Drug Class Review
on
Long-Acting Opioid Analgesics

Final Report

April 2006

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

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TABLE OF CONTENTS

Suggested citation for this report:

Chou R. Drug Class Review on Long-Acting Opioid Analgesics. Final Report. 2006
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 6 months' duration, is a common cause of major disability. It is estimated that one in five adult Americans, or 30 million people, experience chronic pain.[1] Chronic non-cancer pain afflicts a significant subset of chronic pain patients, causing personal suffering, reduced productivity, and substantial health care costs.[2] Opioids have been endorsed by the American Academy of Pain Medicine and the American Pain Society[3] as well as 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 used for cancer patients.

Opioids are a class of medications that act on common receptors and are natural derivatives of morphine.[6] 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 both short- and long-acting preparations, and the use of long-acting opioids for patients with chronic non-cancer pain has become common. Because chronic pain may not resolve with time, use of opioid analgesics for these conditions can be long-term. Despite the widespread use of long-acting opioids, there are few data regarding the comparative efficacy and adverse event profiles associated with specific long-acting opioids in patients who have 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 efficacy and safety, and also whether long-acting opioids as a class are more efficacious or safer than short-acting opioids in the treatment of chronic non-cancer pain. This report was originally commissioned in 2001 and is updated annually. The last update (Update #3) was based on searches conducted in November 2004. The current document (Update #4) is based on new searches conducted in September 2005. Since the last update, extended release hydromorphone was withdrawn from the market after the manufacturer provided data to the Food and Drug Administration showing that drinking alcohol could result in rapid release of the hydromorphone.[8]

Scope and Key Questions

The scope of the review and key questions 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:

1. What is the comparative efficacy 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 effects (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 effects?

Several aspects of the key questions deserve comment:

Population. The population included in this review is adult (greater than 18 years old) 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. "Long-acting" was defined as opioids administered three times a day or less frequently. Long-acting opioids that we identified were transdermal fentanyl and oral oxycodone, morphine, methadone, levorphanol, codeine, dihydrocodeine, hydromorphone, and oxymorphone.

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 analogue or categorical pain scales. Visual analogue scales (VAS) 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 VAS 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, or 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 (e.g., no pain, mild, moderate, or severe). 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.[9] Pain control (improvement in pain) and pain relief (resolution of pain) are also measured using visual analogue 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 have not been consistently utilized in studies investigating this outcome.[10, 11] We recorded any information about abuse and addiction, including rates of death and hospitalization when available.

Because of inconsistent reporting of outcomes, 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 different reasons found that withdrawals were primarily due to adverse events in patients on long-acting oxycodone, but due to inadequate pain control in the patients on placebo.[12] 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.[13-15] 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 evaluated one long-acting opioid against another long-acting opioid provided direct evidence of comparative efficacy and adverse event rates. Trials that compared long-acting opioids to short-acting opioids, non-opioids, or placebos may provide indirect data about comparative effectiveness and safety. 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 assess adverse events, and may select patients at low-risk for adverse events (in order to minimize dropout rates) and utilize methodology inadequate for assessing adverse events. Well-designed observational studies designed to assess adverse event rates may include broader populations, carry out observations over a longer time period, utilize higher quality techniques for assessing adverse events, or examine larger sample sizes.

One unique issue that complicates the interpretation of studies of 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. According to the theory of incomplete cross-tolerance, 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.[16-19]

METHODS

Literature Search

Initial searches to identify articles relevant to each key question, were performed, in order, on the Cochrane Library (2002, Issue 1), MEDLINE (1966-2002), 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 and economic evaluation data to the Evidence-based Practice Center. All citations were imported into an electronic database (EndNote 5.0). Searches on the electronic databases were carried out through March 28, 2002, using updates on electronic databases after the initial searches.

We conducted Update #4 searches of the Cochrane Library (through third quarter, 2005) and MEDLINE (through September week 3 2005) using the same search strategies as for the initial searches. Additional searches were also performed for specific opioids newly available in long-acting formulations: hydromorphone and oxymorphone. Pharmaceutical manufacturers were again invited to submit dossiers, including citations. These submissions were reviewed to identify new citations not previously identified. 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 DERP. We obtained full-text articles if the title and abstract review met the following eligibility criteria:

1. Systematic reviews of the clinical efficacy or adverse event rates of long-acting opioids in patients with chronic non-cancer pain OR
2. Randomized controlled trials 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 trials and observational studies of adverse events associated with a long-acting opioid.

We re-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 are 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.

