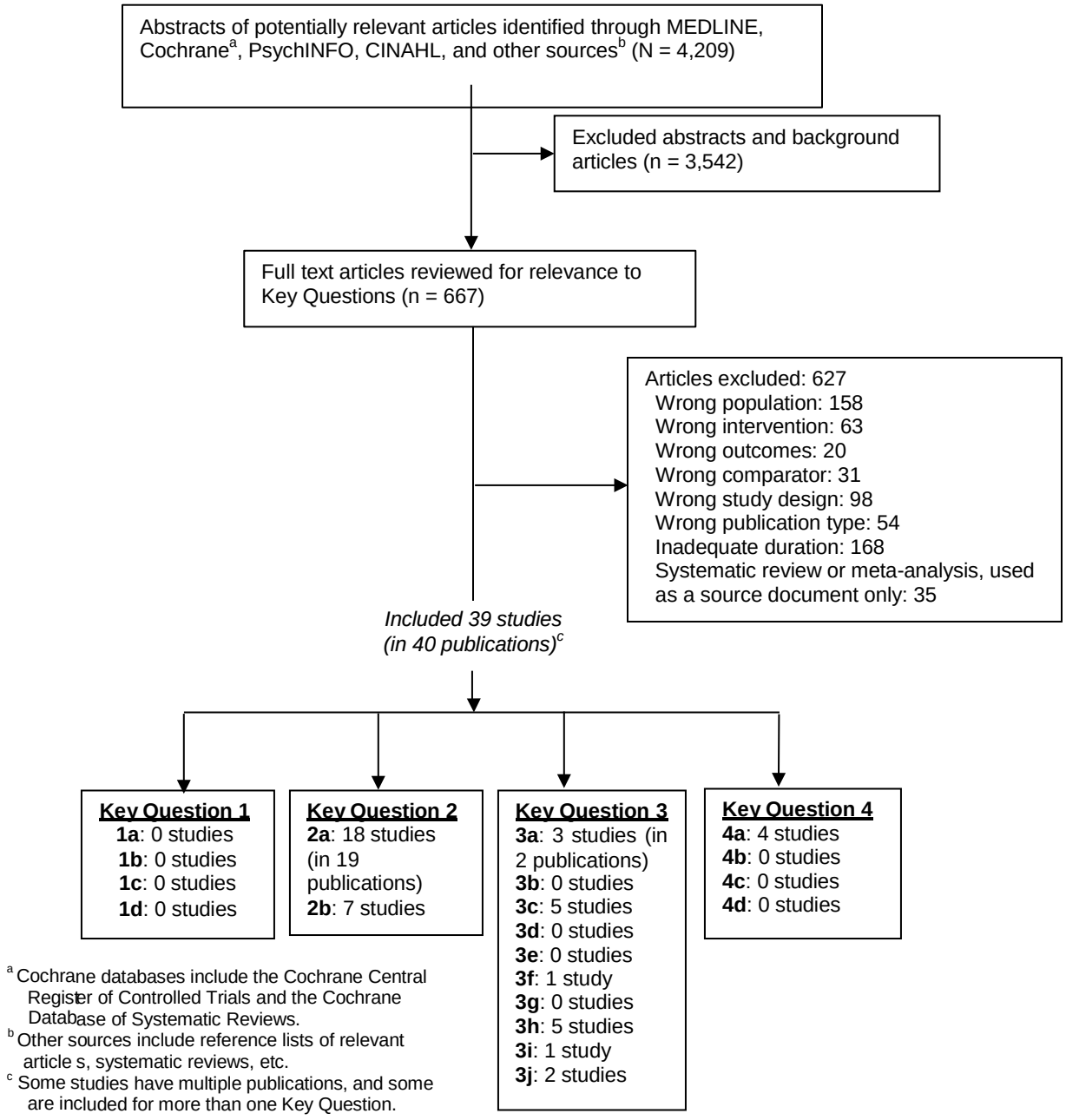
review comments will be made available after AHRQ posts the final CER on the public Web site.

Results

Overview

The search and selection of articles are summarized in the study flow diagram (Figure 2). Database searches resulted in 4,209 potentially relevant articles. After dual review of abstracts and titles, 667 articles were selected for full-text review, and 39 studies (in 40 publications) were determined by dual review at the full-text level to meet inclusion criteria and were included in this review. Data extraction and quality assessment tables for all included studies per Key Question are available in Appendixes E and F.

Figure 2. Literature flow diagram



Key Question 1a

In patients with chronic pain, what is the effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (≥1 year) outcomes related to pain, function, and quality of life?

Key Points

- No study of opioid therapy versus placebo or no opioid therapy evaluated long-term (≥1 year) outcomes related to pain, function, or quality of life (SOE: Insufficient).

Detailed Synthesis

All studies in the 2009 APS review evaluated outcomes related to pain, function, and quality of life at less than 1 year (typically at ≤12 weeks) and did not meet inclusion criteria for the current review. We also identified no studies published since the 2009 APS review that met inclusion criteria. Although a systematic review[8] of long-term opioid therapy included 10 studies of oral opioids and five studies of transdermal opioids that evaluated outcomes after at least 6 months, all were case series or uncontrolled long-term continuations of patients enrolled in clinical trials, with the exception of one head-to-head randomized trial that compared two long-acting opioids (see Key Question 3c).[43] In the systematic review, the pooled estimate for discontinuation due to insufficient pain relief was 10.3 percent (95 percent CI 7.6 to 13.9 percent) with oral opioids and 5.8 percent (95 percent CI 4.2 to 7.9) with transdermal opioids. Among patients who remained on oral opioids for at least 6 months, pain scores were generally reduced, but estimates varied substantially. Effects on quality of life and functional status were inconclusive. Findings of this review are difficult to interpret due to the lack of a nonopioid comparison group in the included studies, marked statistical heterogeneity, and other methodological shortcomings of the studies.

Key Question 1b

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); (3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for addiction)?

Key Points

- No study met inclusion criteria (see Key Question 1a) (SOE: Insufficient).

Detailed Synthesis

No study met inclusion criteria (see Key Question 1a). Although one systematic review[44] reported similar short-term effects of opioids versus placebo on improvement in pain scores for

nociceptive (31 studies) and neuropathic (13 studies) pain, the studies included in the review did not meet inclusion criteria due to the short duration of followup. In the review, 61 of 62 included randomized trials were 16 weeks or shorter in duration, and the other trial was 24 weeks. There were too few trials of fibromyalgia (two studies) or mixed pain conditions (one study) to reliably estimate effects of opioids for these pain conditions.

Key Question 1c

In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacological or nonpharmacological) on outcomes related to pain, function, and quality of life?

Key Points

- No study met inclusion criteria (SOE: Insufficient).

Detailed Synthesis

We identified no study on the comparative effectiveness of long-term opioid therapy versus nonopioid therapies on long-term outcomes related to pain, function, and quality of life.

Key Question 1d

In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacological or nonpharmacological) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?

Key Points

- No study met inclusion criteria (SOE: Insufficient).

Detailed Synthesis

We identified no study on the comparative effectiveness of long-term opioid therapy plus nonopioid interventions versus opioids or nonopioid interventions alone on long-term outcomes related to pain, function, and quality of life.

Key Question 2a

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 accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?

Key Points

- One fair-quality retrospective review of a large database of claims from commercial health plans found long-term (≥91 days supply) prescribed opioid use associated with significantly increased risk of opioid abuse or dependence diagnosis versus no opioid use (1-36 MED/day: OR 15, 95 percent CI 10 to 21; 36-120 MED/day: OR 29, 95 percent CI 20 to 41; ≥120 MED/day: OR 122, 95 percent CI 73 to 206) (SOE: Low).
- In 10 uncontrolled studies, estimates of opioid abuse, addiction, and related outcomes varied substantially even after stratification by clinic setting. Rates of diagnosed opioid abuse were 0.6 percent to 8 percent and rates of dependence were 3 percent to 26 percent in primary care settings. In pain clinic settings, rates of misuse were 8 to 16 percent and addiction 2 to 14 percent, but studies varied in methods used to define and ascertain outcomes. Rates of (variably-defined) aberrant drug-related behaviors (e.g., positive urine drug tests, medication agreement violations) ranged from 5.7 percent to 37.1 percent (SOE: Insufficient).
- One fair-quality retrospective cohort study found recent opioid use to be associated with increased risk of any overdose events (adjusted hazard ratio [HR] 5.2, 95 percent CI 2.1 to 12) and serious overdose events (adjusted HR 8.4, 95 percent CI 2.5 to 28) versus current nonuse in chronic pain patients who had received opioids at some point (SOE: Low).
- One fair-quality cohort study and one good-quality case-control study found use of opioids to be associated with increased risk of fracture (adjusted HR 1.28, 95 percent CI 0.99 to 1.64 and adjusted OR 1.27, 95 percent CI 1.21 to 1.33) though the estimate was not statistically significant in the cohort study and the risk was no longer present with more than 20 cumulative prescriptions in the other (SOE: Low).
- One good-quality case-control study found current opioid use versus nonuse to be associated with increased risk of myocardial infarction (adjusted OR 1.28, 95 percent CI 1.19 to 1.37). The risk was highest with 11 to 50 cumulative prescriptions (OR 1.38, 95 percent CI 1.28 to 1.49). A fair-quality cohort study found chronic opioid therapy, compared to the general population, to be associated with increased risk of myocardial infarction (adjusted incidence rate ratio [IRR] 2.66, 95 percent CI 2.30 to 3.08) and of myocardial infarction or revascularization (adjusted IRR 2.38, 95 percent CI 2.15 to 2.63) (SOE: Low).
- One fair-quality cross-sectional study of men with back pain (n=11,327) found long-term opioid use versus nonuse of opioids to be associated with increased risk for use of

medications for erectile dysfunction or testosterone replacement (adjusted OR 1.5, 95 percent CI 1.1 to 1.9) (SOE: Low)

- No study evaluated the association between long-term opioid therapy for chronic pain versus no opioid therapy and risk of motor vehicle accidents, infections, psychological harms, or cognitive harms.

Detailed Synthesis

Opioid Abuse, Addiction, and Related Outcomes

The 2009 APS review included two systematic reviews on use of opioids for chronic pain and rates of opioid abuse, addiction, or related outcomes.[45, 46] One systematic review that restricted inclusion to studies with at least 1 year of followup reported signs of opioid addiction in 0.27 percent of patients prescribed opioids in studies that reported this outcome.[45] However, none of the studies met inclusion criteria for the current review because addiction was not the primary outcome and they did not describe pre-specified methods for defining or ascertaining these outcomes. The other systematic review focused on patients with low back pain and reported rates of aberrant medication-taking behaviors that ranged from 5 to 24 percent.[46] The studies did not meet inclusion criteria for the current review because they did not include patients with at least 1 year of followup, did not clearly separate abuse and addiction related to opioid use versus other substances, or did not report pre-specified methods for the outcomes, with the exception of one retrospective cohort study.[47] It reported rates of opioid abuse behaviors in patients with chronic pain in primary care settings, based on chart review findings of one or more reports of lost or stolen opioid medications, documented use of other sources to obtain opioid medications, or requests for two or more early refills. Rates of opioid abuse behaviors were 24 percent (12/50) in a VA primary care setting and 31 percent (15/48) in a non-VA, urban hospital-based primary care setting. Factors associated with decreased risk of opioid abuse behaviors were no history of substance use disorder (adjusted OR 0.72, 95 percent CI 0.45 to 1.1) and older age (adjusted OR 0.94, 95 percent CI 0.94 to 0.99).

We identified no randomized trial published since the APS review on risk of opioid abuse, addiction, and related outcomes in patients with chronic pain prescribed long-term opioid therapy. One fair-quality retrospective study of patients in a large administrative database newly diagnosed with chronic (non-cancer) pain and followed for 18 months found prescribed long-term opioid use (receipt of ≥91 days' supply of opioids within a 12-month period), versus no prescribed opioids, associated with increased risk of opioid use disorder (defined as opioid abuse and dependence based on ICD-9 codes) (Appendix E1 and F1).[48] Rates of opioid abuse or dependence were 0.72, 1.28 and 6.1 percent in those prescribed low (1-36 mg MED/day), medium (36-120 mg MED/day) and high (≥120 mg MED/day) opioid doses, respectively, during the 12 months after the new chronic pain diagnosis, versus 0.004 percent in those with no opioid prescription. Compared to no opioid prescription and after adjustment for age, sex, history of substance abuse/dependence diagnosis and other comorbidities, chronic opioid use was associated with significantly increased risk of abuse or dependence for all doses of opioids (low dose: OR 15, 95 percent CI 10 to 21; medium dose: OR 29, 95 percent CI 20 to 41; high dose: OR 122, 95 percent CI 73 to 206).

Ten additional uncontrolled studies (in 11 publications) of patients with chronic pain, the majority of whom were prescribed opioids for at least 1 year, evaluated abuse and related outcomes as a primary outcome using explicit, predefined criteria (Table 1 below; Appendix E1

and F2).[49-58] All were rated fair-quality; none of the studies reported blinding of outcome assessors to patient characteristics, such as risk factors for substance abuse or psychological comorbidities. Another shortcoming in some studies was failure to assess the predefined outcomes in all patients.

Four of the new studies were performed exclusively or primarily in U.S. primary care settings.[47, 49, 50, 53] One study[53] found that 0.6 percent of primary care clinic patients receiving daily prescription opioids (96 percent for more than a year; total n=801) met the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for opioid abuse disorder and 3.1 percent for opioid dependence, based on formal diagnostic interviews. Behaviors indicative of opioid misuse were more common. Thirty-seven percent reported increasing doses on their own, 33 percent feeling intoxicated from pain medication, 24 percent purposeful over-sedation, 16 percent using opioids for purposes other than pain management, and 20 percent drinking alcohol to relieve pain. Twenty-four percent of patients had urine drug screens positive for illicit drugs (mostly cannabinoids).[53] A retrospective study of chronic pain patients receiving long-term opioid therapy in an integrated managed care health system (n=704) found that 13 percent met DSM-IV criteria for opioid dependence and 8 percent met criteria for opioid abuse without dependence, based on structured phone interviews.[49] Another study, which performed diagnostic interviews in 9 primary care and 3 specialty clinics with patients who received 4 or more opioid prescriptions over a year (n=705), found that 26 percent met DSM-IV criteria for current opioid dependence.[50] In multivariate logistic regression models, factors associated with current opioid dependence were age less than 65 years (OR 2.3, 95 percent CI
1.6 to 3.5), history of opioid abuse (OR 3.8, 95 percent CI 2.6 to 5.7), higher lifetime opioid dependence severity (OR 1.9, 95 percent CI 1.4 to 2.5), history of major depression (OR 1.3, 95 percent CI 1.1 to 1.6), and current use of psychotropic medications (OR 1.7, 95 percent CI 1.2 to 2.5). Rates of opioid abuse or misuse behaviors were not reported.

Six other studies were performed in pain clinic settings. Pain clinics may have a higher proportion of patients with opioid abuse and related problems because of referral patterns. Despite initial screening to exclude current substance abuse on entry, one study from a VA pain clinic found that after 1 year of followup, 28 percent of patients prescribed opioids (n=135) were discontinued from the clinic because of medication agreement violations.[51] Among these were 8 percent with specific opioid misuse behaviors such as unsanctioned dose increases or use of opioids other than those prescribed. In a cross-sectional study of Danish pain clinic patients with cancer and noncancer pain (mean duration of opioid use among those taking opioids = 6.8 years),14.4 percent of those using opioids (n=187) met International Classification of Diseases (ICD-10) criteria for "addiction to opioids," which correspond most closely to the DSM-IV criteria for opioid abuse.[54] A cross-sectional study of UK NHS hospital pain clinic patients who had been prescribed opioids (n=104) found that 1.9 percent of the patients self-reported addiction using the Substance Use Questionnaire, 2.9 percent reported that they had craved opioids and 0.9 percent reported that they used alcohol to enhance the effects of opioids.[52] A prospective registry study of patients who had participated in five clinical trials of CR oxycodone and who continued to take this medication (n=227) found that 5.7 percent of the patients were identified by their physicians as exhibiting problematic drug-related behaviors, based on a brief physician- completed questionnaire.[55] However, verification by an independent panel resulted in a lower rate of 2.2 percent. A chart review conducted in a single pain clinic (n=197) reported that 15.7 percent of patients had aberrant drug-related behaviors noted in their charts and 8.7 percent had positive urine drug tests.[57] Finally, a cross-sectional study of patients attending five pain clinics (n=622) 0 found that 37.1 percent had positive urine drug tests (defined as presence of an illicit substance or unprescribed opioid), while 24 percent had positive scores $\geq$2 (the cutoff for "high risk") on the Prescription Opioid Therapy

Questionnaire and 29.1 percent had scores ≥11 (the cutoff for "at risk") on the Prescription Drug Use Questionnaire.[58]

A challenge in interpreting the evidence on rates of opioid abuse, addiction, and related outcomes is inconsistency in how these outcomes were defined, as well as variability in methods used to ascertain these outcomes. In addition, definitions and usage of these terms have changed over time. The studies described above were all conducted prior to the American Psychiatric Association's new DSM-V[59] diagnostic criteria for current opioid use disorder.

Overall, because of methodological limitations in the available studies and because estimates for opioid abuse, addiction, and related outcomes were highly variable even after stratifying by clinical setting, the SOE was rated Insufficient.

Table 1. Uncontrolled studies of long-term opioid use and abuse, misuse, and related outcomes

Author, Year Duration, If Applicable	Sample Characteristics Opioid Dose, Opioid Duration, and Pain Type	Method of Ascertaining and Defining Abuse/Misuse	Main Results
Banta-Green, 2009[49] Cross-sectional	n=704 Integrated group practice patients in a nonprofit healthcare system in Washington State Mean age: 55 years Female sex: 62% Race: 89% non-Hispanic White Dose: mean 50 mg/day MED, past year Duration: NR Pain type: NR	Composite International Diagnostic Interview (CIDI) for DSM-IV opioid diagnoses	Opioid dependence: 13% (91/704) Opioid abuse without dependence: 8% (56/704)
Boscarino, 2010[50] Cross-sectional	n=705 Primary and specialty care patients in integrated healthcare system in Pennsylvania who received 4+ opioid prescriptions in past 12 months Age: 18-64 years: 79% 65+ years: 21% Female sex: 61% White race: 98% Dose: NR Duration: mean of 10.7 opioid prescriptions over 1 year Pain type: non-cancer, otherwise not described	Composite International Diagnostic Interview (CIDI) for DSM-IV criteria for opioid dependence UDT: not examined	25.8% (95% CI: 22.0-29.9) met criteria for current opioid dependence; 35.5% (95% CI: 31.1-40.2) met criteria for lifetime dependence Factors associated with current dependence: Age <65 years (OR 2.3, 95% CI 1.6 to 3.5) History of opioid abuse (OR 3.8, 95% CI 2.6 to 5.7) History of high dependence severity (OR 1.9, 95% CI 1.4 to 2.5) History of major depression (OR 1.3, 95% CI 1.1 to 1.6) Current use of psychotropic medications (OR 1.7, 95% CI 1.2 to 2.5)

Table 1. Uncontrolled studies of long-term opioid use and abuse, misuse, and related outcomes (continued)

Author, Year Duration, If Applicable	Sample Characteristics Opioid Dose, Opioid Duration, and Pain Type	Method of Ascertaining and Defining Abuse/Misuse	Main Results
Carrington Reid, 2002[47] Retrospective cohort	n=98 (50 at VA and 48 at urban primary care clinic) patients with 6+ months of opioid prescriptions during 1 year VA primary care clinic vs. urban hospital primary care clinic Median age: 54 vs. 55 years Female sex: 8% vs. 67% Race: 88% White, 12% Black vs. 52% White, 36% Black, 10% Hispanic Median duration of pain: 10 vs. 13 years Dose: NR Duration: 6+ months of opioid prescriptions during past year Pain type: Non-cancer, Various (low back 44% vs 25%)	Chart review for reports of lost or stolen opioids, documented use of other sources to obtain opioids, and requests for ≥2 early refills UDT: not examined	VA site vs. urban primary care site Opioid abuse behaviors: 24% (12/50) vs. 31% (15/48) Median time to onset of abuse behaviors: 24 months Factors associated with odds of opioid abuse behaviors: History of substance use disorder (adjusted OR 3.8, 95% CI 1.4 to 10.8) Age (adjusted OR 0.4, 95% CI 0.9 to 1.0) Number of medical diseases (adjusted OR 0.7, 95% CI 0.5-1.1)
Compton, 2008[51] 1 year	n=135 veterans at a VA pain clinic Mean age: 53 years Female sex: 6% Race: NR Baseline mean usual pain VAS (0-10) rating: 6.75 Dose: NR Duration: NR Pain type: 77% musculoskeletal, 19% neuropathic, 4% multi-category	Chart review for opioid discontinuation due to medication agreement violation (including for opioid misuse or abuse) UDT: not examined	Discontinuation due to medication agreement violation: 28% (38/135) Discontinuation due to specific problematic opioid misuse behaviors: 8% (11/135)
Cowan, 2003[52] Cross-sectional	n=104 patients who had been prescribed opioids at a pain clinic in a UK NHS hospital Mean age: 55.4 years Female sex: 39% Race: NR Mean duration of pain: 10.5 years Dose: NR Duration: mean 14.1 months; 57% of the 104 patients had permanently stopped opioid therapy Pain type: 34% degenerative disease other than OA, 24% failed back/neck surgery syndrome, 10% complex regional pain syndrome, 10% osteoarthritis	SUQ UDT: not examined	Self-reported addiction: 1.9% (2/104) Craving opioids: 2.9% (3/104) Has taken drugs to enhance the effect of opioids: 0.9% (1/104) Has used alcohol to enhance the effect of opioids: 0.9% (1/104)

Table 1. Uncontrolled studies of long-term opioid use and abuse, misuse, and related outcomes (continued)

Author, Year Duration, If Applicable	Sample Characteristics Opioid Dose, Opioid Duration, and Pain Type	Method of Ascertaining and Defining Abuse/Misuse	Main Results
Fleming, 2007[53] See also: Saffier, 2007[56] Cross-sectional	n=801 primary care patients on daily opioid therapy Mean age: 48.6 years Female sex: 68% Race: 75.6% White; 23.1% African American; 1% other Disability income: 48% Mean daily dose: 92 mg MED Duration: 96% prescribed COT for ≥12 mos. Pain type: Degenerative aarthritis: 24%; low back pain: 21%; migraine headache 8%; neuropathy 5.5%	In-person interviews with Addiction Severity Index (ASI); Substance Dependence Severity Scale (SDSS); Aberrant Behavior 12-item List UDT: sample collected at end of interview	Met DSM-IV criteria for opioid dependence: 3.1% Met DSM-IV criteria for opioid abuse: 0.6% Any illicit drug on UDT: 24% (mostly marijuana) Purposely over-sedated: 24% (186/785) Felt intoxicated from pain medication: 33% (260/785) Requested early refills: 45% (359/785) Increased dose on own: 37% (288/785) Medications lost or stolen: 30% (236/785) Used opioid for purpose other than pain: 16% (125/785) Drank alcohol to relieve pain: 20% (154/785)
Hojsted, 2010[54] Cross-sectional	n=253 patients at a pain clinic (236 non-cancer and 17 cancer pain) Mean age: 52 years Female sex: 64% Race: NR Receiving opioids: 74% (187/253) Dose: Median daily dose = 90 mg MED among those taking opioids Duration: mean 6.8 years among those taking opioids who returned a questionnaire Pain type: 28% nociceptive pain, 33% neuropathic pain, 39% mixed nociceptive and neuropathic	Addiction screening by physician and nurse (blinded to each other) using the ICD-10 and Portenoy's Criteria; a positive screen by either provider was considered positive UDT: not examined	Addiction to opioids or hypnotics, ICD-10: total sample 11% (28/253); among those taking addictive drugs 13%; among those taking opioids 14% Addiction to opioids, ICD-10, among those taking opioids: 14.4% (27/187) Addiction to opioids or hypnotics, Portenoy's Criteria. among those taking opioids: 19% (36/187) Addiction to opioids, Portenoy's Criteria: 19% (36/187)
Portenoy, 2007[55] 3 years	n=227 patients enrolled in a registry study of patients who had participated in a previous controlled clinical trial of CR oxycodone for noncancer pain and who continued to take CR oxycodone Mean age: 56 years Female sex: 57% Race: 90% White BPI average pain score: 6.4 Dose: mean 52.5 mg MED/day Duration: mean 541 days Pain type: 38% osteoarthritis pain, 31% diabetic neuropathy, 31% low back pain	Physician-completed brief questionnaire assessing problematic drug-related behavior with verification by an independent panel of experts UDT: not examined	Problematic drug-related behavior identified by physicians: 5.7% (13/227) Problematic drug-related behavior adjudicated by expert panel as meeting DSM-IV criteria for drug abuse or dependence: 0 Problematic drug-related behavior adjudicated by expert panel as positive: 2.2% (5/227) Problematic drug-related behavior adjudicated by expert panel as possible: 0.4% (1/227) Problematic drug-related behavior adjudicated by expert panel as withdrawal but no indication of abuse: 0.4% (1/227) Problematic drug-related behavior adjudicated by expert panel as suspected abuse/dependence but insufficient information to draw definitive conclusion: 2.2% (5/227) Problematic drug-related behavior

Table 1. Uncontrolled studies of long-term opioid use and abuse, misuse, and related outcomes (continued)

Author, Year Duration, If Applicable	Sample Characteristics Opioid Dose, Opioid Duration, and Pain Type	Method of Ascertaining and Defining Abuse/Misuse	Main Results
			adjudicated by expert panel as no evidence of abuse, dependence, or euphoria: 0.4% (1/227) Overdose deaths: 1 (phenylpropanolamine, oxycodone, and alcohol)

Table 1. Uncontrolled studies of long-term opioid use and abuse, misuse, and related outcomes (continued)

Author, Year Duration, If Applicable	Sample Characteristics Opioid Dose, Opioid Duration, and Pain Type	Method of Ascertaining and Defining Abuse/Misuse	Main Results
Schneider, 2010[57] Retrospective chart review	n=197 patients treated by a pain specialist for at least one year Mean age: 49 years Female sex: 67% Race: NR Dose: mean 180 mg/day MED (long-acting), 49 mg/day MED (short-acting) Duration: mean 4.7 years Pain type: 51% back pain, 10% neck pain, 9% fibromyalgia, 8% other myofascial pain	UDT: immunoassay followed by confirmatory GC/MS	Positive UDT: 8.7% (14/161) Aberrant drug-related behaviors noted in chart: 15.7% (31/197)
Wasan, 2009[58] Cross-sectional	n=622 chronic noncancer pain patients from pain management centers on long-term opioid therapy Mean age: 50.4 years Female sex: 55% Race: 80% White Mean pain rating (0-10): 5.96 Dose: NR Duration: mean 6.2 years Pain type: 61% low back pain	POTQ, PDUQ, and UDT (immunoassay and confirmatory GCMS)	Positive scores of ≥2 on POTQ: 24% (115/480) Score ≥11 on PDUQ: 29.1% (130/447) Positive UDT: 37.1% (134/356)

Abbreviations: ASI= Addiction Severity Index, CI=confidence interval, CIDI=Composite International Diagnostic Interview, DSM-IV= Diagnostic and Statistical Manual Fifth Edition, GC/MS=gas chromatography mass spectrometry, ICD-10=International Statistical Classification of Diseases and Related Health Problems Version 10, MED=morphine-equivalent dose, NA=not applicable, NR= not reported, OR=odds ratio, PDUQ=Prescription Drug Use Questionnaire, POTQ=Prescription Opioid Therapy Questionnaire, SDSS=Dependence Severity Scale, SUQ=Self-report Substance Use Questionnaire, UDT=urine drug test, VA=Veterans Affairs.

Overdose

The 2009 APS review identified no studies on the risk of overdose in patients with chronic pain prescribed long-term opioid therapy versus placebo or no opioid. Epidemiological studies that reported opioid-related deaths did not have a nonopioid control group, did not have denominators for the numbers of people prescribed opioids, were not designed to distinguish deaths related to prescribed opioids from deaths related to illicit use of opioids, or did not focus on patients on long-term opioid therapy.[60]

We identified one fair-quality retrospective cohort study published since the APS review that reported risk of overdose with opioid use versus nonuse in patients (n=9,940) in a U.S. integrated health care system with a new episode of opioid use (defined as no opioid prescription in the past 6 months), a chronic noncancer pain diagnosis within 2 weeks before the initial opioid prescription, and at least 3 opioid prescriptions in the first 90 days of the episode (Appendix E2 and F1).[61] The mean duration of followup was 42 months, and short-acting opioids were the most frequently prescribed type; only 10 percent of the patients received predominantly long- acting opioids. Overdoses were identified through ICD-9 codes and a State mortality registry, with verification through medical record review. Risk estimates were based on recently dispensed opioids at the time of the overdose event. Therefore, results may be interpreted as risk of overdose with current use versus nonuse in people previously prescribed opioid therapy for several months.

The annual overdose rate was 256 per 100,000 person-years in patients who recently received prescribed opioids versus 36 per 100,000 person-years in people who did not. After adjustment for smoking, depression, substance abuse, comorbid conditions, pain site, age, sex, recent sedative-hypnotic prescription, and recent initiation of opioid use, recent receipt of any prescribed opioids, compared to no opioid receipt, was associated with increased risk of any overdose events (HR 5.2, 95 percent CI 2.1 to 12.5) and serious overdose events (HR 8.4, 95 percent CI 2.5 to 28) (SOE: Low).

