

The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop

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Background: Increases in prescriptions of opioid medications for chronic pain have been accompanied by increases in opioid overdoses, abuse, and other harms and uncertainty about long-term effectiveness.

Purpose: To evaluate evidence on the effectiveness and harms of long-term (>3 months) opioid therapy for chronic pain in adults.

Data Sources: MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, PsycINFO, and CINAHL (January 2008 through August 2014); relevant studies from a prior review; reference lists; and ClinicalTrials.gov.

Study Selection: Randomized trials and observational studies that involved adults with chronic pain who were prescribed long-term opioid therapy and that evaluated opioid therapy versus placebo, no opioid, or nonopioid therapy; different opioid dosing strategies; or risk mitigation strategies.

Data Extraction: Dual extraction and quality assessment.

Data Synthesis: No study of opioid therapy versus no opioid therapy evaluated long-term (>1 year) outcomes related to pain, function, quality of life, opioid abuse, or addiction. Good- and

fair-quality observational studies suggest that opioid therapy for chronic pain is associated with increased risk for overdose, opioid abuse, fractures, myocardial infarction, and markers of sexual dysfunction, although there are few studies for each of these outcomes; for some harms, higher doses are associated with increased risk. Evidence on the effectiveness and harms of different opioid dosing and risk mitigation strategies is limited.

Limitations: Non-English-language articles were excluded, meta-analysis could not be done, and publication bias could not be assessed. No placebo-controlled trials met inclusion criteria, evidence was lacking for many comparisons and outcomes, and observational studies were limited in their ability to address potential confounding.

Conclusion: Evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. Evidence supports a dose-dependent risk for serious harms.

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Chronic pain, often defined as pain lasting longer than 3 months or past the normal time for tissue healing, is common and is a major cause of decreased quality of life and disability (1, 2). Prescriptions of opioid medications for chronic pain have increased dramatically (3-5). This trend has been accompanied by greatly increased levels of prescription opioid overdose, abuse, addiction, and diversion (6-15). Compared with placebo, opioid therapy has been found to be associated with alleviation of pain in the short term (16, 17). However, most opioid trials do not extend beyond 6 weeks and are of limited relevance to long-term opioid use. Furthermore, clinical decision making for long-term opioid therapy is complex and requires individualized benefit-risk assessments; opioid selection and dose initiation and titration strategies; integration of risk assessment and mitigation strategies; and consideration of alternative, nonopioid therapies (18).

The purpose of this review was to evaluate the evidence on the effectiveness and harms of opioid therapy for chronic pain. We updated a prior review (19) and expanded on it by focusing on long-term benefits and harms of opioid therapy, risk for overdose and injuries, dosing strategies, and risk assessment and mitigation.

METHODS

Detailed methods and data for this review, including the detailed key questions, analytic framework, search strategies, inclusion criteria, and study data extraction and quality rating methods, are available in the full report (20). The protocol was developed by using a standardized process (21) with input from experts and the public and is registered in the PROSPERO database (CRD42014007016) (22). This review focuses on adults with chronic pain and addresses the following key questions:

What is the effectiveness of long-term opioid therapy versus placebo, no opioid therapy, or nonopioid therapy for long-term (>1 year) outcomes related to pain, function, and quality of life?

What are the risks of opioids versus placebo or no opioids on opioid abuse, addiction, and related out-

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comes; overdose; and other harms, including falls, fractures, motor vehicle accidents, endocrinological harms, and cardiovascular events?

What is the comparative effectiveness of opioid dosing strategies on pain; function; quality of life; and risk for overdose, addiction, abuse, or misuse?

What is the accuracy of risk assessment before initiation of opioid therapy for predicting risk for opioid overdose, addiction, abuse, or misuse?

What is the effectiveness of risk mitigation strategies on outcomes related to overdose, addiction, abuse, or misuse?

“Opioid dosing strategies” refers to opioid selection, dose initiation and titration, scheduled and continuous versus as-needed dosing, dose escalation versus maintenance, opioid rotation versus continuation of current therapy, methods for discontinuation of opioid therapy, tapering of doses versus continuation of therapy, and different tapering method. Risk mitigation strategies include patient education; opioid therapy plans; urine drug screening; and use of prescription drug monitoring program data, monitoring instruments, more frequent monitoring intervals, pill counts, and abuse-deterrent formulations.

Data Sources and Searches

A research librarian searched MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, PsycINFO, and CINAHL for English-language articles published from January 2008 through August 2014. We also included relevant studies from a prior review (19), reviewed reference lists, and searched ClinicalTrials.gov.

Study Selection

Two investigators independently reviewed abstracts and full-text articles against prespecified eligibility criteria. We included studies of adults (aged ≥ 18 years) with chronic pain (>3 months) who were prescribed long-term opioid therapy (defined as opioid use on most days for >3 months). We included studies of long-term opioid therapy versus placebo, no therapy, another drug, or nondrug therapy; studies of different opioid dosing strategies; and studies of risk mitigation strategies that evaluated the outcomes described in the key questions. We focused on outcomes reported after at least 1 year of opioid therapy. For overdose and injuries (such as fractures, falls, and motor vehicle accidents), we included studies with any duration of opioid prescription for chronic pain because such outcomes can occur early during therapy. We also included studies of any duration on dose initiation and titration and opioid therapy discontinuation.

Studies of parenteral opioids and tramadol (a dual-mechanism medication with weak opioid μ -receptor affinity) were excluded. We included studies that did not report pain duration if the average duration of opioid therapy was more than 3 months and studies that did not report the duration of therapy if patients were prescribed long-acting opioids, which are not recommended for short-term use. We also included studies of patients with cancer pain who were not at the end of

life. Studies of acute pain, addiction treatment, and pregnant or breastfeeding women were excluded.

We included randomized trials and observational studies (cohort studies with concurrent controls, cross-sectional studies, and case-control studies) that controlled for potential confounders. We also included observational studies without a nonopioid control group that involved patients with chronic pain who were prescribed opioid therapy for at least 1 year and assessed abuse, misuse, or addiction as a primary outcome by using predefined methods. Finally, we included studies on the accuracy of risk prediction instruments administered before initiation of opioid therapy for predicting misuse, abuse, or addiction.

Data Extraction and Quality Assessment

One investigator extracted details about the study design, patient sample, setting, opioid therapy characteristics, and results. Another investigator verified the extracted data for accuracy. Two investigators independently assessed risk of bias for each study (including studies in the prior review) as good, fair, or poor by using predefined criteria for randomized trials (23), observational studies (24), and risk prediction instruments (25-27), in conjunction with the approach recommended in the Agency for Healthcare Research and Quality (AHRQ) methods guides (21, 25). Discrepancies were resolved through a consensus process.

Data Synthesis and Analysis

We assessed the overall strength of each body of evidence as high, moderate, low, or insufficient by using the approach described in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (28), based on aggregate study quality, precision, consistency, and directness. We did not attempt meta-analyses because of the small number of studies; variability in study designs, patient samples, and interventions; and methodological shortcomings of the studies.

Role of the Funding Source

The AHRQ funded the review, and a working group convened by the National Institutes of Health assisted in developing the review's scope and key questions. Both had no role in study selection, quality assessment, or synthesis. The investigators are solely responsible for the content.

