Drug Class Review

Long-Acting Opioid Analgesics

Final Update 6 Report

July 2011

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

STRUCTURED ABSTRACT

Purpose

We compared the effectiveness and harms of long-acting opioids and of long-acting opioids compared with short-acting opioids in adults with chronic noncancer pain.

Data Sources

To identify published studies, we searched MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and reference lists of included studies. We also searched the US Food and Drug Administration Center for Drug Evaluation and Research website for additional unpublished data and solicited dossiers of information from pharmaceutical manufacturers.

Review Methods

Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to standard Drug Effectiveness Review Project review methods.

Results and Conclusions

Although we identified 10 head-to-head trials comparing 2 or more long-acting opioids, the evidence was insufficient to determine if there are differences among long-acting opioids in effectiveness or harms. Eight trials found no statistical difference in pain relief or function between long-acting opioids. The 2 trials which found a significant difference were both open-label, rated poor quality, and were inconsistent with higher-quality trials evaluating the same comparison that found no significant differences. A shortcoming of the currently available evidence is that comparisons between specific long-acting opioids have been evaluated in only 1 to 3 trials each (most with small sample sizes), which may limit statistical power for detecting true differences. Studies that provided indirect data were too heterogeneous in terms of study design, patient populations, interventions, assessed outcomes, and results to make accurate judgments regarding comparative efficacy or adverse event rates. Evidence was insufficient to determine if long-acting opioids as a class are more effective or associated with fewer harms than short-acting opioids. There was also insufficient evidence to draw conclusions about comparative effectiveness or safety in subgroups.

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INTRODUCTION

Chronic pain, typically defined as pain for at least 3 to 6 months, is a common cause of major disability. An estimated 1 in 5 adult Americans, or 30 million people, experience chronic pain.[1] Chronic noncancer pain afflicts a significant subset of patients, causing personal suffering, reduced productivity, and substantial health care costs.[2] Opioids have been endorsed by the American Academy of Pain Medicine, the American Pain Society,[3] and the Canadian Pain Society,[4] among others, as appropriate treatment for refractory chronic noncancer pain in the general population and in older patients,[5] when used judiciously and according to guidelines similar to those followed with cancer patients.

Opioids are natural derivatives of morphine.[6] As a class, these medications act on common receptors. They are the most potent medications available for treatment of most types of severe pain. They are also associated with a variety of adverse events, including abuse and addiction. Opioids are available in short- and long-acting preparations. Because chronic pain may not resolve with time, use of opioid analgesics for these conditions is commonly long term. Despite the widespread use of long-acting opioids, there is little data regarding the comparative benefits and harms associated with specific long-acting opioids for chronic noncancer pain.[7]

The purpose of this report is to determine whether there is evidence that 1 or more long-acting opioid is superior to others in terms of benefits and harms and whether long-acting opioids as a class are superior to short-acting opioids when used for treatment of chronic noncancer pain.

Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. They focus on the strength and limits of evidence from studies about the effectiveness of a clinical intervention. Systematic reviews begin with careful formulation of research questions. The goal is to select questions that are important to patients and clinicians then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix A and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are preferred over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in each group, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant between groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat is the number of patients who would need be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of the evidence, allowing a greater contribution from studies that meet high methodological standards and, thereby, reducing the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed randomized controlled trials are considered better evidence than results of cohort, case-control, and cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, well-conducted cohort designs are preferred for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well conducted.

Systematic reviews pay particular attention to whether results of *efficacy studies* can be generalized to broader applications. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. For many drug classes, including the antipsychotics, unstable or severely impaired patients are often excluded from trials. In addition, efficacy studies frequently exclude patients who have comorbid disease, meaning disease other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that are impractical in typical practice settings. These studies often restrict options that are of value in actual practice, such as combination therapies and switching to other drugs. Efficacy studies also often examine the short-term effects of drugs that in practice are used for much longer periods. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the “average” patient than results from the highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures, such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling a study as either an efficacy or an effectiveness study, although convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one’s practice or to a particular patient.

Studies anywhere on the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how large the quantity, may have limited applicability to practice. Clinicians can judge the relevance of study results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

The key questions and scope of the review were originally developed and refined by the Oregon Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of different long-acting opioids in reducing pain and improving functional outcomes in adult patients being treated for chronic noncancer pain?

2. What is the comparative effectiveness of long-acting opioids compared with short-acting opioids in reducing pain and improving functional outcomes when used for treatment of adults with chronic noncancer pain?

3. What are the comparative harms (including addiction and abuse) of different long-acting opioids in adult patients being treated for chronic noncancer pain?

4. What are the comparative harms of long-acting opioids compared with short-acting opioids in adult patients being treated for chronic noncancer pain?

5. Are there subpopulations of patients (specifically by race, age, sex, socioeconomic status type of pain, or comorbidities) with chronic noncancer pain for which one long-acting opioid is more effective or associated with fewer harms?

6. Are there subpopulations of patients (specifically by race, age, sex, socioeconomic status, type of pain, or comorbidities) with chronic noncancer pain for which long-acting opioids are more effective or associated with fewer harms than short-acting opioids?

   Several aspects of the key questions deserve comment:

Population. The population included in this review was adult (18 years old or greater) patients with chronic noncancer pain. We defined chronic noncancer pain as continuous or recurring pain for at least 6 months. Cancer patients and patients with HIV were excluded from this review.

Drugs. We included oral or transdermal long-acting opioids. Although dosing frequency varies for an individual formulation of morphine, we refer to dosing twice daily in a trial as "sustained-release" and once daily as "extended-release". "Long-acting" was defined as opioids administered 3 times daily or less frequently. Included drugs are shown below in Table 1. Black box warnings of the included drugs are provided in Appendix B. Although extended-release tapentadol is available in Canada and Europe, the participating organizations of Drug Effectiveness Review Project elected to exclude it from this review because it is not yet available in the United States. Extended-release Tramadol was also excluded because its mechanism of action is different from the other included long-acting opioids. It is believed that tramadol works through binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Table 1. Included drugs

Drug	Trade name(s)	Forms	Recommended usual dosing frequency (times per day)
Buprenorphine	Butrans™	ER transdermal film	Every 7 days
Codeine	Codeine Contin[a]	ER oral tablet	2
Dihydrocodeine	DHC Continus®[b]	Oral tablet	2
Fentanyl	Duragesic®	ER transdermal film	Every 72 hours
Hydromorphone	Exalgo®	ER oral tablet	1
Levorphanol[c]	Generic	Oral tablet	3-4
Methadone	Dolophine®	Oral tablet	2-3
Morphine	Avinza® Kadian® MS Contin® Oramorph SR®	ER oral capsule ER oral capsule ER oral tablet ER oral tablet	1 1-2 1-3 2-3
Morphine sulfate and naltrexone hydrochloride	Embeda™	ER oral capsule	1-2
Oxycodone	OxyContin®	ER oral tablet	2
Oxymorphone	Opana ER®[c]	ER oral tablet	2

Abbreviations: ER, extended release; SR, sustained release.
[a] Only available in Canada.
[b] Only available in Europe.
[c] Not available in Canada.

Outcomes. The main efficacy measures were pain intensity, pain relief, and function. There is no single accepted standard regarding how to measure these outcomes.

Most studies measure pain intensity using either visual analog or categorical pain scales. Visual analog scales consist of a line on a piece of paper labeled 0 at one end, indicating no pain, and a maximum number (commonly 100) at the other, indicating excruciating pain. Patients designate their current pain level on the line. An advantage of visual analog scales is that they provide a continuous range of values for relative severity. A disadvantage is that the meaning of a pain score for any individual patient depends on the patient's subjective experience of pain. This poses a challenge in objectively comparing scores between patients, and even different scores from the same patient. Categorical pain scales, on the other hand, consist of several pain category options from which a patient must choose (for example, no pain, mild pain, moderate pain, or severe pain). A disadvantage of categorical scales is that patients must chose between categories that may not accurately describe their pain. The best approach may be to utilize both methods.[8] Pain control (improvement in pain) and pain relief (resolution of pain) are also measured using visual analog and categorical scales.

Studies usually evaluate function using the Medical Outcomes Study Short Form-36 (SF-36), Short Form-12 (SF-12), or other multi-question assessments. These questionnaires measure how well an individual functions physically, socially, cognitively, and psychologically. Another approach to measuring function is to focus on how well the medication helps commonly faced problems in daily living by patients with chronic pain, such as getting enough sleep or staying focused on the job. Some studies also report effects on mood and the preference for a medication over another.

The following adverse events were specifically reviewed: abuse, addiction, nausea, vomiting, constipation, dizziness, somnolence, and confusion. These were felt to be the most common and troubling adverse events in clinical practice. We recorded rates of these adverse events as well as rates of discontinuation due to specific adverse events when reported. In some studies, only "serious" adverse events or adverse events "thought related to treatment medication" were reported. Many studies did not define these terms.

We specifically examined whether opioids differ in the risk of *abuse and addiction*. Although standardized definitions for abuse and addiction have been proposed, they are not used consistently in studies investigating this outcome.[9, 10] We recorded any information about abuse and addiction, including rates of death and hospitalization, when available.

Because of inconsistent reporting of outcomes, trial *withdrawal rates* may be a more reliable measure in studies of opioids. This outcome may be a surrogate measure for either clinical efficacy or adverse events. One trial that examined reason for withdrawal found that withdrawals were primarily due to adverse events in patients on long-acting oxycodone, but in patients on placebo, withdrawals were due to inadequate pain control.[11] High withdrawal rates therefore probably indicate some combination of poor tolerability and ineffectiveness. An important subset is *withdrawal due to any adverse event* (those who discontinue specifically because of adverse events).

Study types. We included controlled clinical trials to evaluate efficacy. The validity of controlled trials depends on how they are designed. Randomized, properly blinded clinical trials are considered the highest level of evidence for assessing efficacy.[12-14] Clinical trials that are not randomized or blinded and those that have other methodological flaws are less reliable, but are also discussed in our report.

Trials that compare a long-acting opioid with another long-acting opioid ("head-to-head" trials) or a long-acting opioid with a short-acting opioid provide direct evidence of comparative benefits and harms. Trials that compare a long-acting opioid with placebo may provide indirect data about comparative benefits and harms. However, reliable comparisons from such trials may not be possible if they evaluate significantly different populations, interventions, or outcomes, or if the trials have important methodological flaws.

To evaluate adverse event rates, we included clinical trials and observational cohort studies designed to assess adverse events between different long-acting opioids. Clinical trials are often not designed to, or use inadequate methods to, assess adverse events and may select patients at lower risk for adverse events (in order to minimize dropout rates and maximize potential benefits). Well-designed observational studies designed to assess adverse events may include broader populations more applicable to real-world practice, carry out observations over a longer time period, use higher-quality techniques for assessing adverse events, or examine larger sample sizes.

One issue that complicates the interpretation of studies of opioids for chronic pain is "incomplete cross-tolerance." In medical jargon, a patient who finds that a particular opioid is less effective over time is said to have become "tolerant" to that drug. "Incomplete cross-tolerance" means that a patient's "tolerance" for an opioid may not carry over to other opioids. If incomplete cross-tolerance occurs, individuals who have been taking a specific opioid may do better if they switch to a different opioid—not because the new one is a better drug, but simply because it is not the one they have been taking. In observational studies of both cancer and noncancer patients, there is some evidence that incomplete cross-tolerance occurs.[15-18]

METHODS

Literature Search

Searches to identify articles relevant to each key question were performed of the Cochrane Central Register of Controlled Trials® (4th Quarter, 2010), Cochrane Database of Systematic Reviews® (2005 to January 2011), Database of Abstracts of Reviews of Effects (1st Quarter 2011), MEDLINE® (1966-January Week 4, 2011), EMBASE (1980-2001), and reference lists of included studies and review articles. In electronic searches, we combined terms for pain with terms for opioid analgesics and narcotics and relevant research designs (see Appendix C for complete search strategies). In addition, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote® X2, Thomson Reuters).

Data Abstraction

We abstracted information on population characteristics, interventions, subject enrollment, and results for efficacy, effectiveness, and harms outcomes for trials, observational studies, and systematic reviews. Equianalgesic doses of opioid medications were estimated using published tables.[19] We recorded intent-to-treat results if they were available and the trial did not report high overall loss to follow-up. In trials with crossover, because of the potential for differential withdrawal prior to crossover and drug carryover effects biasing subsequent results, outcomes for the first intervention were recorded if available. A second reviewer checked all data.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria (see www.ohsu.edu/drugeffectiveness). These criteria are based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom) criteria.[12, 13] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intent-to-treat analysis. Trials that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are *likely* to be valid, while others are only *possibly* valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist. A particular randomized trial might receive 2 different ratings, 1 for effectiveness and another for adverse events.