Gastrointestinal Harms

The APS review identified no studies on risk of gastrointestinal harms with long-term opioid therapy versus placebo or nonuse, and we identified no studies published since the APS review meeting inclusion criteria. Systematic reviews included in the APS review were based on short-term trials that reported frequent nausea, constipation, and vomiting in patients prescribed opioids.[22, 62, 63]

Fractures

The APS review included a systematic review of six observational studies of the association between opioid use and fracture. All six studies reported a statistically significant association, with a pooled RR of 1.38 (95 percent CI 1.15 to 1.66).[64] The APS review also included a case-control study not in the systematic review that also found use of various opioids to be associated with increased risk of fracture (OR estimates ranged from 1.1 to 2.2).[65] However, none of these studies meet inclusion criteria for the current review, because they did not specifically evaluate patients with chronic pain or on long-term opioid therapy. In addition, the studies had important methodological limitations, including failure to adjust for important confounders. Other studies published since the 2009 APS review also evaluated the association between opioid use and fractures, but did not meet inclusion criteria for similar reasons.[66-70]

We identified one cohort study[18] and one case-control study[71] published since the APS review on the association between opioid use and fracture in patients with chronic pain or on long-term opioid therapy (Appendix E3, F1, and F3). The cohort study identified patients 60 years and older with a diagnosis of noncancer pain initiating a new episode of opioid use (no opioid prescription fills in the prior 6 months) who had at least three opioid prescriptions in the first 90 days of the episode.[18] Patients were followed for a mean of 33 months. The overall annual confirmed nonvertebral fracture rate was 5 percent (6 percent among current opioid users and 4 percent among people not currently using opioids; HR 1.28, 95 percent CI 0.99 to 1.64, adjusted for demographic factors, prior fractures, comorbidities, and concomitant medication use). The most commonly prescribed opioids were hydrocodone (42 percent), oxycodone (24 percent), and codeine combinations (14 percent). The study was rated fair-quality due to failure to report loss to followup and unclear blinding of outcomes assessors.

One good-quality case-control study evaluated 21,739 people with hip, humerus, or wrist fractures from the UK General Practice Research Database and 85,326 nonfracture controls matched on age, sex, date of fracture diagnosis, and practice site.[71] Although the study did not specifically focus on patients with chronic pain, the analysis was stratified by duration of opioid use, based on the cumulative number of opioid prescriptions before the index date. After adjustment for a number of factors, including smoking status, comorbidities, concomitant medications, type of pain, and recent or past opioid use, current opioid therapy was associated with increased risk of fracture versus nonuse (OR 1.27, 95 percent CI 1.21 to 1.33). The risk was

highest with one prescription (OR 2.70, 95 percent CI 2.34 to 3.13) and decreased with higher numbers of prescriptions, with no increased risk for patients with more than 20 cumulative prescriptions, suggesting that increased risk of fracture may be associated with more recent initiation of opioid therapy.

The SOE for the association between opioid use versus non-use and risk of fractures was rated Low.

Motor Vehicle Accidents

The APS review included two systematic reviews[72, 73] (25 and 48 observational studies) and five other observational studies[74-78] on the association between opioid use and driving safety, but none of the studies met inclusion criteria for the current review because they did not report duration of opioid use, included individuals treated for opioid addiction or using opioids illicitly, focused on surrogate markers of driving safety such as simulated driving tests or measures of cognitive performance rather than actual motor vehicle accidents, or did not include a comparison arm of chronic pain patients not prescribed opioids. We identified no studies published since the APS review on risk of motor vehicle accidents in patients with chronic pain on long-term opioid therapy versus no opioid therapy.

Cardiovascular Events

The APS review did not evaluate the association between opioid therapy for chronic pain and risk of cardiovascular events. We identified one cohort study[79] and one case-control study[80] on the association between long-term opioid use for chronic pain and risk of myocardial infarction (Appendix E4, F2, and F3). The cohort study included individuals with claims for opioids or a nonselective cyclo-oxygenase-2 (COX-2) inhibitor over a cumulative period of $\geq$180 days over a 3.5 year period.[79] Individuals were excluded if they had cancer pain or a history of myocardial infarction or cancer and were matched on age, sex and cohort entry date to people in the general population who did not receive $\geq$180 days of opioids or COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs). Compared to the general population, chronic opioid therapy was associated with increased risk of myocardial infarction (adjusted IRR 2.66, 95 percent CI 2.30 to 3.08) and of myocardial infarction or revascularization (adjusted IRR 2.38, 95 percent CI 2.15 to 2.63), after controlling for age, sex, cardiovascular and other comorbidities, and concomitant medication use. The study was rated fair quality because there was no attempt to match patients on pain condition or severity of pain, or to adjust for these factors.

A good-quality case-control study compared 11,693 people with myocardial infarction from the UK General Practice Research Database to 44,897 controls with no myocardial infarction matched on age, sex, index date, and practice site.[80] The most commonly prescribed opioids were codeine, propoxyphene, and dihydrocodeine. Although it did not specifically enroll patients with chronic pain, the study included an analysis stratified by duration of opioid use, based on the number of cumulative opioid prescriptions at the time of myocardial infarction. After adjustment for a number of factors, including smoking status, comorbidities, concomitant medications, type of pain, and recent or past opioid use, it found current opioid therapy use associated with increased risk of myocardial infarction versus nonuse (adjusted OR 1.28, 95 percent CI 1.19 to 1.37). Recent (within 31 to 365 days) use was also associated with increased risk (OR 1.17, 95 percent CI 1.10 to 1.24). The risk was highest with 11 to 50 cumulative prescriptions (OR 1.38, 95 percent CI 1.28 to 1.49) but was statistically significant with 1-2, 3-10, or >50 cumulative prescriptions (OR range 1.09 to 1.25).

The SOE for the association between opioid use versus non-use and risk of myocardial infarction was rated Low.

We identified no study on the association between long-term opioid therapy for chronic pain versus no opioid therapy and risk of arrhythmia or sudden death.

Endocrinological Harms

The APS review included four studies on the effects of oral opioid use on endocrinological effects. One cross-sectional study of women with chronic pain (n=37, mean duration of opioid use 31 months) found no association between opioid use versus nonuse and growth hormone, corticotrophin, cortisol, thyroxine, thyrotropin, prolactin, estradiol, follicle stimulating hormone, luteinizing hormone, or testosterone levels, but did not meet inclusion criteria because it did not adjust for potential confounders.[81] Three other cross-sectional studies found opioid use to be associated with decreased levels of gonadal hormone or dehydroepiandrosterone sulfate in men and women, but it was unclear in two of the studies whether patients had chronic pain, the duration of opioid use was not reported, none of the studies adjusted for potential confounders, and it was unclear how patients were selected, making it difficult to determine whether patients on opioids with signs of sexual or endocrinological dysfunction were preferentially enrolled.[23, 24, 82]

We identified one study published since the APS review on the association between opioid use versus nonuse and endocrinological harms (Appendix E5 and F2).[11] In a cross-sectional analysis of men with back pain (n=11,327) in an integrated health care system, long-term opioid use (defined as $\geq$120 days or >90 days with 10 or more fills), compared with no opioid use, was associated with increased likelihood of use of medications for erectile dysfunction or testosterone replacement (adjusted OR 1.5, 95 percent CI 1.1 to 1.9), after adjustment for age, co-morbidities, hospitalizations, use of sedative-hypnotics, dose of opioids, type of opioid, depression, and smoking status. Median opioid dose in men on chronic opioids was 30 mg morphine equivalent dose (MED)/day (19 percent received $\geq$120 mg) and 42 percent received long-acting opioids. A limitation of this study is that the patient sample was a mix of acute, subacute, and chronic back pain, and the study could not control for duration of pain. In all studies, the cross-sectional design makes it impossible to determine whether endocrinological problems preceded opioid use or resulted from opioid use. One other cross-sectional study published since the prior APS review reported an association between long-term opioid use and laboratory markers of endocrinological dysfunction, but did not meet inclusion criteria because it did not perform adjustment for potential confounders.[83]

The SOE for the association between opioid use versus non-use and risk of endocrinological harms was rated Low.

Other Harms

We identified no studies on the association between long-term opioid therapy for chronic pain versus no opioid use and risk of falls, infections, cognitive harms, or psychological harms. These outcomes were not evaluated in the APS review.

Key Question 2b

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 abuse disorder or at high risk for addiction); (4) the dose of opioids used?

Key Points

- No study evaluated how harms associated with long-term opioid therapy vary depending on the specific type or cause of pain, patient demographics, or patient comorbidities (SOE: Insufficient).
- One fair-quality retrospective database 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 to 21) for 1-36 mg MED/day, 29 (95 percent CI 20 to 41) for 36-120 mg MED/day, and 122 (95 percent CI 73 to 206) for ≥120 mg MED/day (SOE: Low).
- One fair-quality retrospective cohort study and one good-quality nested case-control study found an association between higher doses of long-term opioid therapy and risk of overdose. In the cohort study, versus 1 to 19 mg MED/day, the adjusted HR for an overdose event was 1.44 (95 percent CI 0.57 to 3.62) with 20 to 49 mg MED/day and increased with higher doses to 8.87 (95 percent CI 3.99 to 19.72) for ≥100 mg MED/day. The risk for serious overdose showed a similar pattern, with HRs of 1.19 (95 percent CI 0.4 to 3.6) for 20 to <50 mg MED/day, 3.11 (95 percent CI 1.01 to 9.51) for 50 to 99 mg/day, and 11.18 (95 percent CI 4.80 to 26.03) for ≥100 mg/day (all relative to 1-19 mg/day). In the case-control study, versus 1 to 19 mg MED/day, the adjusted OR for an opioid-related death was 1.32 (95 percent CI 0.94 to 1.84) for 20 to 49 mg MED/day and increased to 2.88 (95 percent CI 1.79 to 4.63) for ≥200 mg MED/day (SOE: Low).
- One fair-quality cohort study found that risk of fracture increased from an adjusted HR of 1.20 (95 percent CI 0.92 to 1.56) at 1 to <20 mg MED/day to 2.00 (95 percent CI 1.24 to 3.24) at ≥50 mg MED/day; the overall test for dose response did not reach statistical significance (P = 0.06) (SOE: Low).
- One fair-quality cohort study found that relative to a cumulative dose of 0 to <1350 mg MED over 90 days, the adjusted IRR for myocardial infarction for 1350 to <2700 mg was 1.21 (95 percent CI 1.02 to 1.45), for 2700 to <8100 mg was 1.42 (95 percent CI 1.21 to 1.67), for 8100 to <18,000 mg was 1.89 (95 percent CI 1.54 to 2.33), and for ≥18,000 mg was 1.73 (95 percent CI 1.32 to 2.26) (SOE: Low).
- One good-quality case-control study found no association between opioid dose and odds of road trauma injury among drivers and passengers.

Doses of opioids >20 mg MED/day were associated with increased odds of road trauma injury when the analysis was restricted to drivers. There was no dose-dependent association at doses higher than 20 mg MED/day. Relative to 1 to <20 mg MED/day, the adjusted odds of road trauma injury among drivers were 1.21 (1.02 to 1.42) for 20 to 49 (1.02 to 1.49) for >200 mg. (SOE: Low).

One fair-quality cross-sectional study of men found a daily opioid dose of ≥120 mg MED/day to be associated with increased odds of use of medications for erectile dysfunction or testosterone replacement versus 0 to <20 mg MED/day (adjusted OR 1.6, 95 percent CI 1.03 to 2.4). Odds were not increased at doses of 20 to <120 mg MED/day (SOE: Low).

Detailed Synthesis

We identified no study on how harms associated with long-term opioid therapy vary depending on the specific type or cause of pain, patient demographics, or patient comorbidities, including those with a history of or at high risk for addiction.

The APS review identified no studies on the association between opioid dose and risk of harms in patients with chronic pain on long-term opioid therapy. We identified six studies published since the APS review on the association between opioid dose and risk of opioid-related deaths or overdose,[61,84] fractures,[18] myocardial infarction,[79] motor vehicle accidents,[20] and endocrinological effects.[11]

Opioid Abuse, Addiction, and Related Outcomes

A previously described (see KQ 2a) fair-quality retrospective database study found a dose-dependent association between dose of long-term opioid therapy for chronic pain and risk of abuse or dependence.[48] Based on ICD-9 diagnosis codes, rates of abuse or dependence were 0.7 percent with low-dose opioids (1-36 mg MED/day), 1.3 percent with medium-dose (36-120 mg MED/day), and 6.1 percent with high-dose (≥120 mg MED/day). Compared to no opioid prescription, the odds ratio for abuse or dependence after adjustment for age, sex, history of substance abuse and other comorbidities was 15 (95 percent CI 10 to 21) for low-dose, 29 (95 percent CI 20 to 41) for medium-dose, and 122 (95 percent CI 73 to 205) for high-dose opioids (Appendix E1) (SOE: Low).

Overdose

Two studies found an association between opioid dose and risk of overdose (Appendix E2, F1, and F3).[61, 84] A previously described (see KQ 2a), fair-quality retrospective cohort study of patients (n=9,940) with recently diagnosed noncancer pain and prescribed opioid therapy followed patients for a mean duration of 42 months.[61] Fifty-one patients experienced overdose events (148 per 100,000 person-years); 40 were serious overdose events (116 per 100,000 person-years) and 6 were fatal overdose events (17 per 100,000 person-years). After adjusting for smoking, depression, substance abuse, comorbid conditions, pain site, age, sex, recent sedative-hypnotic prescription, and recent initiation of opioid use, higher opioid dose was associated with increased risk of any overdose event. Relative to 1 to 19 mg MED/day, 20 to 49 mg/day was associated with a HR of 1.44 (0.57-3.62), 50-99 mg/day with a HR of 3.73 (1.47-9.5), and ≥100 mg/day with a HR of 8.87 (3.99-19.72). The risk for serious overdose showed a similar pattern, with HRs of 1.19 (95 percent CI 0.4 to 3.6) for 20 to 49 mg MED/day, 3.11 (95 percent CI 1.01 to 9.51) for 50 to 99 mg/day, and 11.18 (95 percent CI 4.80 to 26.03) for ≥100 mg/day (all relative to 1-19 mg/day).

A good-quality, population-based, nested case-control study of Canadian patients eligible for publicly funded prescription drug coverage who had received an opioid for noncancer pain identified 498 cases of opioid-associated deaths.[84] Cases were matched on age, sex, index year, the Charlson comorbidity index, and a disease risk index based on comorbidities to 1714 controls. Opioid-associated deaths were identified using coroner records and defined as deaths in which the coroner identified a combination of drugs including at least one opioid or in which forensic toxicology testing showed an opioid concentration sufficiently high to cause death.

Mean duration of opioid use was 5 years in cases and 4 years in controls. Long-acting opioids were dispensed at some point in the exposure period to 46 percent of cases and 30 percent of controls. After adjusting for previous drugs used, number of drugs, duration of opioid treatment, the number of physicians prescribing opioids, the number of pharmacies dispensing opioids, and prescribing of long-acting opioids, higher doses of opioids were associated with increased odds of opioid-associated mortality. Relative to 1 to 19 mg MED/day, the adjusted OR for opioid-associated mortality was 1.32 (95 percent CI 0.94 to 1.84) for 20 to 49 mg/day, 1.92 (95 percent CI 1.30 to 2.85) for 50 to 99 mg/day, 2.04 (95 percent CI 1.28 to 3.24) for 100 to 199 mg/day, and 2.88 (95 percent CI 1.79 to 4.63) for ≥200 mg/day (SOE: Low).

Three other observational studies also found an association between higher opioid doses and risk of opioid overdose-related deaths, but did not meet inclusion criteria because duration of opioid use was not reported,[16, 85] emergency room visits for opioid-related overdose events were combined with emergency room visits for alcohol,[86] or it did not evaluate patients with chronic pain prescribed long-term opioid therapy.[85]

Fractures

A previously described, fair-quality cohort study (see Key Question 2a) on the association between current use of opioids and risk of fractures in people aged 60 and older found that risk of fracture increased from an adjusted hazard ratio of 1.20 (95 percent CI 0.92 to 1.56) at 1 to <20 mg MED/day to 2.00 (95 percent CI 1.24 to 3.24) at ≥50 mg MED/day, although the overall test for dose response did not reach statistical significance (p = 0.06) (Appendix E3 and F2) (SOE: Low).[18]

Cardiovascular Events

A previously described fair-quality cohort study (see Key Question 2a) on the association between current use of opioids and risk of myocardial infarction in patients using long-term opioid therapy found a trend towards increased risk of myocardial infarction with higher cumulative opioid exposure (Appendix E4 and F1).[79] Compared to a cumulative dose of 0 to <1350 mg MED over 90 days, the adjusted IRR for myocardial infarction for 1350 to <2700 mg was 1.21 (95 percent CI 1.02 to 1.45), for 2700 to <8100 mg was 1.42 (95 percent CI 1.21 to 1.67), for 8100 to <18,000 mg was 1.89 (95 percent CI 1.54 to 2.33), and for ≥18,000 mg was 1.73 (95 percent CI 1.32 to 2.26) (SOE: Low).

Motor Vehicle Accidents

We identified one good-quality case-control study (n=10,600) on the association of opioid dose with risk of motor vehicle accidents in Ontario, Canada among individuals eligible for provincial prescription drug coverage who received at least one opioid prescription (Appendix E6 and F3).[20] It identified 5,300 cases who visited an emergency department with an injury related to road trauma. Cases were matched on sex, age, index year, and disease risk index to

5300 controls who did not visit the emergency department for road trauma. Although it did not specifically identify chronic pain patients on long-term opioid therapy, the average duration of opioid use was 7.1 years in cases and 6.8 years in controls. Individuals prescribed methadone were excluded because methadone is typically used to treat addiction in this area. Although there was no association between opioid dose and risk of road trauma in drivers or passengers at the time of the accident, doses of opioids >20 mg MED/day were associated with increased odds of road trauma when the analysis was restricted to drivers. There was no dose-dependent association at doses higher than 20 mg MED/day. Relative to 1 to <20 mg MED/day, the odds of road trauma among drivers after adjustment for age, alcoholism history, concomitant medication use, total number of drugs, and number of physician and emergency department visits was 1.21 (95 percent CI 1.02 to 1.42) for 20 to 49 mg, 1.29 (95 percent CI 1.06 to 1.57) for 50-99 mg, 1.42 (95 percent CI 1.15 to 1.76) for 100 to 199 mg, and 1.23 (95 percent CI 1.02 to 1.49) for ≥200 mg (SOE: Low).

Endocrinological Harms

One previously described fair-quality study cross-sectional analysis of men with back pain (n=11,327) found a daily opioid dose of ≥120 mg MED/day associated with increased risk of use of medications for erectile dysfunction or testosterone replacement versus 0 to <20 mg MED/day (OR 1.6, 95 percent CI 1.03 to 2.4), after adjustment for duration of opioid use, age, co-morbidities, hospitalizations, use of sedative-/hypnotics, type of opioid, depression, and smoking status (Appendix E5 and F2) (SOE: Low).[11] There was no increased risk at doses of 20 to <120 mg MED/day.

Key Question 3a

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 overdose, addiction, abuse, or misuse; and doses of opioids used?

Key Points

- Evidence from three trials on effects of titration with immediate-release versus sustained-release opioids reported inconsistent results on outcomes related to pain and are difficult to interpret due to additional differences between treatment arms in dosing protocols (titrated versus fixed dosing) and doses of opioids used (SOE: Insufficient).
- No trial was designed to assess risk of addiction, abuse, or misuse (SOE: Insufficient).

Detailed Synthesis

The APS review included three fair-quality, open-label trials of sustained-release versus immediate release opioids for titrating patients to stable pain control (Appendix E7 and F4).[87, 88] Two trials comparing controlled-release (CR) versus immediate-release (IR) oxycodone were reported in one publication.[87] The first involved a sample of 48 patients with cancer pain and dose titration for a period up to 21 days.[87] The second trial titrated 57 patients with low back pain for a period of up to 10 days.[87] Most patients in both trials were converted to oxycodone from other opioids. Results of both trials showed no difference between CR and IR oxycodone with

respect to the percentage of patients achieving stable pain control, the time to achieve stable pain control, and the degree of pain control achieved. Another trial found titrated doses of sustained-release morphine plus immediate-release oxycodone slightly superior to fixed-dose, immediate-release oxycodone for pain intensity, but no differences on measures of function, sleep, and psychological distress.[88] Results of this trial are difficult to interpret because maximum doses of opioids varied in the two arms (up to 200 mg MED/day in titrated dose arm, versus up to 20 mg/day in the fixed-dose oxycodone arm), and average doses of opioids were not reported. None of the three trials was designed to assess outcomes related to risk of overdose, addiction, abuse, or misuse. Due to study limitations, inconsistent results, and differences between study arms other than use of sustained-release versus immediate-release opioids, the SOE was rated Insufficient.

We identified no study published since the APS review on the comparative effectiveness of different methods for initiating and titrating opioids.

Key Question 3b

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

Key Points

- No study compared effectiveness of short- versus long-acting opioids on long-term outcomes in patients with chronic pain (SOE: Insufficient).

Detailed Synthesis

The APS review included a systematic review[89] of seven trials[87, 88, 90-94] of short- versus long-acting opioid formulations, but none of the trials met inclusion criteria for the current review. Six trials[87, 90-94] were 30 days or shorter in duration and the other[88] was 16 weeks in duration. Five of the trials found no difference between sustained-release and immediate-release opioid formulations in pain control.[87, 90, 91, 93, 94] Although two trials found regimens including sustained-release preparations more effective for pain control than regimens restricted to immediate-release preparations, results are difficult to interpret because the regimens were not given at therapeutically equivalent doses.[88, 92] No trial was designed to evaluate risk of overdose, addiction, abuse, or misuse.

We identified no trials of short- versus long-acting opioids published since the APS review that met inclusion criteria.

Key Question 3c

In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; and risk of overdose, addiction, abuse, or misuse?

Key Points

- Three randomized, head-to-head trials of various long-acting opioids found no differences in long-term outcomes related to pain or function (SOE: Low).
- No trial was designed to assess risk of overdose, addiction, abuse, or misuse (SOE: Insufficient).
- One cohort study found sustained-release methadone to be associated with lower mortality risk (presumably related to accidental overdose) as compared to morphine in a propensity-adjusted analysis (SOE: Low).
- Another cohort study found some differences between long-acting opioids in rates of adverse outcomes related to abuse, but outcomes were nonspecific for opioid-related adverse events, precluding reliable conclusions (SOE: Insufficient).

Detailed Synthesis

The APS review included one fair-quality, open-label randomized trial (n=680) of transdermal fentanyl versus sustained-release morphine in patients with chronic low back pain that evaluated outcomes through 13 months[43] (Table 2 below; Appendix E8a, E8b, and F4). The study found no differences between these long-acting opioids in pain relief, pain intensity, use of supplemental analgesic medications, work loss, and quality of life. The study was not designed to assess overdose and addiction or related outcomes, and no cases of these outcomes were reported. The APS review also included a fair-quality retrospective cohort study based on Oregon Medicaid administrative data (n=5,684) that evaluated abuse and other related outcomes in patients with cancer or noncancer pain and at least one new 28-day prescription of methadone, sustained-release oxycodone, sustained-release morphine, or transdermal fentanyl over a 4-year timeframe.[95] Adverse events were based on clinical encounters and ICD-9 codes and defined as emergency department (ED) visits or hospitalization for opioid-related events, all-cause ED visits or hospitalizations, opioid poisoning, overdose symptoms, and death. After adjusting for opioid dose, co-morbidities, concomitant medications, and other potential confounders, sustained-release oxycodone was associated with lower risk than sustained-release morphine of an ED encounter or hospitalization involving an opioid-related adverse event (HR 0.45, 95 percent CI 0.26 to 0.77) or death (HR 0.71, 95 percent CI 0.54 to 0.94). Among patients with noncancer pain, compared with sustained-release morphine, fentanyl was associated with higher risk of ED encounters (HR 1.27, 95 percent CI 1.02 to 1.59) and methadone was associated with greater risk of overdose symptoms (HR 1.57, 95 percent CI 1.03 to 2.40). There were no significant differences between methadone and long-acting morphine in risk of death (adjusted HR 0.71, 95 percent CI 0.46 to 1.08) or overdose symptoms. Some limitations of this study include large, statistically significant differences in baseline characteristics between patients prescribed different long-acting opioids and analysis of outcomes not specific for opioid-related adverse events. For example, overdose symptoms were defined as alteration of consciousness, malaise, fatigue, lethargy, or respiratory failure.

We identified two randomized trials[96, 97] and one retrospective cohort study[98] published since the APS review that compared different long-acting opioids in patients receiving long-term opioid therapy. One large (n=1,117) fair-quality trial of patients with chronic low back pain or osteoarthritis pain found no difference between sustained-release tapentadol and sustained-release oxycodone in pain intensity through 1 year.[97] Methodological limitations included open-label design and high attrition. A smaller (n=46), poor-quality trial of patients with various types of chronic noncancer pain (61 percent low back pain) found no clear differences between transdermal buprenorphine versus transdermal fentanyl in pain intensity, pain relief, quality of life, function, or psychological symptoms through 1 year.[96] It was rated poor-quality due to high attrition and open-label design. In addition, statistical analyses comparing results between groups were not reported for most outcomes and the study was not designed to measure efficacy. No deaths were reported in either study, and the studies were not designed to assess risk of addiction, abuse, or misuse. In both trials, opioid doses were titrated to effect.

A fair-quality retrospective cohort study based on national VA system pharmacy data compared all-cause mortality among chronic pain patients prescribed methadone (n=28,554) or long-acting morphine (n=79,938).[98] The study excluded patients prescribed methadone for opioid dependence or in palliative care settings. The mean daily doses of methadone and long acting morphine were 25.4 mg and 67.5 mg, respectively. Compared to the morphine cohort, the methadone group was younger and had fewer comorbid medical conditions, but higher rates of psychiatric conditions, substance use, and back pain. To help control for these and other differences, the study analyzed patients based on their propensity for being prescribed methadone. The baseline characteristics in each propensity quintile were very similar across the two groups. In both groups, all-cause mortality was highest in propensity quintile 1 (patients with the least propensity to receive methadone and most medically ill) and least in quintile 5 (highest propensity to receive methadone). In the propensity-stratified analysis, overall risk of mortality was lower with methadone than with morphine (adjusted HR 0.56, 95 percent CI 0.51 to 0.62).

For propensity quintile 1, the adjusted HR was 0.36 (95 percent CI 0.26 to 0.49); similar trends were observed for quintiles 2 to 4. For quintile 5, there was no difference between methadone and morphine in risk of all-cause mortality (adjusted HR 0.92, 95 percent CI 0.74 to 1.2). The main limitation of this study is the possibility of residual confounding by indication. Although the study stratified patients based on their propensity for being prescribed methadone and performed adjustment on potential confounders, unmeasured confounders could still have been present. The likely effects of residual confounding on estimates is difficult to predict, because people prescribed methadone had features associated both with decreased risk of mortality (younger age and fewer co-morbid medical conditions) as well as with increased risk (more psychiatric conditions and substance abuse).

The SOE was rated Low for no difference between different long-acting opioids in pain or function, Low for mortality risk associated with methadone versus morphine, and Insufficient for abuse and related outcomes.

Table 2. Head-to-head trials and observational studies of different long-acting opioids

Author Year Study Design Duration	Setting/ Data Source Country	Interventions, N	Results	Quality
Allan, 2005[43] Randomized trial 13 months	Multicenter (number of sites not clear) Europe	A: Transdermal fentanyl (titrated from 25 mcg/hr) (Mean dose 57 mcg/hr) (N=338) B: Sustained-release morphine (titrated from 30 mg q 12 hrs) (Mean dose: 140 mg) (N=342)	A vs. B Pain score (mean, 0-100 VAS) at 56 weeks (N=608): 56.0 vs. 55.8 Severe pain at rest (per protocol analyses, N=248 and 162): 22/248 (9%) vs. 20/162 (12%), p=0.030 (no significant differences in ITT analysis, but data not provided) Severe pain on movement (per protocol): 70/248 (28%) vs. 43/162 (27%), p=0.611 Severe pain during the day (per protocol): 48/248 (19%) vs. 40/162 (25%), p=0.385 Severe pain at night (per protocol): 25/248 (10%) vs. 26/162 (16%) , p=0.003 (no significant differences in ITT analysis, but data not provided) Rescue strong opioids use: 154/296 (52%) vs. 154/291 (53%) Quality of life (SF-36): No differences between interventions Loss of working days: No differences between interventions Withdrawal due to lack of efficacy: 18/335 (5%) vs.15/342 (4%)	Fair

Table 2. Head-to-head trials and observational studies of different long-acting opioids (continued)

Author Year Study Design Duration	Setting/ Data Source Country	Interventions, N	Results	Quality
Hartung, 2007[95] Retrospective cohort study Duration not applicable	U.S. Medicaid claims	A. Transdermal fentanyl (n=1,546) B. Methadone (n=974) C. ER oxycodone (n=1,866) D. ER morphine (n=1,298)	A vs. B vs. C (reference: D) Mortality: adjusted HR 0.71 (95% CI 0.46 to 1.08) vs. HR 0.71 (95% CI 0.54 to 0.94) vs. 0.80 (95% CI 0.63 to 1.02) ED encounter or hospitalization involving an opioid-related adverse event (HR 0.45, 95% CI 0.26 to 0.77) Among patients with noncancer pain: Fentanyl associated with higher risk of ED encounters than sustained-release morphine (HR 1.27, 95% CI 1.02 to 1.59) Methadone associated with greater risk of overdose symptoms than sustained-release morphine (HR 1.57, 95% CI 1.03 to 2.40) No significant differences between methadone and long-acting morphine in risk of death (adjusted HR 0.71, 95% CI 0.46 to 1.08)	Fair
Krebs, 2011[98] Retrospective cohort study Duration not applicable	U.S. VA	A: Methadone (n=28,554) B: Long-acting morphine sulfate (MS) (n=79,938)	All-cause mortality: Unadjusted: 3,347 (3.4%) patients died; highest mortality within 1st 30 days (1.2% in methadone and 3.7% in MS); raw death rates from MS higher than methadone for all 30-day intervals; Death rate: Quintile #1 (0.042 vs 0.133); Quintile #2 (0.034 vs 0.078); Quintile #3 (0.025 vs 0.053); Quintile #4 (0.022 vs 0.034); Quintile #5 (0.017 vs 0.020); Propensity adjusted mortality (HR): Overall risk of mortality lower with methadone than morphine (adjusted HR 0.56, 95% CI 0.51 to 0.62) Quintile #1: 0.36 (95% CI: 0.26, 0.49); Quintile #2: 0.46 (0.37, 0.56); Quintile #3: 0.50 (0.41, 0.61); Quintile #4: 0.66 (0.54, 0.81); Quintile #5: 0.92 (0.74, 1.16); Results robust in validation dataset	Fair
Mitra, 2013[96] Randomized trial 12 months	Townsville, Australia (1 site)	A: Transdermal buprenorphine (TDB) initial dose=-5 mcg/h (n=22) B: Transdermal fentanyl (TDF) initial dose=12.5 mcg/h (n=24) Both titrated to optimal doses over 4 weeks; increased doses beyond that given as clinically indicated	Sleep quality: No significant difference between groups (data not provided) Pain VAS: 3-point (scale 1-10) reduction in pain in 11% in each treatment group (data not provided) DASS21: TDB had relatively better score at 12 mos (data not provided) PDI: Appears similar (data not provided)	Poor

Table 2. Head-to-head trials and observational studies of different long-acting opioids (continued)

Author Year Study Design Duration	Setting/ Data Source Country	Interventions, N	Results	Quality
Wild, 2010[97] Randomized trial 12 months	53 sites in North America; 36 sites in Europe	A. Tapentadol ER 100-250 mg BID (adjustable) (n=894) B. Oxycodone CR 20-50 mg BID (adjustable) (n=223)	Mean (SE) pain intensity score: decreased from 7.6 (0.05) and 7.6 (0.11) at baseline to 4.4 (0.09) and 4.5 (0.17) Global assessment, very much improved or much improved: 48.1% (394/819) vs 41.2% (73/177) Concomitant nonopioid analgesics (NSAIDS, ASA, acetaminophen): 19.9% (178/894) vs. 17% (38/223)	Fair

Abbreviations: ASA=aspirin, BID=twice daily, CI=confidence interval, CR=controlled release, DASS21=Depression, Anxiety, and Stress Scale-21 Items, ER=extended release, HR=hazard ratio, ITT=intent to treat, MS=long-acting morphine sulfate, NSAID=nonsteroidal anti-inflammatory drug, PDI=Physical Disability Index, q=every, SE=standard error, TDB= transdermal buprenorphine, TDF= transdermal fentanyl, US=United States, VA=Veterans Affairs, VAS=Visual Analogue Scale.

