Drug Class Review

Long-Acting Opioid Analgesics

Final Update 5 Report

April 2008

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.

Update 4: April 2006
Update 3: April 2005
Update 2: April 2004
Update 1: September 2003
Original Report: November 2002

The literature on this topic is scanned periodically.

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The medical literature relating to the topic is scanned periodically (see http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for scanning process description). The Drug Effectiveness Review Project governance group elected to proceed with another update of this report based on the information contained in the scan. Please see timeline on the DERP website for details on the date of its release. Prior versions of this report can be accessed at the DERP website.

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Suggested citation:

Roger Chou R, Carson S. Drug class review on long-acting opioid analgesics. 2008. http://www.ohsu.edu/drugeffectiveness/reports/final.cfm

Funding:

The funding source, the Center for Evidence-based Policy, is supported by 17 organizations, including 15 state Medicaid programs. These organizations selected the topic and had input into the Key Questions for this review. The content and conclusions of the review are entirely determined by the Evidence-based Practice Center researchers. The authors of this report have no financial interest in any company that makes or distributes the products reviewed in this report.

INTRODUCTION

Chronic pain, typically defined as pain of at least 3 to 6 months' duration, is a common cause of major disability. An estimated one in five adult Americans, or 30 million people, experience chronic pain.[1] Chronic non-cancer 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 non-cancer 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 non-cancer pain.[7]

The purpose of this report is to determine whether there is evidence that one 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 non-cancer pain. This report was originally commissioned in 2001 and has been updated annually to biennially. The last update of this report (Update #4) was based on searches conducted in September 2005. The current document (Update #5) is based on searches conducted in September 2007.

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 (DERP). The participating organizations of DERP 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:

Key Questions

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 non-cancer pain?

    a. In head-to-head comparisons, have one or more long-acting opioid been shown to be superior to other long-acting opioids in reducing pain and improving functional outcomes when used for treatment of adults with chronic non-cancer pain?

b. In trials comparing long-acting opioids to other types of drugs or to placebo, is there a pattern to suggest that one long-acting opioid is more effective than another?

c. Have long-acting opioids been shown to be superior to short-acting opioids in reducing pain and improving functional outcomes when used for treatment of adults with chronic non-cancer pain?

2. What are the comparative incidence and nature of adverse events (including addiction and abuse) of long-acting opioid medications in adult patients being treated for chronic non-cancer pain?

   a. In head-to-head comparisons, have one or more long-acting opioid been shown to be associated with fewer adverse events compared to other long-acting opioids when used for treatment of adults with chronic non-cancer pain?

   b. In trials comparing long-acting opioids to other types of drugs or to placebo, is there a pattern to suggest that one long-acting opioid is associated with fewer adverse events than another?

   c. Have long-acting opioids been shown to have fewer adverse events than short-acting opioids when used for treatment of adults with chronic non-cancer pain?

3. Are there subpopulations of patients (specifically by race, age, sex, or type of pain) with chronic non-cancer pain for which one long-acting opioid is more effective or associated with fewer adverse events?

Several aspects of the key questions deserve comment:

Population. The population included in this review is adult (18 years old or greater) patients with chronic non-cancer pain. We defined chronic non-cancer pain as continuous or recurring pain of at least 6 months' duration. 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 a day in a trial as "sustained-release" and once a day as "extended-release". "Long-acting" was defined as opioids administered three times a day or less frequently. Included drugs are shown below.

List of included drugs

Active ingredient	Brand name	Recommended usual dosing frequency (times per day)
Oxycodone	Oxycontin	2
Morphine	Avinza	1
Morphine	Kadian	1-2
Morphine	MS-Contin, generic	1-3
Morphine	Oxycontin	2
Methadone	Dolophine, generic	2-3
Fentanyl	Duragesic, generic	Every 72 hours
Levorphanol	Generic	3-4
Codeine	Codeine Contin	2
Dihydrocodeine	DHC Continus	2
Oxymorphone	Opana ER	2

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 different patients' scores, 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 problems in daily living commonly faced 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 one 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" are reported. Many studies do 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 effects).

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 one long-acting opioid against another long-acting opioid ("head-to-head" trials) or a long-acting opioid versus a short-acting opioid provide direct evidence of comparative benefits and harms. Trials that compare a long-acting opioid to 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 one opioid may not carry over to other opioids. If incomplete cross-tolerance occurs, individuals who have been taking one 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 non-cancer 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 Library (2007, Issue 3), MEDLINE (1966-September Week 1, 2007), EMBASE (1980-2001), and reference lists of review articles. In electronic searches, we combined terms for pain with terms for opioid analgesics and narcotics and relevant research designs (see Appendix A for complete search strategy). In addition, a submission protocol was created and disseminated

to pharmaceutical manufacturers for the submission of clinical data to the Center for Evidence-based Policy. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

All English-language titles and abstracts and suggested additional citations were reviewed for inclusion using criteria developed by the research team with input from participating organizations in the Drug Effectiveness Review Project. We obtained full-text articles if the title and abstract review met the following eligibility criteria:

1. Systematic review of the clinical efficacy or adverse event rates of long-acting opioids in patients with chronic non-cancer pain; OR
2. Randomized controlled trial that compared a long-acting opioids to another long-acting opioid, a short-acting opioid, a non-opioid, or placebo in adult patients with chronic non-cancer pain; OR
3. Randomized controlled trial or observational study of adverse events associated with a long-acting opioid.

We then applied these eligibility criteria to the full-text articles, ensuring that the clinical efficacy or adverse event rates from specific opioids were reported or could be calculated. While studies of longer duration were preferred, we had no lower limit on the length of followup, but excluded "single-dose studies," which examine the effects of a single dose of medication rather than a course of treatment.

Data Abstraction

One reviewer abstracted the following data from included trials: Study design, setting, and population characteristics (including sex, age, race, diagnosis); eligibility and exclusion criteria; interventions (dose and duration); comparisons; numbers screened, eligible, enrolled, and lost to followup; method of outcome ascertainment (scales used); and results for each outcome. Equianalgesic doses of opioid medications were estimated using published tables.[19] We recorded intention-to-treat results if they were available and the trial did not report high overall loss to followup. 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.

Quality Assessment

We assessed quality of trials based on the predefined criteria listed in Appendix B. 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 followup, and the use of intention-to-treat analysis. External validity of trials was assessed based on adequate description of the study population, similarity of patients to other populations to whom the intervention would be applied, control group receiving comparable treatment, source of funding, and role of the funder.

Overall quality was assigned based on criteria developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).[12, 13] Trials that had a fatal flaw in one or more categories were rated poor quality. Trials that met all criteria were rated good quality. The remainder was 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 *unlikely* to be valid, while others are *probably* or *likely to be* valid. A poor quality trial is not valid; the results are at least as likely to reflect flaws in the study design rather than true differences between the compared drugs. A particular randomized trial might receive two different ratings, one for efficacy and another for adverse events.

Appendix C shows the criteria we used to rate observational studies of adverse events. These criteria 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 six or more of the seven pre-defined criteria, fair quality if they met three to five criteria, and poor quality if they met two or fewer criteria.

Two reviewers independently assigned quality ratings. Overall quality rating and quality rating scores (for studies on adverse event assessment) were compared between reviewers. Differences were resolved by consensus.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. Poor quality studies would usually be excluded from evidence tables, but we included them to ensure that users of this report become familiar with the studies' limitations.

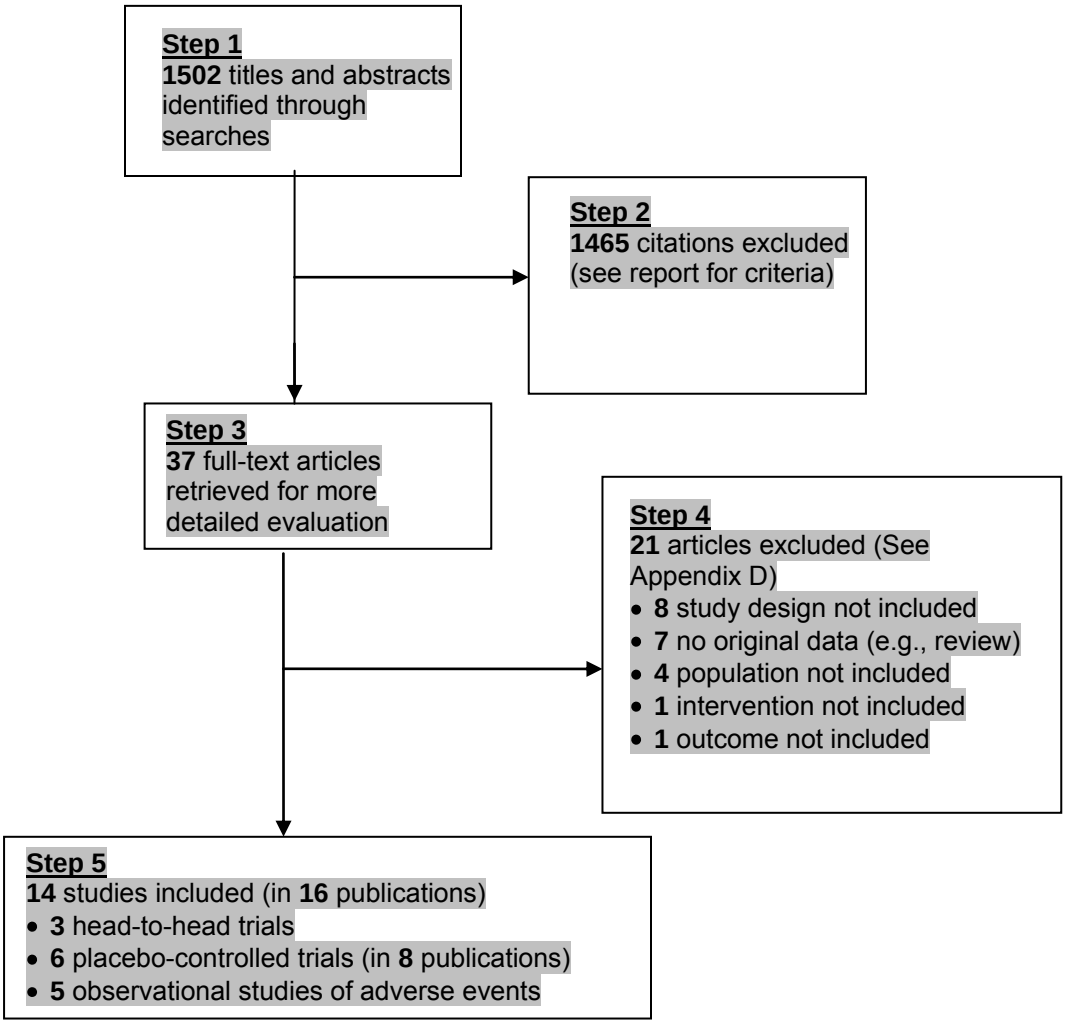
To assess the overall strength of evidence for a body of literature about a particular key question, we examined the consistency of study designs, patient populations, interventions, and results. Consistent results from good quality studies across a broad range of populations would suggest a high degree of certainty that the results of the studies were true (that is, the entire body of evidence would be considered good quality). For a body of fair quality studies, consistent results may indicate that biases in the same direction are operating in all the studies. For a body of poor quality studies, conclusions are likely to be unreliable.

RESULTS

Literature Search Results for Update #5

Through Update #4, a total of 25 randomized trials were included (5 head-to-head trials of long-acting opioids, 13 placebo- or active-controlled trials of long-acting opioids, and 7 trials of long-acting versus a short-acting opioid). Results of literature searches for Update #5 are shown in Figure 1. Searches identified 1502 citations. Full-text citations of 1465 of these were retrieved for further review and 10 studies were included. Excluded studies for Update #5 are listed in Appendix D.