The criteria used to rate observational studies of adverse events reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met 6 or

more of the 7 predefined criteria, fair quality if they met 3 to 5 criteria, and poor quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality. We rated the internal validity based a clear statement of the questions(s); reporting of inclusion criteria; methods used for identifying literature (the search strategy), validity assessment, and synthesis of evidence; and details provided about included studies. Again, these studies were categorized as good when all criteria were met.

Two reviewers independently assigned quality ratings. Overall quality rating and quality rating scores were compared between reviewers. Differences were resolved by consensus.

Grading the Strength of Evidence

We graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.[20] Developed to grade the overall strength of a body of evidence, this approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias.

Table 2 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer key questions on the comparative effectiveness, efficacy, and harms of different long-acting opioids and long-acting opioids compared with short-acting opioids. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals. Two reviewers independently assessed each domain for each outcome and differences were resolved by consensus.

Strength of evidence was graded for each key outcome measure and was limited to head-to-head comparisons except where a case could be made for assessing the strength of indirect evidence.

Table 2. Definitions of the grades of overall strength of evidence[21]

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Studies that evaluated 1 long-acting opioid against another or a long-acting opioid

compared with a short-acting opioid provided direct evidence of comparative effectiveness and adverse event rates. Where possible, these data are the primary focus. Direct comparisons were preferred over indirect comparisons; similarly, effectiveness and long-term safety outcomes were preferred to efficacy and short-term tolerability outcomes.

In theory, trials that compare long-acting opioids with other drug classes or with placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily heterogeneity of trial populations, interventions, and outcomes assessment. Data from indirect comparisons are used to support direct comparisons, where they exist, and are used as the primary comparison where no direct comparisons exist. Indirect comparisons should be interpreted with caution.

Quantitative analyses were conducted using meta-analyses of outcomes reported by a sufficient number of studies that were homogeneous enough that combining their results could be justified. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. When meta-analysis could not be performed, the data were summarized qualitatively.

Public Comment

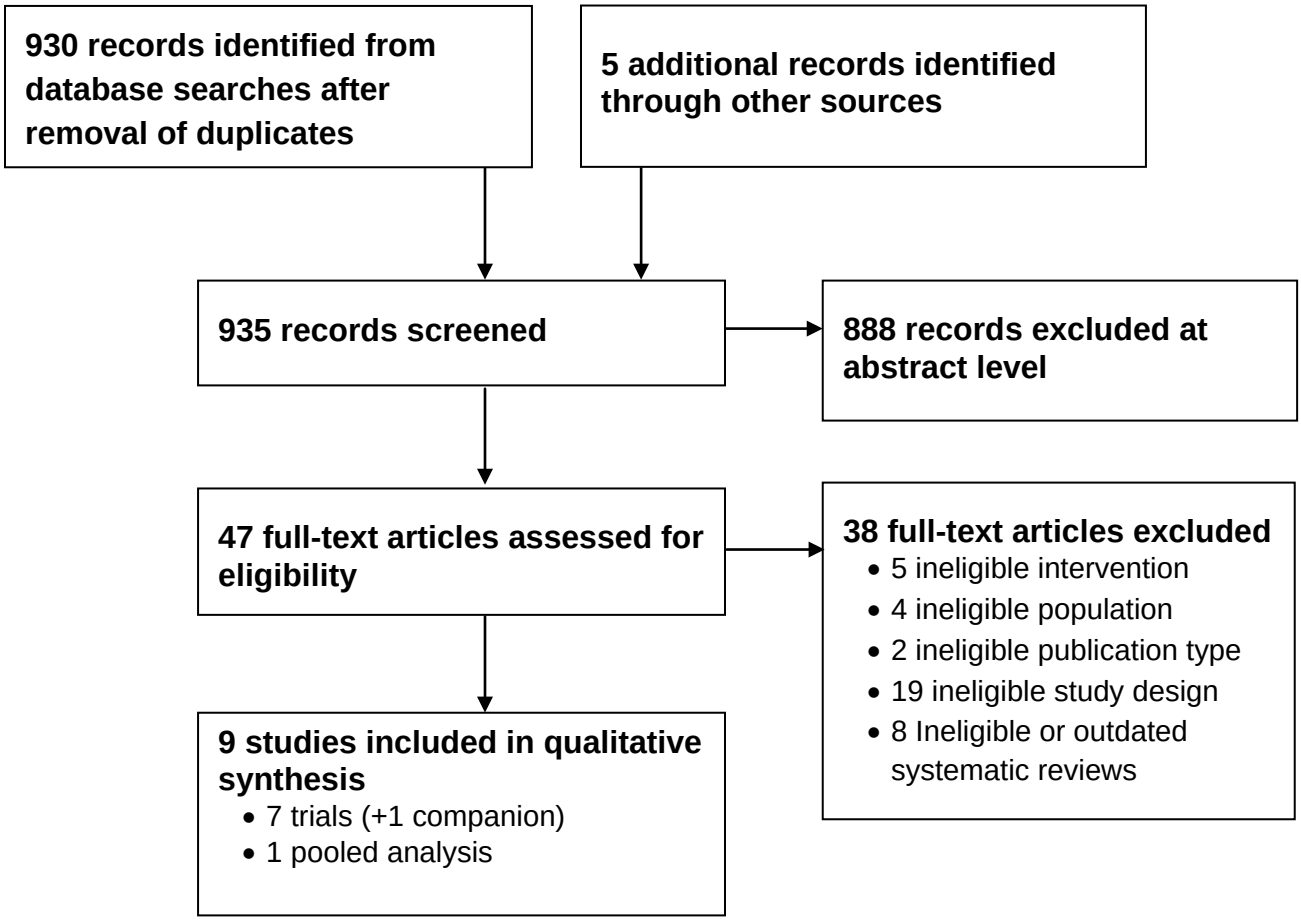
This report was posted to the Drug Effectiveness Review Project website for public comment. We received comments from 3 pharmaceutical companies, 1 representing professional or advocacy organization.

RESULTS

Literature Search Results for Update 6

Through Update 5, a total of 34 randomized trials were included (8 head-to-head trials of long-acting opioids, 19 placebo-controlled or active-control trials of long-acting opioids, and 7 trials of long-acting vs. a short-acting opioid). Results of literature searches for Update 6 are shown in Figure 1. Searches identified 935 citations. Full-text citations of 47 of these were retrieved for further review and 9 studies were included. Excluded studies for Update 6 are listed in Appendix D.

Figure 1. Results of literature search for Update 6[a]



[a] The Drug Effectiveness Review Project uses a modified PRISMA flow diagram.[22]

Overview of Included Trials

We identified 41 randomized trials (6113 patients enrolled) that evaluated long-acting opioids for chronic noncancer pain. Ten trials compared a long-acting opioid to another (Evidence Tables 1, 2, and 4).[23-32] Seven trials compared a long-acting opioid to a short-acting opioid,[33-39] and 27 compared a long-acting opioid to a nonopioid or placebo.[11, 25, 26, 28, 40-63] Eleven trials used a crossover design.[24, 32, 35, 36, 40, 41, 43-45, 47, 50] We identified trials of long-acting oxycodone,[11, 26, 34, 36, 39, 47, 50, 56, 57, 60, 64] long-acting morphine,[23-25, 37, 41-45] long-acting dihydrocodeine,[35, 38] long-acting codeine,[33, 40, 46] long-acting oxymorphone,[26, 52-54] transdermal fentanyl,[23, 24, 55] levorphanol,[51] methadone,[49] and extended-release hydromorphone.[59] One trial[65] cited in reference lists[2, 40] could not be located despite searches for journal, title, and author. This paper was described as being small, with a very high rate of withdrawal (14/20), making it unlikely that including its results would change the results of this review.[2]

Nearly all of the trials were of relatively short duration, ranging from 5 days[33] to 24 weeks.[29] The 1 exception was a head-to-head trial of transdermal fentanyl compared with oral

long-acting morphine that was 13 months in duration.[23] All trials excluded persons with past or current substance abuse. The majority of trials recruited patients from specialty clinics, most commonly from rheumatology or pain practices, and the majority were multicenter. Race was rarely reported. Women were the slightly predominant gender (slightly greater than 50%). The average age (in years) of enrollees was in the 50s.

Key Question 1. What is the comparative effectiveness of different long-acting opioids in reducing pain and improving functional outcomes in adult patients being treated for chronic noncancer pain?

Summary of findings

- There was insufficient evidence from 10 head-to-head trials to suggest that a long-acting opioid is superior to another in terms of efficacy in adult patients with chronic noncancer pain.
    - Three trials (2 fair quality, 1 poor quality) directly compared transdermal fentanyl to oral long-acting morphine.
    - Two fair-quality trials directly compared long-acting oxymorphone to long-acting oxycodone.
    - Two trials (1 fair quality, 1 poor quality) directly compared extended-release (once daily) morphine with long-acting (twice daily) oxycodone.
    - One fair-quality trial compared extended-release (once daily) with sustained-release (twice daily) morphine.
    - One fair-quality trial compared morphine/naltrexone with extended-release morphine.
    - One poor-quality trial compared extended-release hydromorphone with oxycodone.
- Eight trials found no significant difference in pain relief or function between long-acting opioids; the 2 trials which found a significant difference (1 trial of transdermal fentanyl vs. oral long-acting morphine and 1 trial of extended-release morphine vs. sustained-release oxycodone) were both open-label, rated poor quality, and were inconsistent with higher quality trials evaluating the same comparison that found no differences.
- There were no trials evaluating the effectiveness of opioid rotation compared with other approaches such as dose escalation of a single opioid in patients with chronic noncancer pain.
- No useful indirect evidence for determining the comparative efficacy of long-acting opioids was found in 27 placebo-controlled trials; the studies were generally of insufficient quality and too diverse in terms of study designs, patient populations, interventions, and assessed outcomes to conduct indirect comparisons on efficacy.
- We were unable to perform meta-analysis on any subgroup of trials; the trials were not designed to evaluate rates of abuse or addiction.

Detailed assessment

Direct evidence

Ten trials directly compared the efficacy of a long-acting opioid with another in chronic pain of noncancer origin (Table 3, Evidence Tables 1, 2, and 4).[23-32] Three trials were rated poor quality[24, 30, 31] and the rest were fair.

Table 3. Head-to-head trials of long-acting opioids

Author, year (Quality)	Comparisons (mean daily dose)	Pain type	N Duration	Main Results
Allan 2005[23] (FAIR)	A: Transdermal fentanyl 57 mcg/hr B: Oral morphine 140 mg (twice daily)	Low back pain	683 13 months	No significant differences in intent-to-treat analyses for pain relief using 0-100 VAS (56.0 vs. 55.8) (analysis only included 608 patients); severe pain at rest, on movement, during the day, or at night; breakthrough medication use; loss of working days; or quality of life (SF-36).
Allan 2001[24] (POOR)	A: Transdermal fentanyl 57 mcg/hr B: Oral morphine 133 mg (twice daily)	Miscellaneous	212 4 weeks	Patient preference, pain intensity score at end of treatment, and pain relief at end of treatment significantly better for transdermal fentanyl using 5 point categorical scale (65% vs. 28% "preferred" or "very much preferred"; *P*<0.001), 0-100 VAS (57.8 vs. 62.9; *P*<0.001) and undefined categorical scale (35% vs. 23% "good" or "very good"; *P*=0.002).
Niemann 2000[27] (FAIR)	A: Transdermal fentanyl 56 mcg/hr B: Oral morphine 128 mg (twice daily)	Chronic pancreatitis	18 4 weeks	No significant differences between treatments for preference or global pain control using unspecified methods or quality of life using SF-36.
Hale 2005[26] (FAIR)	A: Oxymorphone 79 mg (twice daily) B: Oxycodone 155 mg (twice daily) C: Placebo	Low back pain	235 18 days	No significant differences between long-acting oxymorphone and long-acting oxycodone for pain intensity (0-100 VAS and 5-point categorical scale), pain relief (0-100 VAS), interference with activities (0-10 scale), rescue medication use, or global assessment using 5-point categorical scale.
Matsumoto 2005[28] (FAIR)	A: Oxymorphone 40 mg (twice daily) B: Oxymorphone 20 mg (twice daily) C: Oxycodone 20 mg (twice daily) D: Placebo	Osteoarthritis	467 4 weeks	No clear differences between oxymorphone and oxycodone. Both active treatments were superior to placebo at 4 weeks for measures for pain (0-100 VAS), physical function (WOMAC), and quality of life.
Rauck 2006[30] (POOR)	A: Morphine 64 mg (once daily) B: Oxycodone 53 mg (twice daily)	Low back pain	392 8 weeks	A vs. B: Brief Pain Inventory score (0 to 10, mean improvement from baseline): -3.1 vs. -2.8 (*P* not reported). Proportion with >2 point improvement in Brief Pain Inventory: 55% (73/132) vs. 44% (59/134); *P*=0.03. Pittsburgh Sleep Quality Index (mean improvement from baseline): 33% vs. 17%; *P*=0.006. Rescue medication use: 2595 vs. 3154 doses; *P*<0.0001.