Key Question 3d

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 overdose, addiction, abuse, or misuse; and doses of opioids used?

The APS review identified no trial of short- plus long-acting opioids versus long-acting opioids alone. We also identified no study published since the APS review that addressed this question (SOE: Insufficient).

Key Question 3e

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?

Key Points

- No study compared long-term opioid therapy using scheduled, continuous dosing versus as-needed dosing (SOE: Insufficient).

Detailed Synthesis

The 2009 APS review included one trial of scheduled, around-the-clock dosing of codeine versus as-needed dosing, but it did not meet inclusion criteria for the current review because duration of followup was five days.[92] In addition, results of this trial were difficult to interpret because the interventions varied on factors other than whether the opioid was dosed around-the-clock, including use of sustained-release versus immediate-release codeine formulations and different doses (200 versus 71 mg/day of codeine).

We identified no study published since the APS review on long-term opioid therapy using scheduled, continuous dosing versus as-needed dosing (SOE: Insufficient).

Key Question 3f

In patients 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?

Key Points

- One fair-quality randomized trial of more liberal dose escalation versus maintenance of current doses found no difference in outcomes related to pain or function, or risk of

withdrawal due to opioid misuse, but achieved limited separation between groups in opioid doses (52 versus 40 mg MED/day at the end of the trial) (SOE: Low).

Detailed Synthesis

The APS review did not address the comparative effectiveness of dose escalation versus dose maintenance or use of dose thresholds. We identified one relevant fair-quality randomized trial (n=140) published since the APS review (Appendix E9 and F4).[99] It compared more liberal dose escalation (doses increased for inadequate pain relief using preset dosing guidelines) versus maintenance of current doses (doses only increased if medically necessary due to clear dosage tolerance or acute injury). The subjects were VA patients with primarily musculoskeletal chronic pain[99] (defined as >6 months duration). Over 90 percent of enrollees were male and initial opioid doses were about 30 mg morphine equivalents/day. Both short- and long-acting opioids were prescribed, with long-acting opioids used more at higher doses. Average pain at baseline was about 7 on a 0 to 10 scale, and mean Oswestry Disability Index (ODI) score was about 48 (indicating moderate functional disability). The trial was fair-quality, primarily due to high attrition. Although doses at the end of the 12-month trial were higher in the dose escalation group, an important limitation of this trial is that the difference in opioid doses prescribed at the end of the trial was relatively small (mean 52 versus 40 mg morphine equivalents/day).

The trial found no difference between groups at 12 months in mean Visual Analogue Scale (VAS) pain ratings (5.6 for escalating dose versus 6.2 for stable dose, p=0.11), proportion with $\geq$1.5 point improvement in VAS pain rating (28 percent versus 20 percent, RR 1.4, 95 percent CI 1.76 to 2.5), mean ODI scores (46 versus 45, p=0.85), proportion with $\geq$10 point improvement in ODI score (29 percent versus 23 percent, RR 1.0, 95 percent CI 0.61 to 1.8), or use of various nonopioid medications or physical therapy. There was also no significant difference in all-cause withdrawals (49 percent versus 56 percent, RR 0.88, 95 percent CI 0.64 to 1.2). Withdrawal due to opioid misuse was frequent in both groups, with no difference between groups (24 percent versus 30 percent, RR 0.79, 95 percent 0.46 to 1.4) (SOE: Low).

Key Question 3g

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?

Key Points

- No study compared opioid rotation versus maintenance of long-term opioid therapy (SOE: Insufficient).

Detailed Synthesis

The APS review identified no randomized trials or controlled observational studies on opioid rotation versus maintenance of current therapy. We identified no studies published since the APS review that addressed this Key Question (SOE: Insufficient).

Key Question 3h

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?

Key Points

- Two good-quality randomized trials found buccal fentanyl more effective than placebo for treating acute exacerbations of pain and three randomized trials found buccal fentanyl or intranasal fentanyl more effective than oral opioids for treating acute exacerbations of pain in patients on long-term opioid therapy, based on outcomes measured up to 2 hours after dosing. (SOE: Moderate).
- No study evaluated long-term benefits or harms (SOE: Insufficient).

Detailed Synthesis

The APS review included two placebo-controlled, randomized trials (n=77 and 79) of buccal fentanyl for acute exacerbations of pain in people prescribed opioid therapy for chronic pain (Table 3 below, Appendix E10 and F4).[100, 101] Both found buccal fentanyl to be more effective than placebo at relieving acute pain exacerbations based on outcomes measured up to 2 hours after dosing, for up to nine episodes over a 3-week period. Neither trial was designed to evaluate benefits or harms associated with longer-term use of buccal fentanyl, including outcomes related to abuse and associated outcomes. Use of a run-in period in both trials could limit generalizability of findings, as about one-quarter of patients were excluded during an open-label run-in period due to lack of efficacy or adverse events.

We identified three subsequent head-to-head trials of buccal or intranasal fentanyl versus oral opioids for acute exacerbations of chronic pain.[102-104] As in the prior trials, all were funded by the manufacturer of buccal or intranasal fentanyl or conducted by researchers affiliated with the manufacturer. All used a double-blind, double-dummy crossover design and enrolled patients prescribed ≥60 mg MED/day and with one to four episodes of pain exacerbations per day. Like the prior trials, they focused on immediate outcomes following administration and used a run-in period. Two good-quality trials (n=183 and 137) found fentanyl buccal tablets to be more effective than oxycodone in reducing pain intensity (pain reduction 0.82 versus 0.60 and 0.88 versus 0.76 on a 0-10 scale; both $p<0.001$) and meaningful pain relief (undefined) (16 percent versus 12 percent at 15 minutes, $p<0.05$ and 46 percent versus 38 percent at 30 minutes, $p<0.01$).[102, 104] The pain condition in most patients in both trials was back or neck pain, osteoarthritis, fibromyalgia, traumatic injury, or complex regional pain syndrome. A fair-quality trial (n=84) of cancer patients found fentanyl pectin nasal spray more effective than immediate-release morphine sulfate at reducing pain intensity by >33 percent at 15 minutes (52 percent versus 44 percent of episodes; $p<0.01$).[103] It was unclear how many of the patients in the study were at end of life.

The SOE for the effectiveness of buccal or nasal fentanyl for immediate pain relief was rated Moderate.

Table 3. Trials of different strategies for treating acute exacerbations of chronic pain in patients on long-term opioid therapy

Author, Year Study Design Duration	Sample	Interventions, N	Results	Quality
Ashburn, 2011[102] Randomized trial (crossover) Duration: up to 42 days total	n=183 Patients aged 18 to 80 years with >3 months of chronic pain receiving >60 mg/day MED, with 1-4 episodes of breakthrough pain per day Mean age: 48.8 years Female sex: 62% Race: 92% White, 5% Black, 3% other Pain intensity in 24 hours prior to enrollment: 5.1 Indication (most common): 57% back pain, 11% osteoarthritis, 8% neck pain, 9% fibromyalgia, 4% traumatic injury, 4% complex regional pain syndrome	A. Fentanyl buccal tablet (n=183) B. Oxycodone (n=183)	A vs. B Pain intensity difference (from before drug administration; 0-10 scale) at 15 minutes: 0.82 vs. 0.60 (p<0.0001) Pain relief (0-5 scale) at 15 minutes: 0.69 vs. 0.53 (p<0.05) Meaningful pain relief within 15 minutes: 16% vs. 12% of episodes (p<0.05)	Good
Davies, 2011[103] Randomized trial (crossover) 3 to 21 days	n=84 Patients with histologically confirmed cancer, receiving a fixed-schedule opioid regimen at a total daily dose equivalent >60 mg MED, with 1 to 4 episodes of breakthrough pain per day Mean age: 55.9 years Female sex: NR Race: NR	A. Fentanyl pectin nasal spray (n=106 for safety and n=84 for efficacy) B. Immediate-release morphine sulfate (n=106 for safety and n=84 for efficacy)	A vs. B ≥2-point reduction in pain intensity at 10 minutes: 52.4% vs. 45.4% (p<0.05) ≥2 pain relief at 15 minutes: 60.2% vs. 53.4% (p<0.05) Total pain relief ≥33% at 15 minutes: 52.3% vs. 43.5% (p<0.01)	Fair

Table 3. Trials of different strategies for treating acute exacerbations of chronic pain in patients on long-term opioid therapy (continued)

Author, Year Study Design Duration	Sample	Interventions, N	Results	Quality
Portenoy, 2007[100] Randomized trial 3 weeks	n=77 Patients aged 18 to 80 years with chronic low back pain Mean age: 47 years Female gender: 55% Nonwhite race: 12% Baseline pain intensity: 5.1 (10 point scale) Primary etiology of low back pain degenerative disc disease: 68%	A. Buccal fentanyl 100 to 800 mcg for an episode of breakthrough pain B. Placebo (n=77) Dose of buccal fentanyl: 800 mcg 56%; 600 mcg 24%; 400 mcg 15%; 200 mcg 5%	A vs. B Sum of the pain intensity differences from 5 through 60 minutes: 8.3 vs. 3.6 Proportion of breakthrough pain episodes with "meaningful" pain reduction: 70% (289/413) vs. 30% (63/207) (p<0.0001) Proportion of breakthrough pain episodes with ≥33% reduction in pain intensity after 30 minutes: 42% (172/413) vs. 18% (18/207) (p<0.0001) Proportion of breakthrough pain episodes with ≥50% reduction in pain intensity after 30 minutes: 30% (122/413) vs. 13% (27/207) (p<0.0001) Proportion of breakthrough pain episodes with ≥33% reduction in pain intensity after 120 minutes: 65% (269/413) vs. 28% (57/207) (p<0.0001) Proportion of breakthrough pain episodes with ≥50% reduction in pain intensity after 120 minutes: 48% (198/413) vs. 16% (33/207) (p<0.0001)	Good

Table 3. Trials of different strategies for treating acute exacerbations of chronic pain in patients on long-term opioid therapy (continued)

Author, Year Study Design Duration	Sample	Interventions, N	Results	Quality
Simpson, 2007[101] Randomized trial (crossover) 3 weeks	n=79 18 to 80 years old, >3 months history of chronic neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, traumatic injury, or complex regional pain syndrome, on chronic opioids (at least 60 mg/day or morphine or equivalent), pain intensity <7 on a 0 to 10 scale, 1 to 4 daily episodes of breakthrough pain	A. Buccal fentanyl 100 to 800 mcg for an episode of breakthrough pain B. Placebo (n=79) Dose of buccal fentanyl: 800 mcg 54%; 600 mcg 19%; 400 mcg 18%; 200 mcg 5%, 100 mcg 5%	A vs. B Sum of the pain intensity differences from 5 through 60 minutes: 9.63 vs. 5.73 (p<0.001) Proportion of breakthrough pain episodes with 'meaningful' pain reduction: 69% vs. 36% (p<0.0001) Proportion of breakthrough pain episodes with ≥50% reduction in pain intensity after 15 minutes: 12% vs. 5% (p≤0.0001), p<0.0001 for each subsequent time point from 30 to 120 minutes Use of supplemental medication: 14% (59/432) vs. 36% (77/213) (OR 0.28, 95% CI 0.18 to 0.42)	Good
Webster, 2013[104] Randomized trial (crossover) Up to 42 days	N=274 Mean age: 50.8 years Female sex: 58% Race: 91% white, 7% black, 2% other Pain intensity in 24 hours prior to enrollment: 5.1	A. Fentanyl buccal tablet (n=137) B. Oxycodone (n=137)	A vs. B Pain intensity difference (from before drug) at 15 minutes: 0.88 vs. 0.76 (0-10 scale) (p<0.001) Pain relief at 15 minutes: 38% vs. 34% (p<0.05) Meaningful pain relief within 15 minutes: 17% vs. 16% (p=NS) Meaningful pain relief within 30 minutes: 46% vs. 38% (p<0.01)	Good

Abbreviations: CI=confidence interval, MED=morphine equivalent dose, NR=not reported, NS=not significant, OR=odds ratio.

Key Question 3i

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?

Key Points

- One small (n=10), poor-quality crossover trial found abrupt cessation of morphine to be associated with increased pain and decreased function compared to continuation of morphine (SOE: Insufficient).

Detailed Synthesis

The APS review included one small (n=10), poor-quality crossover trial that found abrupt cessation of morphine to be associated with increased pain and decreased function compared to continuation of morphine (Appendix E11 and F4).[105] Three patients (30 percent) reported opioid withdrawal symptoms following abrupt cessation of morphine, though there were no differences in physiologic parameters (vital signs and pupil size). Average dose of morphine prior to entry into was 42 mg/day (range 30 to 120 mg/day). Results of this trial may not apply to the general population of patients with chronic pain, as patients who did not have pain

adequately controlled by immobilization and alternative medications were excluded from study entry. We identified no study published since the APS review addressing this question.

Key Question 3j

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 Points

- Two poor-quality, nonrandomized prospective trials found no clear differences between different methods for opioid discontinuation or tapering (inpatient, patient controlled versus fixed reduction schedule or detoxification plus counseling versus detoxification plus maintenance) in likelihood of opioid abstinence after 3 to 6 months (SOE: Insufficient).

Detailed Synthesis

The APS review included two poor-quality, nonrandomized prospective trials that reported similar rates of opioid abstinence after 3 to 6 months in patients allocated to different methods for opioid discontinuation or tapering (Appendix E12 and F4).[106, 107] In one study (n=108), patients either chose inpatient, patient-controlled reduction of opioids or a fixed reduction schedule.[106] Mean opioid dose on study entry was 36 mg MED/day; duration of opioid therapy was not reported. In the second study, patients (n=42) received detoxification plus counseling or detoxification with maintenance therapy if detoxification was unsuccessful.[107] Mean duration of opioid use was 7.2 years in the detoxification plus counseling group and 9.2 years in the detoxification plus maintenance group; opioid doses ranged widely (e.g., codeine daily doses ranged from 240 to 2400 mg/day). Neither study evaluated effects of different methods for discontinuing opioids on pain, function, quality of life, or withdrawal symptoms.

We identified no study published since the APS review on the comparative effectiveness of different tapering protocols and strategies in chronic pain patients on long-term opioid therapy.

Key Question 4a

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?

Key Points

- Three studies (one fair-quality, two poor-quality) evaluated the Opioid Risk Tool (ORT); using a cutoff of ≥4. Estimates of diagnostic accuracy were inconsistent, precluding reliable conclusions. Sensitivities ranged from 0.20 to 0.99; specificities for the two in which this could be calculated were 0.88 and 0.16 (SOE: Insufficient).

- Two studies evaluated the Screening and Opioid Assessment for Patients with Pain (SOAPP) Version 1 instrument. In one fair-quality study, based on a cutoff score of ≥8, sensitivity was 0.68 and specificity was 0.38, for a PLR of 1.11 and NLR of 0.83 for predicting aberrant urine drug test. In one poor-quality study, sensitivity for predicting opioid discontinuation due to aberrant drug-related behavior was 0.73 based on a cutoff score of >6 and other diagnostic accuracy indicators could not be determined. (SOE: Low).
- One poor-quality study evaluated the Diagnosis, Intractability, Risk, and Efficacy Inventory (DIRE), but specificity and other diagnostic accuracy indicators could not be determined as patients who were not discontinued from opioids were not included in this study. (SOE: Insufficient)
- One poor-quality study evaluated the Pain Medication Questionnaire (PMQ), and for a cutoff of scores ≥30, sensitivity was low (0.34), specificity was 0.77, and AUROC was 0.57 for predicting opioid discontinuation due to aberrant drug-related behaviors. (SOE: Insufficient)
- One poor-quality study evaluated the Screening and Opioid Assessment for Patients with Pain-Revised (SOAPP-R). For a cutoff of ≥18, sensitivity was 0.39 and specificity was 0.69 and AUROC was 0.54 for predicting opioid discontinuation and discharge due to aberrant drug-related behavior. (SOE: Insufficient)

Detailed Synthesis

The APS review[108] included two fair-quality prospective studies of instruments to predict risk of opioid abuse or misuse completed by patients before initiation of opioid therapy (Table 4 below; Appendix E13 and F5).[109, 110] One study[109] evaluated the 14-item, patient self-administered Screening and Opioid Assessment for Patients with Pain (SOAPP) Version 1 instrument[111] and the other[110] evaluated the 10-item, self-administered Opioid Risk Tool (ORT). The SOAPP is scored on a scale of 0 to 56, while ORT scores can range from 0 to 25. For both instruments, higher scores indicate greater risk of opioid misuse and patients with scores ≥8 are considered high-risk for abuse. Both studies were performed with samples of patients in pain clinics. Methodological shortcomings of both studies included unclear blinding of outcomes assessors to findings of the screening instrument, use of definitions for aberrant drug-related behaviors that were not well standardized or defined, and failure to distinguish less serious from more serious behaviors. Although the APS review included two other studies used to develop the SOAPP Version 1[111] and the Revised SOAPP,[112] both were conducted using samples of patients already on long-term opioid therapy and did not meet inclusion criteria for the current review. In these studies, sensitivities (0.80 and 0.91) and specificities (0.68 and 0.69) were higher than those reported in the study of the SOAPP Version 1[109] conducted in patients evaluated prior to initiation of treatment.

The study of the SOAPP Version 1 instrument[111] reported a sensitivity of 0.68 (95 percent CI 0.52 to 0.81) and specificity of 0.38 (95 percent CI 0.29 to 0.49) based on a cutoff score of ≥8, for a PLR of 1.11 (95 percent CI 0.86 to 1.43) and NLR of 0.83 (95 percent CI 0.50 to 1.36) (Table 5 below).[109] Results were difficult to interpret because the only outcome reported was aberrant urine drug test, urine drug screens were not obtained in most patients, and duration of followup was unclear.

In the study[110] of the ORT, items in the ORT were chosen and weighted before evaluation of diagnostic test characteristics, and cut-off scores for different risk categories appeared to be selected on an a priori basis. Aberrant drug-related behaviors as documented in medical records over 12 months of follow-up were identified in 6 percent (1/18) of patients categorized as low risk (score 0 to 3), compared with 28 percent (35/123) of patients categorized as moderate risk (score 4 to 7) and 91 percent (41/44) of those categorized as high risk (score ≥8), for PLRs of 0.08 (95 percent CI 0.01 to 0.62) for a low-risk score, 0.57 (95 percent CI 0.44 to 0.74) for a moderate-risk score, and 14.34 (95 percent 5.35 to 38) for a high-risk score (Table 5 below).[110]

We identified two subsequent poor-quality retrospective studies that compared the ability of different risk assessment instruments to predict subsequent opioid abuse or misuse.[113, 114] One study compared the ORT, the Revised (24-item) SOAPP (SOAPP-R), the Pain Medication Questionnaire (PMQ), and a semi-structured clinical interview.[113] SOAPP-R scores range from 0 to 24 (scores ≥18 indicate high risk) and PMQ scores range from 0 to 104 (scores ≥30 indicate high risk.) The other compared the SOAPP Version 1, the ORT, the Diagnosis, Intractability, Risk, and Efficacy Inventory (DIRE) instrument, and a semi-structured clinical interview.[114] DIRE scores range from 7 to 21, and unlike the other risk assessment instruments, lower scores (≤13) indicate high-risk for abuse. Both studies appeared to be conducted in the same pain clinic during different time periods. Methodological shortcomings in both studies included exclusion of patients who were not evaluated with all of the risk assessment instruments (in one study, nearly 300 of 347 patients were excluded for this reason,[113] and in the other the proportion excluded was not reported[114]) and use of a case-control design. In both studies, cases were based on opioid discontinuations due to abuse, without further specification. One study also evaluated aberrant behaviors, but this outcome was not clearly defined.[114]

One poor-quality study found the ORT (cutoff >4), PMQ (cutoff ≥30) and SOAPP-R (cutoff ≥18) associated with sensitivities of 0.20, 0.34, and 0.39, respectively, and specificities of 0.88, 1.77 and 0.69, resulting in weak positive likelihood ratios (PLR; range 1.27 to 1.65) and negative likelihood ratios (NLR; range 0.86 to 0.91).[113] The AUROC ranged from 0.54 to 0.57. Results were similar when cases were based on presence of aberrant behaviors not necessarily resulting in opioid discontinuation. The other poor-quality study reported a higher sensitivity with the SOAPP Version 1 (0.73 at cutoff >6) compared with the ORT (0.45 at cutoff ≥4) or DIRE (0.17 at cutoff <14).[114] Because patients who were not discontinued from opioids were not included in this study, specificity and other diagnostic accuracy indicators could not be determined. Both studies also included a semi-structured clinician interview that addressed many of the components included in the risk prediction instruments (e.g., pain source and duration, history of drug or alcohol abuse, psychiatric symptoms or comorbidities). In both studies, the predictive accuracy of the clinician interview was at least as good as that of formal risk instruments.

The only instruments evaluated in more than one study were the ORT (3 studies[110, 113, 114]) and the SOAPP version 1 (two studies).[109, 114] Across the studies, estimates for diagnostic accuracy were extremely inconsistent. Using a cutoff score of >4, the sensitivity of the ORT ranged from 0.20 to 0.99 in three studies[110, 113, 114] and specificity was 0.88 and 0.16 in two studies and could not be calculated in the third study (SOE: Insufficient).[110, 113] The inconsistency could be due in part to differences in study methods and definitions of opioid abuse or misuse. For the SOAPP, cutoff scores of ≥6 and ≥8 had similar sensitivities (0.73 and 0.68, respectively) (SOE: Low), but other measures of diagnostic accuracy could not be compared because one of the studies only included cases.[114]

Table 4. Studies of risk assessment instrument.

Author Year	Population, N	Risk Assessment	Method of Administratio	Reference Standard
Akbik, 2006[109]	n=155 Mean age 43 years (SD 9.6) 33% female 86% White, other races not reported Pain: 39% back	SOAPP (scale 0-56; high risk ≥8)	Self-report	Positive urine drug test
Jones, 2012[113] (Study 2)	n=263 Mean age 48 years (SD 13) 56% female 96% White, other races not reported Pain: 45% low back pain, 21% arthritis or fibromyalgia), 14% joint pain, 10% pelvic or abdominal pain, 7% neck or upper back pain	ORT (scale 0-25; high risk ≥8) PMQ (scale 0-104; high risk ≥30) SOAPP-R (scale 0-24; high risk ≥18 Clinician assessment	Self-report (SOAPP-R, ORT, PMQ); clinician interview	Opioid discontinuation due to abuse
Moore, 2009[114]	n=48 Mean age 44 years (SD 11) 60% female Race not reported Pain not reported	SOAPP (scale 0-56; high risk ≥8) DIRE (scale 7-21; high-risk ≤13) ORT (scale 0-26; high risk ≥8) Clinician assessment	Self-report (SOAPP, DIRE, ORT); clinician interview	Opioid discontinuation due to abuse[a]
Webster, 2005 [110]	n=185 Mean age 44 years (SD 13) 58% female Race not reported Pain: 45% back; 18% head; 16% neuropathic; 16% musculoskeletal; 5% visceral	ORT (scale 0-25; high risk ≥8)	Self-report	Documentation in medical record of aberrant behavior during followup

Abbreviations: DIRE= Diagnosis Intractability Risk and Efficacy Inventory, ORT= Opioid Risk Tool, PMQ=Pain Medication Questionnaire,
SD=standard deviation, SOAPP= Screening and Opioid Assessment for Patients with Pain, SOAPP-R= Screening and Opioid Assessment for Patients with Pain-Revised.

Table 5. Predictive value of risk assessment instruments

Scale	Studies	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	AUROC
DIRE	Moore, 2009[114]	Score <14: 0.17	Not calculable[a]	Not calculable[a]	Not calculable[a]	Not calculable[a]
ORT	Jones, 2012[113]	Score >4: 0.20 (95% CI 0.15 to 0.27)	Score >4: 0.88 (95% CI 0.82 to 0.93)	Score >4: 1.65 (95% CI 0.78 to 3.51)	Score >4: 0.91 (95% CI 0.78 to 1.06)	0.54
	Moore, 2009[114]	Score ≥4: 0.45	Not calculable[a]	Not calculable[a]	Not calculable[a]	Not calculable[a]
	Webster, 2005[110]	Score ≥4: 0.99 (95% CI 0.92 to 0.99)	Score ≥4: 0.16 (95% CI 0.10 to 0.24)	Score ≥4: 0.99 (95% CI 0.92 to 0.999) Score 1-3: 0.08 (95% CI 0.01 to 0.62) Score 4-7: 0.57 (95% CI 0.44 to 0.74) Score ≥8: 14.34 (95% CI 5.35 to 38)	Score ≥4: 0.16 (95% CI 0.10 to 0.24)	Not reported
PMQ	Jones, 2012[113]	Score ≥30: 0.34 (95% CI 0.20 to 0.51)	Score ≥30: 0.77 (95% CI 0.69 to 0.80)	Score ≥30: 1.46 (95% CI 0.87 to 2.45)	Score ≥30: 0.86 (95% CI 0.68 to 1.08)	0.57
SOAPP-R	Jones, 2012[113]	Score ≥18: 0.39 (95% CI 0.26 to 0.54)	Score ≥18: 0.69 (95% CI 0.63 to 0.75)	Score ≥18: 1.27 (95% CI 0.86 to 1.90)	Score ≥18: 0.88 (95% CI 0.70 to 1.10)	0.54
SOAPP	Moore, 2009[114]	Score >6: 0.73	Not calculable[a]	Not calculable[a]	Not calculable[a]	Not calculable
	Akbik, 2006[109]	Score ≥8: 0.68 (95% CI 0.52 to 0.81)	Score ≥8: 0.38 (95% CI 0.29 to 0.49)	Score ≥8: 1.11 (95% CI 0.86 to 1.43)	Score ≥8: 0.83 (95% CI 0.50 to 1.36)	Not reported

[a]Retrospective study; only patients who had discontinued opioids due to aberrant drug-related behavior were included.
Abbreviations: CI=confidence interval, DIRE= Diagnosis Intractability Risk and Efficacy Inventory, ORT= Opioid Risk Tool, PMQ=Pain Medication Questionnaire, SOAPP= Screening and Opioid Assessment for Patients with Pain, SOAPP-R=Screening and Opioid Assessment for Patients with Pain-Revised.

Key Question 4b

In patients with chronic pain, what is the effectiveness of use of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse?

Key Points

- No study evaluated the effectiveness of risk prediction instruments for reducing outcomes related to overdose, addiction, abuse, or misuse (SOE: Insufficient).

Detailed Synthesis

The APS review identified no studies on the effectiveness of risk prediction instruments in reducing outcomes related to overdose, addiction abuse or misuse. We also did not identify any studies published since the APS review addressing this question.

Key Question 4c

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, (pill counts, and (8) use of abuse-deterrent formulations on outcomes related to overdose, addiction, abuse, or misuse?

Key Points

- No study evaluated the effectiveness of risk mitigation strategies for improving outcomes related to overdose, addiction, abuse, or misuse (SOE: Insufficient).

Detailed Synthesis

Like the APS review, we identified no study on the effectiveness of various risk mitigation strategies for improving outcomes related to overdose, addiction, abuse, or misuse.