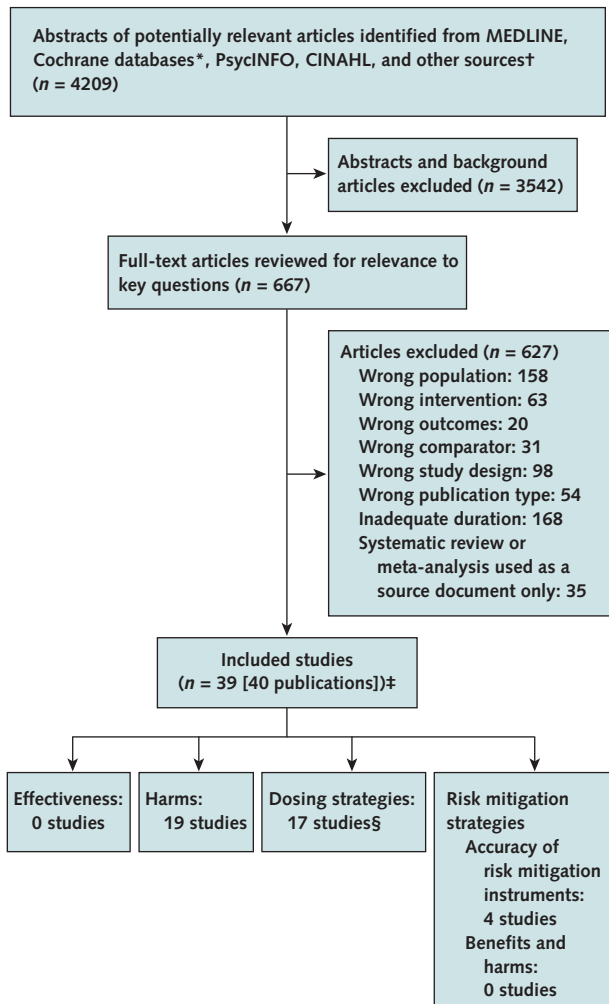
RESULTS

The literature search and selection is summarized in the **Figure**. Database searches resulted in 4209 potentially relevant articles. After dual review of abstracts and titles, 39 studies (in 40 publications) were included. Five of these studies, which assessed immediate effects of opioids used to treat acute pain exacerbations, were omitted here but are discussed in the full report (20).

Long-Term Effectiveness

No study of opioid therapy versus placebo, no opioid therapy, or nonopioid therapy evaluated long-term

Figure. Summary of evidence search and selection.



* Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews.

† Includes reference lists of relevant articles and systematic reviews.

‡ Some studies have multiple publications, and some are included for >1 key question.

§ Includes 5 studies on acute exacerbations of pain, which are discussed in the full report (20).

(>1 year) outcomes related to pain, function, or quality of life.

Harms

Opioid Abuse, Addiction, and Related Outcomes

No randomized trial evaluated opioid abuse, addiction, or related outcomes with long-term opioid therapy versus placebo or no opioid therapy. In 1 fair-quality study that used claims data from a large commercial health plan, long-term opioid therapy (>90 days' supply of opioids within 12 months of a new chronic pain diagnosis) versus no opioid prescription was associated with increased risk for a diagnosis of opioid abuse or dependence (29). Rates of opioid abuse or dependence ranged from 0.7% with low-dose therapy (morphine-equivalent dose [MED] of 1 to 36 mg/d) to 6.1% with high-dose therapy (MED ≥120

mg/d) compared with 0.004% with no opioids; adjusted odds ratios (ORs) ranged from 14.9 (95% CI, 10.4 to 21.5) for low-dose therapy to 122.5 (CI, 72.8 to 206.0) for high-dose therapy.

In 10 fair-quality uncontrolled studies (Appendix Table 1, available at www.annals.org) (30–40), estimates of opioid abuse, addiction, and related outcomes varied substantially, even after stratification by setting. No study reported blinding of outcome assessors to patient characteristics, and some studies also did not assess predefined outcomes in all patients. In primary care settings, prevalence of opioid abuse ranged from 0.6% to 8% and prevalence of dependence ranged from 3% to 26% (30, 31, 34). In pain clinic settings, prevalence of misuse ranged from 8% to 16% and prevalence of addiction ranged from 2% to 14% (32, 33, 35, 36, 38–40). Prevalence of aberrant drug-related behaviors (such as aberrant urine drug test results, medication agreement violations, or other behaviors indicative of misuse) ranged from 6% to 37%. Factors associated with increased risk for misuse included history of substance use disorder, younger age, major depression, and use of psychotropic medications (31, 37).

Definitions of opioid abuse, addiction, and related outcomes and methods used to identify these events varied (Appendix Table 1). All studies were conducted before the introduction of the diagnostic criteria for opioid use disorder in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (41).

Overdose

One large, fair-quality retrospective cohort study (n = 9940) found that, compared with nonuse, recent opioid use was associated with an increased risk for any overdose events (adjusted hazard ratio [HR], 5.2 [CI, 2.1 to 12.5]) and serious overdose events (adjusted HR, 8.4 [CI, 2.5 to 28]) (Appendix Table 2, available at www.annals.org) (42). The annual overdose rate was 256 per 100 000 person-years among patients who had recently received prescribed opioids versus 36 per 100 000 person-years among those who had not. Higher doses were associated with increased risk. Compared with an MED of 1 to 19 mg/d, the adjusted HRs for overdose ranged from 1.44 (CI, 0.57 to 3.62) for an MED of 20 to 49 mg/d to 8.87 (CI, 3.99 to 19.72) for an MED of at least 100 mg/d. A similar pattern was observed for serious overdose.

A good-quality, population-based, nested case-control study (498 case patients) also found a dose-dependent association with risk for overdose (43). Compared with an MED of 1 to 19 mg/d, the adjusted ORs ranged from 1.32 (CI, 0.94 to 1.84) for an MED of 20 to 49 mg/d to 2.88 (CI, 1.79 to 4.63) for an MED of at least 200 mg/d.

Fractures

A fair-quality cohort study (n = 2341 adults aged ≥60 years) found a higher fracture rate among current opioid users (6%) than among current nonusers (4%)

after a mean follow-up of 33 months, but the difference was not statistically significant (adjusted HR, 1.28 [CI, 0.99 to 1.64]) (Appendix Table 2) (13). A test for dose response was also of borderline statistical significance.

One good-quality case-control study (21 739 case patients) found current opioid use to be associated with increased risk for hip, humerus, or wrist fracture versus nonuse (adjusted OR, 1.27 [CI, 1.21 to 1.33]) (44). The risk was highest with 1 prescription (OR, 2.70 [CI, 2.34 to 3.13]) and decreased with higher numbers of prescriptions, with no increased risk with more than 20 cumulative prescriptions.

Cardiovascular Events

One fair-quality cohort study ($n = 297\ 314$) found that a cumulative opioid supply of at least 180 days over a 3.5-year period was associated with an increased risk for myocardial infarction versus no long-term opioid therapy (adjusted incidence rate ratio, 2.66 [CI, 2.30 to 3.08]) (Appendix Table 2) (45). Compared with a cumulative MED of 0 to 1350 mg over 90 days, the adjusted incidence rate ratio for myocardial infarction was 1.21 (CI, 1.02 to 1.45) for an MED of 1350 to less than 2700 mg and ranged from 1.42 to 1.89 for MEDs of at least 2700 mg. A good-quality case-control study (11 693 case patients) found that current opioid therapy versus nonuse was associated with increased odds of myocardial infarction (adjusted OR, 1.28 [CI, 1.19 to 1.37]) (46). No study evaluated associations between long-term opioid therapy and risk for arrhythmia or sudden death.

Endocrinological Harms

One fair-quality cross-sectional study of men with back pain ($n = 11\ 327$) found that, compared with nonuse, long-term opioid use was associated with increased use of medications for erectile dysfunction or testosterone replacement (adjusted OR, 1.45 [CI, 1.12 to 1.87]) (Appendix Table 2) (7). Compared with MEDs of 0 to less than 20 mg/d, an MED of at least 120 mg/d was associated with increased risk (OR, 1.58 [CI, 1.03 to 2.43]), but there was no increased risk at MEDs of 20 to less than 120 mg/d. Sexual dysfunction was not measured directly; other study limitations included unknown duration of pain and inability to determine whether medication use preceded receipt of opioids.

Motor Vehicle Accidents

One good-quality case-control study (5300 case patients) found that MEDs of at least 20 mg/d were associated with increased odds of road trauma among drivers (Appendix Table 2) (47). Compared with MEDs of 1 to less than 20 mg/d, the adjusted ORs ranged from 1.21 to 1.42 for MEDs of at least 20 mg/d.