Figure 1. Results of literature search for Update #5



Overview of Included Trials

We identified 34 randomized trials (3608 patients enrolled) that evaluated long-acting opioids for chronic non-cancer pain. Eight trials compared one long-acting opioid to another (Evidence Table 1.1).[20-27] Seven trials compared a long-acting opioid to a short-acting opioid,[28-34] and 22 compared a long-acting opioid to a non-opioid or placebo.[11, 22, 23, 25, 35-51] Ten trials used a crossover design.[21, 30, 31, 35, 36, 38-40, 42, 45] We identified trials of long-acting oxycodone,[11, 23, 29, 31, 34, 42, 45, 51, 52] long-acting morphine,[20-22, 32, 36-40] long-acting dihydrocodeine,[30, 33] long-acting codeine,[28, 35, 41] long-acting oxymorphone,[23, 47-49] transdermal fentanyl,[20, 21, 50] levorphanol,[46] and methadone.[44] No trials of long-acting hydromorphone met inclusion criteria. One trial[53] cited in reference lists[2, 35] 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]

The trials ranged in size from 12[38] to 683[20] evaluable enrollees, with an average of 106 enrollees. Ten of the trials focused on osteoarthritis,[25, 49-52 11, 22, 29, 33, 41] 10 on back pain,[27, 47, 48 20,

[23, 28, 30-32, 34] seven on neuropathic pain,[36, 37, 42-46] one on phantom limb pain,[38], one on chronic pancreatitis pain,[24] and five on heterogenous chronic non-cancer pain.[21, 26, 35, 39, 40]

Nearly all of the trials were of relatively short duration, ranging from 5 days[28] to 24 weeks.[26] The one exception was a head-to-head trial of transdermal fentanyl versus oral long-acting morphine that was 13 months in duration.[20] 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.

Assigned quality ratings for efficacy or for adverse events did not differ between reviewers. Of the fifteen trials addressing adverse event rates for the original report, assigned scores were identical for twelve and differed by one point for three.[30, 33, 39] None of the difference in point scores resulted in reclassification of overall quality rating for adverse event assessment.

We excluded two systematic reviews of the efficacy and safety of long-acting opioids in non-cancer pain.[54, 55] Neither attempted to assess the comparative efficacy of different long-acting opioids or the efficacy of long-acting compared with short-acting opioids. One of the systematic reviews found that six intermediate-term (median 28 days) studies demonstrated superior efficacy of long-acting opioids over placebo for neuropathic pain.[54] Mean post-treatment pain intensity scores were 14 units lower (0 to100 scale) for opioids than for placebo. Nausea, constipation, somnolence, vomiting, and dizziness were common, but adverse events were not life-threatening. The other systematic review found a mean decrease in pain intensity of at least 30% with opioids in most of 11 trials of long-acting opioids for either neuropathic or musculoskeletal pain.[55] About 80% of patients experienced at least one adverse event, with constipation, nausea, and somnolence being most common. There were insufficient data to assess tolerance and addiction.

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 non-cancer pain?

1a. In head-to-head comparisons, has one or more long-acting opioid been shown to be superior to other long-acting opioids in reducing pain and improving functional outcomes when used for treatment of adults with refractory non-cancer pain?

Summary

There is insufficient evidence from eight head-to-head trials to suggest that one long-acting opioid is superior to another in terms of efficacy in adult patients with chronic non-cancer pain. Three trials (two fair quality, one 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 (one fair quality, one poor quality) directly compared extended-release (once daily) morphine to long-acting (twice daily) oxycodone, and one fair quality trial compared extended-release (once daily) versus sustained-release (twice daily) morphine. Six trials found no difference between long-acting opioids. The two trials which found a significant difference (one trial of transdermal fentanyl versus oral long-acting morphine and

one trial of extended-release morphine versus 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 are no trials evaluating the effectiveness of opioid rotation compared to other approaches such as dose escalation of a single opioid in patients with chronic non-cancer pain.

Detailed assessment

Eight trials directly compared the efficacy of one long-acting opioid to another in chronic pain of non-cancer origin (Table 1.1, Evidence Table 1.1).[20-27] Three trials[20, 21, 24] compared transdermal fentanyl to long-acting (sustained-release) morphine twice a day. Another trial[22] compared an extended-release (once-daily) morphine preparation to a sustained-release (twice-daily) morphine preparation. Two trials compared long-acting oxymorphone to long-acting oxycodone, one in patients with low back pain[23] and another in patients with osteoarthritis.[25] Four[21-24] of the five trials were four weeks or less in duration. We excluded a meta-analysis of transdermal fentanyl versus long-acting morphine because it included studies available only as abstracts or from the drug company sponsor and did not provide enough information to judge their quality, and pooled data across randomized trials and observational studies.[56]

The largest (N=680) and longest duration (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 four weeks prior to enrollment.[20] This study was rated fair quality because it was open-label and did not report intention-to-treat results for some of the outcomes (Evidence Table 1.1). 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.

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

The second trial that compared transdermal fentanyl to long-acting morphine twice a day used a crossover design and compared transdermal fentanyl to long-acting morphine in a population of 256 heterogenous chronic pain patients with an average of 9 years' pain duration.[21] This study was rated poor quality because of several major methodological flaws (Evidence Table 1.1). The most important areas of concern were that neither patients nor investigators were blinded, and in addition many of the trial participants were on one 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 versus oral long-acting morphine is also a concern, it may not be 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 compared with 27.4, p=0.004) and mental health (44.4 compared with 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 make 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 addresses whether patients with chronic non-cancer 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 versus long-acting morphine because it enrolled patients not recently using 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 1.1).[24] This study may not be applicable to the general population of patients with chronic non-cancer pain, since it only included a very small number of patients with a fairly uncommon, specific condition.

One randomized, double-blinded trial compared extended-release (once-daily) to sustained-release (twice-daily) morphine in 295 osteoarthritis patients.[22] 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 1.1). 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 1.1) For sleep, one of seven

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 to twice-daily morphine; all other measures of sleep quality were not significantly different between once- and twice-daily morphine. All three 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 followup for each drug regimen was only 4 weeks, and duration of pain and previous narcotic use in evaluated patients was not reported.

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 intention-to treat-analyses.[23, 25] In addition, the external validity of one 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.[23] 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 versus placebo) and used different doses of oxymorphone (80 mg and 40 mg daily compared to 40 mg daily of oxycodone).[25] There were no clear differences in pain, function, or quality of life between long-acting oxymorphone versus 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.[26, 27] One trial, which evaluated various chronic non-cancer pain conditions, was rated fair quality and found no differences between the drugs for pain relief or quality of life after 24 weeks.[26] The second trial (the ACTION trial[27, 57, 58]), which evaluated low back pain patients, was rated poor quality because it was open-label, reported a high withdrawal rate (32.1%) and did not report an intention-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 reflect methodological shortcomings in the trial, rather than true differences between the drugs.

Withdrawal rates in head-to-head trials are shown in Table 1.2. 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.

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.[59] It found that evidence to support the practice of opioid switching was largely anecdotal or based on observational, uncontrolled studies.

1b. In trials comparing long-acting opioids to other types of drugs or to placebo, is there a pattern to suggest that one long-acting opioid is more effective than another?

Summary

No useful indirect evidence for determining the comparative efficacy of long-acting opioids was found in 22 placebo-controlled trials (3 rated good quality[36, 43, 49]). 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. Withdrawal rates, the most uniformly reported outcome, varied greatly for each long-acting opioid and did not suggest that one long-acting opioid is superior to the others. We were unable to perform meta-analysis on any sub-group of trials. The trials were not designed to evaluate rates of abuse or addiction.

Long-acting oxycodone (6 trials[11, 42, 43, 45; 51, 52]), long-acting morphine (5 trials[36-40]), sustained-release oxymorphone (3 trials[47-49]), long-acting codeine (2 trials[35, 41]), transdermal fentanyl (1 trial[50]) were superior to placebo in at least two trials. Methadone was superior to placebo in one trial that evaluated every other day dosing.[44] One trial found higher-dose levorphanol superior to lower-dose levorphanol (used as an active placebo) for neuropathic pain.[46]

Detailed assessment

We identified 22 trials comparing a long-acting opioid to placebo. 18 trials (3 good quality[36, 43, 49] and the remainder fair quality) compared a long-acting opioid to an inert placebo.[11, 22, 23, 25, 35, 37, 38, 40-44, 47-52] One trial[46] compared higher- versus lower-dose levorphanol (lower-dose levorphanol considered an active control), and three 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[39, 45] or lorazepam[36]).

The trials exhibited a high degree of diversity with respect to patient populations and interventions. Chronic non-cancer pain conditions evaluated in the trials included post-herpetic neuralgia,[42], diabetic neuropathy,[43, 45] various neuropathic pain conditions,[36, 44, 46] phantom limb pain,[38] osteoarthritis,[11, 22, 25, 41, 49-52] back pain,[23, 47, 48] and miscellaneous chronic non-cancer pain.[35, 39, 40] Two trials evaluated long-acting codeine,[35, 41] seven long-acting morphine,[22, 32, 36-40] eight long-acting oxycodone,[11, 23, 25, 42, 43, 45, 51, 52] three sustained-release oxymorphone,[23, 25, 47-49] one transdermal fentanyl,[50] one levorphanol,[46] and one methadone.[44] 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[52] to a mean of 155 mg daily.[23] The duration of follow-up ranged from 5 days to 16 weeks.

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 twenty day period, with no intervention or placebo given on alternate days.[44] Although improved pain intensity was seen on days in which methadone 10 mg bid was taken, results of this study can not be compared to other trials and may not be applicable to clinical practice, where daily administration of methadone results in

different steady-state concentrations of the drug and also affects 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 are not comparable to results from trials using true (inert) placebo.[46]

The most common outcomes assessed were pain intensity, rescue drug use, and withdrawals (Table 1.3). There was no clear pattern from placebo-controlled trials favoring one 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[29] or 0-10 scale,[11, 43]) the Pain and Sleep Questionnaire,[45] the Brief Pain Inventory Sleep score,[36] and visual analog scales (1-100) for trouble falling asleep and needing medication to sleep.[41] 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 also did not suggest a pattern favoring one long-acting opioid versus other long-acting opioids (Table 1.2). For long-acting oxycodone, the withdrawal rate ranged from 12%[52] to 50%.[11] For long-acting morphine, the withdrawal rate ranged from 0%[38] to 30%.[39] 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[36, 43] and one in patients with osteoarthritis.[49] One was a short-term (6 weeks) study that found that controlled-release oxycodone (average titrated dose 42 mg/d) 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.[43] A four-arm, multiple crossover trial (each intervention for five weeks) comparing long-acting morphine (average titrated dose 45 mg/d), gabapentin, the combination of long-acting morphine and gabapentin, and low-dose lorazepam (used as an active placebo) for neuropathic pain[36] 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[49] compared extended-release oxymorphone (40 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 to placebo in the oxymorphone 40 or 50 groups, respectively (p=0.012 and 0.006). All other trials were rated fair quality (see Evidence Tables 1.2 and 1.3) and had at least one of the following methodological problems: inadequate or poorly described randomization and allocation concealment, lack of blinding or unclear blinding methods, or high loss to followup. The main results are summarized in Table 1.3.

The trials generally provided inadequate information to accurately assess external validity 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. Numbers excluded for meeting specific exclusion criteria were usually not reported.

Several excluded trials may be of some interest. Three short-term (6 to 15 days) trials of transdermal buprenorphine were excluded because this formulation is not approved in the US.[60-62] Furthermore, they included patients with cancer pain (33% to 77%) and did not report results in patients with non-cancer pain separately. All appeared to be fair quality. One study[60] found that transdermal buprenorphine was associated with a statistically significant increased response (at least satisfactory pain relief and ≤1 sublingual tablet of buprenorphine as rescue medication per day) compared with placebo; one[61] found no statistically significant difference; and the third[62] found that transdermal buprenorphine was associated with slightly reduced use of rescue buprenorphine sublingual tablets, but no differences for pain relief. A meta-analysis of three studies of transdermal buprenorphine that analyzed results separately for patients with non-cancer pain reported overall response rates of 29% with the lowest dose of transdermal buprenorphine (35 μg/h) and 46% with the highest dose (70 μg/h), compared with 23% for placebo.[63] Statistical significance was not reported. Randomized controlled trials of long-acting hydromorphone[64] (now removed from the market) in patients with non-cancer pain have not yet been published in peer-reviewed journals.

1c. Have long-acting opioids been shown to be superior to short-acting opioids in reducing pain and improving functional outcomes when used for treatment of adults with chronic non-cancer pain?