Key Question 4d

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 Points

- No study evaluated the comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids (SOE: Insufficient).

Detailed Synthesis

Like the APS review, we identified no study on the comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids. Short-term randomized trials generally excluded patients with a past or current history of addiction.

Discussion

Key Findings and Strength of Evidence

The key findings of this review are summarized in the summary of evidence table (Table 6 below) and the factors used to determine the overall SOE grades are summarized in Appendix G. For a number of Key Questions, we identified no studies meeting inclusion criteria. For Key Questions where studies were available, the SOE was rated no higher than low, due to small numbers of studies and methodological shortcomings, with the exception of buccal or intranasal fentanyl for pain relief outcomes within 2 hours after dosing, for which the SOE was rated moderate.

For effectiveness and comparative effectiveness, we identified no studies of long-term opioid therapy in patients with chronic pain versus no opioid therapy or nonopioid alternative therapies that evaluated outcomes at 1 year or longer. No studies examined how effectiveness varies based on various factors, including type of pain and patient characteristics. Most placebo-controlled randomized trials were shorter than 6 weeks in duration[44] and no cohort studies on the effects of long-term opioid therapy versus no opioid therapy on outcomes related to pain, function, or quality of life were found. Although uncontrolled studies of patients prescribed opioids are available,[8] findings are difficult to interpret due to the lack of a nonopioid comparison group.

Regarding harms, new evidence (published since the APS review) from observational studies suggests that being prescribed long-term opioids for chronic pain is associated with increased risk of abuse,[48] overdose,[61] fractures,[18, 71] and myocardial infarction,[80] versus not currently being prescribed opioids. In addition, several recent studies suggest that the risk is dose-dependent, with higher opioid doses associated with increased risk.[11, 18, 48, 61, 79, 84] Although two studies found an association between opioid dose and increased risk of overdose starting at relatively low doses (20 to 49 mg MED/day), estimates at higher doses were variable (adjusted HR 11.18 at >100 mg MED/day versus adjusted OR 2.88 for $\geq$200 mg MED/day).[61, 84] However, few studies evaluated each outcome and the population evaluated and duration of opioid therapy were not always well characterized. In addition, as in all observational studies, findings are susceptible to residual confounding despite use of statistical adjustment and other techniques such as matching. A study also found long-term opioid therapy associated with increased likelihood of receiving prescriptions for erectile dysfunction or testosterone, which may be markers for sexual dysfunction due to presumed endocrinological effects of opioids.[11] However, it did not directly measure sexual dysfunction, and patients may seek or receive these medications for other reasons.

No study assessed the risk of abuse, addiction, or related outcomes associated with long-term opioid therapy use versus placebo or no opioid therapy. In uncontrolled studies, rates of abuse and related outcomes varied substantially, even after restricting inclusion to studies that evaluated patients on opioid therapy for at least one year and used pre-defined methods for ascertaining these outcomes, and stratifying studies according to whether they evaluated primary care populations or patients evaluated in pain clinic settings.[46, 49-58] An important reason for the variability in estimates is differences in patient samples and in how terms such as addiction, abuse, misuse, and dependence were defined in the studies, and in methods used to identify these outcomes (e.g., formal diagnostic interview with patients versus chart review or informal assessment). In one study, estimates of opioid misuse were lower based on independent review than based on assessments by the treating physician.[57] No study evaluated patients with "opioid use disorder" as recently defined in the new DSM-V.[59]

Evidence on the effectiveness of different opioid dosing strategies is also extremely limited. One new trial of a more liberal dose escalation strategy versus maintenance of current doses found no differences in outcomes related to pain, function, or risk of withdrawal from the study due to opioid misuse, but the difference in opioid doses between groups at the end of the trial was small (52 versus 40 mg MED/day).[99] One study from Washington State reported a decrease in the number of opioid-associated overdose deaths after implementing a dose threshold,[115] but did not meet inclusion criteria for this review because it was an ecological, before-after study, and it is not possible to reliably determine whether changes in the number of opioid overdose deaths were related to other factors that could have impacted opioid prescribing practices. Evidence on benefits and harms of different methods for initiating and titrating opioids, short- versus long-acting opioids, scheduled and continuous versus as-needed dosing of opioids, use of opioid rotation, and methods for titrating or discontinuing patients off opioids was not available or too limited to reach reliable conclusions.

We also found limited evidence on the comparative benefits and harms of specific opioids. Three head-to-head trials found few differences in pain relief between various long-acting opioids at 1 year followup,[43, 96, 97] but the usefulness of these studies for evaluating comparative effectiveness may be limited because patients in each arm had doses titrated to achieve adequate pain control. None of the trials was designed to evaluate abuse, addiction, or related outcomes.

Methadone has been an opioid of particular interest because it is disproportionately represented in case series and epidemiological studies of opioid-associated deaths.[116] Characteristics of methadone that may be associated with increased risk of serious harms are its long and variable half-life, which could increase the risk for accidental overdose, and its association with electrocardiographic QTc interval prolongation, which could increase the risk of potentially life-threatening ventricular arrhythmia.[117] However, the highest-quality observational study, which was conducted in VA patients with chronic pain and controlled well for confounders using a propensity-adjusted analysis, found methadone to be associated with lower risk of mortality as compared with sustained-release morphine.[98] These results suggest that in some settings, methadone may not be associated with increased mortality risk, though research is needed to understand the factors that contribute to safer prescribing in different clinical settings.

Although five randomized trials found buccal or intranasal fentanyl more effective than placebo or oral opioids for treating acute exacerbations of chronic pain, all focused on short-term treatment and immediate outcomes in the minutes or hours after administration.[100-104] No study was designed to assess long-term benefits or harms, including accidental overdose, abuse, or addiction. In 2007, the U.S. FDA released a public health advisory due to case reports of deaths and other life-threatening adverse effects in patients prescribed buccal fentanyl.[118]

Evidence also remains limited on the utility of opioid risk assessment instruments, used prior to initiation of opioid therapy, for predicting likelihood of subsequent opioid abuse or misuse. In three studies of the ORT, estimates were extremely inconsistent (sensitivity ranged from 0.20 to 0.99).[110, 114, 119] A study that directly compared the accuracy of the ORT and two other risk assessment instruments reported weak likelihood ratios for predicting future abuse or misuse (PLR 1.27 to 1.65 and NLR 0.86 to 0.91).[119] Risk prediction instruments other than the ORT (such as the SOAPP version 1, revised SOAPP, or DIRE) were only evaluated in one or two studies, and require further validation. Studies on the accuracy of risk instruments for identifying aberrant behavior in patients already prescribed opioids are available,[51, 54, 112, 119-125] but were outside the scope of this review.

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, monitoring instruments, more frequent monitoring intervals, pill counts, or abuse-deterrent formulations on outcomes related to overdose, addiction, abuse or misuse. Studies on effects of risk mitigation strategies were primarily focused on ability to detect misuse (e.g., urine drug testing and prescription monitoring program data) or on effects on markers of risky prescribing practices or medication-taking behaviors,[126] and did not meet inclusion criteria for this review, which focused on effects on clinical outcomes. One study found that rates of poison center treatment incidents and opioid-related treatment admissions increased at a lower rate in States with a prescription drug monitoring program than in States without one, but used an ecological design, did not evaluate a cohort of patients prescribed opioids for chronic pain, and was not designed to account for other factors that could have impacted opioid prescribing practices.[126]

Although evidence indicates that patients with a history of substance abuse or at higher risk for abuse or misuse due to other risk factors are more likely to be prescribed opioids than patients without these risk factors,[127-130] we identified no study on the effectiveness of methods for mitigating potential harms associated with long-term opioid therapy in high-risk patients.

Table 6. Summary of evidence

Key Question Outcome	Strength of Evidence Grade	Conclusion
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 (≥1 year) outcomes related to pain, function, and quality of life?		
Pain, function, quality of life	Insufficient	No study of opioid therapy versus placebo or no opioid therapy evaluated long-term (≥1 year) outcomes related to pain, function, or 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); 3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for addiction)?		
Pain, function, quality of life	Insufficient	No studies
c. In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacological or nonpharmacological) on outcomes related to pain, function, and quality of life?		

Table 6. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
Pain, function, quality of life	Insufficient	No studies

Key Question Outcome	Strength of Evidence Grade	Conclusion
d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacological or nonpharmacological) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?		
Pain, function, quality of life	Insufficient	No studies
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 accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?		
Abuse, addiction	Low	No randomized trial evaluated risk of opioid abuse, addiction, and related outcomes in patients with chronic pain prescribed opioid therapy. One retrospective cohort study found prescribed long-term opioid use associated with significantly increased risk of abuse or dependence versus no opioid use.
Abuse, addiction	Insufficient	In 10 uncontrolled studies, estimates of opioid abuse, addiction, and related outcomes varied substantially even after stratification by clinic setting
Overdose	Low	Current opioid use was associated with increased risk of any overdose events (adjusted HR 5.2, 95% CI 2.1 to 12) and serious overdose events (adjusted HR 8.4, 95% CI 2.5 to 28) versus current nonuse
Fractures	Low	Opioid use associated with increased risk of fracture in 1 cohort study (adjusted HR 1.28, 95% CI 0.99 to 1.64) and 1 case-control study (adjusted OR 1.27, 95% CI 1.21 to 1.33)
Myocardial infarction	Low	Current opioid use associated with increased risk of myocardial infarction versus nonuse (adjusted OR 1.28, 95% CI 1.19 to 1.37 and incidence rate ratio 2.66, 95% CI 2.30 to 3.08)
Endocrine	Low	Long-term opioid use associated with increased risk of use of medications for erectile dysfunction or testosterone replacement versus nonuse (adjusted OR 1.5, 95% CI 1.1 to 1.9)

Table 6. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
Gastrointestinal harms, motor vehicle accidents, infections, psychological harms, cognitive harms	Insufficient	No studies
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)?		
Various harms	Insufficient	No studies
b. How do harms vary depending on the dose of opioids used?		
Abuse, addiction	Low	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 to 21) for 1-36 MED/day, 29 (95 percent CI 20 to 41) for 36-120 MED/day, and 122 (95 percent CI 73 to 205) for ≥120 MED/day.
Overdose	Low	Versus 1 to 19 mg MED/day, 1 cohort study found an adjusted HR for an overdose event of 1.44 (95% CI 0.57 to 3.62) for 20 to 49 mg MED/day that increased to 11.18 (95% CI 4.80 to 26.03) at >100 mg MED/day; 1 case-control study found an adjusted OR for an opioid-related death of 1.32 (95% CI 0.94 to 1.84) for 20 to 49 mg MED/day that increased to 2.88 (95% CI 1.79 to 4.63) at ≥200 mg MED/day
Fracture	Low	Risk of fracture increased from an adjusted HR of 1.20 (95% CI 0.92 to 1.56) at 1 to <20 mg MED/day to 2.00 (95% CI 1.24 to 3.24) at ≥50 mg MED/day; the trend was of borderline statistical significance
Myocardial infarction	Low	Relative to a cumulative dose of 0 to 1350 mg MED over 90 days, the incidence rate ratio for myocardial infarction for 1350 to <2700 mg was 1.21 (95% CI 1.02 to 1.45), for 2700 to <8100 mg was 1.42 (95% CI 1.21 to 1.67), for 8100 to <18,000 mg was 1.89 (95% CI 1.54 to 2.33), and for >18,000 mg was 1.73 (95% CI 1.32 to 2.26)
Motor vehicle accidents	Low	No association between opioid dose and risk of motor vehicle accidents
Endocrine	Low	Relative to 0 to <20 mg MED/day, the adjusted OR for daily opioid dose of ≥120 mg MED/day for use of medications for erectile dysfunction or testosterone replacement was 1.6 (95% CI 1.0 to 2.4)

Table 6. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
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; risks of overdose, addiction, abuse, or misuse; and doses of opioids used?		
Pain	Insufficient	Evidence from three trials on effects of titration with immediate-release versus sustained-release opioids reported inconsistent results on outcomes related to pain and are difficult to interpret due to additional differences between treatment arms in dosing protocols (titrated vs. fixed dosing) and doses of opioids used
Function, quality of life, outcomes related to abuse	Insufficient	No studies
b. In patients with chronic pain, what is the comparative effectiveness of short- versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?		
Pain, function, quality of life, outcomes related to abuse	Insufficient	No studies
c. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; and risk of overdose, addiction, abuse, or misuse?		
Pain and function	Low	No difference between various long-acting opioids
Assessment of risk of overdose, addiction, abuse, or misuse	Insufficient	No studies were designed to assess risk of overdose, addiction, abuse, or misuse
Overdose (as indicated by all-cause mortality)	Low	One cohort study found methadone to be associated with lower all-cause mortality risk than sustained-release morphine in a propensity adjusted analysis
Abuse and related outcomes	Insufficient	Another cohort study found some differences between long-acting opioids in rates of adverse outcomes related to abuse, but outcomes were nonspecific for opioid-related adverse events, precluding reliable conclusions
d. In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids vs. long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?		
Pain, function, quality of life, outcomes related to abuse	Insufficient	No studies
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?		

Table 6. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
Pain, function, quality of life, outcomes related to abuse	Insufficient	No studies
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?		
Pain, function, withdrawal due to opioid misuse	Low	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 vs. 40 mg MED/day at the end of the trial)
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?		
Pain, function, quality of life, outcomes related to abuse	Insufficient	No studies
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?		
Pain	Moderate	Two randomized trials found buccal fentanyl more effective than placebo for treating acute exacerbations of pain and three randomized trials found buccal fentanyl or intranasal fentanyl more effective than oral opioids for treating acute exacerbations of pain in patients on long-term opioid therapy, based on outcomes measured up to 2 hours after dosing
Abuse and related outcomes	Insufficient	No studies
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?		
Pain, function	Insufficient	Abrupt cessation of morphine was associated with increased pain and decreased function compared to continuation of morphine
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?		
Opioid abstinence	Insufficient	No clear differences between different methods for opioid discontinuation or tapering in likelihood of opioid abstinence after 3 to 6 months

Table 6. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
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?		
Diagnostic accuracy: Opioid Risk Tool	Insufficient	Based on a cutoff of >4, three studies (one poor-quality, two poor-quality) reported very inconsistent estimates of diagnostic accuracy, precluding reliable conclusions
Diagnostic accuracy: Screening and Opioid Assessment for Patients with Pain (SOAPP) version 1	Low	Based on a cutoff score of ≥8, sensitivity was 0.68 and specificity of 0.38 in 1 study, for a PLR of 1.11 and NLR of 0.83. Based on a cutoff score of >6, sensitivity was 0.73 in 1 study.
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?		
Outcomes related to abuse	Insufficient	No study evaluated the effectiveness of risk prediction instruments for reducing 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?		
Outcomes related to abuse	Insufficient	No studies
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?		
Outcomes related to abuse	Insufficient	No studies

Abbreviations: CI=confidence interval, HR=hazard ratio, MED= morphine equivalent dose, NLR=negative likelihood ratio, OR=odds ratio,
PLR=positive likelihood ratio, SOAPP= Screening and Opioid Assessment for Patients with Pain.

Findings in Relationship to What is Already Known

Our findings are generally consistent with prior systematic reviews of opioid therapy for chronic pain that also found no long-term, placebo-controlled randomized trials.[8, 44] One systematic review of outcomes associated with long-term opioid therapy concluded that many patients discontinue treatment due to adverse events or insufficient pain relief, though patients who continue opioid therapy experience clinically significant pain relief.[8] However, results of the studies included in this review are difficult to interpret because the studies had no nonopioid therapy control group, reported substantial between-study heterogeneity, and were susceptible to potential attrition and selection bias. Our findings are also consistent with a systematic review on comparative benefits and harms of various long-acting opioids and

short- versus long-acting opioids, which found no clear differences, primarily based on short-term randomized trials.[131]

Our review reported rates of abuse and related outcomes that are higher than a previously published systematic review of long-term opioid therapy that reported a very low rate of opioid addiction (0.27 percent).[8] Factors that may explain this discrepancy are that the prior review included studies that did not report predefined methods for ascertaining opioid addiction, potentially resulting in underreporting, and primarily included studies that excluded high-risk patients. Like a previous systematic review, we found variability in estimates of abuse and related outcomes, with some potential differences in estimates based on clinical setting (primary care versus pain clinic) and patient characteristics (e.g., exclusion of high-risk patients).[132]

Regarding risk mitigation strategies, our findings were similar to a previously published systematic review that found weak evidence with which to evaluate risk prediction instruments.[133] Unlike our review, which found no evidence on effects of risk mitigation strategies on risk of abuse, addiction, or related outcomes, a previously published review found use of opioid management plans and urine drug screens to be associated with decreased risk of misuse behaviors.[14] However, this conclusion was based on four studies that did not meet inclusion criteria for our review because effects of opioid management plans and urine drug screens could not be separated from other concurrent opioid prescribing interventions,[134, 135] use of a historical control group,[136, 137] or before-after study design.[134]

Applicability

A number of issues could impact the applicability of our findings. One challenge was difficulty in determining whether studies focused on patients with chronic pain. Although a number of large observational studies reported harms based on analyses of administrative databases, they were frequently limited in their ability to assess important clinical factors such as the duration or severity of pain. For some of these studies, we inferred the presence of chronic pain from prescribing data, such as the number of prescriptions over a defined period or the use of long-acting opioid preparations. Some potentially relevant studies were excluded because it was not possible to determine whether the sample evaluated had chronic pain or received long- term therapy.[16, 74-78, 85]

Another issue that could impact applicability is the type of opioid used in the studies. Both long-acting and short-acting opioids are often prescribed for chronic pain. In some studies, use of short-acting opioids predominated.[11, 18, 84] Results of studies of short-acting opioids may not generalize to patients prescribed long-acting opioids.

Selection of patients could also impact applicability. The few randomized trials that met inclusion criteria typically excluded patients at high risk of abuse or misuse and frequently used run-in periods prior to allocating treatments. The use of a run-in period preselects patients who respond to and tolerate initial exposure to the studied treatment. Therefore, benefits observed in the trials might be greater and harms lower than seen in actual clinical practice.[138]

Another factor impacting applicability is that most trials were not designed or powered to assess risk of abuse, addiction, or related outcomes. For example, trials of buccal fentanyl for acute exacerbations of chronic pain focused exclusively on immediate (episode-based) outcomes and were not designed to assess long-term outcomes, including outcomes related to the potential for abuse.[100-104] Long-term head-to-head trials of long-acting opioids excluded patients at high risk for these outcomes and reported no events.[43, 96, 97]

The setting in which studies were conducted could also impact applicability. As noted in other sections of this report, rates of overdose, abuse, addiction, and related outcomes are likely to vary based on the clinical setting. Therefore, we stratified studies reporting rates of abuse according to whether they were performed in primary care or pain clinic settings. The highest-quality comparative study of methadone versus another opioid (long-acting morphine) found decreased mortality risk but was conducted in a VA setting,[98] which could limit applicability to other settings, due to factors such as how clinicians were trained in methadone use, policies on opioid prescribing, availability of resources to manage opioid prescribing, or other factors.

Implications for Clinical and Policy Decisionmaking

Our review has important implications for clinical and policy decisionmaking. Based on our review, most clinical and policy decisions regarding use of long-term opioid therapy must necessarily still be made on the basis of weak or insufficient evidence. This is in accordance with findings from a 2009 U.S. guideline on use of opioids for chronic pain, which found 21 of 25 recommendations supported by only low-quality evidence,[108] and a 2010 Canadian guideline,[139] which classified 3 of 24 recommendations as based on (short-term) randomized trials and 19 recommendations as based solely or partially on consensus opinion. Although randomized trials show short-term, moderate improvements in pain in highly selected, low-risk populations with chronic pain, such efficacy-based evidence is of limited usefulness for informing long-term opioid prescribing decisions in clinical practice.

Given the marked increase in numbers of overdose deaths and other serious adverse events that have occurred following the marked increase in opioid prescribing for chronic pain, recent policy efforts have focused on safer prescribing of opioids. A recent review of opioid guidelines found broad agreement regarding a number of risk mitigation strategies despite weak evidence, such as risk-assessment guided patient assessment for opioid therapy, urine drug testing, use of prescription monitoring program data, abuse-deterrent formulations, and opioid management plans.[140] Based on low-quality evidence regarding harms associated with long-term opioid therapy, our review provides some limited support for clinical policy efforts aimed at reducing harms. One area in which there has been less agreement across guidelines is whether dose thresholds that warrant more intense monitoring or used to define maximum ceiling doses should be implemented, and if so, what is the appropriate threshold. Some evidence is now available on dose-dependent harms associated with opioids,[61, 84] which could help inform policies related to dose thresholds. However, research on the effects of implementing dose thresholds on clinical outcomes is limited to a single ecological study.[115] In addition, although two observational studies were consistent in reporting a relationship between higher opioid dose and risk of overdose, estimates were highly variable at similar doses.[61, 84] This makes it difficult to determine an optimal maximum dose threshold based on an objective parameter, such as a dose inflection point where risk rises markedly. Other studies have begun to characterize cardiovascular, endocrinological, and injury-related harms associated with long-term opioid therapy and could be used to inform clinical decisions, though using such information in balanced assessments to inform clinical and policy decision-making remains a challenge given the lack of evidence regarding long-term benefits.

Limitations of the Review Process

We excluded non-English language articles and did not search for studies published only as abstracts. We did not attempt meta-analysis or assess for publication bias using graphical or statistical methods to detect small sample effects due to the paucity of evidence. Although we

found no evidence of unpublished studies through searches on clinical trial registries and regulatory documents and solicitation of unpublished studies through SIP requests, the usefulness of such methods for identifying unpublished observational studies may be limited, as such studies are often not registered. We identified no unpublished randomized trials meeting inclusion criteria. We focused on studies that reported outcomes after at least one year of opioid therapy, though applying a shorter duration threshold for inclusion could have provided additional evidence. However, we identified no placebo-controlled trials of opioid therapy for at least 6 months.

Limitations of the Evidence Base

As noted previously, the critical limitation of our review is the lack of evidence in the target population (patients with chronic pain) and intervention (long-term opioid therapy), despite broadening of inclusion criteria to incorporate studies in which we assumed that patients were being treated for chronic pain due to the type of opioid prescribed (long-acting opioid) or number of prescriptions. We were also unable to determine how benefits and harms vary in subgroups, such as those defined by demographic characteristics, characteristics of the pain condition, and other patient characteristics (e.g., medical or psychological comorbidities). Due to the lack of evidence and methodological shortcomings in the available studies, no body of evidence (with

the exception of buccal or intranasal fentanyl for immediate pain relief) was rated higher than low, meaning that conclusions are highly uncertain.

Research Gaps

Many research gaps limit the full understanding of the effectiveness, comparative effectiveness, and harms of long-term opioid therapy, as well as of the effectiveness of different dosing methods and risk mitigation strategies, and effectiveness in special populations. Longer-term studies of patients clearly with chronic pain comparing those who are prescribed long-term opioid therapy with those receiving other pharmacological and non-pharmacological therapies are needed. Studies that include higher-risk patients, commonly treated with opioids in clinical practice, and that measure multiple important outcomes, including pain, physical and psychological functioning, as well as misuse and abuse, would be more helpful than efficacy studies focused solely on pain intensity. Greater standardization of methods for defining and identifying abuse-related outcomes in studies that report these outcomes are needed. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group recently issued recommendations on measuring abuse liability in analgesic clinical trials.[141]

Additional research is also needed to develop and validate risk prediction instruments, and to determine how using them impacts treatment decisions and, ultimately, patient outcomes. More research is needed on the comparative benefits and harms of different opioids or formulations and different prescribing methods. Studies comparing effectiveness and harms of methadone versus other long-acting opioids, to determine if findings from a study[98] conducted in a VA setting are reproducible in other settings, and to better understand factors associated with safer methadone prescribing.

Research is also needed to understand the effects of risk mitigation strategies such as urine drug screening, use of prescription drug monitoring program data, and abuse-deterrent formulations on clinical outcomes such as rates of overdose, abuse, addiction, and misuse. In one before-after study, the introduction of an abuse-deterrent opioid was followed by patients

switching to other prescription opioids or illicit opioids,[142] underscoring the need for research to understand both the positive and negative clinical effects of risk mitigation strategies.

Long-term randomized trials of opioid therapy are difficult to implement due to attrition, challenges in recruitment, or ethical factors (e.g., long-term allocation of patients with pain to placebo or allocation to non-use of risk mitigation strategies recommended in clinical practice guidelines). Nonetheless, pragmatic and other non-traditional randomized trial approaches could be used to address these challenges.[143] Observational studies could also help address a number of these research questions, but should be specifically designed to evaluate patients with chronic pain prescribed long-term opioid therapy and appropriately measure and address potential confounders. Well-designed clinical registries that enroll patients with chronic pain prescribed and not prescribed chronic opioids could help address the limitations of studies based solely or primarily on administrative databases, which are often unable to fully characterize the pain condition (e.g., duration, type, and severity) or other clinical characteristics and frequently do not have information regarding outcomes related to pain, function, and quality of life. Such registry studies could be designed to extend the observations from randomized trials of opioids versus placebo or other treatments, but would differ from currently available studies by following patients who discontinue or do not start opioids, in addition to those who continue on or start opioid therapy.

Conclusions

Evidence on long-term opioid therapy for chronic pain is very limited, but suggests an increased risk of serious harms that appears to be dose-dependent. Based on our review, most clinical and policy decisions regarding use of long-term opioid therapy must necessarily still be made on the basis of weak or insufficient evidence. More research is needed to understand long-term benefits, risk of abuse and related outcomes, and effectiveness of different opioid prescribing methods and risk mitigation strategies.

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Abbreviations and Acronyms

AUROC	area under receiver operating characteristic curve
ASA	aspirin
ASI	Addiction Severity Index
APS	American Pain Society
BID	twice daily
CI	confidence interval
CIDI	Composite International Diagnostic Interview
CR	controlled release
DASS21	Depression, Anxiety, and Stress Scale-21 Items
DIRE	Diagnosis, Intractability, Risk, and Efficacy Inventory
DSM-V	Diagnostic and Statistical Manual, Fourth Edition DSM-
IV	Diagnostic and Statistical Manual, Fifth Edition
ER	extended release
GC/M	gas chromatography mass spectrometry
HR	hazard ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems Version 10 IRR incidence rate ratio
ITT	intent to treat
MED	morphine equivalent dose
MS	long-acting morphine sulfate
NA	not applicable
NLR	negative likelihood ratio
NR	not reported
NSAID	nonsteroidal anti-inflammatory drug
ODI	Oswestry Disability Index
OR	odds ratio
ORT	Opioid Risk Tool
PDI	Physical Disability Index
PDUQ	Prescription Drug Use Questionnaire
PLR	positive likelihood ratio
PMQ	Pain Medication Questionnaire
POTQ	Prescription Opioid Therapy Questionnaire
RCT	randomized controlled trial
SE	standard error
SDSS	Dependence Severity Scale
SOAPP	Screening and Opioid Assessment for Patients with Pain
SOAPP-R	Screening and Opioid Assessment for Patients with Pain-Revised
SOE	strength of evidence
SUQ	Self-report Substance Use Questionnaire
TDB	transdermal buprenorphine
TDF	transdermal fentanyl
U.S.	United States
UDT	urine drug test
VA	Veterans Affairs
VAS	Visual Analogue Scale

Appendix A. Search Strategies

Database: Ovid MEDLINE(R) Without Revisions

KQ 1 and 2: Comparative Effectiveness and Harms

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. exp Chronic Pain/
6. (chronic adj2 pain).mp.
7. 5 or 6
8. 4 and 7
9. limit 8 to yr="2008 - 2013"
10. limit 9 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or multicenter study or randomized controlled trial)
11. 9 and random$.mp.
12. 10 or 11

KQ 2a: Supplemental Search – Abuse and Addiction Detection

1. Analgesics, Opioid/
2. 1 and 2
3. Substance Abuse Detection/
4. Opioid-Related Disorders/ or Substance-Related Disorders/
5. 3 and (4 or 5)
6. (chronic adj3 pain).mp.
7. 1 and 7
8. 8 not 3
9. 9 and (4 or 5)
10. 6 or 10

KQ 3a-3g; 3i: Dosing Strategies

1. exp Analgesics, Opioid/
2. opioid*.mp. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or

phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
3. or/1-3
4. Opioid-Related Disorders/
5. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
6. Drug Administration Schedule/
7. Pain Management/
8. Clinical Protocols/
9. Breakthrough Pain/
10. Dose-Response Relationship, Drug/
11. ((dose$ or dosing) adj7 (strateg$ or adjust$ or titrat$ or taper$)).mp.
12. exp Chronic Pain/
13. (chronic adj2 pain).mp.
14. or/4-6
15. or/7-12
16. 15 and 16
17. (or/13-14) and 17
18. 18 and (random$ or control$ or trial or cohort or prospective or retrospective).mp.
19. limit 19 to yr="2008 - 2013"

KQ 3h: Dosing Strategies – Tapered Dosing

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. Opioid-Related Disorders/
6. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
7. Drug Administration Schedule/
8. Pain Management/
9. Clinical Protocols/
10. Breakthrough Pain/
11. Dose-Response Relationship, Drug/
12. ((dose$ or dosing) adj7 (strateg$ or adjust$ or titrat$ or taper$)).mp.
13. exp Chronic Pain/
14. (chronic adj2 pain).mp.
15. or/4-6
16. or/7-12
17. 15 and 16
18. (or/13-14) and 17

19. 18 and (random$ or control$ or trial or cohort or prospective or retrospective).mp.
20. 19 and (taper$ or decreas$ or reduc$).mp.
21. limit 20 to yr="1902 - 2007"

KQ 4a-4b: Risk Prediction

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. exp Chronic Pain/
6. (chronic adj2 pain).mp.
7. Opioid-Related Disorders/
8. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
9. 4 and (5 or 6)
10. 7 or 8
11. 9 or 10
12. Decision Support Techniques/
13. "Predictive Value of Tests"/
14. Prognosis/
15. Risk Assessment/
16. Risk Factors/
17. Proportional Hazards Models/
18. "Reproducibility of Results"/
19. "Sensitivity and Specificity"/
20. (sensitivity or specificity).mp.
21. (risk and (predict$ or assess$)).mp.
22. or/12-21
23. 11 and 22
24. limit 23 to yr="2008 - 2013"

KQ 4c: Risk Mitigation

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or

phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. exp Chronic Pain/
6. (chronic adj2 pain).mp.
7. Opioid-Related Disorders/
8. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
9. 4 and (5 or 6)
10. 7 or 8
11. 9 or 10
12. Patient Compliance/
13. Health Services Misuse/
14. Substance Abuse Detection/
15. Drug Monitoring/
16. (urine adj7 (screen$ or test$ or detect$)).mp.
17. (abus$ or misus$ or diversion$ or divert$).mp.
18. (opioid$ adj7 (contract$ or agree$)).mp.
19. Contracts/
20. Patient Education as Topic/
21. Drug Overdose/
22. or/12-21
23. ((risk$ adj7 mitigat$) or reduc$).mp.
24. ("risk evaluation and mitigation" or "rems").mp.
25. Risk Reduction Behavior/ or Risk/
26. or/23-25
27. 11 and 22 and 26
28. limit 27 to yr="2008 - 2013"

KQ 4d: Treatment Strategies

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. Opioid-Related Disorders/
6. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
7. Patient Compliance/
8. Health Services Misuse/
9. Substance Abuse Detection/
10. Drug Monitoring/

11. (urine adj7 (screen$ or test$ or detect$)).mp.
12. (abus$ or misus$ or diversion$ or divert$).mp.
13. (opioid$ adj7 (contract$ or agree$)).mp.
14. Contracts/
15. Patient Education as Topic/
16. Drug Overdose/
17. or/7-16
18. Substance Abuse Detection/
19. Opiate Substitution Treatment/
20. Risk Management/
21. or/18-20
22. or/4-6
23. 17 and 21 and 22
24. treatment outcome.mp. or Treatment Outcome/
25. (treatment and (strateg$ or plan$)).mp.
26. 23 and (24 or 25)

All KQs: Systematic Reviews

1. meta-analysis.mp. or exp Meta-Analysis/
2. (cochrane or medline).tw.
3. search$.tw.
4. 1 or 2 or 3
5. "Review Literature as Topic"/ or systematic review.mp.
6. 4 or 5
7. exp Analgesics, Opioid/
8. opioid*.mp.
9. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
10. 10 (chronic and pain).mp.
11. or/7-9
12. 6 and 10 and 11
13. limit 12 to yr="2008 - 2013"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

KQ 1 and 2: Comparative Effectiveness and Harms

1. exp Analgesics, Opioid/
2. opioid*.mp.