Author, year (Quality)	Comparisons (mean daily dose)	Pain type	N Duration	Main Results
				SF-12 Physical Component Summary (mean improvement from baseline): 23% vs. 19% (NS). SF-12 Mental Component Summary (mean improvement from baseline): 23% vs. 16% (NS). Work Limitations Questionnaire (mean demands score, 0 to 100): 22.1 vs. 20.9.
Nicholson 2006[29] (FAIR)	A: Morphine 79 mg/day (twice daily B: Oxycodone 85 (3 times daily)	Miscellaneous, non-neuropathic	112 24 weeks	No significant differences between groups (A vs. B) in SF-36 Physical Component Scale: +2.5 vs. +2.1 (NS); Pain (0 to 10): -1.9 vs. -1.4 (NS); Patient Global Assessment (-4 to +4): +2.6 vs. +1.7 (NS). Sleep Interference Scale (0 to 10): -2.6 vs. -1.6; *P*<0.05. SF-36 Mental Component Scale: +0.8 vs. +4.2 (*P* for differences between groups not reported, but *P*<0.05 vs. baseline only for oxycodone)
Caldwell, 2002 [25] (FAIR)	A: Morphine 30 mg (once daily a.m.) B: Morphine 30 mg (once daily p.m.) C: Morphine 30 mg (twice daily) D: Placebo	Osteoarthritis	295 4 weeks	No significant differences between active treatments for pain intensity at index joint (0-500 VAS), pain intensity overall (1-100 VAS), physical function (0-1700 VAS), stiffness index (0-200 VAS). A (but not B) significantly superior to C for 1 of 7 sleep measures (overall quality of sleep) using 0-100 VAS (-15 change from baseline for A vs. -12 for B vs. -6 for C (*P*<0.05 for A vs. C).
Katz 2010[32] (FAIR)	A: Morphine/ naltrexone B: Morphine Median morphine dose 80 mg (range 40 to 320 mg)	Osteoarthritis	72 2 weeks	No significant difference between treatments in any pain measure.
Hale 2007[31] (POOR)	A: Hydromorphone 16 mg (once daily) B: Oxycodone 12 mg (twice daily)	Osteoarthritis	138 4 weeks	No significant difference between treatments in any pain measure; no significant differences between treatments in patient or investigator-rated measures of improvement.

Abbreviations: NS, not significant; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

The largest (N=680) and longest (13 months) trial compared transdermal fentanyl to long-acting morphine in 680 patients with chronic low back pain (average duration 10 years) who had not received regular (more than 4 doses over a 7-day period) strong opioids during the 4 weeks prior to enrollment.[23] This study was rated fair quality because it was open-label and did not report intent-to-treat results for some of the outcomes (Evidence Table 4). For the primary outcome of pain relief as measured by visual analog scores, for example, the study reported results for only 608 out of 680 randomized subjects. In addition, even though this trial enrolled only patients who had not recently used regular strong opioids, it did not report the proportion of patients who had been previously exposed to intermittent or more distant strong opioids. The external validity of this trial was difficult to assess because the number of patients who were approached or eligible but did not enroll in the trial was not reported.

After 13 months of treatment, this trial found similar outcomes for patients randomized to either drug for pain relief (visual analog scale); the proportion of patients reporting severe pain at rest, on movement, during the day, or at night (intent-to-treat analyses); use of supplemental analgesia for breakthrough pain; loss of work among patients who were working; and quality of life (SF-36). The dose of the intervention drug was titrated to an average of 57 µg per hour in the transdermal fentanyl group and to 140 mg per day in the oral morphine group. More patients in the sustained-release morphine group completed the study compared with the transdermal fentanyl group (53% vs. 48%). The difference could be attributed to more withdrawals because of adverse events in the transdermal fentanyl group (37% vs. 31%).

The second trial that compared transdermal fentanyl with long-acting morphine twice daily used a crossover design in a population of 256 heterogenous chronic pain patients with an average duration of 9 years of pain.[24] This study was rated poor quality because of several major methodological flaws (Evidence Table 4). The most important areas of concern were that neither patients nor investigators were blinded and many of the trial participants were on 1 of the study drugs prior to entry. Blinding is particularly important in studies using subjective measures. In this trial, lack of blinding may have been an even greater factor because 76% of the enrollees were taking morphine prior to enrollment. Patients who had achieved better results with morphine were probably less likely to enroll. If subjects who were entered into the trial had responded poorly to morphine relative to other patients, they could have been favorably predisposed towards a new medication. Incomplete cross-tolerance could also have biased the results towards transdermal fentanyl simply because it was new. By contrast, although lack of blinding in the larger trial of transdermal fentanyl compared with oral long-acting morphine was also a concern, it may not have been as critical because only subjects who had not recently been using strong opioids regularly were enrolled.

After 4 weeks of treatment, more patients reported “good” or “very good” pain control for fentanyl (40%) than for long-acting morphine (19%). On the other hand, withdrawal rates favored long-acting morphine (9%) over fentanyl (16%). Functional outcomes were assessed using SF-36. Fentanyl was favored for summary measures of physical functioning (28.6 vs. 27.4; P=0.004) and mental health (44.4 vs. 43.1; P=0.030), though absolute differences in scores were small. A post-hoc analysis excluding 24 patients who reported a “bad” or “very bad” score while taking morphine before the study found that 69% expressed a “strong” or “very strong” preference for fentanyl. On the other hand, another subgroup analysis of the 66 enrollees who were naïve to morphine and fentanyl at the beginning of the study found equivalent withdrawal rates between interventions.

Certain aspects of this trial made its external validity difficult to assess. The numbers of patients screened and eligible for entry were not reported. Patients in both groups took immediate-release morphine as needed to supplement their long-acting medication. The dose of long-acting opioid was determined at the beginning of the trial and was increased based only on the amount of immediate-release morphine used. The length of follow-up for each drug regimen was only 4 weeks.

How similar was the study sample to the population of interest to clinical practice? As discussed above, the subjects can best be described as patients who probably have not had a “good” response to morphine or another opioid in the first place. The study addressed whether patients with chronic noncancer pain accustomed to opioids (and who may not have had a “good” response to morphine or another opioid in the first place) prefer a change to transdermal fentanyl. It does not address the question of greater interest to practitioners choosing an initial

long-acting opioid. In unselected patients who have chronic pain requiring treatment with opioids, is transdermal fentanyl more effective than long-acting morphine? This question might be better addressed by the larger trial of transdermal fentanyl compared with long-acting morphine because it enrolled patients who had not recently used regular strong opioids.

A small (N=18), fair-quality (open-label), head-to-head trial of transdermal fentanyl and oral morphine in patients with chronic pancreatitis found no significant differences for patient preference, pain control, or quality of life (Evidence Table 4).[27] This study may not be applicable to the general population of patients with chronic noncancer pain because it only included a very small number of patients with a fairly uncommon, specific condition.

Two trials comparing long-acting oxymorphone with long-acting oxycodone were both rated fair quality. Methodological shortcomings included failure to adequately describe randomization methods or allocation concealment, high withdrawal rates, or lack of intent-to treat-analyses.[26, 28] In addition, the external validity of 1 of the trials was compromised because only about 70% of patients who entered the dose titration phase were eventually entered into the 18-day intervention phase.[26] This trial, which evaluated patients with chronic low back pain, found no significant differences in efficacy at the end of the intervention phase between long-acting oxymorphone and long-acting oxycodone for all measures of pain control, global assessments, or limitations of daily activity. The second trial, which evaluated patients with osteoarthritis, did not assess statistical significance of differences between long-acting oxymorphone and long-acting oxycodone (analyses focused on differences vs. placebo) and used different doses of oxymorphone (80 mg and 40 mg daily vs. 40 mg daily of oxycodone).[28] There were no clear differences in pain, function, or quality of life between long-acting oxymorphone compared with oxycodone at 40 mg daily and differences between oxymorphone 80 mg daily and oxycodone 40 mg daily were small, with uncertain statistical significance.

Two head-to-head trials compared extended-release morphine to sustained-release oxycodone.[29, 30] One trial, which evaluated various chronic noncancer pain conditions, was rated fair quality and found no significant differences between the drugs for pain relief or quality of life after 24 weeks.[29] The second trial (the ACTION trial),[30, 66, 67] which evaluated low back pain in patients, was rated poor quality because it was open-label, reported a high withdrawal rate (32.1%), and did not report an intent-to-treat analysis. In addition, analyzed patients were unbalanced on demographic factors (race, etiology of pain). Although this trial found extended-release morphine superior to sustained-release oxycodone for improvement in pain, quality of sleep, and use of pain medications, these findings may have reflected methodological shortcomings in the trial rather than true differences between the drugs.

One randomized, double-blinded trial compared extended-release (once-daily) to sustained-release (twice-daily) morphine in 295 patients with osteoarthritis.[25] Four treatment groups were evaluated: once-daily morphine in the morning, once-daily morphine in the evening, twice-daily morphine, and placebo. This study was rated fair quality and appeared to use adequate blinding and randomization (Evidence Table 4). Important limitations included high overall withdrawal rates and no explanation of how withdrawn patients were handled in data analysis.

This study found that once-daily morphine was not significantly different than twice-daily morphine for all measures of pain control (Evidence Table 4). For sleep, 1 of 7 measures of sleep quality (overall sleep quality) showed a slight but significant improvement in patients receiving once-daily morphine in the morning (but not once-daily morphine in the evening) compared with twice-daily morphine; all other measures of sleep quality were not significantly

different between once- and twice-daily morphine. All 3 long-acting morphine arms were superior to placebo for most measures of efficacy. Withdrawal rates were similar in all active treatment groups. External validity of this trial was difficult to assess because the numbers of patients screened and eligible for entry were not reported, the length of follow-up for each drug regimen was only 4 weeks, and duration of pain and previous narcotic use in evaluated patients was not reported.

A fair-quality crossover study compared the combination product morphine/naltrexone with extended-release morphine in patients with osteoarthritis.[32] After 2 weeks of treatment, there were no significant differences between groups on measures of pain intensity, mean daily pain score, or physical function. More patients taking morphine/naltrexone rated treatment "good", "very good", or "excellent" (91.5% vs. 78.9%), but the difference was not statistically significant. On the stiffness subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), there was a statistically significant difference in favor of morphine/naltrexone (2.5 vs. 12.3; *P*=0.02) and there were no significant differences between treatments on any other subscales of the WOMAC.

One study compared extended-release hydromorphone to oxycodone in patients with osteoarthritis using a noninferiority analysis and found similar efficacy for pain relief.[31] This trial was rated poor quality. It was not possible to determine whether the results of this trial were valid or due to bias because of unclear randomization methods, inadequate allocation concealment combined with differences between groups at baseline, an open-label design with patient-reported outcomes, and a high attrition rate.

A good-quality Cochrane review found no trials comparing opioid rotation, switching, or substitution to other strategies such as dose escalation of a single opioid in patients with acute or chronic pain.[68] It found that evidence to support the practice of opioid switching was largely anecdotal or based on observational, uncontrolled studies.

Indirect evidence

We identified 27 trials (in 28 publications) comparing a long-acting opioid to placebo (Evidence Tables 2, 3, and 4). Twenty-three trials (3 good quality[41, 48, 54] and the remainder fair quality) compared a long-acting opioid to an inert placebo.[11, 25, 26, 28, 40, 42, 43, 45-49, 52-62, 64] One trial[51] compared higher- with lower-dose levorphanol (lower-dose levorphanol considered an active control) and 3 trials used other "active" placebos. Active placebos mimic some of the adverse events associated with opioids but are not thought to have any analgesic effects (benztropine[44, 50] or lorazepam[41]).

Two trials evaluated long-acting codeine,[40, 46] 7 evaluated long-acting morphine,[25, 37, 41-45] 10 evaluated long-acting oxycodone,[11, 26, 28, 47, 48, 50, 56, 57, 60, 64] 5 evaluated extended-release oxymorphone,[26, 28, 52-54] and 1 trial each evaluated transdermal fentanyl,[55] levorphanol,[51] methadone,[49] extended-release hydromorphone,[59] morphine/naltrexone,[61] and transdermal buprenorphine.[62] One of the trials of oxycodone[57] was designed to measure the efficacy of extended-release tapentadol, a drug not included in this report, but also included a placebo arm. The average opioid dose evaluated in the trials varied greatly. For example, in the trials evaluating long-acting oxycodone, the daily dose ranged from 20 mg daily[64] to a mean of 155 mg daily.[26] The duration of follow-up ranged from 5 days to 16 weeks.