Other Harms

No study evaluated risks for falls; infections; or psychological, cognitive, or gastrointestinal harms among patients with chronic pain who were receiving long-

term opioid therapy versus placebo or no opioid therapy.

Opioid Dosing Strategies

Initiation of Opioid Therapy and Titration of Doses

Although 3 fair-quality, open-label trials (reported in 2 articles) compared sustained- versus immediate-release opioids for titration of doses to stable pain control, results were inconsistent and difficult to interpret because of differences between treatment groups in dosing protocols (titrated vs. fixed dosing) and opioid doses (48, 49).

Comparative Effectiveness and Harms of Long-Acting Opioids

Three randomized, head-to-head trials of various long-acting opioids found no differences in 1-year outcomes related to pain or function (Appendix Table 3, available at www.annals.org) (50-52). Two of the trials (50, 51) were rated fair-quality, and one (52) was rated poor-quality. Methodological limitations included high attrition and open-label design; the poor-quality trial also did not report statistical analyses comparing results between groups for most outcomes. Opioid doses were titrated to effect or were determined during a run-in period, and no trial was designed to assess risk for abuse or addiction.

A fair-quality retrospective cohort study based on national pharmacy data from the Department of Veterans Affairs (VA) system compared all-cause mortality among patients with chronic pain who were prescribed methadone ($n = 28\ 554$) or long-acting morphine ($n = 79\ 938$) (53). In a propensity-stratified analysis, overall risk for death was lower with methadone than with morphine (adjusted HR, 0.56 [CI, 0.51 to 0.62]); a similar pattern was seen in all propensity quintiles except the highest.

A fair-quality retrospective cohort study based on Oregon Medicaid data ($n = 5684$) found that, compared with sustained-release morphine, sustained-release oxycodone was associated with a lower risk for an emergency department visit or hospitalization involving an opioid-related adverse event (adjusted HR, 0.45 [CI, 0.26 to 0.77]) or death (adjusted HR, 0.71 [CI, 0.54 to 0.94]) (54). There were no statistically significant differences between methadone and long-acting morphine in risk for death or overdose symptoms. A limitation of this study was that overdose symptoms (alteration of consciousness, malaise, fatigue, lethargy, or respiratory failure) were nonspecific for opioid-related adverse events.

Dose Escalation

One fair-quality randomized trial ($n = 140$) found no differences between more liberal dose escalation (doses increased according to preset dosing guidelines for inadequate pain relief) versus maintenance of current doses (doses increased only if medically necessary because of clear dosage tolerance or acute injury) after 12 months in pain, function, and use of nonopioid med-

ications or physical therapy (55). There were also no differences in all-cause withdrawals or withdrawals due to opioid misuse. However, the difference in opioid doses prescribed at the end of the trial was relatively small (the mean MED was 52 mg/d with more liberal dosing vs. 40 mg/d with maintenance of current doses).

Other Opioid Dosing Strategies

No study compared the long-term effectiveness of short- versus long-acting opioids; short- plus long-acting opioids versus long-acting opioids alone; scheduled, continuous dosing versus as-needed dosing; or opioid rotation versus maintenance of current therapy. Evidence was limited to small, poor-quality studies (56–58) for the comparative effectiveness of tapering of opioid doses or discontinuation of therapy versus maintenance of therapy and for different strategies for tapering of doses. No study evaluated long-term benefits or harms associated with different strategies for treating acute exacerbations of chronic pain; effects on immediate pain relief are detailed in the full report (20).

Risk Assessment Instruments

Four studies (59–62) evaluated the accuracy of risk assessment instruments, administered before the initiation of opioid therapy, for predicting opioid abuse or misuse (Appendix Tables 4 and 5, available at www.annals.org). Three studies (60–62) (2 fair-quality and 1 poor-quality) reported inconsistent results for the 10-item Opioid Risk Tool. Based on a cutoff score of greater than 4 (on a scale of 0 to 25), sensitivity ranged from 0.20 to 0.99; two of these studies reported specificities of 0.88 and 0.16. Two studies (59, 61) evaluated the accuracy of version 1 of the 14-item Screener and Opioid Assessment for Patients with Pain instrument. One fair-quality study (59) reported a sensitivity of 0.68 (CI, 0.52 to 0.81) and specificity of 0.38 (CI, 0.29 to 0.49) based on a cutoff score of at least 8 (on a scale of 0 to 56), resulting in weak positive and negative likelihood ratios (1.11 and 0.83, respectively). One poor-quality study (61) reported a sensitivity of 0.73, based on a cutoff score of at least 6 (specificity not reported). The accuracy of other risk assessment instruments was evaluated in 1 poor-quality study each. Methodological shortcomings included unclear blinding of outcome assessors to findings of the screening instrument and use of definitions for aberrant drug-related behaviors that were not well-standardized or described. The poor-quality studies (60, 61) also did not apply the risk assessment instruments to all patients or included only patients with abuse or misuse. No study evaluated the effectiveness of risk prediction instruments for improving outcomes related to overdose, addiction, abuse, or misuse.

Risk Mitigation Strategies

No study evaluated the effectiveness of risk mitigation strategies for improving outcomes related to overdose, addiction, abuse, or misuse.

DISCUSSION

The evidence in this review is summarized in the Table. We identified no studies of long-term opioid therapy for chronic pain versus no opioid therapy or nonopioid therapies that evaluated effects on pain, function, or quality of life at 1 year or longer. Most placebo-controlled, randomized trials were shorter than 6 weeks, and almost all were shorter than 16 weeks (17). We did not include uncontrolled studies for these outcomes; reliable conclusions cannot be drawn from such studies because of the lack of a nonopioid comparison group and heterogeneity of the results (63).

More evidence is available on harms of opioid therapy. Controlled observational studies published after our prior review (19) suggest that, compared with no opioid use, opioid therapy for chronic pain is associated with increased risk for overdose (42), opioid abuse and dependence (29), fractures (13), myocardial infarction (46), and use of medications to treat sexual dysfunction (7). For fractures, 1 study found that the risk was highest shortly after the start of opioid therapy (44). For some harms, studies suggest that higher opioid doses are associated with increased risk (7, 13, 29, 42, 43, 45). As with all observational studies, findings are susceptible to residual confounding. Although we restricted inclusion to studies that attempted to control for potential confounders, most studies were based on information available in administrative databases, which are typically limited in their ability to address potentially important confounders.

In uncontrolled studies, rates of abuse and related outcomes varied substantially, even after the studies were stratified by setting (primary care or pain clinic). Studies differed in how addiction, abuse, misuse, and dependence were defined and in the methods used to identify these outcomes. Our review found higher rates of abuse and related outcomes than a previous systematic review that included studies that did not report predefined methods for ascertaining opioid addiction (63). All studies were done before the recent DSM-5 definition of opioid use disorder was published (41).