3. (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. exp Chronic Pain/
6. (chronic adj2 pain).mp.
7. 5 or 6
8. 4 and 7
9. limit 8 to yr="2008 - 2013"

KQ 3a-3g, 3i: Dosing Strategies

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. Opioid-Related Disorders/
6. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
7. Drug Administration Schedule/
8. Pain Management/
9. Clinical Protocols/
10. Breakthrough Pain/
11. Dose-Response Relationship, Drug/
12. ((dose$ or dosing) adj7 (strateg$ or adjust$ or titrat$ or taper$)).mp.
13. exp Chronic Pain/
14. (chronic adj2 pain).mp.
15. or/4-6
16. or/7-12
17. 15 and 16
18. (or/13-14) and 17
19. limit 18 to yr="2008 - 2013"

KQ 3h: Tapered Dosing

1. exp Analgesics, Opioid/
2. opioid*.mp.

3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. Opioid-Related Disorders/
6. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
7. Drug Administration Schedule/
8. Pain Management/
9. Clinical Protocols/
10. Breakthrough Pain/
11. Dose-Response Relationship, Drug/
12. ((dose$ or dosing) adj7 (strateg$ or adjust$ or titrat$ or taper$)).mp.
13. exp Chronic Pain/
14. (chronic adj2 pain).mp.
15. or/4-6
16. or/7-12
17. 15 and 16
18. (or/13-14) and 17
19. 18 and (random$ or control$ or trial or cohort or prospective or retrospective).mp.
20. 19 and (taper$ or decreas$ or reduc$).mp.
21. limit 20 to yr="1902 - 2007"

KQ 4a-b: Risk Prediction

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. exp Chronic Pain/
6. (chronic adj2 pain).mp.
7. Opioid-Related Disorders/
8. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
9. 4 and (5 or 6)
10. 7 or 8
11. 9 or 10

12. Decision Support Techniques/
13. "Predictive Value of Tests"/
14. Prognosis/
15. Risk Assessment/
16. Risk Factors/
17. Proportional Hazards Models/
18. "Reproducibility of Results"/
19. "Sensitivity and Specificity"/
20. (sensitivity or specificity).mp.
21. (risk and (predict$ or assess$)).mp.
22. or/12-21
23. 11 and 22
24. limit 23 to yr="2008 - 2013"

KQ 4c: Risk Mitigation

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. (20690)
4. or/1-3 (22725)
5. exp Chronic Pain/ (79)
6. (chronic adj2 pain).mp. (2585)
7. Opioid-Related Disorders/ (571)
8. (opioid adj2 (abuse or addict* or misuse or diversion)).mp. (116)
9. 4 and (5 or 6) (523)
10. 7 or 8 (630)
11. 9 or 10 (1139)
12. Patient Compliance/
13. Health Services Misuse/
14. Substance Abuse Detection/
15. Drug Monitoring/
16. (urine adj7 (screen$ or test$ or detect$)).mp.
17. (abus$ or misus$ or diversion$ or divert$).mp.
18. (opioid$ adj7 (contract$ or agree$)).mp.
19. Contracts/
20. Patient Education as Topic/
21. Drug Overdose/
22. or/12-21
23. ((risk$ adj7 mitigat$) or reduc$).mp.
24. ("risk evaluation and mitigation" or "rems").mp.

25. Risk Reduction Behavior/ or Risk/
26. or/23-25
27. 11 and 22 and 26
28. limit 27 to yr="2008 - 2013"

KQ 4d: Treatment Strategies

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. Opioid-Related Disorders/
6. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
7. Patient Compliance/
8. Health Services Misuse/
9. Substance Abuse Detection/
10. Drug Monitoring/
11. (urine adj7 (screen$ or test$ or detect$)).mp.
12. (abus$ or misus$ or diversion$ or divert$).mp.
13. (opioid$ adj7 (contract$ or agree$)).mp.
14. Contracts/
15. Patient Education as Topic/
16. Drug Overdose/
17. or/7-16
18. Substance Abuse Detection/
19. Opiate Substitution Treatment/
20. Risk Management/
21. or/18-20
22. or/4-6
23. 17 and 21 and 22
24. treatment outcome.mp. or Treatment Outcome/
25. (treatment and (strateg$ or plan$)).mp.
26. 23 and (24 or 25)

Database: PsycINFO

KQ 1 and 2: Comparative Effectiveness and Harms

1. opioid*.mp.
2. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or

dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
3. (chronic and pain).mp.
4. (1 or 2) and 3
5. (random$ or control$ or trial or cohort or prospective or retrospective).mp.
6. 4 and 5
7. limit 6 to yr="2008 - 2014"
8. limit 7 to human

KQ 3a-3g, 3i: Dosing Strategies

1. opioid*.mp.
2. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
3. (chronic and pain).mp.
4. (1 or 2) and 3
5. 4 and (dose or dosing or dosage).mp.
6. limit 5 to human
7. limit 6 to yr="2008 - 2014"

KQ 3h: Tapered Dosing

1. opioid*.mp.
2. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
3. (chronic and pain).mp.
4. (1 or 2) and 3
5. 4 and (taper$ or decreas$).mp.
6. limit 5 to human

KQ 4a-4c: Risk Prediction and Mitigation

1. opioid*.mp.
2. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
3. (chronic and pain).mp.
4. (1 or 2) and 3
5. risk.mp.
6. 4 and
7. limit 6 to human
8. limit 7 to yr="2008 - 2014"

KQ 4d: Treatment Strategies

1. opioid*.mp
2. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp
3. (chronic and pain).mp
4. (1 or 2) and 3
5. 4 and ((treatment and (strateg$ or plan$).mp
6. 5 and (overdose or abuse or misuse or pain or function or “quality of life” or “qol”).mp
7. limit 6 to human

Database: EBSCO CINAHL Plus with Full Text

All Key Questions (except 3h, 4d)

1. (MH "Analgesics, Opioid") OR (MH "Narcotics") OR (MH "Alfentanil") OR "alfentanil" (MH "Alphaprodine") OR "alphaprodine" OR "beta-casomorphins" (MH "Buprenorphine") OR "buprenorphine" OR "carfentanil" (MH "Codeine") OR "codeine" OR (MH "Oxycodone") OR "deltorphin" OR (MH "Dextromethorphan") OR "dextromethorphan" OR "dezocine" OR "dihydrocodeine" OR "dihydromorphine" OR (MH "Enkephalins") OR "enkephalin" OR "ethylketocyclazocine" OR "ethylmorphine" "etorphine" OR (MH "Fentanyl") OR "fentanyl" (MH "Heroin") OR "heroin" "hydrocodone" OR (MH "Dihydromorphinone") OR "hydromorphone" OR "ketobemidone" OR "levorphanol" OR "lofentanil" OR (MH "Meperidine") OR

"meperidine" OR "meptazinol" OR (MH "Methadone") OR "methadone" OR "methadyl acetate" OR (MH "Morphine") OR "morphine" OR (MH "Nalbuphine") OR (MH "Opium") OR "oxycodone" OR "oxymorphone" OR (MH "Pentazocine") OR "pentazocine" OR "phenazocine" OR "phenoperidine" OR "pirinitramide" OR "promedol" OR (MH "Propoxyphene") OR "propoxyphene" OR "remifentanil" OR (MH "Sufentanil") OR "sufentanil" OR "tilidine" OR (MH "Tapentadol") OR "tapentadol"
2. (MH "Chronic Pain") OR "chronic pain"
3. 1 and 2
4. "random*" OR "control*" OR "trial" OR "cohort" OR "prospective" OR "retrospective"
5. 3 and 4
6. Limit 4 to published date 20080101-20131015

KQ 3h: Tapered Dosing

1. (MH "Analgesics, Opioid") OR (MH "Narcotics") OR (MH "Alfentanil") OR "alfentanil" (MH "Alphaprodine") OR "alphaprodine" OR "beta-casomorphins" (MH "Buprenorphine") OR "buprenorphine" OR "carfentanil" (MH "Codeine") OR "codeine" OR (MH "Oxycodone") OR "deltorphin" OR (MH "Dextromethorphan") OR "dextromethorphan" OR "dezocine" OR "dihydrocodeine" OR "dihydromorphine" OR (MH "Enkephalins") OR "enkephalin" OR "ethylketocyclazocine" OR "ethylmorphine" "etorphine" OR (MH "Fentanyl") OR "fentanyl" (MH "Heroin") OR "heroin" "hydrocodone" OR (MH "Dihydromorphinone") OR "hydromorphone" OR "ketobemidone" OR "levorphanol" OR "lofentanil" OR (MH "Meperidine") OR "meperidine" OR "meptazinol" OR (MH "Methadone") OR "methadone" OR "methadyl acetate" OR (MH "Morphine") OR "morphine" OR (MH "Nalbuphine") OR (MH "Opium") OR "oxycodone" OR "oxymorphone" OR (MH "Pentazocine") OR "pentazocine" OR "phenazocine" OR "phenoperidine" OR "pirinitramide" OR "promedol" OR (MH "Propoxyphene") OR "propoxyphene" OR "remifentanil" OR (MH "Sufentanil") OR "sufentanil" OR "tilidine" OR (MH "Tapentadol") OR "tapentadol"
2. (MH "Chronic Pain") OR "chronic pain"
3. 1 and 2
4. "random*" OR "control*" OR "trial" OR "cohort" OR "prospective" OR "retrospective"
5. 3 and 4
6. "taper*" OR "decreas*"
7. 5 and 6
8. Limit 6 to published date 19920101-20071231

KQ 4d: Treatment Strategies

1. (MH "Analgesics, Opioid") OR (MH "Narcotics") OR (MH "Alfentanil") OR "alfentanil" (MH "Alphaprodine") OR "alphaprodine" OR "beta-casomorphins" (MH "Buprenorphine") OR "buprenorphine" OR "carfentanil" (MH "Codeine") OR "codeine" OR (MH "Oxycodone") OR "deltorphin" OR (MH "Dextromethorphan") OR "dextromethorphan" OR "dezocine" OR "dihydrocodeine" OR "dihydromorphine" OR (MH "Enkephalins") OR "enkephalin" OR "ethylketocyclazocine" OR "ethylmorphine" "etorphine" OR (MH "Fentanyl") OR "fentanyl" (MH "Heroin") OR "heroin" "hydrocodone" OR (MH "Dihydromorphinone") OR "hydromorphone" OR "ketobemidone" OR "levorphanol" OR "lofentanil" OR (MH "Meperidine") OR

"meperidine" OR "meptazinol" OR (MH "Methadone") OR "methadone" OR "methadyl acetate" OR (MH "Morphine") OR "morphine" OR (MH "Nalbuphine") OR (MH "Opium") OR "oxycodone" OR "oxymorphone" OR (MH "Pentazocine") OR "pentazocine" OR "phenazocine" OR "phenoperidine" OR "pirinitramide" OR "promedol" OR (MH "Propoxyphene") OR "propoxyphene" OR "remifentanil" OR (MH "Sufentanil") OR "sufentanil" OR "tilidine" OR (MH "Tapentadol") OR "tapentadol"

2. (MH "Chronic Pain") OR "chronic pain"
3. 1 and 2
4. "random*" OR "control*" OR "trial" OR "cohort" OR "prospective" OR "retrospective"
5. 3 and 4
6. "treatment" AND ("strateg*" OR "plan*")
7. 5 and 6
8. Limit 7 to published date 19920101-20071231

Database: EBM Reviews – Cochrane Database of Systematic Reviews

All KQs: Systematic Reviews

1. (opioid$ or alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).ti.
2. 1 and (chronic and pain).mp.
3. limit 2 to full systematic reviews

Appendix B. PICOTS

PICOT	Include	Exclude
Population and Conditions of Interest	• For all KQs: Adults (age >18 years) with various types of chronic pain (defined as pain lasting >3 months), including patients with acute exacerbations of chronic pain (KQ Ig) • For KQs 1b, 2b: Subgroups as defined by specific pain condition, patient demographics (e.g., age, race, ethnicity, sex), comorbidities (including medical comorbidities and mental health disorders, including past or current alcohol or substance abuse and related disorders, and those at high risk for addiction); • For KQ 2b: Subgroups also defined by the dose of opioids used	• Patients with pain at end of life, acute pain, pregnant or breastfeeding, patients treated with opioids for addiction
Interventions	• For KQs 1, 2, 3: Long- or short-acting opioids (including tapentadol) used as long-term therapy (defined as use of opioids on most days for >3months) • For KQ 1d: Also include combination of opioid plus nonopioid therapy (pharmacological or nonpharmacological) • For KQ 1Va, b: Risk prediction instruments • For KQ 1Vc: 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, use of abuse deterrent formulations • For KQ 1Vd: Opioid management strategies	• Intravenous or intramuscular administration of opioids • Tramadol
Comparators	• For KQs 1a, 1b, 2a, 2b: Opioid vs. placebo or nonopioid therapy (including usual care) • For KQ 1c: Opioid vs. nonopioid therapy (pharmacological or nonpharmacological [e.g., exercise therapy, cognitive behavioral therapy, interdisciplinary rehabilitation]) • For KQ 1d: Opioid plus nonopioid therapy (pharmacological or nonpharmacological) vs. opioid or nonopioid therapy alone • For KQ 3a: Comparisons of different dose initiation and titration strategies • For KQ 3b: Short- vs. long-acting opioids • For KQ 3c: One long-acting opioid vs. another long-acting opioid • For KQ 3d: Short- plus long-acting opioid vs. long-acting opioid • For KQ 3e: Scheduled, continuous vs. as-needed dosing of opioid • For KQ 3f: Dose escalation vs. dose maintenance or use of maximum dosing thresholds • For KQ 3g: Opioid rotation vs. continuation of current opioid • For KQ 3h: Comparisons of different methods for treating acute exacerbations of chronic pain • For KQ 3i: Decreasing or tapering opioid doses vs. continuation of opioids • For KQ 3j: Comparisons of different tapering protocols and strategies • For KQ 4a: Risk prediction instruments vs. reference standard for overdose or opioid addiction, abuse or misuse • For KQ 4b: Risk prediction instruments vs. nonuse of risk prediction instruments • For KQ 4c: Risk mitigation strategies (see Interventions above) vs. nonuse of risk mitigation strategies • For KQ 4d: Comparisons of treatment strategies for managing patients with addiction to prescription opioids	

PICOT	Include	Exclude
Outcomes	• For KQs 1, 3, 4: Pain (intensity, severity, bothersomeness), function (physical disability, activity limitations, activity interference, work function), and quality of life (including depression), doses of opioids used • Also for KQs 2, 3, 4: Overdose, opioid use disorder, addiction, abuse, and misuse; other opioid-related harms (including gastrointestinal, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)	• Intermediate outcomes (e.g., pharmacokinetics/pharmacodynamics, drug-drug interactions, dose conversions)
Timing	• Any duration for outcomes related to overdose and injuries (falls, fractures, motor vehicle accidents), studies on treatment of acute exacerbations of chronic pain, studies on dose initiation and titration, and studies on discontinuation of opioid therapy • For other outcomes: >1 year	
Setting	• Outpatient settings (e.g., primary care, pain clinics, other specialty clinics)	• Addiction treatment settings, inpatient settings
Study Design	• For all KQs, randomized controlled trials, controlled cohort studies, and case-control studies (controlled observational studies must have performed adjustment on potential confounders) • For all KQs, we excluded uncontrolled observational studies, case series, and case reports, with the exception of KQ 2a for which we included uncontrolled observational studies of patients with chronic pain prescribed long-term opioid therapy for at least one year that used predefined methods to assess rates of abuse, misuse, or addiction • For KQ 4a, we included studies that evaluated the predictive ability of risk prediction instruments, and excluded studies that did not evaluate the performance of a risk prediction instrument against a reference standard.	

KQ, key question; PICOT=populations, interventions, comparators, outcomes, timing, setting.

Appendix C. Included Studies*

Akbik H, Butler SF, Budman SH, et al. Validation and clinical application of the screener and opioid assessment for patients with pain (SOAPP). J Pain Symptom Manage. 2006;32(3):287-93. PMID: 16939853.

Allan L, Richarz U, Simpson K, et al. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naive patients with chronic low back pain. Spine. 2005;30(22):2484-90. PMID: 16284584.

Ashburn MA, Slevin KA, Messina J, et al. The efficacy and safety of fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic pain. Anesth Analg. 2011;112(3):693-702. PMID: 21304148.

Banta-Green CJ, Merrill JO, Doyle SR, et al. Opioid use behaviors, mental health and pain--development of a typology of chronic pain patients. Drug Alcohol Depend. 2009;104(1-2):34-42. PMID: 19473786.

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(10):1776-82. PMID: 20712819.

Carman WJ, Su S, Cook SF, et al. Coron0ary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. Pharmacoepidemiol Drug Saf. 2011;20(7):754-62. PMID: 21567652.

Compton PA, Wu SM, Schieffer B, et al. Introduction of a self-report version of the prescription drug use questionnaire and relationship to medication agreement noncompliance. J Pain Symptom Manage. 2008;36(4):383-95. PMID: 18508231.

Cowan DT, Wilson-Barnett J, Griffiths P, et al. A survey of chronic noncancer pain patients prescribed opioid analgesics. Pain Med. 2003;4(4):340-51. PMID: 14750910.

Cowan DT, Wilson-Barnett J, Griffiths P, et al. 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(2):113-21. PMID: 15773875.

Davies A, Sitte T, Elsner F, et al. Consistency of efficacy, patient acceptability, and nasal tolerability of fentanyl pectin nasal spray compared with immediate-release morphine sulfate in breakthrough cancer pain. J Pain Symptom Manage. 2011;41(2):358-66. PMID: 21334555.

Deyo RA, Smith DH, Johnson ES, et al. Prescription opioids for back pain and use of medications for erectile dysfunction. Spine. 2013;38(11):909-15. PMID: 23459134.

Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study.[summary for patients in Ann Intern Med. 2010;152(2):I-42]. Ann Intern Med. 2010;152(2):85-92. PMID: 20083827.

Edlund MJ, Martin BC, Russo JE, et al. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain. Clin J Pain. 2014;30(7):557-64. PMID: 24281273.

Fleming MF, Balousek SL, Klessig CL, et al. Substance use disorders in a primary care sample receiving daily opioid therapy. J Pain. 2007;8(7):573-82. PMID: 17499555.

Gomes T, Mamdani MM, Dhalla IA, et al. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med. 2011;171(7):686-91. PMID: 21482846.

Gomes T, Redelmeier DA, Juurlink DN, et al. Opioid dose and risk of road trauma in Canada: a population-based study. JAMA Intern Med. 2013;173(3):196-201. PMID: 23318919.

Hartung DM, Middleton L, Haxby DG, et al. Rates of adverse events of long-acting opioids in a state Medicaid program. Ann Pharmacother. 2007;41(6):921-8. PMID: 17504834.

Hojsted J, Nielsen PR, Guldstrand SK, et al. Classification and identification of opioid addiction in chronic pain patients. Eur J Pain. 2010;14(10):1014-20. PMID: 20494598.

Jamison RN, Raymond SA, Slawsby EA, et al. Opioid therapy for chronic noncancer back pain. a randomized prospective study. Spine. 1998;23(23):2591-600. PMID: 9854758.

Jones T, Moore T. Preliminary data on a new opioid risk assessment measure: the Brief Risk Interview. J Opioid Manag. 2013;9(1):19-27. PMID: 23709300.

Krebs EE, Becker WC, Zerzan J, et al. Comparative mortality among Department of Veterans Affairs patients prescribed methadone or long-acting morphine for chronic pain. Pain. 2011;152(8):1789-95. PMID: 21524850.

Li L, Setoguchi S, Cabral H, et al. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. J Intern Med. 2013;273(5):511-26. PMID: 23331508.

Li L, Setoguchi S, Cabral H, et al. 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(4):559-69. PMID: 23639937.

Mitra F, Chowdhury S, Shelley M, et al. A feasibility study of transdermal buprenorphine versus transdermal fentanyl in the long-term management of persistent non-cancer pain. Pain Med. 2013;14(1):75-83. PMID: 23320402.

Moore TM, Jones T, Browder JH, et al. A comparison of common screening methods for predicting aberrant drug-related behavior among patients receiving opioids for chronic pain management. Pain Med. 2009;10(8):1426-33. PMID: 20021601.

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(2):288-96. PMID: 21111684.

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(4):287-99. PMID: 17449988.

Portenoy RK, Messina J, Xie F, et al. Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain: a randomized, placebo-controlled study. Curr Med Res Opin. 2007;23(1):223-33. PMID: 17207304.

Ralphs JA, Williams AC, Richardson PH, et al. Opiate reduction in chronic pain patients: a comparison of patient-controlled reduction and staff controlled cocktail methods. Pain. 1994;56(3):279-88. PMID: 8022621.

Reid MC, Engles-Horton LL, Weber MB, et al. Use of opioid medications for chronic noncancer pain syndromes in primary care. J Gen Intern Med. 2002;17(3):173-9. PMID: 11929502.

Saffier K, Colombo C, Brown D, et al. Addiction severity index in a chronic pain sample receiving opioid therapy. J Subst Abuse Treat. 2007;33(3):303-11. PMID: 17376639.

Salzman RT, Roberts MS, Wild J, et al. 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(4):271-9. PMID: 10534967.

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(4):310-5. PMID: 20049546.

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 Manag. 2010;6(6):385-95. PMID: 21268999.

Simpson DM, Messina J, Xie F, et al. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study. Clin Ther. 2007;29(4):588-601. PMID: 17617282.

Tennant FS, Jr., Rawson RA. Outpatient treatment of prescription opioid dependence: comparison of two methods. Arch Intern Med. 1982;142(10):1845-7. PMID: 6181749.

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(3):193-8. PMID: 19333168.

Webster LR, Slevin KA, Narayana A, et al. Fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic cancer and noncancer pain: a randomized, double-blind, crossover study followed by a 12-week open-label phase to evaluate patient outcomes. Pain Med. 2013;14(9):1332-45. PMID: 23855816.

Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. Pain Med. 2005;6(6):432-42. PMID: 16336480.

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(5):416-27. PMID: 20602712.

***Appendix C is the reference list for all appendixes.**

Appendix D. Excluded Studies

No Author. Use of opioids to control arthritis pain under scrutiny. Increase in falls, fractures in older adults attributed to narcotic painkillers, such as oxycodone, Vicodin or Percocet. Duke Med Health News. 2013;19(5):7. PMID: 23802330. *Excluded: wrong study design*

Abrahamsen B, Brixen K. Mapping the prescriptiome to fractures in men--a national analysis of prescription history and fracture risk. Osteoporos Int. 2009;20(4):585-97. PMID: 18690484. *Excluded: wrong population.*

Adams EH, Breiner S, Cicero TJ, et al. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. J Pain Symptom Manage. 2006;31(5):465-76. PMID: 16716877. *Excluded: wrong study design.*

Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of Tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. Clin Drug Investig. 2010;30(8):489-505. PMID: 20586515. *Excluded: inadequate duration.*

Agarwal S, Polydefkis M, Block B, et al. Transdermal fentanyl reduces pain and improves functional activity in neuropathic pain states. Pain Med. 2007;8(7):554-62. PMID: 17883740. *Excluded: inadequate duration.*

Albert S, Brason FW, 2nd, Sanford CK, et al. Project Lazarus: community-based overdose prevention in rural North Carolina. Pain Med. 2011;12 Suppl 2:S77-85. PMID: 21668761. *Excluded: wrong population.*

Amass L, Bickel WK, Higgins ST, et al. A preliminary investigation of outcome following gradual or rapid buprenorphine detoxification. J Addict Dis. 1994;13(3):33-45. PMID: 7734458. *Excluded: wrong population.*

Amass L, Ling W, Freese TE, et al. Bringing buprenorphine-naloxone detoxification to community treatment providers: the NIDA Clinical Trials Network field experience. American Journal on Addictions. 2004;13 Suppl 1:S42-66. PMID: 15204675. *Excluded: wrong population.*

Amato J-N, Marie S, Lelong-Boulouard V, et al. Effects of three therapeutic doses of codeine/paracetamol on driving performance, a psychomotor vigilance test, and subjective feelings. Psychopharmacology. 2013;228(2):309-20. PMID: 23474890. *Excluded: wrong comparator.*

Amato P. Clinical experience with fortnightly buprenorphine/naloxone versus buprenorphine in Italy: preliminary observational data in an office-based setting. Clin Drug Investig. 2010;30 Suppl 1:33-9. PMID: 20450244. *Excluded: wrong population.*

Anderson VC, Burchiel KJ. A prospective study of long-term intrathecal morphine in the management of chronic nonmalignant pain. Neurosurgery. 1999;44(2):289-300. PMID: 9932882. *Excluded: wrong intervention.*

Annemans L. Pharmacoeconomic impact of adverse events of long-term opioid treatment for the management of persistent pain. Clin Drug Investig. 2011;31(2):73-86. PMID: 21067250. *Excluded: wrong publication type.*

Anonymous. Tapentadol. Acute or chronic pain: No therapeutic advance. Prescrire Int. 2014: 121-4. PMID: 24926510. *Excluded: wrong publication type*

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Appendix E. Data Abstraction Tables

Appendix Table E1. Uncontrolled Studies of Long-term Opioid Use and Abuse, Misuse, and Related Outcomes

Author, Year	Type of Study Setting Duration	Eligibility Criteria	Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse	Main Results	Quality
Banta-Green, 2009	Retrospective cohort Integrated group health system United States	Patients aged 21-79 with chronic opioid prescriptions over at least 3 years (filling ≥10 opioid prescriptions in a 12-month period or filling a prescription for at least a 120-day supply and ≥6 prescriptions in a 12-month period) Exclude: patients with cancers other than benign, nonmelanoma skin cancer	n=704 Mean age: 55 years Female sex: 62% Race: 89% White	Dose: mean 50 mg/day MED Duration: NR Indication: NR	Factor scores based on DSM-IV and PDUQ criteria UDT: not specified	Opioid dependence: 13% (91/704) Opioid abuse without dependence: 8% (56/704)	Fair
Boscarino, 2010	Cross-sectional study, outpatients from nine primary care (83%) and 3 specialty clinics (17%), based on 1 year of observation	≥4 physician orders for opioid therapy in past 12 mos., identified from E.H.R.; mean prescriptions=10.7 Exclude: cancer	n=705 Age: 18-64: 79% 65+: 21% Female sex: 61% White race: 98%	Dose: NR Duration: mean of 10.7 prescriptions over 1 year Indication: noncancer, otherwise not described	Diagnostic interview: CIDI; DSM-IV criteria for opioid dependence	25.8% (95% CI: 22.0-29.9) met criteria for current opioid dependence; 35.5% (95% CI: 31.1-40.2) met criteria for lifetime dependence Factors associated with dependence: Age <65 years (OR 2.3, 95% CI 1.6 to 3.5) History of opioid abuse (OR 3.8, 95% CI 2.6 to 5.7) History of high dependence severity (OR 1.8, 95% CI 1.4 to 2.5) History of major depression (OR 1.3, 95% CI 1.0 to 1.6), Current use of psychotropic medications (OR 1.7, 95% CI 1.2 to 2.5)	Fair