Summary

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 three trials that long- and short-acting oxycodone are equally effective for pain control. No new evidence addressing this key question was identified for Update #5.

Detailed assessment

We identified seven 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 non-cancer origin (Table 1.5). Three studies compared long-acting oxycodone to short-acting oxycodone.[29, 31, 34] One of these studies[31] rerandomized patients who had enrolled in a previous trial.[34] Two studies evaluated long-acting dihydrocodeine,[30, 33] one evaluated long-acting codeine,[28] and one evaluated long-acting morphine.[32] Study designs, patient populations, and outcomes assessed varied between studies (Evidence Table 1.2).

These trials showed no consistent trends demonstrating significant differences in efficacy between long-acting opioids as a class and short-acting opioids (Table 1.5). Three studies that found differences in efficacy favoring long-acting morphine,[32] long-acting dihydrocodeine,[33] and long-acting codeine[28] had features that might invalidate these results. In the trials of long-acting morphine[32] and long-acting codeine,[28] 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,[33] significant differences in pain relief were seen only within the long-acting dihydrocodeine group

when compared to 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 three 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.[29, 31, 34] One of these trials[31] investigated a rerandomized population of patients studied in a previous trial[34] but used a different intervention protocol. These three trials found no significant differences in efficacy (pain relief) between long and short-acting oxycodone. With regard to functional outcomes, one of these trials[29] 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 2. What are the comparative incidence and nature of adverse effects (including addiction and abuse) of long-acting opioid medications in adult patients being treated for chronic non-cancer pain?

A variety of long-acting opioids are used for treatment of chronic non-cancer pain. There continue to be concerns, however, regarding the risk of adverse events.[10] Common adverse events associated with opioid use include nausea, cognitive dysfunction, and constipation. More serious but less common adverse events include respiratory depression, abuse, and addiction. In non-cancer pain patients, data are lacking regarding differential risks for long-acting opioids.[7]

2a. In head-to-head comparisons, has one or more long-acting opioid been shown to be associated with fewer adverse events compared to other long-acting opioids when used for treatment of adults with chronic non-cancer pain?

Summary

There were insufficient data from seven head-to-head trials of long-acting opioids to conclude that any long-acting opioid is associated with fewer harms compared to 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 to oral long-acting morphine.[20, 21] There were no clear or consistent differences in randomized trials comparing long-acting oxycodone and oxymorphone,[25, 47] extended-release morphine and long-acting oxycodone,[26, 27] or extended-release (once-daily) and sustained-release (twice daily) morphine.[22] All head-to-head trials excluded patients at high risk for addiction or abuse and none adequately assessed rates of these complications. No trials evaluate the effectiveness of opioid rotation for management of opioid-induced adverse events in patients with chronic non-cancer pain.

Detailed assessment

As discussed earlier, only eight randomized trials directly compared two long-acting opioids (Table 2.1). One head-to-head trial was a very small (N=18) study of transdermal fentanyl versus twice-daily oral morphine in patients with chronic pancreatitis.[24] 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. Six of the remaining trials compared two different long-acting opioids (transdermal fentanyl versus long-acting oral morphine,[20, 21] long-acting oxymorphone versus long-acting oxycodone,[25, 47] and extended-release morphine versus sustained-release oxycodone[26, 27]) and one[22] compared once- versus twice-daily preparations of oral morphine. All of the trials excluded patients with prior substance abuse. Only one 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.

The largest trial (N=680) compared transdermal fentanyl to long-acting oral morphine in patients with chronic low back pain and was rated fair quality for adverse event assessment, meeting four out of the seven predefined criteria for adverse event assessment (Evidence Table 2.1).[20] 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 intention-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 to 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 one 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% versus 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 2.1).[21] This trial met two out of the seven predefined criteria for adverse event assessment. 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 to 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 versus long-acting oxycodone assessed adverse events (Evidence Table 2.1).[25, 47] The first, which evaluated patients with low back pain, found no significant differences between the two 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 difference in the rate of patients experiencing any adverse event.[25] For specific adverse events, long-acting oxymorphone was associated with more nausea, vomiting, and pruritus compared to long-acting oxycodone, but less headache. However, the statistical significance of the differences was not reported.

Two trials of extended-release morphine versus sustained-release morphine assessed adverse events (Evidence Table 2.1).[26, 27] For constipation, one trial found a higher rate with extended-release morphine,[26] but the other found no difference.[26] There were no clear differences in rates of other adverse events.

The trial that compared once-daily versus twice-daily preparations of oral morphine was also rated poor quality for adverse events (Evidence Table 2.1).[22] This trial met three out of seven predefined criteria for adverse event assessment. 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% compared to 9%). The overall withdrawal rates in patients randomized to any long-acting morphine preparation were 37% to 45%, with withdrawal rates due to adverse events ranging from 23% to 25%.

One meta-analysis[56] was excluded because it included only studies available as abstracts or from the drug company sponsor (2 clinical trials and 2 uncontrolled studies). It found that transdermal fentanyl was associated with a lower risk of any adverse event (87.3% vs. 71.2%, $p<0.001$) and drug-related adverse events (80.7% vs. 62.3%, $p<0.001$) than long-acting morphine, though there were no significant differences for serious adverse events, drug discontinued due to adverse events, and deaths. Constipation (17% vs. 52%), nausea (30% vs. 39%), and somnolence (13% vs. 25%) were all significantly ($p<0.001$) less frequent in patients receiving transdermal fentanyl. The inclusion of uncontrolled and unpublished data severely limits confidence in the validity of these findings.

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

2b. In trials comparing long-acting opioids to other types of drugs or to placebo, is there a pattern to suggest that one long-acting opioid is associated with fewer adverse events than another?

Summary

There is insufficient evidence from 21 placebo-controlled trials to suggest that one long-acting opioid is superior in terms of adverse events than any other in adult patients with chronic non-cancer pain. 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. Rates of abuse and addiction were not reported in the trials. Two fair quality studies based on analyses of administrative databases found long-acting oxycodone[65, 66] associated with higher risk of constipation than transdermal fentanyl. A second fair quality

administrative database study found no differences between methadone, long-acting oxycodone, transdermal fentanyl, or long-acting morphine in risk of constipation, hospitalizations, or overdose symptoms, though transdermal fentanyl was associated with a higher rate of emergency room encounters.[67] Results from these administrative database studies may be susceptible to confounding, given marked differences between groups in a variety of demographic characteristics. Other observational studies of adverse events were of generally poorer quality than the clinical trials and did not provide additional information about comparative adverse event rates. Epidemiologic data show a rise in methadone-associated deaths observed between 1999 and 2002 was proportionate to changes in prescribing patterns. Updated data from the Drug Abuse Warning Network study suggest that during visits to the emergency room, mentions for various opioids have increased but do not report data specifically for long-acting opioids.[68]

Detailed assessment

Randomized Trials. We identified 21 placebo-controlled trials of long-acting opioids that reported adverse events (Evidence Table 2.3).[11, 22, 23, 25, 35-45, 47-52] We excluded one trial of long-acting morphine versus carbamazepine for neuropathic pain[37] was excluded because accurate adverse event rates could not be abstracted from the graphs in the article.

With regard to adverse event assessment, all placebo-controlled trials had at least two important methodological flaws (Table 2.2). 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 to placebo or active placebo (benztropine[39, 45] and lorazepam[36]). In trials that assessed adverse events from different doses of a long-acting opioid,[11, 46] 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).[36] 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/d, for example, rates of nausea ranged from 15%[29] to 50%[34] in five trials (Table 2.2). Withdrawal rates due to adverse events ranged from 4%[31] 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 one long-acting opioid being superior to others for any reported adverse event (Table 2.2).

Observational Studies. We identified 14 cohort studies evaluating the safety of long-acting opioids in patients with non-cancer pain.[11, 22, 35, 65-67, 69-76] None were rated good quality for adverse event assessment (Evidence Table 2.4).

Opioids assessed were long-acting codeine,[35] long-acting morphine,[22, 65, 70, 73, 76] transdermal fentanyl,[65, 66, 69, 72, 74, 75] methadone,[70, 71] and long-acting oxycodone.[11, 65, 66] Two studies evaluated the comparative risk of constipation from different long-acting opioids;[65, 66] 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.[66] Eight were prospective cohort studies[11, 22, 35, 69, 72, 74-76] and five were retrospective cohorts.[65, 66, 70, 71, 73] The prospective cohort studies recruited all[11, 22, 35, 69] or some[72] of their patients from completed

clinical trials. Three of the prospective cohorts[11, 22, 35] 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 1.33-4.89[66] and 1.78, 95% CI 1.05-3.03[65]) after adjusting for patient demographics, co-morbidities, 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 0.80-2.60).[65] 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 suggest 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 is 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 makes it impossible to assess the overall balance of adverse events. This is important because two 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.[20, 21] A third retrospective study of Oregon Medicaid patients found no difference between methadone, long-acting oxycodone, long-acting morphine, and transdermal fentanyl in rates of hospitalizations, mortality, overdose symptoms, or constipation, though transdermal fentanyl was associated with a higher rate of emergency room encounters compared to sustained-release oral morphine (p=2.37, 95% CI 1.02 to 1.59).[67] However, this study was also characterized by the presence of numerous statistically significant differences in baseline characteristics, and many of the assessed outcomes were non-specific for opioid-related events.

Some observational studies reported long-term outcomes and serious adverse events not reported in the trials. The largest (N=530) study[72] reported one death (0.2%, 1/530) thought related to medication, four cases of respiratory depression (1%), and three 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, 22, 35, 69] Rates ranged from 19% for transdermal fentanyl[69] to 54% for long-acting codeine.[35] 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 three Medicaid-based studies,[65-67] 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, 22, 35, 69, 72] resulting in an even more highly selected population than the original trials. In three 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]

Several other observational studies reported serious adverse events from long-acting opioids. A case series of 96 deaths in Hennepin County, Minnesota from 1992 to 2002 in which

methadone was detected found that 15% were chronic pain patients, and about half of this group died from overdose.[77] No information on the numbers of prescriptions for methadone in the county, number of patients prescribed methadone, or on presence of other long-acting opioids was reported. A small (N=17) case series reported episodes of torsades de pointes associated with very high doses of methadone (mean about 400 mg/d).[78] About half of the cases occurred in patients being treated for chronic pain. A more recent case series of 104 methadone-treated patients on lower doses (median 110 mg/d) found that 32% had QTc prolongation, but none had prolongation beyond the value (500 msec) considered a definite risk for torsades de pointes.[79]

The ongoing Drug Abuse Warning Network study reports mentions of drug-related visits for various prescription and non-prescription opioids in emergency departments across the US.[80] Because this study does not report the underlying clinical condition of patients, however, and does not distinguish between long- and short-acting opioids or different modes of administration (intravenous, oral and other), it is not possible to evaluate comparative risk of long-acting opioids in patients with chronic non-cancer pain from these data. Furthermore, in order to assess the comparative risk of various long-acting opioids, it is necessary to utilize some estimate of the rate of overall use (for example, the number of prescriptions or amount dispensed).[1] The most recent (from 1997 through 2002) analysis of the Drug Abuse Warning Network study found that rates of mentions for any fentanyl compound increased by 641% (though the absolute rate of fentanyl mentions remained very low), any morphine compound by 113%, and any oxycodone compound by 347%, while prescribing (as measured by the Automation of Reports and Consolidated Orders System database) increased by 214%, 66%, and 383%, respectively.[68] The Drug Abuse Warning Network methods have recently undergone substantial revision.[81] Data on emergency room mentions associated with different opioid medications using the new methodology will not be directly comparable to the older Drug Abuse Warning Network data when they become available.

Results published by the Office of Communicable Disease and Epidemiology on deaths associated with methadone in the state of Oregon from 1999 through 2002 indicate that although the number of methadone deaths increased from 23 in 1999 to 103 in 2002, the number of deaths appeared roughly proportionate to the increase in methadone distribution (5-fold increase in grams per 100,000 persons between 1997 and 2001).[82] Approximately 28% of the deaths occurred in patients being treated for chronic pain.