Evidence on the effectiveness of different opioid dosing strategies is limited. A trial of a more liberal dose-escalation strategy versus maintenance of current doses found no differences in outcomes, but doses were similar at the end of the trial (55). One study from Washington reported a decrease in the number of opioid-associated overdose deaths after implementation of a guideline that included an MED threshold of 120 mg/d for reassessment and consultation (64), but this study did not meet our inclusion criteria because it was a before-after study in which changes in the number of overdose deaths could have resulted from factors other than use of the dose threshold. Evidence on benefits and harms of methods for initiating opioid therapy and titrating doses, use of short- versus long-acting opioids, scheduled and continuous versus as-needed dosing, use of opioid rotation, and methods

Table. Strength of Evidence

Outcome	Studies	Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence
Effectiveness and comparative effectiveness							
Effectiveness of long-term opioid therapy vs. placebo or no opioid therapy for long-term (>1 y) outcomes							
Pain, function, and quality of life	None	-	-	-	-	-	Insufficient
Harms and adverse events							
Risks of opioids vs. placebo or no opioid on opioid abuse, addiction, and related outcomes; overdose; and other harms							
Abuse or addiction	1 cohort study (n = 568 640)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low
Abuse or addiction	10 uncontrolled studies (n = 3780)	High	Inconsistent	Direct	Precise	Undetected	Insufficient
Overdose	1 cohort study (n = 9940)	Moderate	Unknown (1 study)	Direct	Imprecise	Undetected	Low
Fractures	1 cohort study (n = 2341) and 1 case-control study (21 739 case patients)	Moderate	Consistent	Direct	Precise	Undetected	Low
Myocardial infarction	1 cohort study (n = 426 124) and 1 case-control study (11 693 case patients)	Low	Consistent	Direct	Precise	Undetected	Low
Endocrinological harms	1 cross-sectional study (n = 11 327)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low
How do harms vary depending on the opioid dose used?							
Abuse or addiction	1 cohort study (n = 568 640)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low
Overdose	1 cohort study (n = 9940) and 1 case-control study (593 case patients in primary analysis)	Moderate	Consistent	Direct	Precise	Undetected	Low
Fractures	1 cohort study (n = 2341)	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 (5300 case patients)	Low	Unknown (1 study)	Direct	Precise	Undetected	Low
Endocrinological harms	1 cross-sectional study (n = 11 327)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low
Dosing strategies							
Comparative effectiveness of different methods for initiating opioid therapy and titrating doses							
Pain	2 randomized trials (n = 93)	Moderate	Inconsistent	Direct	Imprecise	Undetected	Insufficient
Comparative effectiveness of different long-acting opioids							
Pain and function	3 randomized trials (n = 1850)	Moderate	Consistent	Direct	Precise	Undetected	Low
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 = 5684)	Moderate	Unknown (1 study)	Direct	Imprecise	Undetected	Insufficient
Dose escalation vs. dose maintenance or use of dose thresholds							
Pain, function, or withdrawal due to opioid misuse	1 randomized trial (n = 140)	Moderate	Unknown (1 study)	Direct	Imprecise	Undetected	Low
Short- vs. long-acting opioids; short- plus long-acting opioids vs. long-acting opioids alone; scheduled and continuous vs. as-needed dosing of opioids; or opioid rotation vs. maintenance of current therapy							
Pain, function, quality of life, and outcomes related to abuse	None	-	-	-	-	-	Insufficient
Comparative effectiveness of different strategies for treating acute exacerbations of chronic pain*							
Pain	5 randomized trials (n = 802)	Moderate	Consistent	Direct	Precise	Undetected	Moderate
Function, quality of life, abuse, and related outcomes	None	-	-	-	-	-	Insufficient
Effects of decreasing or tapering opioid doses vs. continuation of opioid therapy							
Pain and function	1 randomized trial (n = 10)	High	Unknown (1 study)	Direct	Imprecise	Undetected	Insufficient
Comparative effectiveness of different tapering protocols and strategies							
Opioid abstinence	2 nonrandomized trials (n = 150)	High	Consistent	Direct	Imprecise	Undetected	Insufficient

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Table-Continued

Outcome	Studies	Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence
Risk assessment and risk mitigation strategies							
Diagnostic accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or misuse in patients with chronic pain being considered for long-term opioid therapy							
Opioid Risk Tool	3 studies of diagnostic accuracy (n = 496)	Moderate	Inconsistent	Direct	Imprecise	Undetected	Insufficient
SOAPP, version 1	2 studies of diagnostic accuracy (n = 203)	High	Consistent	Direct	Imprecise	Undetected	Low
Effectiveness of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse in patients with chronic pain							
Outcomes related to abuse	None	-	-	-	-	-	Insufficient
Effectiveness of risk mitigation strategies, including opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, and use of abuse-deterrent formulations, on outcomes related to overdose, addiction, abuse, or misuse							
Outcomes related to abuse	None	-	-	-	-	-	Insufficient
Comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids							
Outcomes related to abuse	None	-	-	-	-	-	Insufficient

SOAPP = Screener and Opioid Assessment for Patients with Pain.

* Discussed in detail in the full report (20), which also includes a more detailed strength-of-evidence table.

for tapering doses or discontinuing long-term therapy was insufficient to reach reliable conclusions.

As detailed in the full report (20), evidence on different methods for treating acute exacerbations of chronic pain was limited to trials that evaluated immediate pain relief with buccal or intranasal fentanyl, with no data on long-term outcomes. In 2007, the U.S. Food and Drug Administration released a public health advisory because of case reports of deaths and other life-threatening adverse effects in patients prescribed buccal fentanyl (65).

Limited evidence indicates no clear differences in effectiveness of different long-acting opioids when patients are permitted to have doses titrated for adequate pain control (50-52). However, no randomized trial was designed to assess relative harms, such as overdose, abuse, or addiction. Methadone is disproportionately represented in case series and epidemiologic studies of opioid-associated deaths; this is believed to be related to its long and variable half-life and potential for electrocardiographic QTc interval prolongation (66). However, the highest-quality observational study, which controlled for confounders by using a propensity-adjusted analysis, found methadone to be associated with lower risk for death compared with sustained-release morphine in a VA setting (53). These results suggest that methadone may not be associated with increased risk for death in some settings. More research is needed to understand the factors that contribute to safer prescribing in different clinical settings.

Evidence on the accuracy and effectiveness of risk assessment instruments for predicting opioid abuse or misuse in patients before initiation of long-term opioid therapy was sparse and was characterized by methodological limitations and inconsistent findings, which precluded reliable conclusions (59, 61, 62, 67). No study evaluated the effectiveness of risk mitigation strategies, such as the use of urine drug screening, prescription drug monitoring program data, or abuse-deterrent formulations, in reducing harms. Although a previous review found that opioid management plans

and urine drug screening were associated with decreased risk for misuse behaviors (10), its conclusions were based on 4 studies that did not meet the inclusion criteria for our review because the effects of these strategies could not be separated from those of concurrent opioid prescribing interventions and because the studies used a historical control group or a before-after design.

Our review has limitations. We excluded non-English-language articles and studies published only as abstracts. We did not attempt meta-analysis and could not use graphical or statistical methods to assess for publication bias because of the paucity of evidence, but we identified no unpublished randomized trials that met our inclusion criteria. Studies that evaluated outcomes after less than 1 year might provide evidence that is relevant to long-term prescribing. However, we found no placebo-controlled trials that lasted at least 6 months. Some potentially relevant studies (68-74) were excluded because it was not possible to determine whether patients had chronic pain or received long-term opioid therapy.

Despite these limitations, the lack of scientific evidence on effectiveness and harms of long-term opioid therapy for chronic pain is clear and is in striking contrast to its widespread use for this condition and the large increase in prescription opioid-related overdoses. Although it has been asserted that long-term opioid therapy may be more appropriate for certain types of pain problems or for patients assessed as being at lower risk for overdose or misuse, there was insufficient evidence (as detailed in the full report) to determine how benefits and harms vary in patient subgroups defined by demographic, pain, or other clinical characteristics (20). Studies generally restricted inclusion to persons with noncancer pain or were excluded because it was not possible to determine whether patients with cancer were at the end of life.

Well-designed studies are urgently needed to address the key questions of this review. Randomized trials evaluating benefits and harms of long-term opioid

therapy are challenging to conduct, but more flexible, large pragmatic studies or well-designed controlled observational studies, with assessment of and control for potential confounders, could advance scientific knowledge in this area. Studies that include patients who are potentially at higher risk for adverse outcomes are needed because such patients are commonly prescribed long-term opioid therapy (75–77). Additional research is needed to develop and validate accurate risk prediction instruments and to determine how using them and other risk mitigation strategies affects patient outcomes. More research is needed on the comparative benefits and harms of different opioids, formulations, and dosing protocols and on comparative benefits and harms of long-term opioid therapy in patient subgroups characterized by type of pain problem and other potentially important characteristics. Greater standardization of methods for defining and identifying abuse-related outcomes is also needed (78).