Author, Year	Type of Study Setting Duration	Eligibility Criteria	Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse	Main Results	Quality
Carrington Reid, 2002	Retrospective cohort Two primary care centers United States	Patients who received ≥6 months of opioid prescriptions during a 1-year period for noncancer pain and were not on methadone maintenance.	n=98 (50 at VA and 48 at urban primary care clinic) VA site vs. urban primary care site Median age: 54 vs. 55 years Female sex: 8% vs. 67% Race: 88% White, 12% Black vs. 52% White, 36% Black, 10% Hispanic Mean duration of pain: 10 vs. 13 years	VA site vs. urban primary care site Dose: NR Duration: NR Indication: 44% low back, 10% injury-related, 8% diabetic neuropathy, 16% degenerative joint disease, 4% headache, 10% spinal stenosis vs. 25% low back pain, 13% injury-related, 10% diabetic neuropathy, 13% degenerative joint disease, 13% headache, 4% spinal stenosis	Chart review for lost or stolen opioids, documented use of other sources to obtain opioids, and requests for ≥2 early refills UDT: not specified	VA site vs. urban primary care site Opioid abuse behaviors: 24% (12/50) vs. 31% (15/48) Median time of onset of abuse behaviors: 24 months Factors associated with decreased risk of opioid abuse behaviors: No history of substance use disorder (adjusted OR 0.72, 95% CI 0.45 to 1.1) Age (adjusted OR 0.94, 95% CI 0.94 to 0.99)	Fair
Compton, 2008	Prospective cohort VA pain clinic United States One year	Consecutive chronic nonmalignant pain patients receiving opioids Exclude: patients with diagnosed substance use disorder	n=135 Mean age: 53 years Female sex: 6% Race: NR Baseline VAS score: 6.75	Dose: NR Duration: NR Indication: 77% musculoskeletal, 19% neuropathic, 4% multicategory	Chart review for opioid discontinuation due to medication agreement violation (including for opioid misuse or abuse) UDT: not specified	Discontinuation due to medication agreement violation: 28% (38/135) Discontinuation due to specific problematic opioid misuse behaviors: 8% (11/135) Overdose deaths: none reported	Fair

Author, Year	Type of Study Setting Duration	Eligibility Criteria	Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse	Main Results	Quality
Cowan, 2003	Cross-sectional Pain clinic United Kingdom	Patients attending pain clinic and receiving controlled-release oral morphine sulfate or transdermal fentanyl	n=104 Mean age: 55.4 years Female sex: 39% Race: NR Mean duration of pain: 10.5 years	Dose: NR Duration: mean 14.1 months Indication: 34% degenerative disease, 24% failed back/neck surgery syndrome, 10% complex regional pain syndrome, 10% osteoarthritis	SUQ UDT: not specified	Self-reported addiction: 1.9% (2/104) Craving opioids: 2.9% (3/104) Has taken drugs to enhance the effect of opioids: 0.9% (1/104) Has used alcohol to enhance the effect of opioids: 0.9% (1/104)	Fair
Edlund, 2014	Retrospective HMO, PPO and point-of-service 2000-2005 database review United States	Patients age ≥18 years with a new chronic non-cancer pain diagnosis, no cancer diagnosis, and no opioid use or opioid use disorder diagnosis in prior 6 months	n=568,640 (197,269 prescribed opioids in first year; of these, 5.5% had chronic use (>90 days supply) Mean age not reported; 11% age 18-30, 20% age 31-40, 27% age 41-50, 30% age 51-64, 12% ≥age 65 Female sex: 58% Race: NR Mean duration of pain: all patients newly diagnosed	Dose: Among those with any opioid use, median = 36 mg/day MED. Daily MED categorized as none, low (1-36 mg), medium (36-120 mg), or high (≥120 mg). Duration: Mean NR; users identified as "chronic" had ≥91 days Indication: NR; inclusion criteria required newly diagnosed chronic non-cancer pain	Diagnosis of opioid abuse or dependence (ICD-9-CM code 304.00 or 305.50) within 18 months of first chronic non-cancer pain diagnosis	Opioid abuse or dependence - No opioid prescription: 0.004% (150/371,371) Low dose, chronic: 0.72% (50/6902) Medium dose, chronic: 1.28% (47/3654) High dose, chronic: 6.1% (23/378) Abuse or dependence, opioid use vs. no use - Low dose, chronic: aOR* 15 (95% CI 10 to 21) Medium dose, chronic: aOR 29 (95% CI 20 to 41) High dose, chronic: aOR 122 (95% CI 73 to 206) **Adjusted for age, sex, number of tracer pain sites, number of nonsubstance mental health disorders, previous substance abuse or dependence diagnosis, Charlson score.*	Fair

Author, Year	Type of Study Setting Duration	Eligibility Criteria	Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse	Main Results	Quality
Fleming, 2007 See also: Saffier, 2007	Primary care practices of 235 physicians	Daily opioids over past 3 months; 96% had received opioids for 12 months Exclusions: cancer pain	n=801 Mean age: 48.6 Female sex: 68% Race: 75.6% White; 23.1% African American; 1% other Disability income: 48%	Mean daily dose: 92 MEQ/d Duration: ≥12 mos. For 96% Indication: Osteoarthritis: 24%; low back pain, herniated disc or stenosis: 25%; migraine 8%; neuropathy 5%	In person interviews with ASI; SDSS; Aberrant Behavior 12-item List UDT: collected at end of interview	Met DSM-4 criteria for opioid dependence: 3.1% Met DSM-4 criteria for opioid abuse: 0.6% Any illicit drug on UDS: 24% (mostly marijuana) Aberrant behaviors: purposely oversedated: 24% (186/785) Felt intoxicated from pain med: 33% (260/785) Requested early refills: 45% (359/785) Increased dose on own: 37% (288/785) Meds lost or stolen: 30% (236/785) Used opioid purpose other than pain: 16% (125/785) Drank alcohol to relieve pain: 20% (154/785)	Fair
Hojsted, 2010	Cross-sectional Pain clinic Denmark	Adults with chronic noncancer pain Exclude: patients suffering from cognitive dysfunction, in poor health due to other condition, or did not use any pain medication	n=253, of which 187 were receiving opioid therapy (207 total and 153 receiving opioids returned questionnaire) Mean age: 52 years Female sex: 64% Race: NR Mean pain score: NR Receiving opioids: 74% (187/253) Indication: 93% noncancer pain, 7% cancer pain	Dose: NR Duration: mean 6.8 years (among those who completed questionnaire, n=207) Indication: 28% nociceptive pain, 33% neuropathic pain, 39% mixed nociceptive and neuropathic	Addiction screening by physician and nurse (blinded to each other) using the ICD-10 and Portenoy's Criteria; a positive screen by either provider was considered positive UDT: not specified	Addiction to opioids or hypnotics, ICD-10: 11.1% (28/253) Addiction to opioids, ICD-10: 14.4% (27/187) Addiction to opioids or hypnotics, Portenoy's Criteria: 14.6% (37/253) Addiction to opioids, Portenoy's Criteria: 19.3% (36/187) Overdose deaths: NA	Fair

Author, Year	Type of Study Setting Duration	Eligibility Criteria	Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse	Main Results	Quality
Portenoy, 2007	Prospective registry study 35 pain clinics United States Three years (mean duration 23.8 months)	Adult patients who had participated in any of five previous CCTs of CR oxycodone for noncancer pain	n=227 Mean age: 56 years Female sex: 57% Race: 90% White BPI average pain score: 6.4	Dose: mean 52.5 mg/day Duration: mean 541.5 days Indication: 38% osteoarthritis, 31% diabetic neuropathy, 31% low back pain	Physician-completed brief questionnaire assessing problematic drug-related behavior with verification by an independent panel of experts UDT: not specified	Problematic drug-related behavior identified by physicians: 5.7% (13/227) Problematic drug-related behavior adjudicated by expert panel as positive and meeting DSM-IV criteria: 0 Problematic drug-related behavior adjudicated by expert panel as positive: 2.2% (5/227) Problematic drug-related behavior adjudicated by expert panel as possible: 0.4% (1/227) Problematic drug-related behavior adjudicated by expert panel as withdrawal: 0.4% (1/227) Problematic drug-related behavior adjudicated by expert panel as alleged: 2.2% (5/227) Problematic drug-related behavior adjudicated by expert panel as negative: 0.4% (1/227) Overdose deaths: 1 (phenylpropanolamine, oxycodone, and alcohol)	Fair

Author, Year	Type of Study Setting Duration	Eligibility Criteria	Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse	Main Results	Quality
Schneider, 2010	Chart review Single center pain clinic United States	Patients receiving opioid therapy for ≥1 year	n=197 Mean age: 49 years Female sex: 67% Race: NR	Dose: mean 180 mg/day MED (long acting), 49 mg/day MED (short acting) Duration: mean 4.7 years Indication: 51% back pain, 10% neck pain, 9% fibromyalgia, 8% other myofascial pain	UDT: immunoassay followed by confirmatory GC/MS	Positive UDT: 8.7% (14/161) Aberrant drug-related behaviors noted in chart: 15.7% (31/197)	Fair
Wasan, 2009	Cross-sectional 5 pain clinics United States	Patients with noncancer chronic pain receiving opioid therapy	n=622 Mean age: 50.4 years Female sex: 55% Race: 80% White Mean pain score: 5.96	Dose: NR Duration: mean 6.2 years Indication: 61% low back pain	POTQ, PUDQ, and UDT	Positive scores of ≥2 on POTQ: 24% (115/480) Score ≥11 on PDUQ: 29.1% (130/447) Positive UDT: 37.1% (134/356)	Fair

Note: The references are located in Appendix C.

ASI=Addiction Severity Index; CCT=case control trial; CR=case report; CI=confidence interval; CIDI= Composite International Diagnostic Interview; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-V=Diagnostic and Statistical Manual of Mental Disorders, 5th edition; GC/MS= Gas Chromatography with Mass Spectrometry confirmatory test; ICD-10=International Statistical Classification of Diseases and Related Health Problems, tenth revision; MED=morphine equivalent dose; MEQ/d=milliequivalent/hydrogen; NR=not relevant; PDUQ= Prescription Drug Use Questionnaire; POTQ=Prescription opioid therapy questionnaire; SDSS= Substance dependence severity scale; UDT=urine drug testing; VA=Veterans Administration; VAS= Visual Analog Scale

Appendix Table E2. Observational Studies of Long-Term Opioid Use and Overdose

Author, year	KQ	Type of study, setting	Eligibility criteria	Comparison groups	Population characteristics	Method for Assessing Outcomes and Confounders
Dunn, 2010	KQ2a, b	Retro-spective cohort (Group Health) United States	Age > 18 years starting new episode of opioid use (no opioids in past 6 mos) from 1997 -2005; having 3 or more opioid scripts filled in first 90 days of episode; diagnosis of chronic noncancer pain in 2 wks before first opioid script.	Morphine equivalent doses: A. 1-<20 mg/day B. 20-<49 mg/day C. 50-<99 mg/day D. >=100 mg/day	Mean (SD; range) age (years): 54 (16.8; 18-99) Female sex: 59.6% Race: NR Smoking: 29.5% Depression: 26.9% Substance abuse: 6.2% Charlson Score, mean (SD; range): 0.71 (1.48;0-14) Pain diagnosis: 37.9% back; 30.3% extremity; 12.7% osteoarthritis; 12.3% injury, contusion, or fracture;8.9% neck Opioid dose, mean (median): 13.3 mg (6.0 mg) Sedative-hypnotic use, any: 74.7% Muscle relaxant: 52.3% Benzodiazepine: 42.7% Opioid: Hydrocodone: 46.3% Oxycodone: 24.5% Codeine combination: 11.6% Long-acting morphine: 6.2% Any short acting opioid: 90.4% Any long-acting opioid: 9.6%	All patients in HMO meeting inclusion criteria

Author, year	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Dunn, 2010	Screened: Not reproted Eligible: Not reported Enrolled: 9,940 Mean duration of follow-up (range): 42 mos (<1-119); Analyzed: All included in analysis Loss to followup: 61% had complete followup from cohort entry until end of study or event occurred; 32% left GHC during study; 7% died	Sedative-hypnotic use as time-varying covariate Age Sex Smoking Depression diagnosis Substance abuse diagnosis Index pain diagnosis Chronic disease comorbidity adjustors (RxRisk & Charlson)	51 patients with overdose events (148 per 100,000 person-years); 40 serious overdose events (116 per 100,000 person-years); 6 fatal overdose events (17 per 100,000 person-years) Rate of any overdose per 100,000 person-years (95% CI); HR (95% CI) No opioid: 36 (13-70); 0.31 (0.12-0.80); 6 overdose events A. (referent): 160 (100-233); 1.0 B. 260 (95-505); 1.44 (0.57-3.62) C. 677 (249-1317); 3.73 (1.47-9.5) D. 1791 (894-2995); 8.87 (3.99-19.72) Opioid dose, any: 256 (187-336); 5.16 (2.14-12.48); 45 overdose events HR, serious events (95% CI) No opioid: 0.19 (0.05-0.68); A. (referent): 1.0 B. 1.19 (0.4-3.6); C. 3.11 (1.01-9.51); D. 11.18 (4.8-26.03); Opioid dose, any: 8.39 (2.52-27.98)	National Institute of Drug Abuse and Wellcome Trust	Fair

Author, year	KQ	Type of study, setting	Eligibility criteria	Comparison groups	Population characteristics	Method for Assessing Outcomes and Confounders
Gomes, 2011	KQ2b	Case-Control Canada	Residents aged 15-64 with public drug coverage and an opioid for nonmalignant pain (1997-2006)	Cases: Died of an opioid-related cause (n=498 matched a control) Controls: received opioids (n=1714) A. 1-<20 mg/day B. 20-<50 mg/day C. 50-<100 mg/day D. 100-<200 mg/day E. >=200 mg/day	Total cohort n= 607,156 Mean age (years): 44.49 vs 44.72 Gender (not reported which one): 58.8% vs 58.0%	Controls matched on disease risk index (0.2 standard deviation caliper), age, gender, index year, and Charlson

Note: The references are located in Appendix C.

CI=confidence interval; EtOH=ethanol; GHC=Group Health Cooperative; HMO=Health Maintenance Organization; HR=hazard ratio; ICES= Institute for Clinical Evaluative Sciences; MOHLTC= Ontario Ministry of Health and Long-Term Care; NR=not relevant; RxRisk=drug index for prescription drugs

Author, year	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Gomes, 2011	Screened: 1463 Eligible:1179 Primary-analysis: 593 with 498 matched Secondary-analysis: 873 with 781 matching	Opioid exposure categorized by Average Daily Dose: <20mg, 20-49mg, 50-99mg, 100-199mg, 200+mg. Logistic models adjusted for: duration, income, history of EtOH abuse, interacting prescription drugs, total number of different opioids dispensed, long-acting opioid used, number of physicians prescribing opioids, number of pharmacies dispensing opioids	Risk estimates reported as adjusted OR Risk of opioid overdose death A. 1 (reference) B. 1.32 (0.94-1.84) C. 1.92 (1.30-2.85) D. 2.04 (1.28-3.24) E. 2.88 (1.79-4.63) Secondary using 120-day exposure window risk of opioid overdose death A. 1 (reference) B. 0.93 (0.60-1.42) C. 1.31 (0.86-1.99) D. 1.47 (0.98-2.19) E. 2.24 (1.62-3.10)	MOHLTC Drug Innovation Fund and ICES, a nonprofit research institute sponsored by the Ontario MOHLTC	Good

Appendix Table E3. Observational Studies of Long-Term Opioid Use and Fractures

Author, year	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics
Li, 2013	KQ2a	Nested case control United Kingdom	Cohort: Patients with non-cancer pain with at least 1 opioid prescription between 1/1/90 and 12/31/08 in the General Practice Research Database Cases (n=21,739): First-time diagnosed fracture of the hip, humerus, or wrist during 1990-2008, age 18-80 years, >2 years of medical history before index date; excluding patients with cancer, dementia, metabolic bone disease, Cushing syndrome, hyperparathyroidism, long-term immobiliation, or alcohol or drug abuse, fracture within 2 years, MVA within 90 days, osteoporosis diagnosis prior to index date Controls (n=85,326): Up to 4 controls without fracture selected for each case, matched on age, sex, index date, and general practice	A. Opioid nonuse B. Current cumulative opioid use 1 prescription C. 2-3 opioid prescriptions D. 4-5 opioid prescriptions E. 6-20 opioid prescriptions F. 21-50 opioid prescriptions G. 51-100 opioid prescriptions H. >100 opioid prescriptions 1. Opioid nonuse 2. Current use 3. Recent use 4. Past use	Mean age (years): 62 Female sex: 77% Race: NR Pain condition: NR Pain duration: NR Pain severity: NR Mean dose:NR Most commonly prescribed opioids: dihydrocodeine, codeine, propoxyphene, tramadol

Author, year	Method For Assessing Outcomes and Confounders	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Li, 2013	Used General Practice Research Database, in which drug exposures and diagnoses (including fracture) have been validated	Screened: NR Eligible: NR Enrolled: NR Analyzed: 21,739 fracture cases and 85,326 controls Number not analyzable: NR	Smoking, BMI, number of general practice visits, recorded years before index date, opioid use (new vs. prevalent), comorbidities, comedications, types of pain, recent/past opioid use (matched on age, sex, index date, and general practice)	Adjusted OR for risk of hip, humerus, or wrist fracture A. 1 (reference) B. 2.70 (95% CI 2.34-3.13 C. 1.90 (95% CI 1.67-2.17) D. 1.44 (95% CI 1.22-1.69) E. 1.17 (95% CI 1.08-1.27) F. 1.06 (95% CI 0.98-1.15) G. 1.06 (95% CI 0.96-1.16) H. 1.12 (95% CI 0.99-1.25) 1. 1 (reference) 2. 1.27 (95% CI 1.21-1.33) 3. 1.05 (95% CI 0.99-1.13) 4. 0.96 (95% CI 0.92-1.01)	None	Good

Author, year	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics
Saunders, 2010	KQ2a, b	Cohort, Group Health Cooperative United States	Age 60+, initiating opioids (no opioid prescriptions in prior 6 months) with 3+ prescriptions in 90 days and a diagnosis of non-cancer pain 2-3 weeks prior to the index prescription. Exclusions: Cancer, <270 days enrollment in health plan in the year prior to index.	Opioid dose per day (mg/day): A: Not currently using B: 1-<20 mg/day C: 20-<50 mg/day D: ≥50 mg/day E: Any use	Mean age (years): 73 Female sex: 66% Race: NR Depression diagnosis: 22% Substance abuse diagnosis: 3.8% Dementia diagnosis: 4.8% Prior fracture: 2.6% HRT/bisphosphonate use: 34% Rxrisk score, mean (SD): 4272 (2455) Charlson Index , mean (SD): 1.32 (2.0) Pain diagnosis at index visit 42% back pain, 4.8% neck pain, 25% osteoarthritis, 2.4% headache, 34% extremity pain, 5.3% abdominal pain/hernia, 0.6% menstrual/menopausal pain, 0.2% temporomandibular disorder pain Mean morphine equivalent daily dose (mg): (s.d.) 12.8 mg (17.0) Sedative hypnotic use: 60% Antidepressant use: 57% Opioid prescribed: Hydrocodone: 42% Oxycodone: 24% Codeine combination: 14% Long-acting morphine: 8.3%

Note: The references are located in Appendix C.

CI=confidence interval; HRT=hormone replacement therapy; ICD-9=International Classification of Diseases; KQ=key question; NR=not relevant; RxRisk= drug index for prescription drugs

Author, year	Method For Assessing Outcomes and Confounders	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Saunders, 2010	Fractures initially identified by ICD-9 codes (800xx-804xx; 807xx-809xx; 810xx-829xx; 2000-2006, excluded vertebral fractures) and verified by medical record review; medication data from Group Health Cooperative automated pharmacy files (over 90% of prescriptions); covariates from automated health care data	Screened: ~500,000 Eligible, enrolled, and analyzed: 2,341 Loss to followup: Not reported Duration of followup (mean, person-months) (SD): 32.7 (21.3)	Age, sex, tobacco use, depression diagnosis, substance abuse diagnosis, dementia diagnosis, index pain diagnosis, chronic disease comorbidity adjustors, sedative-hypnotic use, antidepressant use, HRT/bisphosphonate use, and prior fractures.	Fracture rate: 5.0%/year Adjusted HRs for risk of fracture A: 1 (reference) B: 1.20 (95% CI 0.92, 1.56) C: 1.34 (95% CI 0.89, 2.01) D: 2.00 (95% CI 1.24, 3.24) E: 1.28 (95% CI 0.99, 1.64)	National Institute of Drug Abuse	Fair

Appendix Table E4. Observational Studies of Long-Term Opioid Use and Cardivascular Outcomes

Author, Year	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics
Carman, 2011	KQ2a, b	Retrospective cohort United States	Claim submitted for dispensing of opioids or COX-2 inhibitors for ≥180 days from July 2002 to December 2005, patients aged ≥18 years; controls from general populations matched on age, sex, and cohort entry date Exclude: History of MI or revascularization, cancer	A. Opioids (n=148,657) B. Rofecoxib (n=44,236) C. Celecoxib (n=64,072) D. Valdecoxib (n=20,502) E. General population not using opioids or COX-2 inhibitors (n=148,657) 1. 0 to <1350 mg MED per 90 days 2. 1350 to <2700 mg MED per 90 days 3. 2700 to <8100 mg MED per 90 days 4. 8100 to <18,000 mg MED per 90 days 5. ≥18,000 mg MED per 90 days	**A vs. B vs. C vs. D vs. E** Age 18-29 years: 4.7% vs. 1.2% vs. 0.8% vs. 1.2% vs. 4.7% Age 30-39 years: 16.3% vs. 5.4% vs. 4.1% vs. 5.3% vs. 16.3% Age 40-49 years: 33.9% vs. 20.7% vs. 17.6% vs. 20.1% vs. 33.9% Age 50-64 years: 36.7% vs. 56.0% vs. 56.3% vs. 56.5% vs. 36.7% Age ≥65 years: 8.4% vs. 16.6% vs. 21.2% vs. 16.9% vs. 8.4% Female sex: 40.3% vs. 39.5% vs. 39.6% vs. 34.9% vs. 40.3% Diabetics: 11.7% vs. 10.2% vs. 12.4% vs. 11.1% vs. 4.1% Pain condition: NR Duration of pain: NR severity of pain: NR Opioids prescribed: NR

Appendix Table E4. Observational Studies of Long-Term Opioid Use and Cardivascular Outcomes

Author, Year	Method For Assessing Outcomes and Confounders	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Carman, 2011	All relevant claims in database during study period	Screened: NR Eligible, enrolled, analyzed: 426,124	Incidence rates adjusted for age and sex; incidence rate ratio adjusted for age sex, CV and other other comorbidities, and use of concomitant medications	Adjusted incidence rate of MI, incidence rate ratio A: 5.93 (95% CI 5.58 to 6.30); IRR 2.66 (95% CI 2.30 to 3.08) B: 3.54 (95% CI 3.11 to 4.01); IRR 1.94 (95% CI 1.65 to 2.29) C: 3.53 (95% CI 3.15 to 3.94); IRR 1.79 (95% CI 1.53 to 2.10) D: 3.40 (95% CI 2.76 to 4.14); IRR 1.74 (95% CI 1.41 to 2.16) E: 1.58 (95% CI 1.40 to 1.78); IRR 1 (reference) Adjusted incidence rates of MI or revascularization, incidence rate ratio A. 11.91 (95% CI 11.40 to 12.43); IRR 2.38 (95% CI 2.15 to 2.63) B. 7.98 (95% CI 7.33 to 8.67); IRR 1.93 (95% CI 1.72 to 2.15) C. 7.94 (95% CI 7.36 to 8.54); IRR 1.81 (95% CI 1.62 to 2.01) D. 7.53 (95% CI 6.56 to 8.60); IRR 1.75 (95% CI 1.50 to 2.01) E. 3.38 (95% CI 3.12 to 3.67); IRR 1 (reference) Dosing Compared to a cumulative dose of 0 to 1350 mg MED over 90 days, the IRR for 1350 to <2700 was 1.21 (95% CI 1.02 to 1.45), for 2700 to <8100 mg was 1.42 (95% CI 1.21 to 1.67), for 8100 to <18,000 mg was 1.89 (95% CI 1.54 to 2.33), and for >18,000 mg was 1.73 (95% CI 1.32 to 2.26)	GlaxoSmithKline	Fair

Author, Year	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics
Li, 2013	KQ2a	Case-Control UK General Practice Research Database United Kingdom	Cases (n=11,693): Age 18-80 years, 2 years of medical history data before index (onset of MI symptoms) Controls: (n=44,897): Up to 4 controls matched on age, gender, index date, and practice site using risk-set sampling Excluded: History of cancer, ischemic heart disease, heart failure, stroke, congenital heart disorders, heart transplat, arrhythmias, treated hypertension, diabetes, ETOH/Drug abuse, hepatic or renal disease before index, cardiac surgery in the 90 days prior to index.	A. Non-use B. Current (0-30 days from index) C. Recent (31-365 days out) D. Past Use (366-730 days out) Cumulative use (number of prescriptions): 1. 1-2 2. 3-10 3. 11-50 4. >50	Mean age (years): 61.8 vs. 61.6 Female sex: : 31.1% vs. 31.3% Current smoker: 38.6% vs. 23.3% Low BMI (<18.5): 1.2% vs. 1.2% Normal BMI: 25.8% vs. 28.9% Overweight: 31.7% vs. 30.2% Obese: 13.8% vs. 11.3% Arthritis: 25% vs. 24.2% Rheumatoid arthritis: 3.2% vs. 1.8% Fibromyalgia: 1.1% Duration or severity of pain: NR Codeine: 16% vs. 15% Dihydrocodeine: 9.6% vs. 8.1% Propoxyphene: 13% vs. 11%

Note: The references are located in Appendix C.

BMI=body mass index; CI=confidence interval; CV= cardiovascular; IRR=incidence rate ratio; KQ=key question; MI=myocardial infarction; NR=not relevant

Author, Year	Method For Assessing Outcomes and Confounders	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Li, 2013	Used General Practice Research Database, which has been validated on drug exposure and diagnoses (including MI)	Screened: 1,700,000 Eligible: Not reported Enrolled: 11,693 cases and 44,897 controls Analyzed: 11,693 cases and 44,897 controls	Age, gender, smoking, body mass index, number of general practice visits, years of medical history, opioid new versus prevalent use, co-morbidities, concomitant medications, abdominal and pelvic pain and other pain	Risk of MI (adjusted OR) A. 1 (reference) B. 1.28 (95% CI 1.19–1.37) C. 1.17 (95% CI 1.10–1.24) D. 1.06 (95% CI 0.98–1.14) 1. 1.10 (95% CI 1.03–1.18) 2. 1.09 (95% CI 1.02–1.17) 3. 1.38 (95% CI 1.28–1.49) 4. 1.25 (95% CI 1.11–1.40)	None disclosed	Good

Appendix Table E5. Observational Studies of Long-Term Opioid Use and Endocrine Outcomes

Author,	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders
Deyo, 2013	KQ2a, b	Cross-sectional Integrated healthcare United States	Ambulatory males aged ≥18 years with diagnoses associated with low back pain Exclude: patients with evidence of systemic disease or trauma	A. Patients prescribed medication for erectile dysfunction or testosterone replacement (n=909) B. Patients not prescribed medication for erectile dysfunction or testosterone replacement (n=10,418)	**A vs. B** Mean age (years): 55.7 vs. 48.0 Female sex: 0% Race: 89% White, 3% Black, 3% Asian/Pacific Islander, 1% American Indian, 3.9% other (among records with race/ethnicity data available, 59% of total sample) Sedative-hypnotic use: 24.4% vs. 15.6% Diagnosis of depression: 17.3% vs. 11.3%	Review of medical and pharmacy records

Note: The references are located in Appendix C.

KQ=key question; MED=morphine equivalent dose; NIH/NCRR=National Institutes of Health/National Center for Research

Author, year	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Deyo, 2013	Screened: NR Eligible: 11,327 Enrolled: 11,327 Analyzed: 11,327	Age, comorbidity score, number of hospitalizations, sedative-hypnotic use, duration of opioid use, morphine dose at last dispensing, type of opioid (short- vs. long-acting), depression, and smoking status	No opioid use vs. short-term use vs. episodic use vs. long-term use Prescription for sildenafil, tadalafil, or vadenafil 6 months before or after index visit: 6.3% (294/4,655) vs. 6.9% (324/4,696) vs. 7.3% (12/164) vs. 11.3% (204/1,812); p<0.001 Testosterone replacement 6 months before or after index visit: 0.5% (25/2,655) vs. 0.6% (30/4,696) vs. 1.2% (2/164) vs. 2.4% (44/1,812); p<0.001 Testosterone replacement or erectile dysfunction treatment: 6.7% (312/4,655) vs. 7.4% (346/4,696) vs. 7.9% (13/164) vs. 13.1% (238/1,812); p<0.001; OR 1.5, 95% CI 1.1 to 1.9 Dosing Daily opioid dose of >120 mg MED/day associated with increased risk of use of medications for erectile dysfunction or testosterone replacement versus 0 to <20 mg MED/day (OR 1.6, 95% CI 1.0 to 2.4)	NIH/NCRR	Fair

Appendix Table E6. Observational Studies of Long-Term Opioid Use and Motor Vehicle Accidents

Author, year	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Sampling Strategy
Gomes, 2013	KQ2b	Case-Control Canada	Residents aged 15-64 with public drug coverage and an opioid prescription (excluding methadone (2003-2011) at least 6 months of continuous eligibility for public drug coverage before their index date and at least 1 opioid prescrip-tion with a duration that overlapped their index date. Cases and controls were excluded if they had invalid patient identifiers, had missing information about age or sex, received palliative care services in the 6 months before their index date, lived in a long-term care home at the index date, or had a prescription for a nonstudy opioid with a duration that overlapped the index date.	Cases: ED with an external cause of injury related to road trauma (codes V00 to V89 from ICD-10) (n=5,300 matched a control) Controls: (n=5300) A. 1-<20 mg/day B. 20-<50 mg/day C. 50-<100 mg/day D. 100-<200 mg/day E. ≥200 mg/day	**Cases vs. Controls** Mean age (years): 45.76 vs 45.75 Female sex: 48.6% Urban resident: 83.75% vs. 83.98 Social Assistance:22% vs. 21% Disability support: 67.9% vs. 66.6% Duration of use (years): 7.09 vs. 6.84 Charlson score No hospitalization:61.7% vs. 62.3% 0: 23.4% vs. 22.4% 1: 6.85% vs. 6.32% ≥2: 7.96% vs. 8.49%	Incidence density sampling Cases were matched to controls by sex, age (within 3 years), index year (within 1 year), ED visit for road trauma in the past year, and disease risk index (within 0.2 SD). Cases with no matched controls were excluded from analyses.