The Substance Abuse and Mental Health Services Administration (SAMHSA) issued a report on methadone-associated mortality in 2004.[83] It concluded that observed increases in methadone-associated mortality in several states since the late 1990's appeared largely related to increased accessibility of methadone obtained outside of licensed opioid treatment programs. Methadone-associated deaths were usually associated with other central nervous system depressant agents (such as benzodiazepines, alcohol, and other opioids). The report did not compare mortality rates for different long-acting opioids.

A report from the federal General Accounting Office investigated factors that may have contributed to long-acting oxycodone abuse and diversion.[84] It did not provide information about rates of abuse or assess rates of abuse and diversion of long-acting oxycodone compared to other long-acting opioids. It noted that the Food and Drug Administration changed the black box warning on long-acting oxycodone in 2001 to state that it has an abuse potential comparable to morphine.

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 are variable and somewhat unpredictable.[85]

Additional observational studies identified for Update #5 were non-comparative and therefore did not provide useful data on relative harms of different long-acting opioids.[86-89]

2c. Have long-acting opioids been shown to be have fewer adverse events than short-acting opioids when used for treatment of adults with chronic non-cancer pain?

Summary

There is 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. No new evidence for this key question was added this update.

Detailed assessment

Study characteristics of the seven randomized trials directly comparing long-acting opioids with short-acting opioids have already been reviewed in this report and are summarized in Evidence Table 1.2.[28-34] None of the studies were designed to assess rates of addiction or abuse.

In the single trial in this group rated fair quality,[32] adverse events were not prespecified or defined and patients and investigators were not blinded. Furthermore, patients in one arm of this trial received higher doses of opioids than in the other. Adverse events would be expected to be more common in the group receiving higher doses, as observed for most reported adverse events (Table 2.2).

Across all trials, no pattern favoring either long-acting or short-acting opioids was evident for any of the reported adverse events (Table 2.2). In the three most comparable studies, which investigated roughly equivalent daily doses of oxycodone in short-acting and long-acting preparations,[29, 31, 34] no trends favoring one formulation over the other were seen for the outcomes of dizziness, somnolence, vomiting, and constipation. This was also true in the two studies[31, 34] that investigated the same (re-randomized) population.

Withdrawals due to adverse events were reported in five trials (Table 2.2). Three favored short-acting opioids,[28, 33, 34] one favored long-acting,[29] and one was equivocal.[31] These data are limited by the poor quality of the trials for adverse event assessment and the fact that two of the trials evaluated the same (re-randomized) population.

Key Question 3. Are there subpopulations of patients (specifically by race, age, sex, or type of pain) with chronic non-cancer pain for which one long-acting opioid is more effective of associated with fewer adverse effects?

Summary

The evidence regarding differential efficacy or adverse event risk from long-acting opioids in subpopulations of patients with non-cancer pain is severely limited in quantity and

quality. There is almost no information regarding the comparative efficacy of long-acting opioids for specific subpopulations as characterized by race, gender, or age. 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.[66] For specific types of chronic non-cancer pain, the trials are limited by problems with internal validity, external validity, heterogeneity, and small numbers of trials for each subpopulation. It is not possible to draw reliable conclusions regarding comparative efficacy or adverse event rates for any subpopulation from these data.

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; 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 one study[42] evaluated patients with an average age of 70 years. Two trials[11, 29] performed very limited subgroup analysis on older patients. Neither trial directly compared one long-acting opioid to another; they provide 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 to transdermal fentanyl was higher in patients older than 65 years (adjusted odds ratio 7.33, 95% CI 1.98-27.13) than in all patients included in the study (adjusted odds ratio 2.55, 95% CI 1.33-4.89).[66] Because there is a high likelihood for unmeasured or unknown confounders, firm conclusions from this subgroup analysis are not possible.

Several specific types of chronic non-cancer pain patients were studied in some of the reviewed trials. These categories included back pain,[20, 23, 28, 30-32, 34] osteoarthritis, [11, 29, 33, 41] phantom limb pain,[38] and neuropathic pain.[36, 37, 42-46] Only two trials were rated good quality for assessment of clinical efficacy;[36, 43] all were rated and poor or fair quality for adverse event assessment (trial quality reviewed in previous sections of this report). Subgroups of trials for specific types of pain have the same problems with heterogeneity in interventions, outcomes assessed, and findings that were encountered in examining general efficacy and adverse events. They are further limited by the smaller number of available trials for each type of pain. These trials provide insufficient indirect evidence that one long-acting opioid is superior to any other in any subpopulation of patients with chronic pain.

SUMMARY

Results for each of the key questions are summarized in Table 3. It is important to note that only one clinical trial of methadone[44] and one trial of levorphanol[46] in adult patients with chronic non-cancer pain are available. Both of these trials used designs (methadone compared with placebo randomly administered only every other day and high strength levorphanol compared with low strength levorphanol) that made it difficult to compare their results with trials of other long-acting opioids. Two or more clinical trials have been published for transdermal fentanyl and long-acting oral oxycodone, morphine, codeine, and dihydrocodeine. In general,

long-term data on effectiveness or safety of long-acting opioids in patients with chronic non-cancer pain are lacking, with only one trial[20] longer than 6 months in duration.

In general, there was insufficient evidence to prove that one long-acting opioid is more effective or associated with fewer harms than another. Among eight higher quality trials, only two[21, 27] found one long-acting opioid superior to another, but both were characterized by a number of methodological shortcomings (including open-label design in both trials) and were rated poor quality. The other six head-to-head trials found no clear differences between long-acting opioids.[20, 22-26] A shortcoming of the currently available evidence is that comparisons between specific long-acting opioids have been evaluated in only one to three trials each (some 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. Two fair quality retrospective cohort studies found a higher risk of constipation with long-acting oxycodone compared to transdermal fentanyl, but concerns about unmeasured or residual confounding and a narrow focus on constipation (without considering other adverse events) limit interpretation of these findings.[65, 66] The comparative efficacy and overall balance of adverse events associated with different long-acting opioids in adult patients with chronic non-cancer pain remains uncertain.

There was also insufficient evidence to determine whether long-acting opioids as a class are more effective or associated with fewer adverse events than short-acting opioids. A subgroup of three studies investigating long-acting oxycodone versus short-acting oxycodone[29, 31, 34] was more homogeneous and provided fair evidence that long-acting and short-acting oxycodone are equally effective for pain control. It is not clear whether media attention and case reports of abuse and addiction from long-acting opioids represent a true increased risk or are proportionate to prescribing pattern changes.[1] There also may be other reasons (such as convenience, improved compliance, or more consistent pain relief) for prescribing long-acting opioids, but these outcomes were not assessed in the reviewed trials.

Opioid rotation has been proposed as a strategy to improve the balance between analgesia and side effects, but no clinical trials of opioid rotation in patients with non-cancer pain are available, and supporting evidence primarily consists of anecdotal data and uncontrolled observational studies.

Essentially no good quality data are available to assess comparative efficacy and adverse event risks in subpopulations of patients with chronic non-cancer pain.

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Table 1.1. Main results of head-to-head trials of long-acting opioids for chronic non-cancer pain

Author Year (Quality)	Long acting opioids (average dose/day)	Pain type	Duration	N	Pain intensity score	Scale	Main results
Allan, 2005 (FAIR)	A: Transdermal fentanyl 57 mcg/hr B: Oral morphine 140 mg (twice daily)	Low back pain	13 months	683	Not reported	0-100 VAS	No significant differences in intention-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 (POOR)	A: Transdermal fentanyl 57 mcg/hr B: Oral morphine 133 mg (twice daily)	Miscellaneous	4 weeks	212	A: 57.8 B: 62.9	0-100 VAS	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 (FAIR)	A: Transdermal fentanyl 56 mcg/hr B: Oral morphine 128 mg (twice daily)	Chronic pancreatitis	4 weeks	18	Not calculable	5 point Cat.	No significant differences between treatments for preference or global pain control using unspecified methods, or quality of life using SF-36.
Hale, 2005 (FAIR)	A: Oxymorphone 79 mg (twice daily) B: Oxycodone 155 mg (twice daily) C: Placebo	Low back pain	18 days	235	Not reported	0-100 VAS	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 (FAIR)	A: Oxymorphone 40 mg (twice daily) B: Oxymorphone 20 mg (twice daily) C: Oxycodone 20 mg (twice daily) D: Placebo	Osteoarthritis	4 weeks	467	Not reported	0-100 VAS	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.

Author Year (Quality)	Long acting opioids (average dose/day)	Pain type	Duration	N	Pain intensity score	Scale	Main results
Rauck (POOR)	A: Morphine 64 mg (once daily) B: Oxycodone 53 mg (twice daily)	Low back pain	8 weeks	392	A. 6.5 B: 6.6	0-10 VAS	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 BPI: 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: 2,595 vs. 3,154 doses (p<0.0001) 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 (FAIR)	A: Morphine 79 mg/day (twice daily B: Oxycodone 85 (three times daily)	Miscellaneous, non-neuropathic	24 weeks	112	Not reported	0-10 VAS	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 (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	4 weeks	295	A: 313 B: 326 C: 322 D: 317	0-500 WOMAC	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).

Table 1.2. Withdrawal rates in head-to-head trials of long-acting opioids for chronic non-cancer pain

Author Year	Long acting opioid	Duration	Sample size	Overall withdrawal rates	Pre-randomization titration withdrawal	Withdrawal rates per drug	Withdrawal due to inadequate pain control	Withdrawal due to adverse events	Withdrawal for other reasons
Allan, 2005[39]	A: Transdermal fentanyl B: Oral morphine (twice daily)	13 months	683	49%	N/A	A: 52% (177/338) B: 47% (162/342)	18 15	125 104	34 43
Allan, 2001[52]	A: Transdermal fentanyl B: Morphine (twice daily)	4 weeks	212	23%	N/A	A: 16% (39/250) B: 9% (21/238)	N/A	27 10	N/A
Hale, 2005[38]	A: Oral oxymorphine (twice daily) B: Oral oxycodone (twice daily) C: Placebo	18 days	235	41%	A: 32% (53/166), 25 for adverse events B: 26% (42/164), 26 for adverse events	A: 28% (22/80) B: 26% (21/80) C: 71% (53/75)	16 13 44	2 4 5	4 4 4
Matsumoto	A: Oxymorphone 40 mg (twice daily) B: Oxymorphone 20 mg (twice daily) C: Oxycodone 20 mg (twice daily) D: Placebo	4 weeks	467	45%	N/A	A: 56% (68/121) B: 48% (58/121) C: 40% (50/125) D: 37% (46/124)	9 5 13 34	57 46 31 6	2 7 6 6

Author Year	Long acting opioid	Duration	Sample size	Overall withdrawal rates	Pre-randomization titration withdrawal	Withdrawal rates per drug	Withdrawal due to inadequate pain control	Withdrawal due to adverse events	Withdrawal for other reasons
Rauck	A: Morphine 64 mg (once daily) B: Oxycodone 53 mg (twice daily)	8 weeks	392	44%		A: 46% (93/203) B: 42% (79/189)	NR	38 27	NR
Nicholson	A: Morphine 79 mg/day (twice daily B: Oxycodone 85 (three times daily)	24 weeks	112	54%		A: 57% (30/53) B: 51% (30/59)		15 13	
Caldwell, 2002[53]	A: Morphine (once daily a.m.) B: Morphine (once daily p.m.) C: Morphine (twice daily) D: Placebo	4 weeks	295	38%	N/A	A: 37% (27/73) B: 45% (33/73) C: 37% (28/76) D: 32% (23/72)	9 12 8 14	17 18 18 5	1 3 2 4
Niemann, 2000[21]	A: Transdermal fentanyl B: Oral morphine (twice daily)	4 weeks	18	6%	N/A	A: 6% (1/18) B: 0% (0/18)	Not clear	Not clear	N/A