The trials exhibited a high degree of diversity with respect to patient populations and interventions. Chronic noncancer pain conditions evaluated in the trials included postherpetic neuralgia,[47] diabetic neuropathy,[48, 50, 60] various neuropathic pain conditions,[41, 49, 51] phantom

limb pain,[43] osteoarthritis,[11, 25, 28, 46, 54-57, 61, 62, 64] back pain,[26, 52, 53, 59] and miscellaneous chronic noncancer pain.[40, 44, 45]

Included trials also differed in terms of use of a crossover design, use of a run-in period, methods of dose titration, target doses, allowance of rescue medications, blinding, use of an active or true placebo, and other important study design characteristics. One fair-quality trial, for example, used a design in which patients with neuropathic pain randomly received either methadone or placebo every other day over a 20-day period with no intervention or placebo given on alternate days.[49] Although improved pain intensity was seen on days in which methadone 10 mg twice daily was taken, results of this study could not be compared with other trials and may not be applicable to clinical practice, where daily administration of methadone resulted in different steady-state concentrations of the drug and also affected the development of tolerance to pain relief and side effects. Results of another fair-quality trial that found high-dose levorphanol superior to low-dose levorphanol for pain intensity and relief in patients with neuropathic pain were not comparable to results from trials using true (inert) placebo.[51]

The most common outcomes assessed were pain intensity, rescue drug use, and withdrawals. There was no clear pattern from placebo-controlled trials favoring a long-acting opioid over another. However, methods for assessing outcomes varied across trials. For pain intensity, for example, placebo-controlled trials of oxycodone used a 0 to 100 visual analog scale, various categorical scales (0 to 3, 0 to 4, 0 to 5, or 0 to 10), the Brief Pain Inventory, or the WOMAC Pain Index. For sleep, the most commonly reported functional outcome, measurement tools included sleep quality (1-5 scale[34] or 0-10 scale,[11, 48]), the Pain and Sleep Questionnaire,[50] the Brief Pain Inventory Sleep score,[41] and visual analog scales (1-100) for trouble falling asleep and needing medication to sleep.[46] Other trials did not measure effects on sleep at all. Because of the heterogeneity of scales used to measure sleep quality, meaningful comparisons between long-acting opioids could not be made. Other functional outcomes were less commonly reported and when reported were also characterized by measurement using different scales.

Withdrawal rates were reported in all studies and did not suggest a pattern favoring a long-acting opioid compared with other long-acting opioids. For long-acting oxycodone, the withdrawal rate ranged from 12%[64] to 50%.[11] For long-acting morphine, the withdrawal rate ranged from 0%[43] to 30%.[44] The wide variation in withdrawal rates for studies evaluating the same drug could reflect differences in populations, dosing of medications in trials, use of a run-in period, methods used to keep patients in trials, or other factors.

Two good-quality trials were conducted in patients with neuropathic pain[41, 48] and 1 in patients with osteoarthritis.[54] One was a short-term (6 weeks) study that found that controlled-release oxycodone (average titrated dose 42 mg daily) was more effective than placebo for overall average daily pain intensity in 159 patients with diabetic neuropathy (4.1 for oxycodone, 5.3 for placebo) using a 0 (no pain) to 10 (worst pain) scale.[48] A 4-arm, multiple crossover trial (each intervention for 5 weeks) comparing long-acting morphine (average titrated dose 45 mg daily), gabapentin, the combination of long-acting morphine and gabapentin, and low-dose lorazepam (used as an active placebo) for neuropathic pain[41] found that long-acting morphine was superior to placebo for mean pain intensity (3.70 for morphine, 4.49 for placebo on a 0 to 10 scale), depression (Beck Depression Inventory score), and some measures of the short-form McGill Pain Questionnaire, Brief Pain Inventory, and SF-36 Health Survey. The combination of morphine plus gabapentin was superior to morphine alone for pain intensity even though the average dose of morphine was lower in the combination arm. The third good-quality trial[54] compared extended-release oxymorphone (40 mg or 50 mg twice daily) to placebo in 370

patients with knee or hip osteoarthritis. After 2 weeks, pain intensity decreased by 62.8% and 70.9% compared with placebo in the oxymorphone 40 mg or 50 mg groups, respectively (P=0.012 and 0.006). All other trials were rated fair quality and had at least 1 of the following methodological problems: inadequate or poorly described randomization and allocation concealment, lack of blinding or unclear blinding methods, or high loss to follow-up. The main results are summarized in Evidence Table 6.

Key Question 2. What is the comparative effectiveness of long-acting opioids compared with short-acting opioids in reducing pain and improving functional outcomes when used for treatment of adults with chronic noncancer pain?

Summary of evidence

- In 7 fair-quality trials directly comparing a long-acting opioid to a short-acting opioid there was no good-quality evidence to suggest superior efficacy of long-acting opioids as a class over short-acting opioids.
- For oxycodone specifically, there was fair-quality evidence from 3 trials that long- and short-acting oxycodone are equally effective for pain control.

Detailed assessment

Direct evidence

We identified 7 randomized clinical trials (568 patients enrolled), all rated fair quality, which directly compared the efficacy of long-acting opioids to short-acting opioids in patients with chronic pain of noncancer origin (Table 4).

Table 4. Main results of trials of long-acting opioid compared with short-acting opioid

Author Year (Quality rating)	Pain type	Duration	Patients	Findings
Oxycodone				
Caldwell 1999[34] (FAIR)	Osteo-arthritis	30 days	107	LA oxycodone and IR oxycodone plus acetaminophen are equally effective for pain control and improvement of sleep.
Hale 1999[36] (FAIR)	Back pain	6 days	47	LA oxycodone and IR oxycodone are equally effective for pain control.
Salzman 1999[39] (FAIR)	Back pain	10 days	57	LA oxycodone and IR oxycodone are equally effective when titrated for pain control.
Codeine				
Hale 1997[33] (FAIR)	Back pain	5 days	83	LA codeine plus acetaminophen together are more effective for pain control than IR codeine plus acetaminophen together, however, these drugs were not given at therapeutically equivalent dose.
Dihydrocodeine				
Gostick 1989 (FAIR)	Back pain	2 weeks	61	LA dihydrocodeine and IR dihydrocodeine are equally effective for pain control.
Lloyd 1992[38] (FAIR)	Osteo-arthritis	2 weeks	86	LA dihydrocodeine and IR dihydrocodeine are equally effective for pain control when compared directly.
Morphine				
Jamison 1998[37] (FAIR)	Back pain	16 weeks	36	LA morphine plus IR oxycodone together are more effective for pain control than IR. Oxycodone, however, these drugs were not given at therapeutically equivalent doses.

Abbreviations: IR, immediate release; LA, long acting.

Three studies compared long-acting oxycodone to short-acting oxycodone.[34, 36, 39] One of these studies[36] rerandomized patients who had enrolled in a previous trial.[39] Two studies evaluated long-acting dihydrocodeine,[35, 38] 1 evaluated long-acting codeine,[33] and 1 evaluated long-acting morphine.[37] Study designs, patient populations, and outcomes assessed varied between studies (Evidence Table 5).

The trials did not show any trends demonstrating significant differences in efficacy between long-acting opioids as a class and short-acting opioids (Table 4). Three studies that found differences in efficacy favoring long-acting morphine,[37] long-acting dihydrocodeine,[38] and long-acting codeine[33] had features that might invalidate these results. In the trials of long-acting morphine[37] and long-acting codeine,[33] the average daily doses of opioid in the long-acting arm were higher than the average daily doses given in the short-acting group. In the other study,[38] significant differences in pain relief were seen only within the long-acting dihydrocodeine group when compared with baseline ratings, but no significant differences were found when results for the long-acting opioid arm were compared directly to the short-acting opioid arm. In all trials,

functional outcomes were examined inconsistently or measured with heterogeneous scales. Other important outcomes such as improved compliance or more consistent pain control were not examined.

A subgroup of 3 trials of 281 enrolled patients evaluated roughly equivalent doses of long- and short-acting oxycodone and appeared to be the most homogeneous of this group of trials.[34, 36, 39] One of these trials[36] investigated a rerandomized population of patients studied in a previous trial[39] but used a different intervention protocol. These 3 trials found no significant differences in efficacy (pain relief) between long- and short-acting oxycodone. With regard to functional outcomes, 1 of these trials[34] reported improved sleep quality with long-acting oxycodone, but baseline sleep scores were significantly better in patients randomized to this intervention, which could invalidate this finding.

Key Question 3. What are the comparative harms (including addiction and abuse) of different long-acting opioids in adult patients being treated for chronic noncancer pain?

Summary of evidence

- There were insufficient data from 10 head-to-head trials of long-acting opioids to conclude that any long-acting opioid was associated with fewer harms compared with others. None of the trials were designed to specifically assess harms and no trial was rated good quality for adverse event assessment.
- Two trials found transdermal fentanyl associated with slight trends towards less constipation but more withdrawals due to any adverse event compared with oral long-acting morphine.
- There were no clear or consistent differences in randomized trials comparing long-acting oxycodone and oxymorphone, extended-release morphine and long-acting oxycodone, extended-release (once daily) and sustained-release (twice daily) morphine, extended-release hydromorphone and oxycodone, or morphine/naltrexone and extended-release morphine.
- All head-to-head trials excluded patients at high risk for addiction or abuse and none adequately assessed rates of these complications.
- No trials evaluated the effectiveness of opioid rotation for management of opioid-induced adverse events in patients with chronic noncancer pain.
- There was insufficient evidence from 27 placebo-controlled trials to suggest that a long-acting opioid was superior in terms of adverse events than any other in adult patients with chronic noncancer pain as the trials are too clinically diverse and of insufficiently high quality to perform indirect comparisons of common opioid-associated adverse event rates as well as withdrawal rates due to adverse events.
- Withdrawal rates varied greatly for each long-acting opioid and did not suggest that a long-acting opioid was superior to the others.

Detailed assessment

Direct evidence

Ten randomized trials directly compared 2 long-acting opioids.[23-32] Adverse events reported in these trials are shown in Table 5. One head-to-head trial was a very small (N=18) study of transdermal fentanyl compared with twice-daily oral morphine in patients with chronic pancreatitis.[27] Because of its very small size and limited focus on adverse events, it did not provide usable information about comparative adverse event rates and is not further reviewed here. All of the trials excluded patients with prior substance abuse. Only 1 trial reported rates of addiction and reported no cases, but did not state how addiction was defined or ascertained. No trial reported rates of opioid abuse. No deaths were reported in any study.

Table 5. Specific adverse events in head-to-head trials of long-acting opioids

Study	Interventions	Nausea	Vomiting	Constipation	Drowsiness or somnolence	Dizziness
Allan, 2005[23]	Transdermal fentanyl	54%	29%	52%	27%	25%
	Long-acting morphine	50%	26%	65%	30%	24%
Allan, 2001[24]	Transdermal fentanyl	26%	10%	16%	18%	11%
	Long-acting morphine	18%	10%	22%	14%	4%
Niemann, 2000[27]	Transdermal fentanyl	NR	NR	NR	NR	NR
	Long-acting morphine	NR	NR	NR	NR	NR
Caldwell, 2002[25]	Once-daily morphine a.m.	21%	6%	49%	16%	10%
	Once-daily morphine p.m.	32%	16%	40%	12%	10%
	Twice-daily morphine	26%	8%	29%	12%	12%
	Placebo	10%	1%	4%	0%	1%
Hale, 2005[26]	Long-acting oxymorphone	NR	NR	35%	17%	NR
	Long-acting oxycodone	NR	NR	29%	20%	NR
	Placebo	NR	NR	11%	2%	NR
Matsu-moto 2005[28]	Oxymorphone 40 mg (twice daily)	59.5%	33.9%	32.2%	31.4%	31.4%
	Oxymorphone 20 mg (twice daily)	61.3%	22.7%	40.3%	30.3%	28.6%
	Oxycodone 20 mg (twice daily)	43.2%	10.4%	36.0%	27.2%	25.6%
	Placebo	10.5%	1.6%	11.3%	4.8%	4.0%

Study	Interventions	Nausea	Vomiting	Constipation	Drowsiness or somnolence	Dizziness
Nicholson 2006[29]	Morphine 79 mg/day (twice daily	14.0%	NR	26.0%	10.0%	2.0%
	Oxycodone 85 (three times daily)	13.8%	NR	10.3%	6.9%	5.2%
Rauck 2006[30]	Morphine 70 mg (once daily)	50%	24%	87%	85%	58%
	Oxycodone 61 mg (twice daily)	47%	19%	89%	84%	64%
Katz 2010[32]	Morphine/ Naltrexone	9.9%	8.5%	15.5%	9.9%	1.4%
	Morphine	8.5%	4.2%	12.7%	8.5%	7.0%
Hale 2007[31]	Hydromorphone	35.2%	16.9%	29.6%	25.4%	14.1%
	Oxycodone	29.9%	11.9%	25.4%	17.9%	22.4%

Abbreviation: NR, not reported.