In summary, reliable conclusions about the effectiveness of long-term opioid therapy for chronic pain are not possible due to the paucity of research to date. Accumulating evidence supports the increased risk for serious harms associated with long-term opioid therapy, including overdose, opioid abuse, fractures, myocardial infarction, and markers of sexual dysfunction; for some harms, the risk seems to be dose-dependent. Research is needed to understand long-term patient outcomes, the risks for opioid abuse and related problems, and the effects of different opioid prescription methods and risk mitigation strategies.

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Appendix Table 1. Uncontrolled Studies of Long-Term Opioid Use and Abuse, Misuse, and Related Outcomes

Study, Year (Reference)	Study Duration	Study Design	Sample Characteristics	Opioid Dose (MED)	Opioid Duration	Pain Type	Method of Ascertaining and Defining Abuse/Misuse	Primary Results
Banta-Green et al, 2009 (30)	NA	Cross-sectional	704 patients who used opioids in past 90 d Integrated group practice patients in a nonprofit health care system in Washington Mean age: 53 y Female: 62% Race: 89% non-Hispanic white	Mean in past year, 50 mg/d	NR	NR	CIDI for DSM-IV criteria for opioid diagnoses	Opioid dependence: 13% (91 of 704) Opioid abuse without dependence: 6% (56 of 704)
Boscarino et al, 2010 (31)	NA	Cross-sectional	705 primary and specialty care patients in an integrated health care system in Pennsylvania who received ≥4 opioid prescriptions in past 12 mo Aged 18–64 y: 79% Aged ≥65 y: 21% Female: 61% White: 98%	NR	Mean, 10.7 prescriptions over 1 y	Noncancer, no other description	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% (CI, 31.1%–40.2%) met criteria for lifetime dependence Factors associated with current dependence: Age <65 y (OR, 2.3 [CI, 1.6–3.5]) History of opioid abuse (OR, 3.8 [CI, 2.6–5.7]) History of high dependence severity (OR, 1.9 [CI, 1.4–2.5]) History of major depression (OR, 1.3 [CI, 1.1–1.6]) Current use of psychotropic medications (OR, 1.7 [CI, 1.2–2.5])
Reid et al, 2002 (37)	NA	Retrospective cohort	98 patients with ≥6 mo of opioid prescriptions in 1 y VA primary care clinic (n = 50) vs. urban hospital primary care clinic (n = 48) Median age: 54 vs. 55 y Female: 8% vs. 67% Race: 88% white, 12% black vs. 52% white, 36% black; 10% Hispanic Median duration of pain: 10 vs. 13 y	NR	≥6 mo of prescriptions in past year	Noncancer, 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	Opioid abuse behaviors: 24% (12 of 50) vs. 31% (15 of 48) Median time to onset of abuse behaviors: 24 mo Factors associated with odds of opioid abuse behaviors: History of substance use disorder (adjusted OR, 3.8 [CI, 1.4–10.8]) Age (adjusted OR, 0.4 [CI, 0.9–1.0]) Number of medical diseases (adjusted OR, 0.7 [CI, 0.5–1.1])
Compton et al, 2008 (32)	1 y	Prospective cohort	135 veterans at VA pain clinic Mean age: 53 y Female: 6% Race: NR Baseline mean usual pain VAS rating: 6.75 on scale of 0–10	NR	NR	Musculoskeletal (77%), neuropathic (19%), multicategory (4%)	Chart review for discontinuation of opioid therapy due to medication agreement violation (including for opioid misuse or abuse) UDT: not examined SUO UDT: not examined	Discontinuation due to medication agreement violation: 28% (38 of 135) Discontinuation due to specific problematic opioid misuse behaviors: 8% (11 of 135)
Cowan et al, 2003 (33)	NA	Cross-sectional	104 patients who had been prescribed opioids at a pain clinic in a U.K. NHS hospital Mean age: 55.4 y Female: 39% Race: NR Mean duration of pain: 10.5 y	NR	Mean, 14.1 mo; 57% of patients had permanently stopped opioid therapy	Degenerative disease other than osteoarthritis (34%), failed back/neck surgery syndrome (24%), complex regional pain syndrome (10%), osteoarthritis (10%)	SUO UDT: not examined	Self-reported addiction: 1.9% (2 of 104) Craving opioids: 2.9% (3 of 104) Has used drugs to enhance the effect of opioids: 0.9% (1 of 104) Has used alcohol to enhance the effect of opioids: 0.9% (1 of 104)
Fleming et al, 2007 (34); Saffier et al, 2007 (38)	NA	Cross-sectional	801 primary care patients receiving daily opioid therapy Mean age: 48.6 y Female: 66% Race: 73.6% white, 23.1% African American, 1% other Disability income: 48%	Mean, 92 mg/d	96% prescribed chronic opioid therapy for ≥12 mo	Degenerative arthritis (24%), low back (21%), migraine (8%), neuropathy (5.5%)	In-person interviews with ASJ, SDSS, and 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 oversedated: 24% (186 of 785) Felt intoxicated from pain medication: 33% (260 of 785) Requested early refills: 45% (359 of 785) Independently increased dose: 37% (288 of 785) Medications lost or stolen: 30% (236 of 785) Used opioid for purpose other than pain: 16% (125 of 785) Drank alcohol to relieve pain: 20% (154 of 785)

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Appendix Table 1—Continued

Study, Year (Reference)	Study Duration	Study Design	Sample Characteristics	Opioid Dose (MED)	Opioid Duration	Pain Type	Method of Ascertaining and Defining Abuse/Misuse	Primary Results
Højsted et al, 2010 (35)	NA	Cross-sectional	253 patients at pain clinic (236 with noncancer pain and 17 with cancer pain) Mean age: 52 y Females: 64% Race: NR Receiving opioids: 74% (187 of 253)	Median among opioid recipients, 90 mg/d	Mean among opioid recipients who returned a questionnaire, 6.8 y	Noiceptive (28%), neuropathic (33%), mixed noiceptive and neuropathic (39%)	Addition screening by physician and nurse (blinded to each other) using CD-10 and Portenoy criteria; positive screening result by either provider was required UDT: not examined	Addiction to opioids or hypnotics (ICD-10): Total sample: 11% (28 of 253) Among those using addictive drugs: 13% Among those using opioids: 14% Addiction to opioids (ICD-10) among those using opioids: 14.4% (27 of 187) Addiction to opioids or hypnotics (Portenoy criteria) among those using opioids: 19% (36 of 187) Addiction to opioids (Portenoy criteria): 19% (36 of 187)
Portenoy et al, 2007 (36)	3 y	Prospective registry study	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 continued using CR oxycodone Mean age: 56 y Female: 57% Race: 90% white Average BPI pain score: 6.4	Mean, 52.5 mg/d	Mean, 541 d	Osteoarthritis (38%), diabetic neuropathy (31%), low back (31%)	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 physician: 5.7% (13 of 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 of 227) Problematic drug-related behavior adjudicated by expert panel as possible: 0.4% (1 of 227) Problematic drug-related behavior adjudicated by expert panel as withdrawal, but no indication of abuse: 0.4% (1 of 227) Problematic drug-related behavior adjudicated by expert panel as suspected abuse/dependence, but insufficient information to draw definitive conclusion: 2.2% (5 of 227) Problematic drug-related behavior adjudicated by expert panel as no evidence of abuse, dependence, or euphoria: 0.4% (1 of 227) Overdose deaths: 1 (phenylpropionolamine, oxycodone, and alcohol)
Schneider and Kirsh, 2010 (39)	NA	Retrospective chart review	197 patients treated by a pain specialist for ≥ 1 y Mean age: 49 y Female: 67% Race: NR	Mean, 180 mg/d (long-acting) and 47 mg/d (short-acting)	Mean, 4.7 y	Back (51%), neck (10%), fibromyalgia (9%), other myofascial (8%)	UDT: immunoassay followed by confirmatory GC/MS	Positive UDT result: 8.7% (14 of 161) Aberrant drug-related behaviors noted in chart: 15.7% (31 of 197)
Wasan et al, 2009 (40)	NA	Cross-sectional	622 patients with chronic noncancer pain receiving long-term opioid therapy from pain management centers Mean age: 50.4 y Female: 55% Race: 80% white Mean pain rating: 5.96 on scale of 0–10	NR	Mean, 6.2 y	Low back (61%)	POTO, PDUQ, and UDT (immunoassay and confirmatory GC/MS)	Score ≥ 2 on POTO: 24% (115 of 480) Score ≥ 11 on PDUQ: 29.1% (130 of 447) Positive UDT result: 37.1% (134 of 356)