Table 1.3. Main results in placebo-controlled trials of long-acting opioids

Author Year (Quality)	Pain type	Duration	N	Mean daily dose	Pain scale	Main outcomes
Long-acting oxycodone						
Caldwell 1999 (FAIR)	Osteoarthritis	30 days	167	40 mg	1.3 0-4 Cat.	Long-acting oxycodone superior to placebo for pain control and improvement of sleep.
Gimbel, 2003 (GOOD)	Diabetic neuropathy	6 weeks	159	42 mg	0-10 Cat.	Long-acting oxycodone superior to placebo for pain intensity, pain right now, and worst pain using 0-10 numeric analog scale, satisfaction using 1-6 categorical scale, sleep quality using 0-10 scale, brief pain inventory for 9 of 14 subscales. No significant differences for SF-36, Rand Mental Health Inventory, and only 1 of 16 Sickness Impact Profile subscales.
Hale, 2005 (FAIR)	Back pain	18 days	155	Mean 155 mg	0-100 VAS 0-5 Cat.	Long-acting oxycodone superior to placebo 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, and global assessment using 5 point categorical scale.
Markenson, 2005 (FAIR)	Osteoarthritis	90 days	109	44 mg	0-10 Brief Pain Inventory and 0-100 WOMAC	Long-acting oxycodone superior to placebo for pain relief using the WOMAC Pain scale and for function using the WOMAC Physical Function and Brief Pain Inventory scales.
Matsumoto, 2005 (FAIR)	Osteoarthritis	4 weeks	249	40 mg	0-100 VAS	Long-acting oxycodone superior to placebo at 4 weeks for measures for pain (0-100 VAS), physical function (WOMAC), and quality of life.
Roth, 2000 (FAIR)	Osteoarthritis	2 weeks	133	40 mg	0-3 Cat.	Long-acting oxycodone superior to placebo for mean pain intensity using 0-3 categorical scale; quality of sleep using 1-5 categorical scale, brief pain inventory results (6 domains, each assessed using 0-10 VAS)
Watson, 2003 (FAIR)	Diabetic polyneuropathy	4 weeks	45	40 mg	0-100 VAS 0-4 Cat.	Long-acting oxycodone superior to benztropine(active placebo) for mean pain intensity using 0-100 VAS and 0-4 categorical scale; pain relief using 0-5 categorical scale, pain and disability suing Pain Disability Index, and patient preference
Watson, 1998 (FAIR)	Postherpic neuralgia	4 weeks	50	45 mg	0-100 VAS 0-4 Cat.	Long-acting oxycodone superior to placebo for main daily pain intensity using 0-100 VAS and 0-4 categorical scale; pain relief using 0-6 categorical scale; steady pain, paroxysmal pain, allodynia using 0-100 VAS and 0-6 categorical scales; disability and treatment effectiveness using 0-3 categorical scales, and patient preference.
Zautra (FAIR)	Osteoarthritis	2 weeks	107	20 mg	0-10 Cat.	Long-acting oxycodone superior to placebo for pain using 0-10 categorical scale, alson on measures of coping and helplessness.

Author Year (Quality)	Pain type	Duration	N	Mean daily dose	Pain scale	Main outcomes
Long-acting oxymorphone						
Hale 2007 (FAIR)	Back pain	12 weeks	143	87 mg	0-100 VAS	Long-acting oxymorphone superior to placebo for pain intensity using a 0 to 100 VAS and patient global rating using a categorical scale.
Hale, 2005	Back pain	18 days	155	Mean 79 mg	0-100 VAS 0-5 Cat.	Long-acting oxymorphone superior to placebo 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, and global assessment using 5 point categorical scale.
Katz 2007 (FAIR)	Back pain	12 weeks	205	40 mg	0-100 VAS	Long-acting oxymorphone superior to placebo for pain intensity using 0 to 100 VAS, patient global rating using a categorical scale.
Kivitz 2006 (GOOD)	Osteoarthritis	2 weeks	370	Fixed dose 10 mg, 40 mg, 50 mg	0-100 VAS	Long-acting oxymorphone superor to placebo for pain using 0-100 VAS, function using the WOMAC Physical Function score and SF-36 Physical Component Summary, and sleep using the Chronic Pain Sleep Inventory
Matsumoto, 2005 (FAIR)	Osteoarthritis	4 weeks	364	40 mg and 80 mg	0-100 VAS	Long-acting oxymorphone at either 40 mg or 80 mg daily superior to placebo at 4 weeks for measures for pain (0-100 VAS), physical function (WOMAC), and quality of life.
Transdermal fentanyl						
Langford 2006 (FAIR)	Osteoarthritis	6 weeks	416	Median 1.7 patches/ day at 25 mcg/ h	0-100 VAS WOMAC Pain score	Transdermal fentanyl superior to placebo for pain using 0-100 VAS, WOMAC pain score (0 to 10), and SF-36 Pain Index and for function using the WOMAC Physical Functioning score and SF-36 Physical component.
Long-acting codeine						
Arkinstall, 1995 (FAIR)	Miscellaneous	7 days	46	353 mg	0-100 VAS	Long-acting codeine superior to placebo for pain intensity using 0-100 VAS, disability index using 0-70 VAS, rescue drug use, and patient preference.
Peloso, 2000 (FAIR)	Osteoarthritis	4 weeks	103	159 mg	0-100 VAS	Long-acting codeine superior to placebo for daily pain intensity using 0-500 VAS; weekly pain intensity, pain over last 24 hours, stiffness, trouble falling asleep, need medication to sleep, and pain on awakening using 0-100 VAS; physical function using 1-1700 VAS, and rescue drug use.
Levorphanol						
Rowbotham, 2003 (FAIR)	Neuropathic pain	4 weeks	81	9 mg	0-100 VAS	High-dose levorphanol superior to low-dose levorphanol (comparator) for pain intensity using 0-100 VAS; no differences for pain relief using 0-5 categorical scale, mood disturbance/cognitive impairment using

Author Year (Quality)	Pain type	Duration	N	Mean daily dose	Pain scale	Main outcomes
						Profile of Mood States or Symbol-Digit Modalities Test, or quality of life using Multidimensional Pain Inventory
Methadone						
Morley, 2003 (FAIR)	Neuropathic pain	2 phases of 20 days each	19	10 mg	0-100 VAS	Trend towards methadone 5 mg bid superior to placebo for pain intensity using 0-100 VAS; methadone 10 mg bid superior to placebo for pain intensity using 0-100 VAS
Long-acting morphine						
Caldwell, 2002 (FAIR)	Osteoarthritis	4 weeks	295	30 mg	0-4 Cat.	Extended-release (once daily) and sustained-release (twice-daily) morphine superior to placebo for pain relief using the WOMAC Pain scale and on some sleep measures.
Gilron, 2005 (GOOD)	Neuropathic pain	5 weeks	57	45 mg	0-10 VAS	Long-acting morphine superior to placebo for pain intensity using 0-10 VAS, some measures of McGill Pain Questionnaire (sensory, total, present pain intensity), some measures on Brief Pain Inventoy (general activity, mood, normal work, sleep, enjoyment of life), some measures of SF-36 (role-physical, bodily pain, mental health), and mood using Mood Depression Inventory. Combination of morphine and gabapentin superior to morphine alone for pain intensity, and some measures (Sensory, Affective, 10-cm VAS) on McGill Pain Questionnaire.
Harke, 2001 (FAIR)	Neuropathic pain	8 days	38	83 mg	0-10 VAS	Methods used to report results (stratified by responders, partial responders, and nonresponders) makes interpretation of results difficult. Total of 14 partial responders or responders on long-acting morphine versus 11 on placebo (p not reported). Pain intensity assessed using 0-10 VAS and time to spinal cord stimulation reactivation also recorded.
Huse, 2001 (FAIR)	Phantom limb pain	4 weeks	12	115 mg	0-10 VAS	Long-acting morphine superior to benztropine (active placebo) for mean pain intensity using 0-10 VAS; no significant differences for main pain rating index using 0-100 VAS, mean pain relief using 0-10 VAS, functional status using unspecified scale, and mean daily rescue drug use.
Maier, 2002 (FAIR)	Various pain conditions	1 week	49	100 mg	0-10 scale	Long-acting morphine superior to placebo for successful response (greater than 50% reduction in pain or pain intensity <5 on 0-10 scale, tolerability of pain 3 or lower on 0 to 6 scale, and tolerable adverse effects)
Moulin, 1996 (FAIR)	Miscellaneous	6 weeks	61	83.4 mg	0-100 VAS	Long-acting morphine superior to benztropine (active placebo) for mean pain intensity using 0-10 VAS; no significant differences for main pain rating index using 0-100 VAS, mean pain relief using 0-10 VAS,

Author Year (Quality)	Pain type	Duration	N	Mean daily dose	Pain scale	Main outcomes
						functional status using unspecified scale, and mean daily rescue drug use.

Table 1.4. Withdrawal rates in placebo-controlled trials of long-acting opioids

Author Year	Duration	Sample size	Overall withdrawal rates	Pre-randomization titration withdrawal	Withdrawal rates per drug	Withdrawal due to inadequate pain control	Withdrawal due to adverse events	Other
Long-acting oxycodone								
Caldwell, 1999	4 weeks	107	34%	22% (36/176) Adv. Ef 10% (17/167) Ineff. Tx 4% (7/167) Other	LA Oxycodone: 21% (7/34) IR Oxycodone: 30% (11/37) Placebo: 50% (18/36)	3 4 13	3 5 3	1 2 2
Gimbel, 2003	6 weeks	159	28%	Not reported	Overall: 28% (44/159) By intervention, not clear	1 11	7 4	12 12
Hale, 2005	18 days	235	41%	26% (42/164) 26 for adverse events	LA Oxycodone: 26% (21/80) Placebo: 71% (53/75)	13 44	4 5	4 4
Markenson, 2005	90 days	109	66%	N/A	LA Oxycodone: 59% (33/56) Placebo: 75% (38/51)	9 34	20 2	4 2
Matsumoto	4 weeks	467	45%	N/A	LA Oxycodone: 40% (50/125) Placebo: 37% (46/124)	13 34	31 6	6 6
Roth, 2000	2 weeks	133	53%	N/A	LA Oxycodone 20mg: 42% (19/44) LA Oxycodone 10mg: 50% (24/44) Placebo: 60% (27/45)	5 12 22	14 12 2	0 0 3
Watson, 2003	4 weeks	45	20%	N/A	LA Oxycodone: 22% (10/45) Placebo: 24% (11/45)	1 7	7 1	2 3

Author Year	Duration	Sample size	Overall withdrawal rates	Pre-randomization titration withdrawal	Withdrawal rates per drug	Withdrawal due to inadequate pain control	Withdrawal due to adverse events	Other
Watson, 1998	4 weeks	50	22%	N/A	LA Oxycodone: 12% (6/50)	0	5	1
					Placebo: 10% (5/50)	1	3	1
Zautra	2 weeks	107	66%	N/A	LA Oxycodone: 59% (33/56)	9	20	4
					Placebo: 75% (38/51)	34	2	2
Long-acting oxymorphone								
Hale 2005	18 days	235	41%	32% (53/166) 25 for AEs	LA Oxycodone: 28% (22/80)	16	2	4
					Placebo: 71% (53/75)	44	5	4
Hale 2007	12 weeks	143	51%	40% (101/251) 47 for AEs	LA Oxymorphone: 29% (20/70)	8	7	5
					Placebo: 73% (53/73)	39	8	6
Katz 2007	12 weeks	205	42%	37% (120/326) 59 for AEs	LA Oxymorphone:: 32% (34/105)	12	9	13
					Placebo: 53% (53/100)	35	8	10
Kivitz 2006	2 weeks	370	46%	N/A	LA Oxymorphone: 52% (146/279)	16	122	8
					Placebo: 29% (26/91)	15	9	2
Matsumoto	4 weeks	467	45%	N/A	LA Oxymorphone: 40 mg: 56% (68/121)	9	57	2
					20 mg: 48% (58/121)	5	46	7
					Placebo: 37% (46/124)	34	6	6

Author Year	Duration	Sample size	Overall withdrawal rates	Pre-randomization titration withdrawal	Withdrawal rates per drug	Withdrawal due to inadequate pain control	Withdrawal due to adverse events	Other
Transdermal fentanyl								
Langford 2006	6 weeks	416	51%		Transdermal Fentanyl: 48% (96/202) Placebo: 53% (104/197)	15 64	54 20	27 20
Codeine								
Arkinstall, 1995	7 days	46	28%	N/A	Codeine: 19% (9/46) Placebo: 9% (4/46)	1 0	7 1	1 3
Peloso, 2000	4 weeks	103	36%	N/A	40% (20/51) Codeine 33% (17/52) Placebo	1 5	15 5	1 0
Levorphanol								
Rowbotham, 2003	4 weeks	81	27%	N/A	Not reported by drug; 31% (25/81) overall	3 overall	15 (high-dose) 3 (low-dose)	4 overall
Methadone								
Morley, 2003	Two phases of 20 days each	Phase I: 19 Phase II: 17	Phase I: 5% Phase II: 35%	N/A	Phase I: Methadone 5 mg bid: 5% (1/19) Placebo: 0% (0/19) Phase II: Methadone 10 mg bid: 18% (3/17) Placebo: 18% (3/17)	NR	Phase I: 1 0 Phase II: 3 3	NR