Note: The references are located in Appendix C.

CI=confidence interval; ED=emergency department; ICD=International Classification of Diseases

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Author, year	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Gomes, 2013	Screened population: 549,878 Eligible Cases:5300 Eligible Controls: 43,736 Controls matched 1:1	Logistic models adjusted for: age, past (3 years) hospitalization for alcoholism, past (1 year) ED visit for alcoholism, duration of opioid treatment, medication use in past 180 days (ie, selective serotonin reuptake inhibitors, other antidepressants, antipsychotics, benzodiazepines and other depressants of the central nervous system, separately), number of drugs dispensed in the past 180 days, and numbers of physician and ED visits in the past 1 year.	Risk estimates reported as adjusted OR Risk of motor vehicle crash A. 1 (reference) B. 1.09 (95% CI 0.97-1.21) C. 1.07 (95% CI 0.94-1.22) D. 1.08 (95% CI 0.93-1.24) E. 1.00 (95% CI 0.88-1.15) Dosing Relative to 1 to <20 mg MED/day, the odds of road trauma among drivers after adjustment for age, alcoholism history, concomitant medication use, total number of drugs , and number of physician and emergency department visits was 1.21 (1.02 to 1.42) for 20 to 49 mg, 1.29 (1.06 to 1.57) for 50-99 mg, 1.42 (1.15 to 1.76) for 100 to 199 mg, and 1.23 (1.02 to 1.49) for >200 mg	MOHLTC Drug Innovation Fund and ICES, a nonprofit research institute sponsored by the Ontario MOHLTC.	Good

Appendix Table E7. Trials of Different Methods for Initiating and Titrating Opioids

Author Year	Study design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup
Jamison, 1998	RCT 16 weeks	Single center Pain clinic United States	Chronic back pain >6 months duration, age 25 to 65 years, average pain intensify >40 on scale of 0 to 100, unsuccessful response to traditional pain treatment Exclude: Cancer, acute osteomyelitis or acute bone disease, spinal stenosis and neurogenic claudication, non-ambulatory, significant psychiatric history, pregnancy, treatment for drug or alcohol abuse, clinically unstable systemic illness, acute herniated disc within 3 months	A. Long acting morphine + short-acting oxycodone (titrated doses) + Naproxen B. Short-acting oxycodone (set dose) + Naproxen C. Naproxen A vs. B vs. C Mean dose 41.1 mg vs. NR (max 20 mg oxycodone/day) vs. NR In all groups, max 1000 mg/day of naproxen 16 weeks	Mean age (years): 43 Female sex: 57% Race: NR Indication: 39% failed back syndrome, 25% myofascial pain syndrome, 19% degenerative spine disease, 14% radiculopathy, 3% discogenic back pain Prior opioid use: NR Mean pain duration: 79 months	Screened: 48 Eligible: NR Enrolled: 36 Analyzed: 36
Salzman, 1999	RCT 10 days	Multicenter Rheumatology clinics and others United States	18 years or older, chronic stable moderate to severe back pain despite analgesic therapy with or without opioids Exclude: Contraindication to opioid history of substance abuse, unable to discontinue nonstudy narcotic, or current oxycodone dose >80 mg/day Titration to 80 mg without achieving pain control	A: Sustained-release Oxycodone (titrated) B: Immediate-release Oxycodone (titrated) Titration comparison Mean dose A: 104 mg/day Mean dose B: 113 mg/day 10 days	Mean age (years): 56 Female sex: 54% Race: 87% White, 13% Hispanic Indication: Intervertebral disc disease, nerve root entrapment, spondylolisthesis, osteoarthritis, and other non-malignant conditions 84% (48/57) Pain duration: NR	Screened: NR Eligible: NR Enrolled: 57 Analyzed: 57

Note: The references are located in Appendix C.
NR=not reported; RCT=randomized control trial; SF=short form

Author Year	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Jamison, 1998	Pain Intensity: timing not specified, Comprehensive Pain Evaluation Questionnaire Functional status: baseline and at end of treatment (SF-36) Symptom checklist: baseline and at end of treatment (Symptom Checklist-90) Weekly activity record at baseline and once a month Medication diary weekly Overall helpfulness during titration and at end of study (categorical scale, 0= no help, 10=extremely helpful)	A vs. B vs. C Average pain (means, 0-100 VAS): 54.9 vs. 59.8 vs. 65.5 Current pain (means, 0-100 VAS): 51.3 vs. 55.3 vs. 62.7 Highest pain (means, 0-100 VAS): 71.4 vs. 75.5 vs. 78.9 Anxiety (means): 11.2 vs. 15.0 vs. 31.6 Depression (means): 10.8 vs. 16.4 vs. 26.9 Irritability (means): 17.7 vs. 20.5 vs. 33.7 Level of activity (means, 0-100 scale): 49.3 vs. 49.3 vs. 51.5 Hours of sleep (means): 5.9 vs. 5.9 vs. 6.1	A vs. B Somnolence: 27% (8/30) vs. 37% (10/27) Nausea: 50% (15/30) vs. 33% (9/27) Vomiting: 20% (6/30) vs. 4% (1/27) Postural hypotension: 0% vs. 0% Constipation: 30% (9/30) vs. 37% (10/27) Pruritus: 30% (9/30) vs. 26% (7/27) Confusion: 3% (1/30) vs. 0% Dry mouth: 0% vs. 11% (3/27) Dizziness: 30% (9/30) vs. 22% (6/27) Nervousness: 0% vs. 7% (2/27) Asthenia: 7% (2/30) vs. 11% (3/27) Headache: 13% (4/30) vs. 26% (7/27) Withdrawal due to adverse events: 20% (6/30) vs. 7% (2/27)	Roxane Laboratories (maker of long-acting morphine and short-acting oxycodone). Not clear if authors employed by Roxane	Fair
Salzman, 1999	Pain Intensity: daily diary, categorical scale (0-3, none-severe) Study Medication Use: daily diary, amount used Rescue Drug Use: daily diary, amount used Achievement of Stable Pain Control: Stable pain control considered achieved if pain intensity rated as 1.5 or less for 48 hours with no more than 2 doses of rescue medication Time to Stable Pain Control: Days	A vs. B Mean decrease in pain intensity (0 to 3 scale): 1.1 vs. 1.3 (NS) Proportion achieving stable analgesia: 87% (26/30) vs. 96% (26/27) (p = 0.36) Time to stable pain control: 2.7 vs. 3.0 days (p = 0.90). Mean number of dose adjustments: 1.1 vs. 1.7 adjustments (p = 0.58)	A vs. B vs. C Withdrawal due to adverse events: 54% (29/54) vs. 34% (20/59) vs. 130% (6/54) (p=0.008 for A or C vs. B) Withdrawal due to nausea and/or vomiting: 46% (25/54) vs. 22% (13/59) vs. 22% (12/54) Any adverse event: 76% vs. 70% vs. 61% Dizziness: 7% vs. 7% vs. 7% Headache: 18% vs. 15% vs. 13% Dry mouth: 0% vs. 2% vs. 6% Constipation: 7% vs. 3% vs. 11% Diarrhea: 7% vs. 5% vs. 2% Vomiting: 18% vs. 12% vs. 7% Nausea: 54% vs. 42% vs. 33% Somnolence: 9% vs. 7% vs. 0% Pruritus: 4% vs. 2% vs. 7%	Purdue Pharma sponsored study 2 authors employees of Purdue Role not otherwise reported.	Fair

Appendix Table E8a. Head-to-Head Trials of Different Long-Acting Opioids

Author Year	Study design Duration	Setting Country	Eligibility criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup	Outcomes Assessed
Allan, 2005	RCT 13 months	Europe Multicenter (number of sites not clear)	Adults with chronic low back pain requiring regular strong opioids Exclude: Receipt of more than 4 doses of strong opioids in a week in the 4 weeks before the study, high risk of ventilatory depression or intolerance to study drugs, prior alcohol or substance abuse, presence of other chronic pain disorders, or life-limiting illness	A: Transdermal fentanyl (titrated from 25 mcg/hr) (Mean dose 57 mcg/h) B: Sustained-release morphine (titrated from 30 mg q 12 hrs) (Mean dose: 140 mg)	Avg. 54.0 years, 61% female Race: not reported, Prior opioid use not reported 35% nociceptive, 4% neuropathic, 46% nociceptive and neuropathic, 3% nociceptive with psychologic factors, 4% neuropathic with psychologic factors, 83% mechanical low back pain, 8% inflammatory 39% trauma/surgery, 1% metabolic, 3% other Pain duration average 124.7 months	Number approached and eligible not reported 683 randomized (338 to transdermal fentanyl and 342 to sustained-release morphine, 3 group assignment not reported)	Pain score (mean, 0-100 VAS) Severe pain at rest Severe pain on movement Severe pain during the day Severe pain at night Rescue strong opioids use Quality of life (SF-36) Loss of working days Withdrawal due to lack of efficacy
Mitra, 2013	RCT 12 months	One site in Townsville, Australia	Inclusion: Patients > 18, reporting persistent pain for greater part of day and night for at least 1 year, opiooid-naïve, appropriate for treatment with transdermal patches after medical assessment, with no comorbid psychiatric history.	A: TDB initial dose=-5 mcg/h, n=22; B: TDF initial dose=12.5 mcg/h, n=24; Both titrated to optimal doses over 4 weeks; increased doses beyond that given as clinically indicated	None reported by treatment group: Age, mean (range): 49 (22-80); Male: 48%; Back pain: 61%; Other types of pain: 39%; Duration of pain, mean (range): 11.7 yrs (6 mos to 50 yrs); Duration of follow-up: 3 mos (35%), 6 mos (13%), 12 mos (52%)	Considered for trial: 82; Enrolled: 46; Completed and analyzed at 12 mos: 30 (TDB-14 pts and TDF-16 pts)	SPAASMS: Activity & mobility: Rescue pain meds: GP/ED visits: Sleep quality: Side effects: Mood: Pain VAS: DASS21: PDI:

Author Year	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Allan, 2005	Transdermal fentanyl (A) vs. sustained-release morphine (B): Pain score (mean, 0-100 VAS) at 56 weeks (N=608): 56.0 (A) vs. 55.8 (B) Severe pain at rest (per protocol analyses, N=248 and 162): 22/248 (9%) (A) vs. 20/162 (12%) (B), p=0.030 (no significant differences in ITT analysis, but data not provided) Severe pain on movement (per protocol): 70/248 (28%) (A) vs. 43/162 (27%) (B), p=0.61 Severe pain during the day (per protocol): 48/248 (19%) (A) vs. 40/162 (25%) (B), p=0.385 Severe pain at night (per protocol): 25/248 (10%) (A) vs. 26/162 (16%) (B), p=0.003 (no significant differences in ITT analysis, but data not provided) Rescue strong opioids use: 154/296 (52%) (A) vs. 154/291 (53%) (B). Quality of life (SF-36): No differences between interventions Loss of working days: No differences between interventions Withdrawal due to lack of efficacy: 18/335 (5%) vs.15/342 (4%)	Transdermal fentanyl (N=338) vs. sustained-release oral morphine (N=342) Any adverse event: 87% vs. 91% Constipation (ITT): 176/338 (52%) vs. 220/338 (65%) (p<0.05) Nausea: 54% vs. 50% Vomiting: 29% vs. 26% Somnolence: 17% vs. 30% Dizziness: 25% vs. 24% Fatigue: 17% vs. 14% Pruritus: 15% vs. 20% Application site reactions: 9% in transdermal fentanyl group. Deaths: None; Addiction: None reported. Use of laxatives: 177/336 (53%) vs. 221/336 (66%) (p<0.001) Use of antiemetics/anticholingergics:38% vs. 36% Use of antihistamines: 21% vs. 12% (p=0.002) Withdrawal (Overall): 52% (177/338) vs. 47% (162/342). Withdrawal (adverse events):125/335 (37%) vs. 104/337 (31%) (p=0.098)	Janssen Pharma-ceutica One author employed by Janssen	Fair
Mitra, 2013	12 month results: 16 of 46 patients continued for 12 mos and gained effective relief; SPAASMS: Score=13/28 possible in both groups at 12 mos (reading from Figure 5d) Activity & mobility: no numbers provided, groups look similar at 12 mos; Rescue pain meds: initially higher in TDF group; higher in TDB group near study end (no numbers provided); GP/ED visits: increase in visit frequency in TDB group near study end (no numbers provided); Sleep quality: No significant difference between groups (no numbers provided) Side effects: see Adverse event column Mood: TDB had relatively better score at 12 mos (no numbers provided); Pain VAS: 3-point (scale 1-10) reduction in pain in 11% in each treatment group (raw numbers not reported); DASS21: TDB had relatively better score at 12 mos (no numbers provided); PDI: looks similar in Figure 5b (no numbers provided)	Discontinued due to AEs or unsatisfactory relief (not separated by AEs only): A: TDB: 8/22 (41%); number patients with side effects at 12 mos≤1 (reading from Figure 4a); number patients with local skin reaction at 12 mos=1 (reading from Figure 4b); B: TDF: 8/24 (37.5%) number patients with side effcts at 12 mos≤1 (reading from Figure 4a); number patients with local skin reaction at 12 mos=0 (reading from Figure 4b)	Private Practice Research Fund of Townsville	Poor

Author Year	Study design Duration	Setting Country	Eligibility criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup	Outcomes Assessed
Wild 2010	RCT 12 months	53 sites in North America; 36 sites in Europe	Inclusion: Men/ nonpregnant, nonlactating women ≥18 yrs, with diagnosis of moderate/ severe knee or hip osteo, or LBP of noncancer origin; ≥ 3 mo history pain prior to screening, dissatisfied with current analgesic; NRS score ≥4 (of 11) at baseline, after 3-7 day washout from previous anagesics. Exclusion: lifelong seizures; mild/moderate TBI, stroke, TIA, brain neoplasm within one year; severe TBI within 15 years; malignancy within 2 years; history of etoh/drug abuse; history of Hep B/C; HIV; allergy to oxycodone/ acetaminophen; participation in previous tapentadol studies; patients with reference joint or back surgery within 3 months or during study; hepatic or renal dysfunction, uncontrolled hypertension, significant pain with conditions other than osteo or LBP.	A. Tapentadol ER 100-250 mg BID (adjustable) (n=894; 413 completed 6 mos; 227 completed 12 mos) B. Oxycodone CR 20-50 mg BID (adjustable) (n=223; 78 completed 6 mos; 44 completed 12 mos)	A vs B Age, mean (SD): 56.8 (12.5) vs 58.1 (11.8); Age category: <65 72.6% vs 70%; Male: 42.4% vs 43.9%; Race: White:88.6% vs 91.0%, Black: 6.7% vs 5.8%, Hispanic: 2.9% vs 1.8%, Other: 1.8% vs 1.3%; BMI: 31.7 vs 31.8; Pain intensity, Mean (SD): 7.6 (1.5) vs 7.6 (1.62); Pain intensity category: Moderate: 10% vs 13%, Severe: 90% vs 87%; Prior opioids: No 47.1% vs 49.8%	Screened: 1123 Randomized: 1121 Received drug: 1117 Discontinued-A: 53.8%; 22.7% to AEs; Discontinued-B: 65.0; 36% to AEs%	AEs; vital signs; physical exams; labs; ECGs; PROs: PAC-SYM; COWS; SOWS; TEAEs

Note: The references are located in Appendix C.

AE=adverse event; ASA=aspirin; ECG=electrocardiogram; BID=twice daily; COWS=Clinical opiate withdrawal scale; DASS2= Depression Anxiety Stress Scale; GmbH=German liability company; GP/ED=general practitioner/emergency department; Hep B/C=Hepatitis B and/or C; HIV=human immunodeficiency virus; LBP=low blood pressure; NSAIDS=non-steroidal anti-inflammatory drug; PDI=physical disability index; ITT=intent to treat; PROs=patient reported outcomes; PAC-SYM=patient assessment of constipation syndrome; RCT=randomized controlled trial; SD=standard deviation; SE=standard error; SOWS=Subjective Opiate Withdrawal Scale; SPAASMS= score, physical, activity level, additional pain medication, additional physician/ER visits, sleep quality, mood, medication side-effects; TBI=traumatic brain injury; TDB=transdermal buprenorphine; TDF=transdermal fentanyl; VAS=visual analog scale; TEAC=treatment emergent adverse criteria; TEAEs=Treatment-Emergent Adverse Event; TIA=transient ischemic attack

Author Year	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Wild 2010	Mean (SE) pain intensity score: decreased 4.4 (0.09) vs 4.5 (0.17); Global assessment, score of (very) much improved: 48.1% (394/819) vs 41.2% (73/177); Median duration of treatment (days): A: 268 (range 1-385) B: 59 (range 1-384); Mean (SD) total daily dose for study completers: A: 380.5 (102.43) mg B: 71.0 (22.89) mg Concomitant nonopioid analgesics (NSAIDS, ASA, acetaminophen): A: 19.9% (178/894) B: 17% (38/223)	Discontinued due to AEs: A: 22.7% B: 36.8%; At least one TEAC: A: 85.7% (766/894) B: 90.6% (202/223); A vs B: Constipation: 22.6% vs 38.6%; Nausea: 18.1% vs 33.2% Vomiting: 7.0% vs 13.5%; Pruritis: 5.4% vs 10.3%; Dizziness: 14.8% vs 19.3%; Serious TEACs: 5.5% vs 4.0%; No relevant AEs on labs, vitals, ECGs; No deaths; Mean change (SE) PAC-SYM: 0.3 (0.05) vs 0.5 (O.14); COWS,5 days post treatment, no withdrawal: 88% (145/166) vs 84% (42/50); Mean SOWS at 2-5 days post treatment - consistent with COWS	J & J; grunenthal GmbH	Fair

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders
Hartung, 2007	Retrospective cohort Medicaid claims United States	Patients prescribed at least one ≥28-day supply of methadone, ER oxycodone, ER morphine, or transdermal fentanyl	A. Transdermal fentanyl (n=1,546) B. Methadone (n=974) C. ER oxycodone (n=1,866) D. ER morphine (n=1,298)	A vs. B vs. C vs. D Mean age: 70.6 vs. 51.1 vs. 57.4 vs. 58.5 years Female sex: 74% vs. 63% vs. 65% vs. 65% Race: 6.1% vs. 10.5% vs. 7.7% vs. 9.6% non-White Mean MED dose: 96 vs. 247 vs. 67 vs. 74 mg Cancer: 19.9% vs. 18.3% vs. 25.2% vs. 26.1% Osteoarthritis: 13.7% vs. 22.6% vs. 19.3% vs. 18.0% Back pain: 17.5% vs. 41.8% vs. 35.0% vs. 27.3%	Review of claims using ICD-9 codes

Author, Year	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Hartung, 2007	Screened: NR Eligible: NR Enrolled: 5,684 Analyzed: 5,684	Age, sex, race, long-term care residence, number of unique prescribers, disease severity, concominant prescriptions known to interact with opioids , type of presumed pain diagnosis, history of abuse or dependence, enrollment in a substance abuse treatment program	A vs. B vs. C (reference: D) Mortality: adjusted HR 0.71 (95% CI 0.46 to 1.08) vs. HR 0.71 (95% CI 0.54 to 0.94) vs. 0.80 (95% CI 0.63 to 1.02) ED encounter or hospitalization involving an opioid-related adverse event (HR 0.45, 95% CI 0.26 to 0.77) Among patients with noncancer pain: Fentanyl associated with higher risk of ED encounters than sustained-release morphine (HR 1.27, 95% CI 1.02 to 1.59) Methadone associated with greater risk of overdose symptoms than sustained-release morphine (HR 1.57, 95% CI 1.03 to 2.40) No significant differences between methadone and long-acting morphine in risk of death (adjusted HR 0.71, 95% CI 0.46 to 1.08) or overdose symptoms	NR	Fair

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders
Krebs, 2011	Retrospective cohort VA United States	New prescription for >= 28 days' supply of PO methadone or LA morphine tabs/caps from a VA outpatient pharmacy between 1/1/2000 and 12/31/2007. Preceded by 30 day window free of LA opioid prescriptions. Excluded: Liquid/IV forms of methadone/morphine; metastatic cancer, palliative care, receiving methadone for addiction; methadone 40 mg diskettes; < 17 or > 100 years of age; missing gender data.	A: Methadone (n=28,554) B: Long-acting morphine sulfate (MS) (n-79,938)	Mean (SD) daily LA MS dose: 67.5 mg (77.4); median (IQR) 46.7 (45); Mean (SD) daily methadone dose: 25.4 mg (25.8); median (IQR): 20 (20); 99th %ile MS: 360-7200 mg; 99th %ile methadone: 124-560 mg; A vs B: Age: mean (SD): 56 (12) vs 59 (13); Race: white: 40% vs 41%; nonwhite: 52% vs 49%; unknown: 8% vs 9%; MI: 9% vs 11%; CHF: 15% vs 19%; PVD: 17% vs 20%; CVD: 15% vs 17%; COPD: 35% vs 38%: Diabetes: 31% vs 33%; Malignancy: 15% vs 26%; Depression: 62% vs 54%; Bipolar: 10% vs 8%; Anxiety: 32% vs 27%; EtOH: 25% vs 22%; Drug disorderz; 25% vs 18%; Tobacco: 47% vs 42% Back pain: 85% vs 76%; Joint/limb pain: 86% vs 82%; Headache: 25% vs 21%; Neuropathic pain: 35% vs 29%	All patients meeting eligibility criteria

Note: The references are located in Appendix C.

CHF=congestive heart failure; CI=confidence interval; COPD=chronic obstructive pulmonary disease; CVD=cardiovascular disease; ER=extended release; EtOH=Ethyl alcohol; HR=hazard ratio; ICD-9=International Classification of Diseases; IQR=interquartile range; LA=long acting; MI=myocardial infarction; MS=morphine sulfate; PO=oral route; PVD=peripheral vascular disease SD=standard deviation; VA=Veterans Affairs; VISN=Veterans integrated service networks

Author, Year	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Krebs, 2011	Screened: Not applicable; Eligible: 133,969; Enrolled: 108,492; Analyzed: 98,068; Loss to followup: 3,347 (died); 94,721 (censored)	Propensity score for receiving methadone was estimated with logistic regression model that included age, gender, race, geographic area (VISN), depression, anxiety, bipolar dx, schizophrenia, etoh, drug, tobacco disorders, back pain, joint/limb pain, headache, neuropathic pain; Medical comorbidities included via Romano adaptation of Charlson Comorbidity Score; Quintiles calculated and then used in Cox model; Interaction term consisting of propensity quintile and opioid group	All-cause mortality: Unadjusted: 3,347 (3.4%) patients died; highest mortality within 1st 30 days (1.2% in methadone and 3.7% in MS); raw death rates form MS higher than methadone for all 30-day intervals; Death rate: Quitile #1 (0.042 vs 0.133); Quintile #2 (0.034 vs 0.078); Quintile #3 (0.025 vs 0.053); Quintile #4 (0.022 vs 0.034); Quintile #5 (0.017 vs 0.020); Propensity adjusted mortality (HR): Overall risk of mortality lower with methadone than morphine (adjusted HR 0.56, 95% CI 0.51 to 0.62) Quintile #1: 0.36 (95% CI: 0.26, 0.49); Quintile #2: 0.46 (0.37, 0.56); Quintile #3: 0.50 (0.41, 0.61); Quintile #4: 0.66 (0.54, 0.81); Quintile #5: 0.92 (0.74, 1.16); Results robust in validation dataset	VA	Fair

Author Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup	Outcomes Assessed
Naliboff 2011	RCT 12 months	VA pain clinic U.S.	Patients referred to chronic pain clinic; nonmalignant chronic pain for at least 6 months; clinician determination that patient was eligible for long-term opioids. Excluded: anticipated surgery, post-op pain, pulmonary disease or CHF, current or history of substance abuse disorder, hospitalization for psych disorder in past 2 years	A. Escalating opioid dose; mean morphine equivalent 52 mg (n=67) B. Stable opioid dose; mean morphine equivalent 40 mg (n=73)	A vs B Mean age 53 vs 52 years 89% vs 99% male Race not reported Pain: -78% vs 77% musculoskeletal -19% vs 19% neuropathic -3% vs 4% complex Initial morphine equivalent 29.2 (SD 19.6) vs 32.3 (SD 23.1) mg Mean usual VAS 7.0 (SD 1.9) vs 6.7 (SD 1.8) Mean worst VAS 8.4 (SD 1.2) vs 8.0 (SD 1.7) Mean ABC score 1.5 (SD 2.0) vs 1.6 (SD 2.1) Mean ODI 48.6 (SD 12.6) vs 47.8 (SD 14.0)	Screened: not reported Eligible: 140 Enrolled: 140 Analyzed: 134 Loss to followup: 10/140 (7%)	Pain Functional disability Use of nonopioid medications

Note: The references are located in Appendix C.