ASI = Addiction Severity Index; BPI = Brief Pain Inventory; CIDI = Composite International Diagnostic Interview; CR = controlled-release; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; GC = gas chromatography; ICD-10 = International Classification of Diseases, 10th Revision; MED = morphine-equivalent dose; MS = mass spectrometry; NA = not applicable; NHS = National Health Service; NR = not reported; OR = odds ratio; PDUQ = Prescription Drug Use Questionnaire; POTO = Prescription Opioid Therapy Questionnaire; SDSS = Substance Dependence Severity Scale; SUQ = Substance Use Questionnaire; UDT = urine drug test; VA = Department of Veterans Affairs; VAS = visual analogue scale.

Appendix Table 2. Studies of Harms

Study, Year (Reference)	Design; Country	Quality	Eligibility Criteria	Comparison Groups
Endocrinological harms				
Deyo et al, 2013 (7)	Cross-sectional; United States	Fair	Ambulatory men aged ≥ 18 y with diagnoses associated with low back pain	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)
Fractures				
Li et al, 2013 (44)	Nested case-control; United Kingdom	Good	Cohort: patients with noncancer pain with ≥ 1 opioid prescription Case patients (n = 21 739): first-time fracture of the hip, humerus, or wrist, aged 18–80 y, >2 y of medical history data before index date Control participants (n = 85 326): ≤ 4 control participants without fracture selected for each case patient, matched on age, sex, index date, and general practice	A: opioid nonuse B: current cumulative opioid use (1 prescription) C: 2 or 3 opioid prescriptions D: 4 or 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
Saunders et al, 2010 (13)	Cohort; United States	Fair	Age ≥ 60 y, initiating opioid therapy (no opioid prescriptions in prior 6 mo) with ≥ 3 prescriptions in 90 d and diagnosis of noncancer pain 2–3 wk before index prescription	Opioid MED: A: not currently using B: 1– <20 mg/d C: 20– <50 mg/d D: ≥ 50 mg/d E: any use
Motor vehicle accident				
Gomes et al, 2013 (47)	Case-control; Canada	Good	Aged 15–64 y with public drug coverage and an opioid prescription (excluding methadone); ≥ 6 mo of continuous eligibility for public drug coverage and ≥ 1 opioid prescription Case patients: ED visit with external cause of injury related to road trauma (n = 5300) Control participants: matched to case patients on age, index year, and disease risk index (n = 5300)	Opioid MED: A: 1– <20 mg/d B: 20– <50 mg/d C: 50– <100 mg/d D: 100– <200 mg/d E: ≥ 200 mg/d
Myocardial infarction				
Carman et al, 2011 (45)	Retrospective cohort; United States	Fair	Patients aged ≥ 18 y with claim submitted for dispensation of opioids or COX-2 inhibitors for ≥ 180 d from July 2002 to December 2005; control participants from general population matched on age, sex, and cohort entry date	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) Opioid cohort stratified by MED (milligrams per 90 d) 1: 0– <1350 2: 1350– <2700 3: 2700– <8100 4: 8100– $<18 000$ 5: $\geq 18 000$
Li et al, 2013 (46)	Case-control; United Kingdom	Good	Case patients (n = 11 693): aged 18–80 y, 2 y of medical history data before index event Control participants: (n = 44 897): ≤ 4 control participants matched on age, sex, index date, and practice site	A: nonuse B: current use (within 0–30 d) C: recent use (within 31–365 d) D: past use (within 366–730 d) Cumulative use (number of prescriptions): 1: 1–2 2: 3–10 3: 11–50 4: >50

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Appendix Table 2—Continued

Population Characteristics	Method for Assessing Outcomes and Confounders	Variables Adjusted for in Statistical Analysis	Primary Results
<p><i>n</i> = 11 327 Mean age: 56 y (A) vs. 48 y (B) Female: 0% Race (data available for 59% of sample): 89% white, 3% black, 3% Asian/Pacific Islander, 1% American Indian, 3.9% other Sedative-hypnotic use: 24% (A) vs. 16% (B) Depression: 17% (A) vs. 11% (B) Duration of opioid use: NR Mean opioid dose: NR</p>	Review of medical and pharmacy records	Age, comorbidity score, number of hospitalizations, sedative-hypnotic use, duration of opioid use, morphine dose at last dispensation, type of opioid (short- vs. long-acting), depression, and smoking status	Testosterone replacement or erectile dysfunction treatment: No opioid use: 6.7% (312 of 4655) Short-term use: 7.4% (346 of 4696) Episodic use: 7.9% (13 of 164) Long-term use: 13.1% (238 of 1812) <i>P</i> < 0.001; OR, 1.45 (95% CI, 1.12-1.87) Opioid MED ≥120 mg/d vs. 0 to <20 mg/d; OR, 1.58 (CI, 1.03-2.43)
<p><i>n</i> = 107 065 Mean age: 62 y Female: 77% Race: NR Duration of opioid use: NR Mean opioid dose: NR</p>	General Practice Research Database, with validated data on drug exposures and diagnoses (including fracture)	Smoking, BMI, number of general practice visits, recorded years before index date, opioid use (new vs. prevalent), comorbid conditions, comedications, types of pain, and recent/past opioid use	Adjusted OR for risk for hip, humerus, or wrist fracture: A: 1.00 (reference) B: 2.70 (CI, 2.34-3.13) C: 1.90 (CI, 1.67-2.17) D: 1.44 (CI, 1.22-1.69) E: 1.17 (CI, 1.08-1.27) F: 1.06 (CI, 0.98-1.15) G: 1.06 (CI, 0.96-1.16) H: 1.12 (CI, 0.99-1.25) 1: 1.00 (reference) 2: 1.27 (CI, 1.21-1.33) 3: 1.05 (CI, 0.99-1.13) 4: 0.96 (CI, 0.92-1.01)
<p><i>n</i> = 2341 Mean age: 73 y Female: 66% Race: NR Depression: 22% Substance abuse: 3.8% Sedative-hypnotic use: 60% Duration of opioid use: NR Mean MED: 12.8 mg/d (SD, 17.0)</p>	Fractures initially identified by ICD-9 codes (excluding vertebral fractures) and verified by medical record review; medication data from automated pharmacy files; covariates from automated health care data	Age; sex; tobacco use; diagnosis of depression, substance abuse, or dementia; index pain; chronic disease comorbidity; sedative-hypnotic use; antidepressant use; hormone replacement therapy or bisphosphonate use; and prior fractures	Fracture rate: 5.0% per year Adjusted HRs for risk for fracture: A: 1.00 (reference) B: 1.20 (CI, 0.92-1.56) C: 1.34 (CI, 0.89-2.01) D: 2.00 (CI, 1.24-3.24) E: 1.28 (CI, 0.99-1.64)
<p><i>n</i> = 5300 Mean age: 46 y (case patients) vs. 46 y (control participants) Female: 49% Duration of opioid use: 7.1 y (case patients) vs. 6.8 y (control participants) Mean opioid dose: NR</p>	Case patients identified on basis of ICD-10 codes for injury related to road trauma; drug claims database used to determine opioid prescriptions; multiple databases used to identify inpatient hospitalizations, ED visits, claims for physician services, physician specialty, and patient demographic characteristics	Age, hospitalization for alcoholism in past 3 y, ED visit for alcoholism in past year, duration of opioid treatment, medication use in past 180 d, number of drugs dispensed in past 180 d, and numbers of physician and ED visits in past year	Risk for motor vehicle crash (adjusted OR): A: 1.00 (reference) B: 1.21 (CI, 1.02-1.42) C: 1.29 (CI, 1.06-1.57) D: 1.42 (CI, 1.15-1.76) E: 1.23 (CI, 1.02-1.49)
<p><i>n</i> = 426 124 Aged 30-39 y: 16% (A) vs. 5.4% (B) vs. 4.1% (C) vs. 5.3% (D) vs. 16% (E) Aged 40-49 y: 34% (A) vs. 21% (B) vs. 18% (C) vs. 20% (D) vs. 34% (E) Aged 50-64 y: 37% (A) vs. 56% (B) vs. 56% (C) vs. 56% (D) vs. 37% (E) Aged ≥65 y: 8.4% (A) vs. 17% (B) vs. 21% (C) vs. 17% (D) vs. 8.4% (E) Female: 40% (A) vs. 40% (B) vs. 40% (C) vs. 35% (D) vs. 40% (E) Duration of pain: NR Mean opioid dose: NR</p>	Claims database	Incidence rates adjusted for age and sex; IRR adjusted for age, sex, cardiovascular and other comorbid conditions, and use of concomitant medications	Adjusted incidence rate of myocardial infarction: A: 5.93 (CI, 5.58-6.30); IRR, 2.66 (CI, 2.30-3.08) B: 3.54 (CI, 3.11-4.01); IRR, 1.94 (CI, 1.65-2.29) C: 3.53 (CI, 3.15-3.94); IRR, 1.79 (CI, 1.53-2.10) D: 3.40 (CI, 2.76-4.14); IRR, 1.74 (CI, 1.41-2.16) E: 1.58 (CI, 1.40-1.78); IRR, 1.00 (reference) Risk, by dose (IRR): 1: reference 2: 1.21 (CI, 1.02-1.45) 3: 1.42 (CI, 1.21-1.67) 4: 1.89 (CI, 1.54-2.33) 5: 1.73 (CI, 1.32-2.26)
<p><i>n</i> = 56 590 Mean age: 62 y (case patients) vs. 62 y (control participants) Female: 31% (case patients) vs. 31% (control participants) Duration of opioid use: NR Mean opioid dose: NR</p>	General Practice Research Database, with validated data on drug exposures and diagnoses (including myocardial infarction)	Age, sex, smoking, BMI, number of general practice visits, years of medical history, new vs. prevalent opioid use, comorbid conditions, concomitant medications, abdominal and pelvic pain, and other pain	Risk for myocardial infarction (adjusted OR): A: 1.00 (reference) B: 1.28 (CI, 1.19-1.37) C: 1.17 (CI, 1.10-1.24) D: 1.06 (CI, 0.98-1.14) 1: 1.10 (CI, 1.03-1.18) 2: 1.09 (CI, 1.02-1.17) 3: 1.38 (CI, 1.28-1.49) 4: 1.25 (CI, 1.11-1.40)