Author Year	Duration	Sample size	Overall withdrawal rates	Pre-randomization titration withdrawal	Withdrawal rates per drug	Withdrawal due to inadequate pain control	Withdrawal due to adverse events	Other
Morphine								
Caldwell 2002	4 weeks	295	38%	N/A	Morphine OD am: 37% (27/73) Morphine OD pm: 45% (33/73) Morphine BID: 37% (28/76) Placebo: 32% (23/72)	9 12 8 14	17 18 18 5	1 3 2 4
Gilron, 2005	5 weeks	57	19%	N/A	Morphine: 25% (4/16) Gabapentin: 23$ (3/13) Morphine + gabapentin: 29% (4/14) Placebo: 0% (0/14)	NR	NR	NR
Harke, 2001	8 days	38	8%	N/A	Morphine: 5% (1/19) Placebo: 11% (2/19)	NR	NR	1 2
Huse, 2001	4 weeks	12	0%	N/A	Morphine: 0% (0/12) Placebo: 0% (0/12)	NR	N/A	N/A
Maier, 2002	1 week	49	6%	N/A	Morphine: 12% (3/25) Placebo: 0% (0/23)	None reported	3 0	NR
Moulin, 1996	6 weeks	61	30%	Morphine: 48% (15/31) Benztropine: 13% (4/30)	3 (group not specified)	NR	NR	NR

Table 1.5. Main results of trials of long-acting opioid versus short-acting opioid

Author Year	Pain type	Duration	Patients	Findings
Oxycodone				
Caldwell 1999 (FAIR)	Osteoarthritis	30 days	107	LA Oxycodone and IR Oxycodone plus Tylenol are equally effective for pain control and improvement of sleep.
Hale 1999 (FAIR)	Back pain	6 days	47	LA Oxycodone and IR Oxycodone are equally effective for pain control.
Salzman 1999 (FAIR)	Back pain	10 days	57	LA Oxycodone and IR Oxycodone are equally effective when titrated for pain control.
Codeine				
Hale 1997 (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 (FAIR)	Osteoarthritis	2 weeks	86	LA Dihydrocodeine and IR Dihydrocodeine are equally effective for pain control when compared directly.
Morphine				
Jamison 1998 (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.

Table 2.1. Adverse events in head-to-head trials of long-acting opioids

Study	Interventions	Quality rating (# of criteria met)	Nausea	Vomiting	Constipation	Drowsiness or somnolence	Dizziness	Confusion or difficulty concentrating	Withdrawal due to AE
Allan, 2005	A: Transdermal fentanyl B: Long-acting morphine	Fair (4)	A: 54% (176/338) B: 50% (169/338)	A: 29% (97/338) B: 26% (89/338)	A: 52% (176/338) B: 65% (220/338)	A: 27% (92/338) B: 30% (102/338)	A: 25% (85/338) B: 24% (81/338)	Not reported	A: 37% (125/335) B: 31% (104/337)
Allan, 2001	A: Transdermal fentanyl B: Long-acting morphine	Poor (2)	A: 26% (64/250) B: 18% (44/238)	A: 10% (25/250) B: 10% (24/238)	A: 16% (41/250) B: 22% (52/238)	A: 18% (45/250) B: 14% (34/238)	A: 11% (28/250) B: 4% (9/238)	Not reported	A: 11% (27/250) B: 4% (10/238)
Caldwell, 2002	A: Once-daily morphine a.m. B: Once-daily morphine p.m. C: Twice-daily morphine D: Placebo	Poor (3)	A: 21% (15/73) B: 32% (23/73) C: 26% (20/76) D: 10% (7/73)	A: 6% (4/73) B: 16% (12/73) C: 8% (6/76) D: 1% (1/73)	A: 49% (36/73) B: 40% (29/73) C: 29% (22/76) D: 4% (3/73)	A: 16% (12/73) B: 12% (9/73) C: 12% (9/76) D: 0%	A: 10% (10/73) B: 10% (10/73) C: 12% (9/76) D: 1% (1/73)	Not reported	A: 23% (17/73) B: 25% (18/73) C: 24% (18/76) D: 7% (5/73)
Hale, 2005	A: Long-acting oxymorphone B: Long-acting oxycodone C: Placebo	Poor (3)	NR	NR	A: 35% (39/110) B: 29% (32/111) C: 11% (12/108)	A: 17% (19/110) B: 20% (22/111) C: 2% (1/108)	NR	NR	A: 15% (25/166) titration, 2.5% (2/80) treatment B: 16% (26/164) titration, 5.0% (4/80) treatment C: 6.7% (5/75) treatment

Study	Interventions	Quality rating (# of criteria met)	Nausea	Vomiting	Constipation	Drowsiness or somnolence	Dizziness	Confusion or difficulty concentrating	Withdrawal due to AE
Matsu-moto	A: Oxymorphone 40 mg (twice daily) B: Oxymorphone 20 mg (twice daily) C: Oxycodone 20 mg (twice daily) D: Placebo	Poor (3)	A: 59.5% B: 61.3% C: 43.2% D:10.5%	A: 33.9% B: 22.7% C: 10.4% D:1.6%	A: 32.2% B: 40.3% C: 36.0% D:11.3%	A: 31.4% B: 30.3% C: 27.2% D:4.8%	A: 31.4% B: 28.6% C: 25.6% D:4.0%	NR	A: 47.1% B: 38.0% C: 24.8% D:4.8%
Nicholson	A: Morphine 79 mg/day (twice daily B: Oxycodone 85 (three times daily)	Fair (4)	A: 14.0% B: 13.8%	NR	A: 26.0% B: 10.3%	A: 10.0% B: 12.1%	A: 2.0% B: 5.2%	A: 4.0% B: 0%	A: 30.0% B: 22.4%
Niemann 2000	A: Transdermal fentanyl B: Long-acting morphine	NA	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	A: 6% (1/18) B: 0%
Rauck	A: Morphine 64 mg (once daily) B: Oxycodone 53 mg (twice daily)	Fair (4)	A: 50% B: 47%	A: 24% B: 19%	A: 87% B: 89%	A: 85% B: 84%	A: 58% B: 64%	Not reported	A: 40.9% B: 31.2%

Table 2.2. Adverse events in trials of long-acting versus short-acting opioids and placebo-controlled trials of long-acting opioids

Study, year	Interventions	Quality rating (# of criteria met)	Nausea	Vomiting	Constipation	Drowsiness	Dizziness	Confusion	Withdrawals
Long-acting oxycodon:									
Caldwell, 1999	A: Long-acting oxycodone B: Short-acting oxycodone + acetaminophen	POOR (3)	A: 15%(5/34) B: 38%(14/37)	A: 6%(2/34) B: 11%(4/37)	A: 71%(24/34) B: 54%(20/37)	A: 53%(18/34) B: 70%(26/37)	A: 12%(4/34) B: 24%(9/37)	Not reported	A: 6% (3/34) B: 14% (5/37)
Gimbel, 2003	A: Long-acting oxycodone B: Placebo	FAIR (4)	A: 36% (30/82) B: 8% (6/77)	A: 21% (17/82) B: 3% (2/77)	A: 42% (35/82) B: 14% (11/77)	A: 40% (33/82) B: 1% (1/77)	A: 32% (26/82) B: 10% (8/77)	Not reported	A: 9% (7/82) B: 5% (4/77)
Hale, 2005	A: Long-acting oxycodone B: Placebo	POOR (3)	Not reported	Not reported	A: 29% (32/111) B: 11% (12/108)	A: 20% (22/111) B: 11% (1/72)	Not reported	Not reported	A: 5% (4/80) B: 7% (5/75)
Hale, 1999	A: Long-acting oxycodone B: Immediate-release oxycodone	POOR (3)	A: 16%(4/25) B: 41%(9/22)	A: 0%(0/25) B: 0%(0/22)	A: 32%(8/25) B: 45%(10/22)	A: 12%(3/25) B: 18%(4/22)	A: 16%(4/25) B: 9%(2/22)	Not reported	A: 4% (2/47) B: 2% (1/47)
Markenson, 2005	A: Long-acting oxycodone B: Placebo	FAIR (4)	A: 41% (23/56) B: 14%(7/51)	A: 12.5% (7/56) B: 2%(1/51)	A: 48% (27/56) B: 10%(5/51)	A: 32% (18/56) B: 10%(5/51)	A: 32% (18/56) B: 6%(3/51)	Not reported	A: 36% (20/56) B: 4%(2/51)
Matsumoto, 2005	A: Long-acting oxycodone B: Placebo	Poor (3)	A: 43% (54/125) B: 11%(13/124)	A: 10% (13/125) B: 2%(2/124)	A: 36% (45/125) B: 11%(14/124)	A: 27% (34/125) B: 5%(6/124)	A: 26% (32/125) B: 4%(5/124)	Not reported	A: 25%(31/125) B: 5%(6/124)

Study, year	Interventions	Quality rating (# of criteria met)	Nausea	Vomiting	Constipation	Drowsiness	Dizziness	Confusion	Withdrawals
Roth, 2000	A1: Long-acting oxycodone 20 mg bid A2: Long-acting oxycodone 10 mg bid B: Placebo	FAIR (5)	A1: 41%(18/44) A2: 27%(12/44) B: 11%(5/45)	A1: 23%(10/44) A2: 11%(5/44) B: 7%(3/45)	A1: 32%(14/44) A2: 23%(10/44) B: 7%(3/45)	A1: 27%(12/44) A2: 25%(11/44) B: 4%(2/45)	A1: 20%(9/44) A2: 30%(13/44)ß B: 9%(4/45)	Not reported	A1: 32%(14/44) A2: 27%(12/44) B: 4%(2/45)
Salzman, 1999	A: Long-acting oxycodone B: Short-acting oxycodone	POOR (3)	A: 50%(15/30) B: 33%(9/27)	A: 20%(6/30) B: 4%(1/27)	A: 30%(9/30) B: 37%(10/27)	A: 27%(8/30) B: 37%(10/27)	A: 30%(9/30) B: 22%(6/27)	A: 3%(1/30) B: 0%(0/27)	A: 20% (6/30) B: 7% (2/27)
Watson, 2003	A: Long-acting oxycodone B: Benztropine	POOR (3)	A: 36% (16/45) B: 18% (8/45)	A: 11% (5/45) B: 4% (2/45)	A: 29% (13/45) B: 9% (4/45)	A: 20% (9/45) B: 24% (11/45)	A: 16% (7/45) B: 7% (3/45)	Not reported	A: 16% (7/45) B: 2% (1/45)
Watson, 1998	A: Long-acting oxycodone B: Placebo	FAIR (4)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Zautra	A: Long-acting oxycodone B: Placebo	FAIR (4)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	A: 36% (20/55) B: 4% (2/49)
Long-acting oxymorphone									
Hale, 2005	A: Long-acting oxymorphone B: Placebo	POOR (3)	Not reported	Not reported	A: 35% (39/110) B: 11% (12/108)	A: 17% (19/110) B: 11% (1/72)	Not reported	Not reported	A: 3% (2/80) B: 7% (5/75)
Hale, 2007	A: Long-acting oxymorphone B: Placebo	FAIR (5)	A: 3% (12/70) B: 11% (1/72)	A: 0% (0/70) B: 1% (1/72)	A: 19% (10/52) B: 16% (8/51)	A: 6% (4/70) B: 1% (1/72)	A: 3% (2/70) B: 0% (0/72)	Not reported	A: 10% (7/70) B: 11% (8/73)