The largest trial (N=680) compared transdermal fentanyl to long-acting oral morphine in patients with chronic low back pain.[23] The main flaws were that patients and assessors were not blinded to the interventions, there was high loss to follow-up (approximately 50% of patients in each arm completed the trial), methods for identifying adverse events other than constipation were not specified, and intent-to-treat analyses were not reported for some outcomes. For example, for the primary adverse event outcome of constipation using a bowel function assessment, rates were 31% for transdermal fentanyl compared with 48% for morphine ($P<0.001$), but results were only reported for 597 of the 680 enrolled subjects. For other adverse events, rates were calculated based on the number of patients receiving at least 1 dose of study drug (N=673) using "last observation carried forward" methods, with no sensitivity analyses of different assumptions (such as "best case" or "worst case" calculations) on the rates of different adverse events. Using last observation carried forward methods, there were no statistically significant differences for any adverse event other than constipation (52% vs. 65% favoring transdermal fentanyl; $P<0.05$).

Although this trial found that rates of constipation were lower for transdermal fentanyl than oral long-acting morphine, it also found a trend towards increased withdrawal due to any adverse event (a marker for intolerable or more severe adverse events) with transdermal fentanyl (37% vs. 31%; $P=0.098$). Reasons for withdrawal included vomiting (24% of withdrawals in transdermal fentanyl group, 20% in morphine group), nausea (37% in both groups), and constipation (11% and 23%). The proportion of withdrawals due to other adverse events, such as skin reactions, somnolence, and dry mouth, was not reported.

A second trial compared transdermal fentanyl to long-acting oral morphine in patients with mixed pain conditions and was rated poor quality for adverse event assessment (Evidence Table 4).[24] This trial found no significant differences in reported rates of overall or "serious" (not defined) complications. Constipation was significantly lower for transdermal fentanyl (29%) compared with long-acting morphine (48%, $P<0.001$) as assessed by a bowel function questionnaire, but was not significantly different when measured by patient-reported or investigator-observed symptoms. The rate of withdrawals due to adverse event for all patients

favored long-acting oral morphine (11% vs. 4%; *P* value not reported), but did not differ significantly in the subgroup not previously on fentanyl or morphine.

Two trials of long-acting oxymorphone compared with long-acting oxycodone assessed adverse events (Evidence Table 4).[28, 52] The first, which evaluated patients with low back pain, found no significant differences between the 2 long-acting opioids in the likelihood of experiencing any adverse event, withdrawal due to adverse events, occurrence of constipation, or occurrence of sedation. Other adverse events were not reported. The second trial, which evaluated patients with osteoarthritis, found no significant difference in the rate of patients experiencing any adverse event.[28] For specific adverse events, long-acting oxymorphone was associated with more nausea, vomiting, and pruritus compared with long-acting oxycodone, but less headache. However, the statistical significance of the differences was not reported.

Two trials of extended-release morphine compared with sustained-release morphine assessed adverse events (Evidence Table 4).[29, 30] For constipation, 1 trial found a higher rate with extended-release morphine[29] but the other found no significant difference.[29] There were no clear differences in rates of other adverse events.

The trial that compared once-daily with twice-daily preparations of oral morphine was also rated poor quality for adverse events (Evidence Table 4).[25] Serious adverse events (not defined) occurred in 6 enrolled patients, but the rates of serious complications were not reported for each treatment group. This trial found a significantly higher rate of constipation in patients on once-daily morphine given in the morning (49%) than twice-daily morphine (29%), but a lower rate of asthenia (1% vs. 9%). The overall withdrawal rates in patients randomized to any long-acting morphine preparation ranged from 37% to 45% and withdrawal rates due to adverse events ranged from 23% to 25%.

Withdrawal rates in head-to-head trials are shown in Table 6. Although there was a wide range of withdrawal rates across studies, within individual trials there were no significant differences between long-acting opioids. There was no pattern to suggest that any long-acting opioid is associated with a higher overall withdrawal rate or higher rate of withdrawals due to inadequate pain relief than any other long-acting opioid.

Table 6. Withdrawal rates in head-to-head trials of long-acting opioids for chronic noncancer pain

Author Year	N/ Duration	Long-acting opioid	Overall	Withdrawal due to inadequate pain control	Withdrawal due to adverse events	Withdrawal for other reasons
Allan 2005[23]	683/ 13 months	Transdermal fentanyl	52% (177/338)	5%	37%	10%
		Oral morphine (twice daily)	47% (162/342)	4%	31%	12%
Allan 2001[24]	256/ 4 weeks	Transdermal fentanyl	16% (39/250)	NR	11%	NR
		Morphine (twice daily)	9% (21/238)	NR	4%	NR
Hale 2005[26]	235/ 18 days	Oral oxymorphone (twice daily)	28% (22/80)	20%	2.5%	4%
		Oral oxycodone (twice daily)	26% (21/80)	16.3%	5%	4%
		Placebo	71% (53/75)	58.7%	6.7%	4%

Author Year	N/ Duration	Long-acting opioid	Overall	Withdrawal due to inadequate pain control	Withdrawal due to adverse events	Withdrawal for other reasons
Niemann, 2000[27]	18/ 4 weeks	Transdermal fentanyl	6% (1/18)	0%	6%	0%
		Oral morphine (twice daily)	0% (0/18)	0%	0%	0%
Matsumoto, 2005[28]	491/ 4 weeks	Oxymorphone 40 mg (twice daily)	56% (68/121)	7.4%	47.1%	2%
		Oxymorphone 20 mg (twice daily)	48% (58/121)	4.1%	38.0%	6%
		Oxycodone 20 mg (twice daily)	40% (50/125)	10.4%	24.8%	5%
		Placebo	37% (46/124)	27.4%	4.8%	5%
Rauck 2006[30]	392/ 8 weeks	Morphine 64 mg (once daily)	46% (93/203)	5%	19%	22%
		Oxycodone 53 mg (twice daily)	42% (79/189)	3%	14%	25%
Nicholson 2006[29]	112/ 24 weeks	Morphine 79 mg/day (twice daily)	57% (30/53)	2%	28%	21%
		Oxycodone 85 (three times daily)	51% (30/59)	7%	22%	20%
Caldwell 2002[25]	295/ 4 weeks	Morphine (once daily a.m.)	37% (27/73)	12.3%	23%	1%
		Morphine (once daily p.m.)	45% (33/73)	16.4%	25%	4%
		Morphine (twice daily)	37% (28/76)	10.5%	24%	3%
		Placebo	32% (23/72)	19.2%	7%	5%
Katz 2010[32]	72/ 2 weeks	Morphine/ Naltrexone	2.7% (1/37)	0%	2.7%	0%
		Morphine	5.7% (2/35)	0%	2.9%	2.9%
Hale 2007[31]	140/ 6 weeks	Hydromorphone	39.4%(28/71)	1.4%	35.2%	2.8%
		Oxycodone	39.1%(27/69)	4.3%	31.9%	2.9%

Abbreviations: NA, not applicable; NR, not reported.

No trials evaluated efficacy of opioid rotation for management of adverse events associated with long-acting opioids in patients with chronic noncancer pain.

Indirect evidence

Randomized trials

We identified 26 placebo-controlled trials of long-acting opioids that reported adverse events (Evidence Tables 2, 3, and 4).[11, 25, 26, 28, 40-50, 52-57, 59-62, 64]

With regard to adverse event assessment, all placebo-controlled trials had important methodological flaws. In addition, these trials had heterogeneous study designs, interventions, outcomes, and patient populations, making meaningful comparisons across studies difficult. Included trials generally found a higher rate of adverse events with long-acting opioids compared with placebo or active placebo (benztropine[44, 50] and lorazepam[41]). In trials that assessed adverse events from different doses of a long-acting opioid,[11, 51] higher doses were associated with more adverse events than lower doses. In the trial that compared morphine to gabapentin plus

morphine, the combination was associated with lower rates of constipation (most likely due to lower doses of morphine) and higher rates of dry mouth (most likely due to the gabapentin).[41] Other adverse events in trials with active placebos were similar.

These trials reported wide ranges for adverse event rates even in studies that evaluated the same long-acting opioid at roughly equivalent doses. For long-acting oxycodone at mean doses of 40 mg daily, for example, rates of nausea ranged from 15%[34] to 50%[39] in 5 trials (Table 6). Withdrawal rates due to adverse events ranged from 4%[36] to 32%[11] in these same studies. Given the uncertainty regarding the rate of adverse events for individual long-acting opioids, it is not surprising that these trials show no discernible pattern of 1 long-acting opioid being superior to others for any reported adverse event.

Observational studies

We identified 14 cohort studies evaluating the safety of long-acting opioids in patients with noncancer pain.[11, 25, 40, 69-79] None were rated good quality for adverse event assessment (Evidence Table 5).

Opioids assessed were long-acting codeine,[40] long-acting morphine,[25, 70, 73, 76, 77] transdermal fentanyl,[69, 72, 74, 75, 77, 78] methadone,[70, 71] and long-acting oxycodone.[11, 77, 78] Two studies evaluated the comparative risk of constipation from different long-acting opioids[77, 78] and the others assessed one long-acting opioid or did not assess comparative safety. The number of patients on long-acting opioids in these studies ranged from 11[71] to 2095.[78] Eight were prospective cohort studies[11, 25, 40, 69, 72, 74-76] and 5 were retrospective cohorts.[70, 71, 73, 77, 78] The prospective cohort studies recruited all[11, 25, 40, 69] or some[72] of their patients from completed clinical trials. Three of the prospective cohorts[11, 25, 40] were open-label extensions of clinical trials included in this review.

Two large, fair-quality retrospective cohort studies of California Medicaid patients found that the rate of a new diagnosis of constipation was significantly higher in patients prescribed long-acting oxycodone than transdermal fentanyl (adjusted odds ratios, 2.55; 95% CI, 1.33 to 4.89[78] and 1.78; 95% CI, 1.05 to 3.03[77]) after adjusting for patient demographics, comorbidities, dose of long-acting opioid, and use of short-acting opioids. One of these studies also assessed the risk of constipation with long-acting morphine compared with transdermal fentanyl and did not find a statistically significant difference (adjusted odds ratio 1.44; 95% CI, 0.80 to 2.60).[77] In these studies, patients on transdermal fentanyl were significantly older, more frequently male, on lower doses of opioids, and more frequently on tricyclic antidepressants. Marked differences in measured confounders suggested a higher risk for residual confounding due to unmeasured or unknown factors. This is important because studies that rely on administrative databases are frequently limited in their ability to measure important potential confounders. Furthermore, it was not clear if assessors were blinded to the long-acting opioid and the makers of transdermal fentanyl sponsored both studies. Finally, both of these studies focused on a single adverse outcome (constipation). Such a narrow focus made it impossible to assess the overall balance of adverse events. This is important because 2 randomized trials of transdermal fentanyl and oral long-acting morphine (reviewed earlier in this report) found that transdermal fentanyl was associated with lower rates of constipation but with higher rates (or a trend towards higher rates) of withdrawal due to any adverse event.[23, 24] A third retrospective study of Oregon Medicaid patients found no significant difference between methadone, long-acting oxycodone, long-acting morphine, and transdermal fentanyl in rates of hospitalizations, mortality, or constipation, though transdermal fentanyl was associated with a higher rate of emergency room encounters (hazard

ratio, 1.27; 95% CI, 1.02 to 1.59) and methadone was associated with a higher rate of overdose symptoms (defined as alteration of consciousness, malaise, fatigue, lethargy, or respiratory failure; hazard ratio, 1.57; 95% CI, 1.03 to 2.40) when each was compared with sustained-release oral morphine.[79] However, interpreting results was a challenge because this study was also characterized by the presence of numerous statistically significant differences in baseline characteristics between groups prescribed different long-acting opioids and many of the assessed outcomes were nonspecific for opioid-related events. Results for opioid poisoning specifically were too imprecise to draw conclusions about comparative risk due to small numbers of events.