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Appendix Table 2—Continued

Study, Year (Reference)	Design; Country	Quality	Eligibility Criteria	Comparison Groups
Overdose				
Dunn et al, 2010 (42)	Retrospective cohort; United States	Fair	Patients aged >18 y starting new episode of opioid use (no opioids in past 6 mo); ≥3 opioid prescriptions filled in first 90 d of episode; diagnosis of chronic noncancer pain in 2 wk before first opioid prescription	MED: A: 1-<20 mg/d B: 20-<49 mg/d C: 50-<99 mg/d D: ≥100 mg/d
Gomes et al, 2011 (43)	Case-control; Canada	Good	Residents aged 15-64 y with public drug coverage and opioid for nonmalignant pain (1997-2006) Case patients: died of opioid-related cause (n = 498) Control participants: matched to case patients on disease risk index, age, sex, index year, and Charlson score (n = 1714)	A: 1-<20 mg/d B: 20-<50 mg/d C: 50-<100 mg/d D: 100-<200 mg/d E: ≥200 mg/d

BMI = body mass index; COX-2 = cyclooxygenase-2; ED = emergency department; HR = hazard ratio; ICD = International Classification of Diseases; IRR = incidence rate ratio; MED = morphine-equivalent dose; NR = not reported; OR = odds ratio; RxRisk = prescription drug index.

Appendix Table 2—Continued

Population Characteristics	Method for Assessing Outcomes and Confounders	Variables Adjusted for in Statistical Analysis	Primary Results
<p>n = 9940 Mean age: 54 y Female: 60% Race: NR Depression: 27% Substance abuse: 6.2% Mean Charlson score, 0.71 (SD, 1.48; range, 0-14) Benzodiazepine use: 43% Duration of opioid use: NR Mean opioid dose: 13.3 mg (median, 6.0 mg)</p>	<p>Claims database</p>	<p>Sedative-hypnotic use as time-varying covariate, age, sex, smoking, depression, substance abuse, index pain diagnosis, and chronic disease comorbidity adjustors (RxRisk and Charlson index)</p>	<p>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)</p> <p>Any overdose event: Adjusted HR, 5.2 (CI, 2.1-12.5) No opioid: 0.31 (CI, 0.12-0.80) A: 1.00 (reference) B: 1.44 (CI, 0.57-3.62) C: 3.73 (CI, 1.47-9.5) D: 8.87 (CI, 3.99-19.72)</p> <p>Serious overdose event: Adjusted HR, 8.4 (CI, 2.5-28) No opioid: 0.19 (CI, 0.05-0.68) A: 1.00 (reference) B: 1.19 (CI, 0.4-3.6) C: 3.11 (CI, 1.01-9.51) D: 11.18 (CI, 4.8-26.03) Opioid dose (any): 8.39 (CI, 2.52-27.98)</p>
<p>n = 2212 Mean age: 44 y (case patients) vs. 45 y (control participants) Female: NR Race: NR Duration of opioid use: NR Mean opioid dose: NR</p>	<p>Case patients identified on basis of coroner's records; drug claims database used to determine opioid prescriptions; multiple databases used to identify inpatient hospitalizations, ED visits, claims for physician services, physician specialty, and patient demographic characteristics</p>	<p>Duration, income, history of alcohol abuse, interacting prescription drugs, total number of different opioids dispensed, long-acting opioid used, number of physicians prescribing opioids, and number of pharmacies dispensing opioids</p>	<p>Adjusted OR for opioid overdose death: A: 1.00 (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)</p> <p>Adjusted OR for opioid overdose death (based on 120-d exposure window): A: 1.00 (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)</p>

Appendix Table 3. Head-to-Head Trials and Observational Studies of Different Long-Acting Opioids