Study, year	Interventions	Quality rating (# of criteria met)	Nausea	Vomiting	Constipation	Drowsiness	Dizziness	Confusion	Withdrawals
Katz, 2007 (FAIR)	A: Long-acting oxymorphone B: Placebo	FAIR (4)	A: 11% (12/105) B: 9% (9/100)	A: 8% (8/105) B: 1% (1/100)	A: 7% (7/105) B: 1% (1/100)	A: 2% (2/105) B: 0% (0/100)	A: 5% (5/105) B: 3% (3/100)	Not reported	A: 8% (9/105) B: 8% (8/100)
Kivitz, 2006 (GOOD)	A: Long-acting oxymorphone B: Placebo	FAIR (5)	A: 4% (10/279) B: 9% (8/91)	A: 24% (66/279) B: 2% (2/91)	A: 22% (62/279) B: 4% (4/91)	A: 18% (49/279) B: 3% (3/91)	A: 23% (63/279) B: 6% (5/91)	Not reported	A: 44% (122/279) B: 10% (9/91)
Matsumoto, 2005 (FAIR)	A: Long-acting oxymorphone B: Placebo	POOR (3)	A: 60% (145/240) B: 11% (13/124)	A: 28% (68/240) B: 2%(2/124)	A: 36% (87/240) B: 11%(14/124)	A: 31% (74/240) B: 5% (6/124)	A: 30% (72/240) B: 4%(5/124)	Not reported	A: 43% (103/240) B: 5% (6/124)
Transdermal fentanyl									
Langford, 2006	A: Transdermal fentanyl B: Placebo	POOR (3)	A: 44% (94/216) B: 19% (37/200)	A: 28% (61/216) B: 3% (5/200)	A: 10% (22/216) B: 2% (3/200)	A: 22% (48/216) B: 4% (7/200)	A: 12% (26/216) B: 5% (10/200)	Not reported	A: 27% (54/202) B: 10% (20/197)
Long-acting codeine									
Arkinstall 1995	A: Long-acting codeine B: Placebo	FAIR (4)	A: 33%[ß] B: 12%	A: 14% B: 3.8%	A: 21% B: 10%	A: 16% B: 5%	A: 21% B: 14%	Not reported	A: 15% (7/46) B: 2% (1/46)
Hale, 1997	A: Long-acting codeine B: Short-acting codeine	POOR (2)	A: 31% (16/52) B: 18% (9/51)	A: 10% (5/52) B: 2% (1/51)	A: 19% (10/52) B: 16% (8/51)	A: 10% (5/52) B: 4% (2/51)	A: 17% (9/52) B: 4% (2/51)	Not reported	A: 13/53 (25%) B: 4/51 (8%)
Peloso, 2000	A: Long-acting codeine B: Placebo	FAIR (4)	Not reported	Not reported	A: 49%(25/51)[ß] B: 11%(6/52)	A: 39%(20/51) B: 10%(5/52)	A: 33%(17/51) B: 8%(4/52)	Not reported	A: 29%(15/51) B: 8%(4/52)

Study, year	Interventions	Quality rating (# of criteria met)	Nausea	Vomiting	Constipation	Drowsiness	Dizziness	Confusion	Withdrawals
Long-acting dihydrocodeine									
Gostick, 1989	A: Long-acting dihydrocodeine B: Short-acting dihydrocodeine	POOR (3)	Not reported	Not reported	A: 55% (23/42)‡ B: 48% (21/44)	Not reported	Not reported	Not reported	26% (16/61) overall, "no treatment differences"
Lloyd, 1992	A: Long-acting dihydrocodeine B:Dextropropoxyphene + paracetamol	POOR (3)	A: 31%(12/39) B: 10%(4/41)	Not reported	A: 8%(3/39) B: 10%(4/41)	A: 26%(10/39) B: 15%(6/41)	Not reported	A: 10%(4/39) B: 5%(2/41)	A: 40%(17/43) B: 9%(4/43)
Levorphanol									
Rowbotham, 2003	A: Levorphanol high-strength B: Levophanol low-strength	FAIR (4)	Not reported	Not reported	Not reported	Not reported	A: 5% (2/43) B: 0% (0/38)	A: 12% (5/43) B: 0% (0/38)	31% overall, not reported by intervention
Methadone									
Morley 2003	A: Methadone B: Placebo	POOR (1)	A: 37% (7/19) for 10 mg/day; 47% (8/17) for 20 mg/day B: 21% (4/19) phase I; 24% (4/17) phase II	A: 21% (4/19) phase I; 6% (1/17) phase II B: 5% (1/19) phase I; 6% (1/17) phase II	A: 11% (2/19) phase I; 18% (3/17) phase II B: 5% (1/19) phase I; 6% (1/17) phase II	A: 11% (2/19) phase I; 18% (3/17) phase II B: 11% (2/19) phase I; 12% (2/17) phase II	A: 32% (6/19) phase I; 18% (3/17) phase II B: 0% (0/19) phase I; 6% (1/17) phase II	Not reported	A: 5% (1/19) phase I; 18% (3/17) phase II B: 0% (0/19) phase I; 18% (3/17) phase II

Study, year	Interventions	Quality rating (# of criteria met)	Nausea	Vomiting	Constipation	Drowsiness	Dizziness	Confusion	Withdrawals
Long-acting morphine:									
Gilron, 2005	A: Long-acting morphine B: Gabapentin C: Long-acting morphine + gabapentin D: Placebo	FAIR (4)	A: 5% B: 0% C: 7% D: 0%	0% in all arms	A: 39% B: 2% C: 21% D: 5%	A: 16% B: 8% C: 21% D: 5%	A: 0% B: 2% C: 0% D: 0%	A: 2% B: 2% C: 7% D: 2%	Not reported
Huse, 2001	A: Long-acting morphine B: Placebo	FAIR (4)	A: 0.74 cm B: 0.4 cm	Not reported	A: 0.03 cm[ß] B: 0.02 cm	A: 2.21 cm B: 1.33 cm	A: 1.27 cm B: 0.71 cm	Not reported	Not reported
Jamison, 1998	A: Long-acting morphine + short-acting oxycodone B: Short-acting oxycodone	FAIR (5)	A: 31% B: 14%	Not reported	A: 30% B: 18%	A: 31% B: 14%	A: 6% B: 19%	A: 0% B: 1.4%	A: 9% (1/11) B: 15% (2/13)
Maier, 2002	A: Long-acting morphine B: Placebo	FAIR (3)	A: 23% (11/48) B: 14% (6/48)	A: 4% (2/48) B: 4% (2/48)	A: 19% (9/48) B: 4% (2/48)	A: 23% (11/48) B: 2% (1/48)	A: 20% (10/48) B: 4% (2/48)	NR	A: 12% (3/25) B: 0% (0/23)
Moulin, 1996	A: Long-acting morphine B: Benztropine	FAIR (5)	A: 39%(18/46)ß B: 7%(3/46)	A: 39%(18/46)ß B: 2%(1/46)	A: 41% (19/46)ß B: 4%(2/46)	Not reported	A: 37%(17/46) B: 2%(1/46)	A: 9%(4/46) B: 15%(7/46)	A: 28% (13/46) B: 2%(1/46)

Table 3. Summary of the evidence by key question

Key Questions	Level of Evidence	Conclusions
Efficacy		
1A. In head-to-head comparisons, has one or more long-acting opioid been shown to be superior to other long-acting opioids in reducing pain and improving functional outcomes when used for treatment of adults with chronic non-cancer pain?	POOR to FAIR	There is insufficient evidence from head-to-head trials to suggest that one long-acting opioid is superior to another in terms of efficacy in adult patients with chronic non-cancer pain. Eight trials (6 fair quality and 2 poor quality) directly compared one long-acting opioid to another. Three trials directly compared transdermal fentanyl to oral long-acting morphine, two trials directly compared long-acting oxymorphone to long-acting oxycodone, two trials directly compared extended-release (once daily) morphine to long-acting (twice daily) oxycodone, and one trial compared extended-release (once daily) versus sustained-release (twice daily) morphine. Six trials found no difference between long-acting opioids. Two trials which found a significant difference (one trial of transdermal fentanyl versus oral long-acting morphine and one trial of extended-release morphine versus sustained-release oxycodone) were open-label, rated poor quality and inconsistent with higher quality trials evaluating the same comparison. No trials evaluate the effectiveness of opioid rotation for management of chronic non-cancer pain.
1B. In trials comparing long-acting opioids to other types of drugs or to placebo, is there a pattern to suggest that one long-acting opioid is more effective than another?	POOR	There is insufficient evidence from 22 placebo-controlled trials to suggest that one long-acting opioid is superior for efficacy in adult patients with chronic non-cancer pain. The longest trial was 16 weeks. The trials are too clinically diverse and of insufficiently high quality to conduct indirect comparisons on efficacy of long acting opioids. One fair quality trial found methadone superior to placebo in patients with neuropathic pain but used an unusual study design in which patients received methadone or placebo only every other day, with no intervention on alternate days. Another trial found that high-strength levorphanol was superior to low-strength levorphanol in patients with neuropathic pain. Long-acting oxycodone, long-acting oxymorphone, transdermal fentanyl, long-acting morphine (extended- or sustained-release), long-acting codeine, and long-acting dihydrocodeine have all been evaluated in two or more clinical trials (placebo-controlled or head-to-head).
1C. Have long-acting opioids been shown to be superior to short-acting opioids in reducing pain and improving functional outcomes when used for treatment in adults with chronic non-cancer pain?	POOR	There is insufficient evidence to suggest superior efficacy of long-acting opioids as a class compared to short-acting opioids in adults with chronic non-cancer pain. Seven fair quality trials directly compare the efficacy of long- and short-acting opioids in patients with chronic non-cancer pain. These trials were highly heterogeneous in terms of study design, patient populations, interventions, and outcomes assessed. There is fair evidence from three more homogeneous trials to suggest that long-acting oxycodone and short-acting oxycodone are equally effective for pain control in adult patients with chronic non-cancer pain.

Key Questions	Level of Evidence	Conclusions
Adverse Events		
2A. In head-to-head comparisons, has one or more long-acting opioid been shown to be associated with fewer adverse events compared to other long-acting opioids when used for treatment of adults with chronic non-cancer pain?	POOR	There was insufficient evidence from eight head-to-head trials to suggest that one long-acting opioid is associated with fewer adverse events compared to any other. Of eight head-to-head trials, none were rated good quality for adverse event assessment (1 fair quality, 4 poor quality). There were no clear differences in overall adverse events or withdrawal due to adverse events. Two trials found transdermal fentanyl associated with slight trends towards less constipation and a higher rate of withdrawals due to any adverse event compared to oral long-acting morphine. There were no clear or consistent differences between long-acting oxycodone and oxymorphone, extended-release morphine and long-acting oxycodone, or extended-release (once-daily) and sustained-release (twice daily) morphine. None of the head-to-head trials were designed to assess risk of abuse or addiction.
2B. In trials comparing long-acting opioids to other types of drugs or to placebo, is there a pattern to suggest that one long-acting opioid is associated with fewer adverse events than another?	POOR	There is insufficient evidence from 21 placebo-controlled trials to suggest that one long-acting opioid is superior in terms of adverse events than any other in adult patients with chronic non-cancer pain. The placebo-controlled trials are too clinically diverse and of insufficiently high quality to perform indirect comparisons of adverse events. Rates of abuse and addiction were not reported in trials. Two fair quality retrospective cohort studies found transdermal fentanyl associated with a lower risk of constipation than long-acting oxycodone and one study found transdermal fentanyl associated with lower risk of emergency room encounters compared to morphine. Other cohort studies on adverse event were of generally poorer quality than the clinical trials and did not provide reliable data on adverse events. Surveillance data from emergency departments in the United States do not provide specific data on long-acting opioid preparations. Epidemiologic data suggests increases in methadone-associated deaths that may be proportionate to changes in prescribing patterns. No trials evaluate opioid rotation for management of opioid-related adverse events. Case reports and uncontrolled observational studies found that effects of opioid rotation are variable and somewhat unpredictable.
2C. Have long-acting opioids been shown to have fewer adverse events than short-acting opioids when used for treatment of adults with chronic non-cancer pain?	POOR	For all assessed adverse events, there is no convincing evidence from 7 heterogeneous randomized controlled trials to suggest lower adverse event rates with long-acting opioids as a class compared to short-acting opioids. None of the 7 trials were rated good quality for adverse event assessment and only 1 was rated fair quality. In a subset of three more homogeneous trials of long-acting versus short-acting oxycodone, there was no pattern suggesting superiority of one formulation over another. There was no data comparing rates of addiction or abuse with long-acting versus short-acting opioids.
Subpopulations		
3. Are there subpopulations of patients (specifically race, age, sex, or type of pain) with chronic non-cancer pain for which one long-acting opioid is more effective or associated with fewer adverse effects?	POOR	One fair quality retrospective cohort study found that long-acting oxycodone was associated with a higher risk of constipation than transdermal fentanyl in older patients compared to all patients included in the study. There is almost no other information regarding the comparative efficacy of long-acting opioids for specific subpopulations as characterized by race, gender, or age. For specific types of chronic non-cancer pain, findings are limited by problems with internal validity, external validity, heterogeneity, and small numbers of trials for each subpopulation. It is not possible to draw reliable conclusions regarding comparative efficacy or adverse event rates for any subpopulation from these data.