Some observational studies reported long-term outcomes and serious adverse events not reported in the trials. The largest (N=530) study[72] reported 1 death (0.2%, 1/530) thought related to medication, 4 cases of respiratory depression (1%), and 3 episodes of drug abuse (0.6%). Two other studies reported rates of abuse[70, 71] but they were retrospective studies with small samples (N=11 and 20) and no inception cohort. Four studies reported rates of long-term use, which could be a long-term measure of tolerability or clinical efficacy.[11, 25, 40, 69] Rates ranged from 19% for transdermal fentanyl[69] to 54% for long-acting codeine.[40] A small (N=28) poor-quality observational study found that sustained-release morphine was not associated with decreased long-term (12 months) neuropsychological performance assessed with a battery of neuropsychologic tests.[76]

Other than in the 3 Medicaid-based studies,[77-79] the patients enrolled in observational studies did not appear to be less selected than those in the controlled trials. In the prospective cohort studies, at least some participants were recruited from completed clinical trials,[11, 25, 40, 69, 72] resulting in an even more highly selected population than the original trials. In 3 retrospective studies, no inception cohort was identified and the population appeared to represent a "convenience" sample of patients for whom data was readily available.[70, 71, 73]

A report from the Federal General Accounting Office investigated factors that may have contributed to long-acting oxycodone abuse and diversion.[80] It did not provide information about rates of abuse or assess rates of abuse and diversion of long-acting oxycodone compared with other long-acting opioids.

An evidence review of strategies to manage the adverse effects of oral morphine found that although there are numerous case reports and uncontrolled series reporting successful reduction in opioid-related side effects after opioid rotation, outcomes of opioid rotation were variable and somewhat unpredictable.[81]

Additional observational studies were excluded because they were noncomparative and therefore did not provide useful data on relative harms of different long-acting opioids.[82-85] A number of observational studies have reported serious adverse events associated with long-acting opioids but did not meet inclusion criteria. Some studies were excluded because they were case series that did not provide information about rates of events or were not designed to compare risk across different opioids.[86-88] For example, studies have linked methadone use with torsades de pointes,[88] QTc prolongation,[86] or sudden death in persons without known cardiac disease,[89] but none were designed to assess risk of methadone in comparison to other long-acting opioids. Large scale epidemiological studies and surveillance studies have reported on deaths associated with use of various opioids, but were excluded because they did not report event rates in inception cohorts of patients exposed to the opioids.[1, 90-93] Rather, they calculated rates indirectly, based on overall opioid prescribing rates. In addition, such studies were generally not designed to distinguish between uses of prescribed compared with nonprescribed opioids, use of opioids for

noncancer compared with cancer pain, or use of long-acting compared with short-acting formulations.

Key Question 4. What are the comparative harms of long-acting opioids compared with short-acting opioids in adult patients being treated for chronic noncancer pain?

Summary of evidence

- There was no convincing evidence from 7 randomized controlled trials to suggest lower adverse event rates with long-acting opioids as a class compared with short-acting opioids for all assessed adverse events.
- There were no data comparing rates of addiction or abuse of long-acting and short-acting opioids.

Detailed assessment

Direct evidence

Study characteristics of the 7 randomized trials directly comparing long-acting opioids with short-acting opioids have already been reviewed in this report and are summarized in Evidence Table 5.[33-39] None of the studies were designed to assess rates of addiction or abuse.

Across all trials, no pattern favoring either long-acting or short-acting opioids was evident for any of the reported adverse events (Table 7). In the 3 most comparable studies, which investigated roughly equivalent daily doses of oxycodone in short-acting and long-acting preparations,[34, 36, 39] no trends favoring 1 formulation over the other were seen for the outcomes of dizziness, somnolence, vomiting, and constipation. This was also true in the 2 studies[36, 39] that investigated the same (rerandomized) population.

Withdrawals due to adverse events were reported in 5 trials. Three favored short-acting opioids,[33, 38, 39] 1 favored long-acting,[34] and 1 was equivocal.[36] These data were limited by the poor quality of the trials for adverse event assessment and the fact that 2 of the trials evaluated the same (rerandomized) population.

Table 7. Adverse events in trials of long-acting compared with short-acting opioids

Study Year (Quality rating)	Opioid	Nausea	Vomiting	Constipation	Drowsiness	Dizziness	Confusion	Withdrawals
Caldwell 1999[34] (POOR)	Long-acting oxycodone	15% (5/34)	6% (2/34)	71% (24/34)	53% (18/34)	12% (4/34)	NR	9% (3/34)
	Short-acting oxycodone + acetaminophen	38% (14/37)	11% (4/37)	54% (20/37)	70% (26/37)	24% (9/37)	NR	14% (5/37)
Hale 1999[36] (POOR)	Long-acting oxycodone	15% (7/47)	2% (1/47)	38% (18/47)	11% (5/47)	13% (6/47)	NR	4% (2/47)
	Immediate-release oxycodone	26% (12/47)	0% (0/47)	36% (17/47)	11% (5/47)	9% (4/47)	NR	2% (1/47)
Salzman 1999[39] (POOR)	Long-acting oxycodone	50% (15/30)	20% (6/30)	30% (9/30)	27% (8/30)	30% (9/30)	3% (1/30)	20% (6/30)
	Short-acting oxycodone	33% (9/27)	4% (1/27)	37% (10/27)	37% (10/27)	22% (6/27)	0% (0/27)	7% (2/27)
Hale 1997[33] (POOR)	Long-acting codeine	31% (16/52)	10% (5/52)	19% (10/52)	10% (5/52)	17% (9/52)	NR	25% (13/52)
	Short-acting codeine	18% (9/51)	2% (1/51)	16% (8/51)	4% (2/51)	4% (2/51)	NR	8% (4/51)
Gostick 1989[35] (POOR)	Long-acting dihydrocodeine	NR	NR	37.7% (23/61)	NR	NR	NR	NR
	Short-acting dihydrocodeine	NR	NR	34.4% (21/61)	NR	NR	NR	NR
Jamison 1998[37] (FAIR)	Long-acting morphine + short-acting oxycodone	31%	NR	30%	39%	6%	0%	9% (1/11)
	Short-acting oxycodone	14%	NR	18%	22%	19%	1.4%	15% (2/13)
Lloyd 1992[38] (POOR)	Long-acting dihydrocodeine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	NR	NR	40% (17/43)
	Dextropropoxyphene + paracetamol	Unable to determine	Unable to determine	Unable to determine	Unable to determine	NR	NR	9% (4/43)

Abbreviation: NR, not reported.

Key Questions 5 and 6. Are there subpopulations of patients (specifically by race, age, sex, socio-economic status type of pain, or comorbidities) with chronic noncancer pain for which one long-acting opioid is more effective or associated with fewer harms, or for which long-acting opioids are more effective or associated with fewer harms than short-acting opioids?

Summary of evidence

- The evidence regarding differential efficacy or adverse event risk from long-acting opioids or between long-acting and short-acting opioids in subpopulations of patients with noncancer pain was severely limited in quantity and quality and it was not possible to draw reliable conclusions regarding comparative efficacy or adverse event rates for any subpopulation from these data.
- One fair-quality observational study found that the risk of constipation was higher for long-acting oxycodone than transdermal fentanyl in patients older than 65 than for all patients included in the study.
- For specific types of chronic noncancer pain, the trials were limited by problems with internal validity, external validity, heterogeneity, and small numbers of trials for each subpopulation.

Detailed assessment

No clinical trials or observational studies were designed to compare the efficacy of long-acting opioids for different races, age groups, or genders. Race was rarely reported in the trials and when it was reported the overwhelming majority of patients were white. Women were well-represented in the trials (slightly over 50%). The average age of included patients was in the mid-50s, though 1 study[47] evaluated patients with an average age of 70 years. Two trials[11, 34] performed very limited subgroup analysis on older patients. Neither trial directly compared a long-acting opioid to another. They provided little information regarding differential efficacy or adverse events within the class of long-acting opioids. One fair-quality retrospective cohort study found that the risk of constipation associated with long-acting oxycodone compared with transdermal fentanyl was higher in patients older than 65 years (adjusted odds ratio, 7.33; 95% CI, 1.98 to 27.13) than in all patients included in the study (adjusted odds ratio, 2.55; 95% CI, 1.33 to 4.89).[78] Because there was a high likelihood for unmeasured or unknown confounders, firm conclusions from this subgroup analysis were not possible.

A post-hoc analysis of 2 placebo-controlled trials examined the effects of age, sex, and prior opioid use on response to extended-release oxymorphone in patients with low back pain.[63] Both trials included a titration phase and a 12-week, randomized treatment phase. Only those patients who responded to oxymorphone treatment in the titration phase continued into the randomization phase (347 of 575; 60.3%). There were no significant effects of age, sex, or prior opioid experience on the visual analogue scale-measured pain intensity and no effect of the measured factors on discontinuations due to lack of efficacy in the oxymorphone group. There were no significant differences in the occurrence of adverse effects based on age or sex. Constipation occurred more frequently in opioid-naïve patients during titration, but the difference was not significant during the treatment phase. Because it included only trials of 1 drug, this analysis did not provide evidence for comparative effectiveness or safety in subgroups.

Different types of chronic noncancer pain patients were studied in trials, including back pain, osteoarthritis, phantom limb pain, and neuropathic pain. Subgroups of trials for specific types of pain had the same problems with heterogeneity in interventions, outcomes assessed, and findings that were encountered in examining general efficacy and adverse events. They were further limited by the smaller number of available trials for each type of pain. These trials provided insufficient indirect evidence that a long-acting opioid is superior to any other in any subpopulation of patients with chronic pain.

SUMMARY

Strength of Evidence

The results of this review are summarized in Table 8, below, and Appendix E summarizes the strength of the evidence for each key question. Although we identified 10 head-to-head trials comparing 2 or more long-acting opioids, the evidence was insufficient to determine if there are differences among the drugs. Eight trials found no significant difference in pain relief or function between long-acting opioids. The 2 trials which found a significant difference (1 trial of transdermal fentanyl vs. oral long-acting morphine and 1 trial of extended-release morphine vs. sustained-release oxycodone) were both open-label, rated poor quality, and were inconsistent with higher-quality trials evaluating the same comparison that found no significant differences.

There was also insufficient evidence to determine whether long-acting opioids as a class are more effective or associated with fewer harms than short-acting opioids. Seven fair-quality trials directly compared a long-acting opioid to a short-acting opioid. These trials were highly heterogeneous in terms of study design, patient populations, interventions, and outcomes assessed. There was fair-quality evidence from 3 more homogeneous trials to suggest that long-acting oxycodone and short-acting oxycodone are equally effective for pain control in adult patients with chronic noncancer pain.

There was insufficient evidence to assess comparative effectiveness or harms in subgroups.

Limitations

This report was limited by a lack of good-quality direct evidence. Most included studies were relatively small, of short duration, and had important methodologic flaws. We were unable to conduct quantitative meta-analyses due to diversity among the trials in populations, outcome measures, and study designs. Methodological limitations of this review within the defined scope included the exclusion of studies published in languages other than English and lack of a specific search for unpublished studies.

Applicability

The trials generally provided inadequate information to accurately assess applicability or showed evidence of having highly selected populations. Most trials did not report numbers of patients screened or eligible for entry and some did not specify exclusion criteria. When exclusion

criteria were specified, patients at risk for drug or substance abuse were typically excluded from trial participation.

Table 8. Summary of evidence

	Strength of evidence	Conclusions
Key Question 1. What is the comparative effectiveness of different long-acting opioids in reducing pain and improving functional outcomes in adult patients being treated for chronic noncancer pain?		
Direct evidence	Fair to poor	There was insufficient evidence from 10 head-to-head trials to suggest that a long-acting opioid is superior to another in terms of efficacy in adult patients with chronic noncancer pain. Eight trials found no significant difference in pain relief or function between long-acting opioids. The 2 trials which found a significant difference (1 trial of transdermal fentanyl vs. oral long-acting morphine and 1 trial of extended-release morphine vs. sustained-release oxycodone) were both open-label, rated poor quality, and were inconsistent with higher-quality trials evaluating the same comparison that found no significant differences.
Indirect Evidence	Insufficient	No useful indirect evidence for determining the comparative efficacy of long-acting opioids was found in 27 placebo-controlled trials. The studies were generally of insufficient quality and too diverse in terms of study designs, patient populations, interventions, and assessed outcomes to conduct indirect comparisons on efficacy.
Key Question 2. What is the comparative effectiveness of long-acting opioids compared with short-acting opioids in reducing pain and improving functional outcomes when used for treatment of adults with chronic noncancer pain?		
Direct evidence	Fair	Seven fair-quality trials directly compared a long-acting opioid to a short-acting opioid. There was no good-quality evidence to suggest superior efficacy of long-acting opioids as a class over short-acting opioids. For oxycodone specifically, there was fair evidence from 3 trials that long- and short-acting oxycodone are equally effective for pain control.
Key Question 3. What are the comparative harms (including addiction and abuse) of different long-acting opioids in adult patients being treated for chronic noncancer pain?		
Direct evidence	Fair to Poor	There were insufficient data from 10 head-to-head trials of long-acting opioids to conclude that any long-acting opioid is associated with fewer harms compared with others. None of the trials were designed to specifically assess harms. All head-to-head trials excluded patients at high risk for addiction or abuse and none adequately assessed rates of these complications.
	Insufficient	There was insufficient evidence from 27 placebo-controlled trials to suggest that a long-acting opioid is superior in terms of adverse events than any other in adult patients with chronic noncancer pain. The trials were too clinically diverse and of insufficiently high quality to perform indirect comparisons of common opioid-associated adverse event rates or withdrawal rates due to adverse events.
Key Question 4. What are the comparative harms of long-acting opioids compared with short-acting opioids in adult patients being treated for chronic noncancer pain?		
	Poor for comparative harms	There was no convincing evidence from 7 randomized-controlled trials to suggest lower adverse event rates with long-acting opioids as a class compared with short-acting opioids for all assessed adverse events.
	Insufficient for comparative risk of addiction and abuse	There were no data comparing rates of addiction or abuse of long-acting and short-acting opioids.