CI=confidence interval, NSAID=nonsteroidal anti-inflammatory drug, ODI=Oswestry Disability Index, RCT=randomized controlled trial, SD=standard deviation, US=United States, VA=Veterans Affairs, VAS=Visual Analog Scale

Author Year	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Naliboff 2011	A vs B Mean VAS usual pain at 12 months: 5.6 (SD 1.5) vs 6.2 (SD 1.5); p=0.11* Usual pain VAS decrease ≥1.5 points: 19/67 (28%) vs 15/73 (20%); RR 1.38; 95% CI 0.76 to 2.49 Mean VAS pain relief at 12 months: 6.0 (SD 1.7) vs 5.3 (SD 1.8); p=0.11* Increase in pain relief ≥1.5 points: 19/67 (29%) vs 11/73 (15%); RR 1.88; 95% CI 0.97 to 3.66 Worst pain VAS decrease ≥1.5 points: 9/67 (14%) vs 4/73 (6%); RR 2.45; 95% CI 0.79 to 7.59 Mean ODI at 12 months: 45.8 (SD 14.8) vs 45.0 (SD 19.4); p=0.85* ODI decrease ≥10 points: 19/67 (29%) vs 20/73 (23%); RR 1.04; 95% CI 0.61 to 1.76 Use of nonopioid treatments (A: n=64; B: n=70): -NSAID: 35/64 (55%) vs 42/70 (60%); RR 0.92; 95% CI 0.68 to 1.22 -Muscle relaxant: 10/64 (15%) vs 14/70 (20%); RR 0.78; 95% CI 0.37 to 1.63 -Anti-seizure: 40/64 (63%) vs 46/70 (66%); RR 0.95; 95% CI 0.74 to 1.23 -Anti-anxiety: 19/64 (29%) vs 24/70 (34%); RR 0.87; 95% CI 0.53 to 1.42 -Antidepressants: 45/64 (71%) vs 48/70 (69%); 1.03; 95% CI 0.82 to 1.28 -Topical: 11/64 (17%) vs 11/70 (16%); RR 1.06; 95% CI 0.49 to 2.28 -Injectable: 17/64 (26%) vs 25/70 (36%); RR 0.74; 95% CI 0.44 to 1.24 -Physical therapy: 31/64 (48%) vs 44/70 (63%); RR 0.77; 95% CI 0.57 to 1.05 **p-value calculated based on completers (A: n=34; B: n=32)*	A vs B All-cause withdrawals: 33/67 (49%) vs 41/73 (56%); RR 0.88; 95% CI 0.64 to 1.20 Withdrawal due to opioid misuse: 16/67 (24%) vs 22/73 (30%); RR 0.79; 95% CI 0.46 to 1.38	Department of Veterans Affairs	Fair

Author year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics
Ashburn, 2011	RCT (crossover) Duration: up to 42 days total (two treatment periods of 10 breakthrough pain episodes each within 21 days)	46 centers United States	Patients aged 18 to 80 years with ≥3 months of chronic pain associated with diabetic neuropathy, postherpetic neuralgia, traumatic injury, complex regional pain syndrome, back pain, neck pain, fibromyalgia, chronic pancreatitis, osteoarthritis, or cancer; receiving ≥60 mg/day MED, with 1-4 episodes of breakthrough pain per day	A. Fentanyl buccal tablet (n=183) B. Oxycodone (n=183)	Mean age: 48.8 years Female sex: 62% Race: 92% White, 5% Black, 3% other Pain intensity in 24 hours prior to enrollment: 5.1 Indication (most common): 57% back pain, 11% osteoarthritis, 8% neck pain, 9% fibromyalgia, 4% traumatic injury, 4% complex regional pain syndrome
Davies, 2011	RCT (crossover) 3-21 days	35 cancer centers Europe and India	Patients with histologically confirmed cancer, receiving a fixed-schedule opioid regimen at a total daily dose equivalent ≥60 mg MED, with 1-4 episodes of breakthrough pain per day	A. Fentanyl pectin nasal spray (n=106 for safety and n=84 for efficacy) B. Immediate-release morphine sulfate (n=106 for safety and n=84 for efficacy)	Mean age: 55.9 years Female sex: NR Race: NR

Author year	Screened, Eligible, Enrolled, Analyzed Loss to Followup	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Ashburn, 2011	Screened: 486 Eligible: 360 Enrolled: 323 (titration phase) Analyzed: 320 (safety), 183 (efficacy)	Pain intensity, pain relief, and total pain relief	A vs. B Pain intensity difference at 15 minutes: 0.82 vs. 0.60 (p<0.001) Pain relief at 15 minutes: 0.69 vs. 0.53 (p<0.05) Meaningful pain relief within 15 minutes: 16% vs. 12% of episodes (p<0.05)	A vs. B Any adverse event: 38% (106/281) vs. 31% (88/284); RR 1.22 (95% CI 0.97 to 1.53)	Cephalon, Inc.	Good
Davies, 2011	Screened: NR Eligible: NR Enrolled: 110 (titration phase) Analyzed: 106 (safety population), 84 (randomized after titration phase)	Pain intensity, pain relief, and total pain relief	A vs. B ≥2-point reduction in pain intensity at 10 minutes: 52.4% vs. 45.4% (p<0.05) ≥2 pain relief at 15 minutes: 60.2% vs. 53.4% (p<0.05) Total pain relief ≥33% at 15 minutes: 52.3% vs. 43.5% (p<0.01)	A vs. B Treatment-emergent adverse events resulting in discontinuation: 6 vs. 2	No financial support provided	Fair

Author year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics
Portenoy, 2007	RCT 3 weeks	Multicenter Clinic setting not described United States	18 to 80 years, chronic low back pain associated with osteoarthritis, degenerative disc disease, or spondylolisthesis resulting in functional disability for at least 3 months, receiving morphing ☐ average pain intensity ☐ scale in 24 hours prior to entry, duration of breakthrough pain less than 4 hours, use of an opioid to treat breakthrough pain described as at least somewhat effective Exclude: Uncontrolled or rapidly escalating pain, allergies or contraindications to study drug, cardiopulmonary disease that might affect safety, psychiatric or medical disease that might affect data collection, alcohol or substance abuse during the past 5 years, lactating, participated in an earlier fentanyl buccal tablet trial, or expected to have surgery during study	A: Buccal fentanyl 100 to 800 mcg for an episode of breakthrough pain B: Placebo Dose of buccal fentanyl: 800 mcg 56%; 600 mcg 24%; 400 mcg 15%; 200 mcg 5%	Not reported for randomization groups Mean age: 47 years Female gender: 55% Non-white race: 12% Baseline pain intensity: 5.1 (10 point scale) Primary etiology of low back pain degenerative disc disease: 68%

Author year	Screened, Eligible, Enrolled, Analyzed Loss to Followup	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Portenoy, 2007	Screened: 124 Eligible: NR Enrolled: 105 (in open-label dose titration), 77 (in randomized phase; randomized to one of 3 treatment sequences consisting of 6 fentanyl buccal tablets and 3 placebo tablets in different orders)	Pain intensity: 0 to 10 scale Pain relief: 5-point scale (0 = none to 4 - complete) Onset time of "meaningful" pain relief	A vs. B Sum of the pain intensity differences from 5 through 60 minutes: 8.3 vs. 3.6 Proportion of breakthrough pain episodes with 'meaningful' pain reduction: 70% (289/413) vs. 30% (63/207) ($p<0.0001$) Proportion of breakthrough pain episodes with $\geq$33% reduction in pain intensity after 30 minutes: 42% (172/413) vs. 18% (18/207) ($p\leq0.0001$) Proportion of breakthrough pain episodes with $\geq$50% reduction in pain intensity after 30 minutes: 30% (122/413) vs. 13% (27/207) ($p\leq0.0001$) Proportion of breakthrough pain episodes with $\geq$33% reduction in pain intensity after 120 minutes: 65% (269/413) vs. 28% (57/207) ($p\leq0.0001$) Proportion of breakthrough pain episodes with $\geq$50% reduction in pain intensity after 120 minutes: 48% (198/413) vs. 16% (33/207) ($p\leq0.0001$)	All data reported only for buccal fentanyl Withdrawn due to adverse event: 1% (1/77) Serious adverse events: 3% (2/77) Nausea: 1% Dizziness: 4% Somnolence: 0% Dysgeusia: 8% Vomiting: 0% Dry mouth: 4%	Cephalon, Inc.	Good

Author year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics
Simpson, 2007	RCT (crossover) 3 weeks	Multicenter Clinic setting not described United States	18 to 80 years old, ≥3 months history of chronic neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, traumatic injury, or complex regional pain syndrome, on chronic opioids (at least 60 mg/day or morphine or equivalent), pain intensity <7 on a 0 to 10 scale, 1 to 4 daily episodes of breakthrough pain, use of opioid therapy for breakthrough pain described as at least partially effective; had to identify effective dose during dose-titration phase to be entered into randomized portion of trial Exclude: Unstable, uncontrolled, or rapidly escalating pain; allergies or other contraindications to study drug; alcohol or substance abuse in past 5 years; significant cardiopulmonary disease; significant medical or psychiatric disease; pregnancy or lactating	A: Buccal fentanyl 100 to 800 mcg for an episode of breakthrough pain B: Placebo Dose of buccal fentanyl: 800 mcg 54%; 600 mcg 19%; 400 mcg 18%; 200 mcg 5%, 100 mcg 5%	NR for randomization groups
Webster, 2013	RCT (crossover) Duration: up to 42 days total (two treatment periods of 10 breakthrough pain episodes each within 21 days)	42 sites Setting not described United States	Patients aged 18 to 80 years with >3 months of chronic pain associated with diabetic neuropathy, postherpetic neuralgia, traumatic injury, complex regional pain syndrome, back pain, neck pain, fibromyalgia, chronic pancreatitis, osteoarthritis, or cancer; receiving >60 mg/day MED, with and average pain intensity ≤6 and 1-4 episodes of breakthrough pain per day Exclude: recent history of substance abuse, positive UDT	A. Fentanyl buccal tablet (n=137) B. Oxycodone (n=137)	Mean age: 50.8 years Female sex: 58% Race: 91% White, 7% Black, 2% other Pain intensity in 24 hours prior to enrollment: 5.1

Note: The references are located in Appendix C.
CI=confidence interval; MED=morphine equivalent dose; NR=not relevant ; RCT=randomized controlled trial

Author year	Screened, Eligible, Enrolled, Analyzed Loss to Followup	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Simpson, 2007	Screened: 129 Eligible: NR Enrolled: 103 (in open-label dose titration), 79 (in randomized phase; randomized to one of 3 crossover treatment sequences consisting of 6 fentanyl buccal tablets and 3 placebo tablets) Discontinued early: 2.5% (2/79)	Pain Intensity: 0 to 10 scale Sum of Pain Intensity differences from 5 through 60 minutes after administration of study drug	A vs. B Sum of the pain intensity differences from 5 through 60 minutes: 9.63 vs. 5.73 (p<0.001) Proportion of breakthrough pain episodes with 'meaningful' pain reduction: 69% vs. 36% (p<0.0001) Proportion of breakthrough pain episodes with ≥50% reduction in pain intensity after 15 minutes: 12% vs. 5% (p≤0.0001), p<0.0001 for each subsequent time point from 30 to 120 minutes Use of supplemental medication: 14% (59/432) vs. 36% (77/213) (OR=0.28, 95% CI 0.18 to 0.42)	All data reported only for buccal fentanyl: Withdrawn due to adverse event: 2.5% (2/79); 12% (12/103) withdrawn due to adverse events during open-label dose titration Nausea: 0% Dizziness: 1% Somnolence: 1% Vomiting: 0% Application site adverse event: 8% (8/103) during open-label dose titration	Cephalon, Inc.	Good
Webster, 2013	Screened: 307 Eligible: NR Enrolled: 213 (titration phase) Analyzed: 211 (safety), 137 (efficacy)	Pain intensity, pain relief, and total pain relief	A vs. B Pain intensity difference at 15 minutes: 0.88 vs. 0.76 (p<0.001) Pain relief at 15 minutes: 38% vs. 34% (p<0.05) Meaningful pain relief within 15 minutes: 17% vs. 16% (p=NS) Meaningful pain relief within 30 minutes: 46% vs. 38% (p<0.01)	A vs. B Any adverse event: 18% (25/138) vs. 14% (20/142); RR 1.29 (95% CI 0.75 to 2.20)	Teva Pharmaceuticals (formerly Cephalon, Inc.)	Good

Author year	Study design Duration	Setting Country	Eligibility criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup
Cowan, 2005	RCT (crossover) 60 hours	Single center Pain clinic United Kingdom	>18 years, chronic noncancer pain on sustained-release oral morphine for ≥30 days, willing to abstain from morphine, able to give regular blood samples Exclude: Pain not adequately controlled by immobilization and alternative medication, patient may require a sudden change in opioid dose, pregnant or lactating	A: Continued sustained-release morphine for 60 hours B: Abrupt cessation of morphine for 60 hours	Mean age: 56 years Female gender: 40% Non-white race: Not reported Pain >5 years: 90% Duration of morphine use: mean 2.2 years Dose ≤60 mg/day: 90%	Screened: 33 Eligible: 11 Enrolled: 10 Analyzed: 10

Note: The references are located in Appendix C.
RCT=randomized controlled trial

Author year	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Cowan, 2005	Effects of cessation of opioids: Unvalidated 19-item questionnaire Brief Pain Inventory Evaluation of physiologic parameters (heart rate, blood pressure, temperature, respiration, pupil size)	Continued sustained-release morphine vs. abrupt cessation Brief Pain Inventory, average pain in last 24 hours (0 to 10): 3.2 vs. 5.3 ($p<0.026$) Pain interference with general activity in last 24 hours (0 to 10): 0.2 vs. 4.3 ($p<0.027$) Physiologic parameters: No differences	Adverse events during cessation of opioids: 3/10 (30%) "Do you have any drug craving?": 0/10 after abrupt cessation of therapy	Janssen-Cilag Ltd., Napp Pharma-ceuticals	Poor

Author Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics
Ralphs, 1994	Non-randomized trial 6 months	Inpatient, single center United Kingdom	Patients referred to inpatient pain management, on opioids, chronic non-cancer pain, with any two of following: widespread disruption in activity due to pain, habitual over-activity leading to increased pain, regular use of analgesics and/or sedatives for >6 months, high affective distress, use of unnecessary aids, high levels of reported or observed pain behaviors, work reduced, impaired, or ceased owing to pain Exclude: Cannot use English, cannot climb stairs, current major psychiatric illness, unavailable for 4-week program, suitable for further physical treatments after medical examinations, pain of less than 1 year's duration, under 18 years old, currently using opioids for treatment of drug dependency	A: Patient-controlled reduction (patient discussed desired rate of reduction, aiming for abstinence by discharge, allowed to take longer if they wished, patients kept pills in room, plans adjusted as appropriate) B: Cocktail method (opioid mixed into a cocktail with dose gradually reduced, patient unaware of reduction schedule)	Mean age: 47 vs. 50 years Female gender: 49% vs. 71% Non-white race: Not reported Pain duration: 124 vs. 101 months Pain distress (0 to 100): 66 vs. 73 Mean opiate dose: 35.8 mg/day
Tennant, 1982	Non-randomized clinical trial 3 to 18 months	Single center Outpatient clinic United States	Patients on opioids who volunteered for outpatient treatment for withdrawing opioids	A: Detoxification/ counseling: Detoxification over 3 weeks with methadone, propoxyphene, clonidine, diphenoxylate, or sedative-hypnotics, followed by weekly psychotherapeutic counseling B: Detoxification/ maintenance: Detoxification as above, with maintenance on opioid if detoxification unsuccessful	Mean age: 33 vs. 44 years Female gender: 48% vs. 52% Nonwhite race: 19% vs. 14% Duration of opioid use: 7.2 vs. 9.2 years Proportion with chronic pain: 62% vs. 71% Back/spine disorder: 24% vs. 19% Use of codeine: 67% vs. 48%

Note: The references are located in Appendix C.
NR=not reported

Author Year	Screened Eligible Enrolled Analyzed Loss to Followup	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Ralphs, 1994	Screened: 132 Eligible: NR Enrolled: 108 (63 to patient-controlled method and 45 to cocktail method) Analyzed: 108 Attrition: 24% (26/108)	Abstinent at discharge Abstinent at 6 month after discharge Use of other drugs, pain, or psychological variables at 6 months	Patient-controlled reduction versus cocktail method Abstinent at discharge: 68% vs. 89% (p<0.05) Abstinent 6 months after discharge: 54% (27/50) vs. 56% (18/32) Use of other drugs, pain, or psychological variables at 6 months: No differences between groups	NR	King Edwards Hospital Fund for London, Special Trustees of St. Thomas Hospital, and the South East Thames Regional Health Authority	Poor
Tennant, 1982	Screened: NR Eligible: NR Enrolled: 42 (21 to detoxification/ counseling and 21 to detoxification/ maintenance) Analyzed: 42	Proportion remaining in treatment past 3 weeks Proportion abstinent from opioids (as judged by history, negative urine test, and no further requests for opioids)	Detoxification/counseling vs. detoxification/maintenance Proportion remaining in treatment past 3 weeks: 24% (5/21) vs. 95% (20/21) Abstinent after 90 days: 10% (2/21) vs. 19% (4/21)	NR	NR	Poor

Author, Year	Study Design	Eligibility Criteria	Population Characteristics	N	Instrument	Method of Administration	Reference Standard	True Positives (n)
Akbik 2006	Prospective cohort	Chronic pain patients attending one of two pain clinics	Mean age 43 years (SD 9.6) 33% female 86% White, other races not reported Pain: 39% back	n=155 (with reference standard, of 397 enrolled)	SOAPP	Self-report	Positive urine screening	SOAPP score ≥8: 30
Jones 2012 (Study 2)	Retrospective cohort	Consecutive pain clinic patients being evaluated for risk of opioid addiction prior to opioid initiation	Mean age 48 years (SD 13) 56% female 96% White, other races not reported Pain: 45% low back pain, 21% arthritis or fibromyalgia, 14% joint pain, 10% pelvic or abdominal pain, 7% neck or upper back pain	n=263	ORT PMQ SOAPP-R Clinician assessment	Self-report; clinician interview	Subsequent opioid discontinuation due to abuse	ORT score >4: 8 PMQ score >30: 13 SOAPP-R score >17: 20 Clinician assessment of high-risk: 27
Moore 2009	Retrospective cohort	New adult patients at a pain clinic	Mean age 44 years (SD 11) 60% female Race not reported Pain not reported	n=48	SOAPP DIRE ORT Clinician assessment	Self-report (SOAPP, DIRE, ORT); clinician interview	Subsequent opioid discontinuation due to abuse	SOAPP: 35 DIRE: 8 ORT: 21 Clinical interview: 37

Author, Year	False Positives (n)	True Negatives (n)	False Negatives (n)	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	AUROC	Quality
Akbik 2006	SOAPP score ≥8: 59	SOAPP score ≥8: 37	SOAPP score ≥8: 14	SOAPP score ≥8: 0.68 (95% CI 0.52 to 0.81)	SOAPP score ≥8: 0.39 (95% CI 0.29 to 0.49)	SOAPP score ≥8: 1.11 (95% CI 0.86 to 1.43)	SOAPP score ≥8: 0.83 (95% CI 0.52 to 1.31)	Not reported	Fair
Jones 2012 (Study 2)	ORT score >4: 19 PMQ score >30: 41 SOAPP-R score >17: 65 Clinician assessment of high-risk: 57	ORT score >4: 142 PMQ score >30: 134 SOAPP-R score >17: Clinician assessment of high-risk: 84	ORT score >4: 33 PMQ score >30: 25 SOAPP-R score >17: Clinician assessment of high-risk: 11	ORT score >4: 0.20 (95% CI 0.15 to 0.27) PMQ score >30: 0.34 (95% CI 0.20 to 0.51) SOAPP-R score >17: 0.39 (95% CI 0.26 to 0.54) Clinician assessment of high-risk: 0.71 (95% CI 0.54 to 0.84)	ORT score >4: 0.88 (95% CI 0.82 to 0.93) PMQ score >30: 0.77 (95% CI 0.69 to 0.80) SOAPP-R score >17: 0.69 (95% 0.63 to 0.75) Clinician assessment of high-risk: 0.60 (95% CI 0.51 to 0.68)	ORT score >4: 1.65 (95% CI 0.78 to 3.51) PMQ score >30: 1.46 (95% CI 0.87 to 2.45) SOAPP-R score >17: 1.27 (95% CI 0.86 to 1.90) Clinician assessment of high-risk: 1.76 (95% CI 1.32 to 2.34)	ORT score >4: 0.91 (95% CI 0.78 to 1.06) PMQ score >30: 0.86 (95% CI 0.68 to 1.08) SOAPP-R score >17: 0.88 (95% CI 0.70 to 1.10) Clinician assessment of high-risk: (0.49 (95% CI 0.29 to 0.81)	ORT 0.53 PMQ 0.57 SOAPP-R 0.54	Poor
Moore 2009	Not calculable	Not calculable	SOAPP: 13 DIRE: 40 ORT: 27 Clinical interview: 11	SOAPP score ≥6: 0.73 DIRE score <14: 0.17 ORT score >4: 0.45 Clinical interview assessment medium or high risk: 0.77	Not reported	Not reported	Not reported	Not reported	Poor

Author, Year	Study Design	Eligibility Criteria	Population Characteristics	N	Instrument	Method of Administration	Reference Standard	True Positives (n)
Webster 2005	Prospective cohort	New chronic pain patients at a pain clinic	Mean age 44 years (SD 13) 58% female Race not reported Pain: 45% back; 18% head; 16% neuropathic; 16% musculoskeletal; 5% visceral	n=185	ORT	Self-report	Documentation of aberrant behavior during followup	ORT score 1-3 (low risk): 1 ORT score 4-7 (moderate risk): 35 ORT score ≥8 (high risk): 40

Note: The references are located in Appendix C.

AUROC=area under receiver operating characteristic curve; CI=confidence interval; DIRE= Diagnosis, Intractability, Risk and Efficacy Inventory; ORT=Opioid Risk Tool; PMQ=Pain Medication Questionnaire; SOAPP-R= Revised Screener and Opioid Assessment for Patients with Pain

Author, Year	False Positives (n)	True Negatives (n)	False Negatives (n)	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	AUROC	Quality
Webster 2005	ORT score 1-3 (low risk): 17 ORT score 4-7 (moderate risk): 88 ORT score high (≥8): 4	ORT score 1-3 (low risk): 92 ORT score 4-7 (moderate risk): 21 ORT score high (≥8): 105	ORT score 1-3 (low risk): 75 ORT score 4-7 (moderate risk): 41 ORT score high (≥8): 36	ORT score ≥4: 0.99 (95% CI 0.92 to 0.999)	ORT score ≥4: 0.16 (95% CI 0.10 to 0.24)	ORT score ≥4: 1.17 (95% CI 1.07 to 1.27) ORT score 1-3 (low risk): 0.08 (95% CI 0.01 to 0.62) ORT score 4-7 (moderate risk): 0.57 (95% CI 0.44 to 0.74) ORT score ≥8 (high risk): 14.34 (95% CI 5.35 to 38)	ORT score ≥4: 0.08 (95% CI 0.01 to 0.65)	Not reported	Fair

Appendix F. Quality Assessment Tables

Appendix Table F1. Quality Assessment of Cohort Studies

Author, Year	KQ	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 followup or overall high loss to followup?	Did the study perform appropriate statistical analyses on potential confounders?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality
Carman, 2011	KQ2a, b myocardial infarction	Yes	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Fair
Dunn, 2010	KQ2a, b overdose	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
Edlund, 2014	KQ2a, b abuse	Yes	Unclear	Yes	Yes	Unclear	No	No	Yes	Yes	Fair
Hartung, 2007	KQ3c	Yes	No	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Fair
Krebs, 2011	KQ3c	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Fair
Saunders, 2010	KQ2a, b fractures	Yes	Unclear	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Fair

Note: The references are available in Appendix C.
Based on United States Preventive Services Task Force Quality Assessment Criteria (see Methods section for details).
KQ=key question

Author, Year	KQ	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were outcome assessors blinded to patient characteristics?	Did the article report attrition?	Is there overall high loss to followup?	Were prespecified outcomes assessed in all patients?	Quality
Banta-Green, 2009	KQ2a abuse	Yes	Unclear	NA	NA	Yes	Fair
Boscarino, 2010	KQ2a abuse	Yes; random	No	NA	NA	No (high proportion of nonrespondents)	Fair
Carrington Reid, 2002	KQ2a abuse	Yes	No	NA	NA	Yes	Fair
Compton, 2008	KQ2a abuse	Yes; consecutive	No	No	Unclear	Yes	Fair
Cowan, 2003	KQ2a abuse	Yes	Unclear	NA	NA	Yes	Fair
Deyo, 2013	KQ2a , b endocrine	Yes	Unclear	NA	NA	Yes	Fair
Fleming, 2007 See also: Saffier, 2007	KQ2a abuse	Yes; all	No	NA	NA	Yes	Fair
Hojsted, 2010	KQ2a abuse	Unclear	No	NA	NA	Yes	Fair
Portenoy, 2007	KQ2a abuse	No (28% of eligible patients enrolled, not clear why most did not enroll)	No	Yes	Yes (Table 3)	Yes	Fair
Schneider, 2010	KQ2a abuse	Yes	No	NA	NA	No; UDT only in 82% of patients	Fair
Wasan, 2009	KQ2a abuse	Unclear	Yes	NA	NA	No	Fair

Note: The references are located in Appendix C.

Based on United States Preventive Services Task Force Quality Assessment Criteria (see Methods section for details).

KQ=key question; NA=not applicable; UDT=urine drug test

Author, Year	KQ	Did the study attempt to enroll all or random sample of cases using predefined criteria?	Were the controls derived from the same population as the cases?	Were the groups comparable at baseline on key prognostic factors?	Were enrollment rates similar in cases and controls invited to participate?	Did the study use accurate methods for identifying outcomes?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Did the study perform appropriate statistical analyses on potential confounders?	Quality
Gomes, 2011	KQ2b overdose	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good
Gomes, 2013	KQ2b, motor vehicle accident	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good
Li, 2013a	KQ2a fractures	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good
Li, 2013b	KQ2a myocardial infarction	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good

Note: The references are available in Appendix C.
Based on United States Preventive Services Task Force Quality Assessment Criteria (see Methods section for details).
KQ=key question

Author, year	KQ	Random-ization	Concealed treatment allocation	Baseline group similarity	Patient blinded	Care provider blinded	Outcome assessor blinded	Cointer-ventions avoided or similar	Compli-ance accept-able in all groups	Attrition reported	Attrition accept-able	Timing of outcome assess-ment in all groups simillar	Intention to treat analysis	Avoid-ance of selective outcomes reporting	Quality
Allan, 2005	KQ3c	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Fair
Ashburn, 2011	KQ3h	Yes	Yes	Yes	Yes	Yes	Unclear; probably yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Cowan, 2005	KQ3i	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	no	Unclear	Yes	Yes	Unclear	Poor
Davies, 2011	KQ3h	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Jamison, 1998	KQ3a	Unclear	Unclear	Unclear	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Mitra, 2013	KQ3c	Yes	No	Unclear	Unclear	No	Yes	Yes	No	Yes	No	Yes	No	No	Poor
Naliboff 2011	KQ3f	Yes	Yes	Yes	Yes	No	Unclear	Yes (similar in both groups)	Unclear	Yes	No	Yes	Yes	Yes	Fair
Portenoy, 2007	KQ3h	Yes	Yes	NA	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Good
Ralphs, 1994	KQ3j	No	No	No	No	No	No	yes	unclear	No	Unclear	yes	yes	unclear	Poor
Salzman, 1999	KQ3a	Unclear	Unclear	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Simpson, 2007	KQ3h	Yes	Unclear	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Tennant, 1982	KQ3j	No	No	No	No	No	No	Unclear	Unclear	No	Unclear	Yes	Yes	Unclear	Poor
Webster, 2013	KQ3h	Yes	Yes	Yes	Yes	Yes	Unclear; probably yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Wild 2010	KQ3c	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Fair

Note: The references are available in Appendix C.
Based on Cochrane Back Review Group Quality Assessment Methods (see Methods section for details).
KQ=key question

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 descripton of screening instrument	Apprioriate criteria included in screening instrument	Adequate descripton 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
Akbik, 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Unclear	Fair
Jones, 2012	Yes	No	No	Yes	Yes	Yes	Yes	No	No	Unclear	Poor
Moore, 2009	Yes	No	No	Yes	Yes	Yes	Yes	No	No	Unclear	Poor
Webster, 2005	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear	Unclear	Unclear	Fair

Note: The references are available in Appendix C.
Based on various methods sources (see Methods section for details).

Appendix G. Strength of Evidence Table

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
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 (>1 year) outcomes related to pain, function, and quality of life?							
Pain, function, quality of life	No studies	-	-	-	-	-	Insufficient
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); 3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for addiction)?							
Pain, function, quality of life	No studies	-	-	-	-	-	Insufficient
c. In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacological or nonpharmacological) on outcomes related to pain, function, and quality of life?							
Pain, function, quality of life	No studies	-	-	-	-	-	Insufficient
d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacological or nonpharmacological) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?							
Pain, function, quality of life	No studies	-	-	-	-	-	Insufficient

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
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 accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?							
Abuse, addiction	1 cohort study (n=568,640)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low
Abuse, addiction	10 uncontrolled studies (n=3,780)	High	Inconsistent	Direct	Precise	Undetected	Insufficient
Overdose	1 cohort study (n=9,940)	Moderate	Unknown (1 study)	Direct	Imprecise	Undetected	Low
Fractures	1 cohort study (n=2,341) and 1 case-control study (21,739 cases)	Moderate	Consistent	Direct	Precise	Undetected	Low
Myocardial infarction	1 cohort study (n=426,124) and 1 case-control study (11,693 cases)	Low	Consistent	Direct	Precise	Undetected	Low
Endocrine	1 cross-section study (n=11,327)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low
Gastrointestinal harms, motor vehicle accients, infections, psychological harms, cognitive harms	No studies	-	-	-	-	-	Insufficient
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)?							
Various harms	No studies	-	-	-	-	-	Insufficient

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
b. How do harms vary depending on the dose of opioids used?							
Abuse, addiction	1 cohort study (n=568,640)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low
Overdose	1 cohort study (n=9,940) and 1 case-control study (593 cases in primary analysis)	Moderate	Consistent	Direct	Precise	Undetected	Low
Fracture	1 cohort study (n=2,341)	Moderate	Unknown (1 study)	Direct	Imprecise	Undetected	Low
Myocardial infarction	1 cohort study (n=426,124)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low
Motor vehicle accidents	1 case-control study (5,300 cases)	Low	Unknown (1 study)	Direct	Precise	Undetected	Low
Endocrine	1 cross-sectional study (n=11,327)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low
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 overdose, addiction, abuse, or misuse; and doses of opioids used?							
Pain	2 randomized trials (n=93)	Moderate	Inconsistent	Direct	Imprecise	Undetected	Insufficient
Function, quality of life, outcomes related to abuse	No studies	-	-	-	-	-	Insufficient
b. In patients with chronic pain, what is the comparative effectiveness of short- versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?							
Pain, function, quality of life, outcomes related to abuse	No studies	-	-	-	-	-	Insufficient

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
c. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; and risk of overdose, addiction, abuse, or misuse?							
Pain and function	3 randomized trials (n=1,850)	Moderate	Consistent	Direct	Precise	Undetected	Low
Assessment of risk of overdose, addiction, abuse, or misuse	No studies	-	-	-	-	-	Insufficient
Overdose (as indicated by all-cause mortality)	1 cohort study (n=108,492)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low
Abuse and related outcomes	1 cohort study (n=5,684)	Moderate	Unknown (1 study)	Direct	Imprecise	Undetected	Insufficient
d. In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids vs. long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?							
Pain, function, quality of life, outcomes related to abuse	No studies	-	-	-	-	-	Insufficient
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?							
Pain, function, quality of life, outcomes related to abuse	No studies	-	-	-	-	-	Insufficient
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 maximum dose ceilings on outcomes related to pain, function, and quality of life?							
Pain, function, withdrawal due to opioid misuse	1 randomized trial (n=140)	Moderate	Unknown (1 study)	Direct	Imprecise	Undetected	Low

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
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?							
Pain, function, quality of life, outcomes related to abuse	No studies	-	-	-	-	-	Insufficient
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?							
Pain	5 randomized trials (n=802)	Moderate	Consistent	Direct	Precise	Undetected	Moderate
Function, quality of life, abuse and related outcomes	No studies	-	-	-	-	-	Insufficient
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 symptoms?							
Pain, function	1 randomized trial (n=10)	High	Unknown (1 study)	Direct	Imprecise	Undetected	Insufficient
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?							
Opioid abstinence	2 nonrandomized trials (n=150)	High	Consistent	Direct	Imprecise	Undetected	Insufficient

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
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?							
Diagnostic accuracy: Opioid Risk Tool	3 studies of diagnostic accuracy (n=496)	Moderate	Inconsistent	Direct	Imprecise	Undetected	Insufficient
Diagnostic accuracy: Screening and Opioid Assesment for Patients with Pain version 1	2 studies of diagnostic accuracy (n=203)	High	Consistent	Direct	Imprecise	Undetected	Low
; with chronic pain, what is the effectiveness of use of risk ;truments on outcomes related to overdose, addiction, abuse, or							
Outcomes related to abuse	No studies	-	-	-	-	-	Insufficient
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?							
Outcomes related to abuse	No studies	-	-	-	-	-	Insufficient
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?							
Outcomes related to abuse	No studies	-	-	-	-	-	Insufficient