Appendix A. Search strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2007>
Search Strategy:
---
1 opioid analgesics.mp. (148)
2 narcotics.mp. (809)
3 analgesics, opioid.mp. (3063)
4 hydromorphone.mp. (178)
5 oxymorphone.mp. (47)
6 1 or 2 or 3 or 4 or 5 (4019)
7 pain.mp. (36851)
8 6 and 7 (2826)

Database: Ovid MEDLINE(R) <1996 to September Week 1 2007>
Search Strategy:
---
1 opioid analgesics.mp. (709)
2 narcotics.mp. (6893)
3 analgesics, opioid.mp. (13796)
4 1 or 2 or 3 (20512)
5 pain.mp. (160651)
6 4 and 5 (9920)
7 opioid analgesics.mp. or exp Analgesics, Opioid/ (26699)
8 narcotics.mp. or exp NARCOTICS/ (23997)
9 7 or 8 (29695)
10 (intractable pain or severe pain or chronic pain).mp. (9417)
11 9 and 10 (1434)
12 limit 11 to human (1285)
13 limit 12 to english language (1113)
14 12 not 13 (172)
15 limit 14 to abstracts (147)
16 13 or 15 (1260)

Database: Ovid MEDLINE(R) <1996 to September Week 2 2007>
Search Strategy:
---
1 opioid analgesics.mp. or exp Analgesics, Opioid/ (26738)
2 narcotics.mp. or exp NARCOTICS/ (24021)
3 1 or 2 (29735)
4 (intractable pain or severe pain or chronic pain).mp. (9439)
5 3 and 4 (1439)
6 limit 5 to human (1289)
7 limit 6 to english language (1116)
8 6 not 7 (173)
9 limit 8 to abstracts (148)

10 7 or 9 (1264)
11 (200509$ or 20051$ or 2006$ or 2007$).ed. (1309060)
12 10 and 11 (349)
13 hydromorphone.mp. or exp HYDROMORPHONE/ (507)
14 oxymorphone.mp. or exp OXYMORPHONE/ (130)
15 11 or 12 (1309060)
16 limit 13 to human (384)
17 limit 14 to english language (130)
18 16 not 17 (335)
19 limit 18 to abstracts (283)
20 17 or 19 (413)
21 4 and 20 (59)
22 11 and 21 (23)
23 22 not 10 (4)
24 from 23 keep 1-4 (4)

Appendix B. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are 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 *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, birth dates or week days
        - not reported
2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients

Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or week days
Open random numbers lists
Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making,

i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Appendix C. Quality abstraction tool for adverse events of opioids

Author	Study_____
Year published	
Citation	
Setting (country, single or multicenter, specialty or primary care clinic)	
INTERNAL VALIDITY	
Selection: 1: Study states "all patients" or "consecutive series" during specified time period (observational study) or describes and accounts for all patients deemed eligible (clinical trial) and has explicit inclusion and exclusion criteria applied to all eligible patients (all study types) 0: Selection not clear, biased selection, inclusion and exclusion criteria not specified, or unable to determine proportion of patients eligible for trial who withdrew or were not entered	
Loss to follow-up: 1: Low overall and differential loss to follow-up (<15% of study population or <25% difference between groups), able to compute adverse effects according to intention-to-treat if low loss to followup 0: High overall or differential loss to follow-up (>15% overall or >25% difference between groups), or unable to calculate intention-to-treat if low loss to follow-up	
Adverse events pre-specified and pre-defined: 1: Study reports definitions used for assessed adverse events in an explicit, reproducible fashion 0: Study does not meet above criteria	
Ascertainment techniques adequately described: 1: Study reports methods used to ascertain complications, including who ascertained, timing, and methods used 0: Study does not meet above criteria	
Non-biased and accurate ascertainment of adverse events: 1: Patients and assessors blinded to intervention and ascertainment techniques go beyond patient self-report alone 0: Study does not meet above criteria	
Statistical analysis of potential confounders: 1: Study examines more than 2 relevant confounders/risk factors using standard acceptable statistical techniques 0: Study does not meet above criteria	
Adequate duration of follow-up: 1: Study reports duration of follow-up and duration at least 7 days 0: Study does not meet above criteria	
Internal validity score (0-7)	

EXTERNAL VALIDITY	
Adequate description of study population: 1: Study reports 2 or more demographic characteristics and both basic clinical characteristics of pain syndrome and average duration of pain 0: Study does not meet above criteria	
Does study report numbers screened and eligible (trial) or inception cohort (observational study)?	
Are exclusion criteria specified and numbers excluded for each criteria reported?	
Who is the funding source?	
Are authors employed by the funding source?	
Are data held by the funding source?	
Are patients in the study on opioids prior to study entry?	

Appendix D. Table of Excluded Studies (Update #5)

Study	Reasons for exclusion
Amabile CM, Bowman BJ. Overview of oral modified-release opioid products for the management of chronic pain. *Annals of Pharmacotherapy.* Jul-Aug 2006;40(7-8):1327-1335	No original data (e.g., letter, editorial, non-systematic review)
Angst Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology.* Mar 2006;104(3):570-587.	Population not included
Bjordal JM, Klovning A, Ljunggren AE, Slordal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomised placebo-controlled trials. *European Journal of Pain: Ejp.* Feb 2007;11(2):125-138.	Intervention not included
Chamberlin KW, Cottle M, Neville R, Tan J. Oral oxymorphone for pain management. *Annals of Pharmacotherapy.* Jul 2007;41(7):1144-1152.	No original data (e.g., letter, editorial, non-systematic review)
Gallagher RM, Welz-Bosna M, Gammaitoni A. Assessment of dosing frequency of sustained-release opioid preparations in patients with chronic nonmalignant pain. *Pain Medicine.* Jan-Feb 2007;8(1):71-74.	Outcome not included
Haythornthwaite JA, Menefee LA, Quatrano-Piacentini AL, Pappagallo M. Outcome of chronic opioid therapy for non-cancer pain. *J Pain Symptom Manage.* 1998;15(3):185-194.	Study design not included
Hojsted J, Sjogren P. Addiction to opioids in chronic pain patients: a literature review. *European Journal of Pain: Ejp.* Jul 2007;11(5):490-518.	No original data (e.g., letter, editorial, non-systematic review)
Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Services Research.* 2006;6:46.	Study design not included
Jensen MK, Thomsen AB, Hojsted J. 10-year follow-up of chronic non-malignant pain patients: opioid use, health related	Study design not included

Study	Reasons for exclusion
quality of life and health care utilization. *European Journal of Pain: Ejp.* Jul 2006;10(5):423-433.	
Kahan M, Srivastava A, Wilson L, Gourlay D, Midmer D. Misuse of and dependence on opioids: study of chronic pain patients. *Canadian Family Physician.* Sep 2006;52(9):1081-1087.	No original data (e.g., letter, editorial, non-systematic review)
Kahan M, Srivastava A, Wilson L, Mailis-Gagnon A, Midmer D. Opioids for managing chronic non-malignant pain: safe and effective prescribing. *Canadian Family Physician.* Sep 2006;52(9):1091-1096	No original data (e.g., letter, editorial, non-systematic review)
Katz N. Methodological issues in clinical trials of opioids for chronic pain. *Neurology.* Dec 29 2005;65(12 Suppl 4):S32-49.	Study design not included
Mercadante S, Bruera E. Opioid switching: a systematic and critical review. *Cancer Treatment Reviews.* Jun 2006;32(4):304-315.	Population not included
Mitchell TB, White JM, Somogyi AA, Bochner F. Switching between methadone and morphine for maintenance treatment of opioid dependence: impact on pain sensitivity and mood status. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions.* 2006;15(4):311-315	Population not included
Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Research & Therapy.* 2005;7(5):R1046-1051.	Study design not included
Moulin DE, Clark AJ, Gilron I, et al. Pharmacological management of chronic neuropathic pain - consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manage.* 2007;12(1):13-21.	No original data (e.g., letter, editorial, non-systematic review)
Schieffer BM, Pham Q, Labus J, et al. Pain medication beliefs and medication misuse in chronic pain. *J Pain.* Sep 2005;6(9):620-629.	Study design not included

Study	Reasons for exclusion
Sittl R. Transdermal buprenorphine in the treatment of chronic pain. *Expert Review of Neurotherapeutics.* May 2005;5(3):315-323.	No original data (e.g., letter, editorial, non-systematic review)
Wasan AD, Butler SF, Budman SH, Benoit C, Fernandez K, Jamison RN. Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. *Clin J Pain.* May 2007;23(4):307-315	Study design not included
Won A, Lapane KL, Vallow S, Schein J, Morris JN, Lipsitz LA. Long-term effects of analgesics in a population of elderly nursing home residents with persistent nonmalignant pain. *Journals of Gerontology Series A-Biological Sciences & Medical Sciences.* Feb 2006;61(2):165-169.	Study design not included
Zernikow B, Michel E, Anderson B. Transdermal fentanyl in childhood and adolescence: a comprehensive literature review. *J Pain.* Mar 2007;8(3):187-207.	Population not included

Appendix E. Quality ratings of trials added for Update #5

Author	Year	Randomization method adequate?	Allocation concealment method adequate?	Groups similar at baseline?	Inclusion criteria specified?	Exclusion criteria specified?	Outcome assessors masked?	Care provider masked?
Hale	2007	Method not described	Method not described	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Katz	2007	Yes	Method not described	Yes	Yes	Yes		Yes
Kivitz	2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Langford	2006	Yes	Yes	Yes	Yes	Yes	Unclear, reported as double blind	Yes
Markenson	2005	Yes	Yes	Yes	Yes	Yes	Unclear, reported as double blind	Yes
Matsumoto	2005	Yes	Method not described	Yes	Yes	Yes	Yes	Yes
Nicholson	2006	Yes	Method not described	Yes Females 61% vs. 40%, p<0.05	Yes	Yes	No	No
Rauck (ACTION Trial)	2006, 2007	Method not described	Yes	No	Yes	Yes	No	No
Zautra	2005	Method not described	Method not described	Yes	Yes	Yes	Unclear, reported as double blind	Yes

Appendix E. Quality ratings of trials added for Update #5

Author	Patients masked?	Attrition reported?	Withdrawal rate differential or high?	Loss to followup differential or high?	ITT analysis?	Post- randomization exclusions?	Rating
Hale	Unclear, reported as double blind	Yes	Yes	No	Yes	Yes	FAIR
Katz	Yes	Yes	Yes	No	Yes	Unable to determine	FAIR
Kivitz	Yes	Yes	Yes	No	Yes	Unable to determine	GOOD
Langford	Yes	Yes	Yes	No	Unable to determine	Unable to determine Discrepancy between number randomized and number in each randomization group	FAIR
Markenson	Yes	Yes	Yes	No	Yes	Yes	FAIR
Matsumoto	Yes	Yes	Yes	No	Yes	Yes	FAIR
Nicholson	No	Yes	Yes	Yes (6%)	No	Yes	FAIR
Rauck (ACTION Trial)	No	Yes	Yes	Unable to determine	No	Unable to determine	POOR
Zautra	Yes	Yes	Yes	No	Yes	No	FAIR