	Strength of evidence	Conclusions
Key Questions 5 and 6. Are there subpopulations of patients (specifically by race, age, sex, socio-economic status type of pain, or comorbidities) with chronic noncancer pain for which one long-acting opioid is more effective or associated with fewer harms, or for which long-acting opioids are more effective or associated with fewer harms than short-acting opioids?		
	Insufficient	The evidence regarding differential efficacy or adverse event risk from long-acting opioids or between long-acting and short-acting opioids in subpopulations of patients with noncancer pain was severely limited in quantity and quality. It was not possible to draw reliable conclusions regarding comparative efficacy or adverse event rates for any subpopulation from these data.

CONCLUSION

The evidence was insufficient to determine if there are differences among long-acting opioids in effectiveness or harms. A shortcoming of the currently available evidence is that comparisons between specific long-acting opioids have been evaluated in only 1 to 3 trials each (most with small sample sizes), which may limit statistical power for detecting true differences. Studies that provided indirect data were too heterogeneous in terms of study design, patient populations, interventions, assessed outcomes, and results to make accurate judgments regarding comparative efficacy or adverse event rates. Evidence was insufficient to determine if long-acting opioids as a class are more effective or associated with fewer harms than short-acting opioids. There was also insufficient evidence to draw conclusions about comparative effectiveness or safety in subgroups.

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Appendix A. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An **adverse event** for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term

in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity.*

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intent to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intent to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the

effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intent-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo-controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo-controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix B. Boxed warnings of included drugs[1-11]

Active ingredient	Trade name(s)	Boxed warnings
Buprenorphine	Butrans™	WARNING: IMPORTANCE OF PROPER PATIENT SELECTION, POTENTIAL FOR ABUSE, AND LIMITATIONS OF USE Proper Patient Selection Butrans™ is a transdermal formulation of buprenorphine indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. Potential for Abuse Butrans™ contains buprenorphine which is a mu opioid partial agonist and a Schedule III controlled substance. Butrans™ can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the abuse potential when prescribing or dispensing Butrans™ in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Assess patients for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. Routinely monitor all patients receiving opioids for signs of misuse, abuse and addiction. Limitations of Use Do not exceed a dose of one 20 mcg/hour Butrans™ system due to the risk of QTc interval prolongation. Avoid exposing the Butrans application site and surrounding area to direct external heat sources. Temperature-dependent increases in buprenorphine release from the system may result in overdose and death.
Fentanyl	Duragesic®	FOR USE IN OPIOID-TOLERANT PATIENTS ONLY DURAGESIC® contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (DURAGESIC®) may be a particular target for abuse and diversion. DURAGESIC® is indicated for management of persistent, moderate to severe chronic pain that: • requires continuous, around-the-clock opioid administration for an extended period of time, and • cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids DURAGESIC® should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to DURAGESIC® 25 mcg/h. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid.

Active ingredient	Trade name(s)	Boxed warnings
Fentanyl (Continued)	Duragesic® (Continued)	Because serious or life-threatening hypoventilation could occur, DURAGESIC® (fentanyl transdermal system) is contraindicated: • in patients who are not opioid-tolerant • in the management of acute pain or in patients who require opioid analgesia for a short period of time • in the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies) • in the management of mild pain • in the management of intermittent pain (e.g., use on an as needed basis [prn]) (See CONTRAINDICATIONS for further information.) Since the peak fentanyl concentrations generally occur between 20 and 72 hours of treatment; prescribers should be aware that serious or life threatening hypoventilation may occur, even in opioid-tolerant patients, during the initial application period. The concomitant use of DURAGESIC® with all cytochrome P450 3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving DURAGESIC® and any CYP3A4 inhibitor should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted (see CLINICAL PHARMACOLOGY – Drug Interactions, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION for further information). The safety of DURAGESIC® has not been established in children under 2 years of age. DURAGESIC® should be administered to children only if they are opioid-tolerant and 2 years of age or older (see PRECAUTIONS Pediatric Use). DURAGESIC® is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. Overestimating the DURAGESIC® dose when converting patients from another opioid medication can result in fatal overdose with the first dose (see DOSAGE And ADMINISTRATON – Initial DURAGESIC® Dose Selection). Due to the mean half-life of approximately 20-27 hours, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours. DURAGESIC® can be abused in a manner similar to other opioid agonists, legal or illicit. This risk should be considered when administering, prescribing, or dispensing DURAGESIC® in situations where the healthcare professional is concerned about increased risk of misuse, abuse, or diversion.

Active ingredient	Trade name(s)	Boxed warnings
Fentanyl (Continued)	Duragesic® (Continued)	Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse, and addiction. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require intensive monitoring for signs of misuse, abuse or addiction. DURAGESIC® patches are intended for transdermal use (on intact skin) only. Do not use a DURAGESIC® patch if the pouch seal is broken or the patch is cut, damaged, or changed in any way. Avoid exposing the DURAGESIC® application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, saunas, hot tubs, and heated water beds, while wearing the system. Avoid taking hot baths or sunbathing. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death. Patients wearing DURAGESIC® systems who develop fever or increased core body temperature due to strenuous exertion should be monitored for opioid side effects and the DURAGESIC® dose should be adjusted if necessary.

Active ingredient	Trade name(s)	Boxed warnings
Hydromorphone	Exalgo®	WARNING: POTENTIAL FOR ABUSE, IMPORTANCE OF PROPER PATIENT SELECTION AND LIMITATIONS OF USE Potential for Abuse EXALGO® contains hydromorphone, an opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid analgesics. EXALGO® can be abused in a manner similar to other opioid agonists, legal or illicit. These risks should be considered when administering, prescribing, or dispensing EXALGO in situations where the healthcare professional is concerned about increased risk of misuse, abuse, or diversion. Schedule II opioid substances which include hydromorphone, morphine, oxycodone, fentanyl, oxymorphone and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression. Proper Patient Selection EXALGO® is an extended release formulation of hydromorphone hydrochloride indicated for the management of moderate to severe pain in opioid tolerant patients when a continuous around-the-clock opioid analgesic is needed for an extended period of time. Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl/hour, 30 mg of oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg of oral oxymorphone/day or an equianalgesic dose of another opioid, for a week or longer. EXALGO® is for use in opioid tolerant patients only. Fatal respiratory depression could occur in patients who are not opioid tolerant. Accidental consumption of EXALGO®, especially in children, can result in a fatal overdose of hydromorphone. Limitations of Use EXALGO® is not indicated for the management of acute or postoperative pain. EXALGO® is not intended for use as an as needed analgesic. EXALGO® tablets are to be swallowed whole and are not to be broken, chewed, dissolved, crushed or injected. Taking broken, chewed, dissolved or crushed EXALGO® or its contents leads to rapid release and absorption of a potentially fatal dose of hydromorphone.

Active ingredient	Trade name(s)	Boxed warnings
Methadone	Dolophine®	Deaths, cardiac and respiratory, have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioid agonists. It is critical to understand the pharmacokinetics of methadone when converting patients from other opioids (see DOSAGE AND ADMINISTRATION). Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration. Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration. In addition, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Methadone treatment for analgesic therapy in patients with acute or chronic pain should only be initiated if the potential analgesic or palliative care benefit of treatment with methadone is considered and outweighs the risks. Conditions For Distribution And Use Of Methadone Products For The Treatment Of Opioid Addiction Code of Federal Regulations, Title 42, Sec 8 Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment. Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program.

Active ingredient	Trade name(s)	Boxed warnings
Morphine	Avinza®	WARNING: AVINZA® capsules are a modified-release formulation of morphine sulfate indicated for once daily administration for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time. AVINZA® CAPSULES ARE TO BE SWALLOWED WHOLE OR THE CONTENTS OF THE CAPSULES SPRINKLED ON APPLESAUCE. THE CAPSULE BEADS ARE NOT TO BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE. PATIENTS MUST NOT CONSUME ALCOHOLIC BEVERAGES WHILE ON AVINZA THERAPY. ADDITIONALLY, PATIENTS MUST NOT USE PRESCRIPTION OR NON-PRESCRIPTION MEDICATIONS CONTAINING ALCOHOL WHILE ON AVINZA THERAPY. CONSUMPTION OF ALCOHOL WHILE TAKING AVINZA MAY RESULT IN THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.
Morphine	Kadian® MS Contin®	Following black box warnings is found in the Kadian® package insert. Similar black box warnings have been issued for MS-Contin®. KADIAN® contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. Kadian® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing KADIAN® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. KADIAN® capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. KADIAN® Capsules are NOT for use as a prn analgesic. KADIAN® 100 mg and 200 mg Capsules ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. Ingestion of these capsules or of the pellets within the capsules may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids. Kadian® capsules are not to be swallowed whole or the contents of the capsules sprinkled on applesauce. The pellets in the capsules are not to be chewed, crushed or dissolved due to the risk of rapid release and absorption of a potentially fatal dose of morphine
Morphine	Oramorph SR®	NOTE: THE SUSTAINED RELEASE OF MORPHINE FROM ORAMORPH SR® SHOULD BE TAKEN INTO CONSIDERATION IN THE EVENT OF AN OVERDOSAGE.

Active ingredient	Trade name(s)	Boxed warnings
Morphine sulfate and naltrexone hydrochloride	Embeda™	WARNING *See full prescribing information for complete boxed warning*. • EMBEDA™ capsules contain pellets of morphine sulfate, an opioid receptor agonist with a sequestered core of naltrexone hydrochloride, an opioid receptor antagonist, and is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. • EMBEDA™ is to be swallowed whole or the contents of the capsules sprinkled on apple sauce. The pellets in the capsules are not to be crushed, dissolved, or chewed. Misuse or abuse of EMBEDA™ by tampering with the formulation, crushing or chewing the pellets, causes the rapid release and absorption of both morphine and naltrexone. The resulting morphine dose may be fatal, particularly in opioid-naïve individuals. In opioid-tolerant individuals, the absorption of naltrexone may increase the risk of precipitating withdrawal. • EMBEDA™ is NOT intended for use as a prn analgesic. • EMBEDA™ 100 mg/4mg capsules ARE FOR USE IN OPIOIDTOLERANT PATIENTS ONLY (2). • Patients should not consume alcoholic beverages or use prescription or non-prescription medications containing alcohol while on EMBEDA™ therapy.

Active ingredient	Trade name(s)	Boxed warnings
Oxycodone	OxyContin®	WARNING: IMPORTANCE OF PROPER PATIENT SELECTION AND POTENTIAL FOR ABUSE OxyContin® contains oxycodone which is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. OxyContin® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. OxyContin® is a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. OxyContin® is not intended for use on an as-needed basis. Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer. OxyContin® 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in opioid-tolerant patients, as they may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory-depressant or sedating effects of opioids. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction. OxyContin® must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved. Taking cut, broken, chewed, crushed or dissolved OxyContin tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone. The concomitant use of OxyContin® with all cytochrome P450 3A4 inhibitors such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse effects and may cause potentially fatal respiratory depression. Patients receiving OxyContin® and a CYP3A4 inhibitor should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted.

Active ingredient	Trade name(s)	Boxed warnings
Oxymorphone	Opana ER®	WARNING: POTENTIAL FOR ABUSE, IMPORTANCE OF PROPER PATIENT SELECTION AND LIMITATIONS OF USE Potential for Abuse OPANA ER® contains oxymorphone, which is a morphine-like opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OPANA ER® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Proper Patient Selection OPANA ER® is an extended-release oral formulation of oxymorphone indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Limitations of Use OPANA ER® is NOT intended for use as an as needed analgesic. OPANA ER® TABLETS are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed OPANA ER® TABLETS leads to rapid release and absorption of a potentially fatal dose of oxymorphone. Patients must not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on OPANA ER® therapy. The co-ingestion of alcohol with OPANA ER® may result in increased plasma levels and a potentially fatal overdose of oxymorphone.