Study, Year (Reference)	Design	Duration	Number of Sites/Data Source	Location	Interventions	Results	Quality
Allan et al, 2005 (50)	Randomized trial	13 mo	Multicenter (number of sites not clear)	Europe	A: transdermal fentanyl (titrated from 25 mcg/h; mean dose, 57 mcg/h) (n = 338) B: sustained-release morphine (titrated from 30 mg every 12 h; mean dose, 140 mg) (n = 342)	Mean VAS pain score (scale of 0-100) at 56 wk: 56.0 (A) vs. 55.8 (B) Severe pain (per protocol analyses): 22 of 248 (9%) (A) vs. 20 of 162 (12%) (B); P = 0.030 (no significant difference in ITT analysis, but data not provided) Severe pain on movement (per protocol analyses): 0 of 248 (28%) (A) vs. 43 of 162 (27%) (B); P = 0.611 Rescue opioid use: 154 of 296 (52%) (A) vs. 154 of 291 (53%) (B) Quality of life (SF-36): no difference Loss of working days: no difference Withdrawal due to lack of efficacy: 18 of 335 (5%) (A) vs. 15 of 342 (4%) (B)	Fair
Hartung et al, 2007 (54)	Retrospective cohort study	January 2000–December 2004	Medicaid claims	United States	A: methadone (n = 974) B: ER oxycodone (n = 1866) C: transdermal fentanyl (n = 1546) D: ER morphine (n = 1298)	Adjusted HR for mortality: A: 0.71 (95% CI, 0.46–1.08) B: 0.71 (CI, 0.54–0.94) C: 0.80 (CI, 0.63–1.02) D: 1.00 (reference) Adjusted HR for ED encounter or hospitalization involving opioid-related adverse event: A: 0.71 (CI, 0.39–1.29) B: 0.45 (CI, 0.26–0.77) C: 0.73 (CI, 0.44–1.23) D: 1.00 (reference) Adjusted HR for opioid poisoning: A: 3.22 (CI, 0.60–17.25) B: 0.87 (CI, 0.14–5.25) C: 0.46 (CI, 0.04–5.12) D: 1.00 (reference) Adjusted HR for overdose symptoms: A: 1.11 (CI, 0.85–1.44) B: 0.89 (CI, 0.70–1.13) C: 0.97 (CI, 0.75–1.24) D: 1.00 (reference)	Fair
Krebs et al, 2011 (53)	Retrospective cohort study	January 2000–December 2007	VA database	United States	A: methadone (n = 28 554) B: long-acting morphine sulfate (n = 79 938)	All-cause mortality: 3347 patients (3.4%) Propensity-adjusted mortality, A vs. B (adjusted HR): Overall: 0.56 (CI, 0.51–0.62) Quintile 1: 0.36 (CI, 0.25–0.49) Quintile 2: 0.46 (CI, 0.37–0.56) Quintile 3: 0.50 (CI, 0.41–0.61) Quintile 4: 0.66 (CI, 0.54–0.81) Quintile 5: 0.92 (CI, 0.74–1.16)	Fair
Mitra et al, 2013 (52)	Randomized trial	12 mo	Single center	Australia	A: transdermal buprenorphine (initial dose, 5 mcg/h) (n = 22) B: transdermal fentanyl (initial dose, 12.5 mcg/h) (n = 24) Both were titrated to optimal doses over 4 wk; increased doses beyond that given as clinically indicated	Pain VAS: 3-point (scale of 1–10) reduction in pain in 11% of patients in each treatment group (data otherwise not provided) Sleep quality: no significant difference between groups (data not provided) Physical Disability Index: seemed similar (data not provided)	Poor
Wild et al, 2010 (51)	Randomized trial	12 mo	Multicenter	Europe and United States	A: ER tapentadol, 100–250 mg twice daily (adjustable) (n = 894) B: oxycodone CR, 20–50 mg twice daily (adjustable) (n = 223)	Mean pain intensity score (±SE) decreased from 7.6 ± 0.05 (A) and 7.6 ± 0.11 (B) at baseline to 4.4 ± 0.09 (A) and 4.5 ± 0.17 (B) Global assessment (very much improved or much improved): 48.1% (394 of 819) (A) vs. 41.2% (73 of 177) (B) Concomitant nonopioid analgesics (NSAIDs, ASA, acetaminophen): 19.9% (178 of 894) (A) vs. 17% (88 of 223) (B)	Fair

ASA = aspirin; CR = controlled-release; ED = emergency department; ER = extended-release; HR = hazard ratio; ITT = intention-to-treat; NSAID = nonsteroidal anti-inflammatory drug; SF-36 = Short Form-36; VA = Department of Veterans Affairs; VAS = visual analogue scale.

Appendix Table 4. Studies of Risk Assessment Instruments

Study, Year (Reference)	Participants, n	Female, %	Race	Pain	Mean Age (SD), y	Risk Assessment Instrument	Method of Administration	Reference Standard
Akbik et al, 2006 (59)	155	33	White (86%), other races NR	Back (39%)	43 (9.6)	SOAPP (scale of 0-56; high risk ≥8)	Self-report	Positive urine drug test result
Jones et al, 2012 (60) (study 2)	263	56	White (96%), other races NR	Low back (45%), arthritis or fibromyalgia (21%), joint (14%), pelvic or abdominal (10%), neck or upper back (7%)	48 (13)	ORT (scale of 0-25; high risk ≥8) PMQ (scale of 0-104; high risk ≥30) SOAPP-R (scale of 0-24; high risk ≥18) Clinician assessment	Self-report (SOAPP-R, ORT, PMQ); clinician interview	Discontinuation of opioid therapy due to abuse
Moore et al, 2009 (61)	48	60	NR	NR	44 (11)	SOAPP (scale of 0-56; high risk ≥8) DIRE (scale of 7-21; high risk ≤13) ORT (scale of 0-25; high risk ≥8) Clinician assessment	Self-report (SOAPP, DIRE, ORT); clinician interview	Discontinuation of opioid therapy due to abuse
Webster and Webster, 2005 (62)	185	58	NR	Back (45%), head (18%), neuropathic (16%), musculoskeletal (16%), visceral (5%)	44 (13)	ORT (scale of 0-25; high risk ≥8)	Self-report	Documentation in medical record of aberrant behavior during follow-up

DIRE = Diagnosis, Intractability, Risk, and Efficacy tool; NR = not reported; ORT = Opioid Risk Tool; PMQ = Pain Medication Questionnaire; SOAPP = Screener and Opioid Assessment for Patients with Pain; SOAPP-R = Screener and Opioid Assessment for Patients with Pain-Revised.

Appendix Table 5. Predictive Value of Risk Assessment Instruments

Study, Year (Reference)	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	AUROC
DIRE					
Moore et al, 2009 (61)	Score <14: 0.17	Not calculable*	Not calculable*	Not calculable*	Not calculable*
ORT					
Jones et al, 2012 (60)	Score >4: 0.20 (95% CI, 0.15-0.27)	Score >4: 0.88 (CI, 0.82-0.93)	Score >4: 1.65 (CI, 0.78-3.51)	Score >4: 0.91 (CI, 0.78-1.06)	0.54
Moore et al, 2009 (61)	Score ≥4: 0.45	Not calculable*	Not calculable*	Not calculable*	Not calculable*
Webster and Webster, 2005 (62)	Score ≥4: 0.99 (CI, 0.92-0.99)	Score ≥4: 0.16 (CI, 0.10-0.24)	Score of 1-3: 0.08 (CI, 0.01-0.62) Score of 4-7: 0.57 (CI, 0.44-0.74) Score ≥8: 14.34 (CI, 5.35-38)	Score ≥4: 0.16 (CI, 0.10-0.24)	NR
PMQ					
Jones et al, 2012 (60)	Score ≥30: 0.34 (CI, 0.20-0.51)	Score ≥30: 0.77 (CI, 0.69-0.80)	Score ≥30: 1.46 (CI, 0.87-2.45)	Score ≥30: 0.86 (CI, 0.68-1.08)	0.57
SOAPP-R					
Jones et al, 2012 (60)	Score ≥18: 0.39 (CI, 0.26-0.54)	Score ≥18: 0.69 (CI, 0.63-0.75)	Score ≥18: 1.27 (CI, 0.86-1.90)	Score ≥18: 0.88 (CI, 0.70-1.10)	0.54
SOAPP					
Moore et al, 2009 (61)	Score >6: 0.73	Not calculable*	Not calculable*	Not calculable*	Not calculable*
Akbik et al, 2006 (59)	Score ≥8: 0.68 (CI, 0.52-0.81)	Score ≥8: 0.38 (CI, 0.29-0.49)	Score ≥8: 1.11 (CI, 0.86-1.43)	Score ≥8: 0.83 (CI, 0.50-1.36)	NR

AUROC = area under the receiver-operating characteristic curve; DIRE = Diagnosis, Intractability, Risk, and Efficacy tool; NR = not reported; ORT = Opioid Risk Tool; PMQ = Pain Medication Questionnaire; SOAPP = Screener and Opioid Assessment for Patients with Pain; SOAPP-R = Screener and Opioid Assessment for Patients with Pain-Revised.

* Retrospective study. Only patients who had discontinued opioid therapy because of aberrant drug-related behavior were included.