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Appendix C. Search strategies Update 6

Database: Ovid MEDLINE(R) <1996 to November Week 2 2010>
Search Strategy:
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1 opioid analgesics.mp. or exp Analgesics, Opioid/ (34952)
2 narcotics.mp. or exp Narcotics/ (30985)
3 (intractable pain or severe pain or chronic pain).mp. (14103)
4 1 or 2 (38525)
5 3 and 4 (2179)
6 hydromorphone.mp. or exp Hydromorphone/ (637)
7 oxymorphone.mp. or exp Oxymorphone/ (199)
8 morphine sulfate.mp. (457)
9 naltrexone hydrochloride.mp. (46)
10 8 and 9 (5)
11 5 or 6 or 7 or 10 (2875)
12 butrans.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (0)
13 codeine contin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (1)
14 dhc continus.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (2)
15 duragesic.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (28)
16 exalgo.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (0)
17 levo-dromoran.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (0)
18 dolophine.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (3)
19 methadose.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (2)
20 avinza.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (13)
21 kadian.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (14)
22 ms-contin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (27)
23 oramorph sr.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (7)
24 embeda.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (6)

25 oxycontin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (101)
26 roxicodone.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (2)
27 opana.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (9)
28 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (190)
29 11 or 28 (3023)
30 limit 29 to (english language and humans and yr="2007 -Current") (927)

Database: Ovid MEDLINE(R) without Revisions <1996 to January Week 4 2011>
Search Strategy:
---
1 opioid analgesics.mp. or exp Analgesics, Opioid/ (157322)
2 narcotics.mp. or exp Narcotics/ (45493)
3 (intractable pain or severe pain or chronic pain).mp. (14364)
4 1 or 2 (166546)
5 3 and 4 (2383)
6 hydromorphone.mp. or exp Hydromorphone/ (644)
7 oxymorphone.mp. or exp Oxymorphone/ (203)
8 morphine sulfate.mp. (456)
9 naltrexone hydrochloride.mp. (48)
10 8 and 9 (6)
11 5 or 6 or 7 or 10 (3087)
12 butrans.mp. (1)
13 codeine contin.mp. (1)
14 dhc continus.mp. (2)
15 duragesic.mp. (29)
16 exalgo.mp. (0)
17 levo-dromoran.mp. (0)
18 dolophine.mp. (3)
19 methadose.mp. (2)
20 avinza.mp. (13)
21 kadian.mp. (14)
22 ms-contin.mp. (27)
23 oramorph.mp. (11)
24 embeda.mp. (7)
25 oxycontin.mp. (102)
26 roxicodone.mp. (2)
27 opana.mp. (9)

28 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (198)
29 11 or 28 (3240)
30 limit 29 to (english language and humans) (2503)
31 (201011$ or 201012$ or 2011$).ed. (163173)
32 30 and 31 (55)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2010>
Search Strategy:
---
1 opioid analgesics.mp. or exp Analgesics, Opioid/ (10213)
2 narcotics.mp. or exp Narcotics/ (10057)
3 (intractable pain or severe pain or chronic pain).mp. (2340)
4 1 or 2 (10602)
5 3 and 4 (441)
6 hydromorphone.mp. or exp Hydromorphone/ (245)
7 oxymorphone.mp. or exp Oxymorphone/ (57)
8 morphine sulfate.mp. (328)
9 naltrexone hydrochloride.mp. (33)
10 8 and 9 (3)
11 5 or 6 or 7 or 10 (690)
12 butrans.mp. (0)
13 codeine contin.mp. (4)
14 dhc continus.mp. (1)
15 duragesic.mp. (4)
16 exalgo.mp. (0)
17 levo-dromoran.mp. (0)
18 dolophine.mp. (0)
19 methadose.mp. (0)
20 avinza.mp. (7)
21 kadian.mp. (11)
22 ms-contin.mp. (37)
23 oramorph.mp. (7)
24 embeda.mp. (1)
25 oxycontin.mp. (23)
26 roxicodone.mp. (0)
27 opana.mp. (3)
28 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (84)
29 11 or 28 (758)
30 limit 29 to yr="2010 -Current" (16)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 2011>
Search Strategy:
---
1 opioid analgesics.mp. or exp Analgesics, Opioid/ (58)
2 narcotics.mp. or exp Narcotics/ (72)
3 (intractable pain or severe pain or chronic pain).mp. (366)
4 1 or 2 (120)
5 3 and 4 (32)
6 hydromorphone.mp. or exp Hydromorphone/ (18)
7 oxymorphone.mp. or exp Oxymorphone/ (5)
8 morphine sulfate.mp. (4)
9 naltrexone hydrochloride.mp. (0)
10 8 and 9 (0)
11 5 or 6 or 7 or 10 (44)
12 butrans.mp. (1)
13 codeine contin.mp. (0)
14 dhc continus.mp. (0)
15 duragesic.mp. (0)
16 exalgo.mp. (0)
17 levo-dromoran.mp. (0)
18 dolophine.mp. (2)
19 methadose.mp. (2)
20 avinza.mp. (0)
21 kadian.mp. (1)
22 ms-contin.mp. (2)
23 oramorph.mp. (2)
24 embeda.mp. (0)
25 oxycontin.mp. (6)
26 roxicodone.mp. (2)
27 opana.mp. (0)
28 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (12)
29 11 or 28 (52)
30 limit 29 to yr="2010 -Current" (15)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2011>
Search Strategy:
---
1 opioid analgesics.mp. or exp Analgesics, Opioid/ (7)
2 narcotics.mp. or exp Narcotics/ (33)
3 (intractable pain or severe pain or chronic pain).mp. (139)
4 1 or 2 (40)
5 3 and 4 (2)

6 hydromorphone.mp. or exp Hydromorphone/ (7)
7 oxymorphone.mp. or exp Oxymorphone/ (4)
8 morphine sulfate.mp. (0)
9 naltrexone hydrochloride.mp. (1)
10 8 and 9 (0)
11 5 or 6 or 7 or 10 (12)
12 butrans.mp. (0)
13 codeine contin.mp. (0)
14 dhc continus.mp. (0)
15 duragesic.mp. (0)
16 exalgo.mp. (0)
17 levo-dromoran.mp. (0)
18 dolophine.mp. (0)
19 methadose.mp. (0)
20 avinza.mp. (0)
21 kadian.mp. (0)
22 ms-contin.mp. (0)
23 oramorph.mp. (0)
24 embeda.mp. (0)
25 oxycontin.mp. (0)
26 roxicodone.mp. (0)
27 opana.mp. (0)
28 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (0)
29 11 or 28 (12)

Appendix D. Excluded trials Update 6

The following full-text publications were considered for inclusion but failed to meet the criteria for this report. See previous versions of the report on the Drug Effectiveness Review Project website for studies excluded previously.

Exclusion codes: 3=ineligible intervention, 4=ineligible population

Excluded trials	Exclusion code
Active-control trials	
Karlsson M, Berggren A-C. Efficacy and safety of low-dose transdermal buprenorphine patches (5, 10, and 20 microg/h) versus prolonged-release tramadol tablets (75, 100, 150, and 200 mg) in patients with chronic osteoarthritis pain: a 12-week, randomized, open-label, controlled, parallel-group noninferiority study. *Clin. Ther.* Mar 2009;31(3):503-513	3
Shram MJ, Sathyan G, Khanna S, et al. Evaluation of the abuse potential of extended release hydromorphone versus immediate release hydromorphone. *J. Clin. Psychopharmacol.* Feb 2010;30(1):25-33.	4
Placebo-controlled trials	
Corsinovi L, Martinelli E, Fonte G, et al. Efficacy of oxycodone/acetaminophen and codeine/acetaminophen vs. conventional therapy in elderly women with persistent, moderate to severe osteoarthritis-related pain. *Arch. Gerontol. Geriatr.* 2009;49:378-382.	3
Vondrackova D, Leyendecker P, Meissner W, et al. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. *Journal of Pain.* Dec 2008;9(12):1144-1154	3

Appendix E. Strength of evidence

Table 1: Comparative effectiveness of long-acting opioids for pain relief and quality of life

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% CI)**	**High, moderate, low, insufficient**
Transdermal fentanyl vs. oral morphine						
2; 701 (683 from one trial)	Fair RCTs	Unable to determine	Direct	Imprecise	Not able to pool data; outcomes differed No significant differences between treatments on VAS (56.0 vs. 55.8) or other pain and quality of life outcomes	Low
Oxymorphone vs. oxycodone						
2; 702	Fair RCTs	Unable to determine (data insufficient)	Direct	Imprecise	Unable to pool data; data insufficient and doses differed No significant differences on measures of pain or function	Low
Long-acting morphine vs. oxycodone						
1; 112	Fair RCT	NA	Direct	Imprecise	No significant differences between groups in SF-36 Physical Component Scale: +2.5 vs. +2.1(NS); Pain (0 to 10): -1.9 vs. -1.4 (NS); Patient Global Assessment (-4 to +4): +2.6 vs. +1.7 (NS)	Low
Extended-release (once-daily) vs. sustained-release (twice-daily) morphine						
1; 295	Fair RCT	NA	Direct	Imprecise	No significant differences between active treatments for pain intensity at index joint (0-500 VAS), pain intensity overall (1-100 VAS), physical function (0-1700 VAS), stiffness index (0-200 VAS).	Low
Morphine/naltrexone vs. extended-release morphine						
1; 72	Fair RCT	NA	Direct	Imprecise	No significant differences between treatments on any pain measure.	Low

Abbreviations: NA, not applicable; NS, not significant; RCT, randomized controlled trial; VAS, visual analogue scale.

Table 2: Comparative effectiveness of long-acting and short-acting opioids for pain relief and quality of life

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% CI)**	**High, moderate, low, insufficient**
Long-acting oxycodone vs. short-acting oxycodone						
3; 211	Fair RCTs	Consistent	Direct	Imprecise	Not able to pool data due to heterogeneity among studies No significant differences between treatments for pain control.	Moderate
Long-acting dihydrocodeine vs. immediate-release dihydrocodeine						
2; 147	Fair RCTs	Consistent	Direct	Imprecise	Not able to pool data due to heterogeneity among studies No significant differences between treatments for pain control.	Low
Long-acting codeine plus acetaminophen vs. immediate-release dihydrocodeine plus acetaminophen						
1	Fair RCT	NA	Direct	Imprecise	LA codeine plus acetaminophen together are more effective for pain control than IR codeine plus acetaminophen together, however, these drugs were not given at therapeutically equivalent doses.	Insufficient
Long-acting dihydrocodeine vs. immediate-release dihydrocodeine						
1; 36	Fair RCT	NA	Direct	Imprecise	LA morphine plus IR oxycodone together are more effective for pain control than IR. Oxycodone, however, these drugs were not given at therapeutically equivalent doses.	Insufficient

Abbreviations: IR, immediate release; LA, long acting; NA, not applicable; RCT, randomized controlled trial.

Table 3: Comparative safety of long-acting opioids

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% CI)**	**High, moderate, low, insufficient**
Transdermal fentanyl vs. oral morphine: Constipation						
2; 701 (683 from one trial)	Fair RCTs	Consistent	Direct	Imprecise	31% vs. 48% (*P*<0.001) 29% vs. 48% (P<0.001)	Low
Transdermal fentanyl vs. oral morphine: Withdrawals due to adverse events						
2; 701 (683 from one trial)	Fair RCTs	Inconsistent	Direct	Imprecise	37% vs. 31% (*P*=0.098) 4% vs. 11% (*P* not reported)	Low
Oxymorphone vs. oxycodone						
2; 702	Fair RCTs	Unable to determine	Direct	Imprecise	No significant differences between treatments in occurrence of constipation or sedation. Oxymorphone associated with more nausea, vomiting, and pruritus, but less headache (statistical significance not reported)	Insufficient
Extended-release (once-daily) vs. sustained-release (twice-daily) morphine: Specific adverse events						
2	Fair RCTs	Inconsistent	Direct	Imprecise	One trial found more constipation with extended-release morphine, the other found no difference. No differences in rates of other adverse events	Insufficient
Morphine/naltrexone vs. extended-release morphine						
1; 72	Fair RCT	NA	Direct	Imprecise	No significant differences in specific adverse events or withdrawals due to adverse events	Low

Abbreviations: NA, not applicable; RCT, randomized controlled trial.

Table 4: Comparative safety of long-acting and short-acting opioids

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% CI)**	**High, moderate, low, insufficient**
Long-acting oxycodone vs. short-acting oxycodone: Specific adverse events						
3; 211	Fair RCTs	Consistent	Direct	Imprecise	Not able to pool data due to heterogeneity among studies No trends favoring one formulation over the other for the outcomes of dizziness, somnolence, vomiting, and constipation	Moderate
Other comparisons: Specific adverse events						
4	Fair RCTs	Unable to determine	Direct	Imprecise	Studies did not compare equipotent doses; Quality of methods of adverse event assessment was low	Insufficient

Abbreviations: RCT, randomized controlled trial.