Original searches identified 3,495 citations: 1081 from the Cochrane Library, 1106 from Medline, 1,205 from EMBASE, 42 from reference lists, and 60 from pharmaceutical company submissions. We identified 1,225 clinical trials and excluded 1195 of these (see Appendix C for detailed search results). 921 clinical trials were excluded because they did not evaluate an included population (most excluded studies evaluated patients with acute pain or cancer pain), 252 were excluded because they did not evaluate an included intervention (oral or transdermal long-acting opioid), and 22 were excluded because they did not evaluate an included outcome (pain control, pain relief, or function). Thirty trials were retrieved for more detailed evaluation. After this second review, we excluded 14 trials: 10 because they did not evaluate an included intervention and 4 because they did not evaluate an included population. One additional randomized trial was excluded because it used either long-acting morphine or oxycodone in its opioid intervention group, and did not provide separate results for each long-acting opioid.[20] Sixteen randomized controlled trials provided usable data and were included in the original report.

Results for annual updates are as follows: 646 new citations were identified for update #1, 176 for update #2, and 769 for update #3. From these citations, we identified 5 clinical trials (one head-to-head[21], one comparing higher to lower doses of a long-acting opioid,[22] and three placebo-controlled[23-25]) and 5 cohort studies[26-30] that met inclusion criteria. We also reviewed updated results of the Drug Abuse Warning Network (DAWN) study[31] and from the Oregon Department of Human Services[32] regarding adverse events from long-acting opioids.

For Update #4, we found 581 new citations from electronic databases: 465 were from the Cochrane Central Register of Controlled Trials and 107 from Medline. Nine additional citations came from hand searches or reference lists. We received five dossiers from three pharmaceutical companies: Purdue Pharma L.P. (MS Contin, Palladone, and Oxycontin)[33-35], Janssen Pharmaceutica Products, L.P. (Duragesic)[36], and Organon Pharmaceuticals USA Inc. (Avinza)[37]. Of the new citations, seven reported results from clinical trials and appeared to meet initial

screening criteria for inclusion. Fourteen other trials were excluded at the title and abstract review stage for the following reasons: nine did not evaluate an included patient population (cancer pain, acute pain, or post-surgical), four did not evaluate an included drug or formulation (intravenous, epidural, or short-acting opioid, or other non-included drug), and one used an excluded study design (pharmacokinetic study). Of the citations that met initial screening criteria and were retrieved for full-text review, four[38-41] met inclusion criteria. One of the trials[39] compared transdermal fentanyl and oral long-acting morphine in patients with chronic low back pain, and had previously been identified when only available as an abstract.[42] Another trial compared long-acting oxymorphone and long-acting oxycodone in patients with low back pain.[38] The other two trials evaluated long-acting morphine; one[41] was a placebo-controlled trial in patients with various pain conditions, and the other[40] compared morphine, gabapentin, placebo, and the combination of morphine and gabapentin in patients with neuropathic pain. One trial[43] was excluded because it evaluated transdermal buprenorphine (not available in the U.S.), one trial[44] of transdermal fentanyl was excluded because it was only available as an abstract, and one trial[45] of long-acting versus short-acting hydromorphine was excluded because it evaluated patients primarily with cancer pain. No new observational studies met inclusion criteria. We excluded two new systematic reviews of long-acting opioids for non-cancer pain because they were not designed to assess comparative efficacy or safety.[46, 47] A previously identified meta-analysis comparing the efficacy and safety of transdermal fentanyl and long-acting morphine was excluded because it included studies available only as abstracts, did not provide enough information about unpublished studies to assess their quality, and pooled data across controlled and uncontrolled studies.[48] We identified no published trials meeting inclusion criteria that evaluated long-acting hydromorphone. Three trials of long-acting hydromorphone that evaluated cancer pain patients were excluded.[45, 49, 50]

Data Abstraction

One reviewer abstracted the following data from included trials: study design, setting, 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 (e.g., scales used), and results for each outcome. Equianalgesic doses of opioid medications were estimated using published tables.[51] We recorded intention-to-treat results if 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 adequately describing the study population, similarity of patients to other populations to whom the intervention would be applied, control group receiving comparable treatment, funding source, 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).[13, 14] 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 were rated fair-quality. As the "fair-quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *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 if they met three to five criteria, and poor 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 are familiar with their 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, however, consistent results may indicate that similar biases are operating in all the studies.

RESULTS

Overview of Included Trials

We identified 25 randomized trials (2,752 patients enrolled) that evaluated long-acting opioids in chronic non-cancer pain populations (Table 1.1). Only five of the 24 trials compared one long-acting opioid to another.[21, 39, 52, 53] Three[21, 39, 52] was compared transdermal fentanyl to long-acting morphine; one[53] compared a once-daily morphine preparation to a twice-daily morphine preparation; and the fifth[38] compared long-acting oxymorphone to long-acting oxycodone. Of the three head-to-head trials of transdermal fentanyl and long-acting morphine, one[21] was a very small (n=18) study of patients specifically with chronic pancreatitis. Seven trials compared a long-acting opioid to a short-acting opioid,[54-60] and thirteen compared a long-acting opioid to a non-opioid or placebo.[12, 22-25, 40, 41, 61-66] Ten trials used a crossover design.[24, 40, 41, 52, 56, 57, 61, 63, 64, 66] We identified trials of long-acting oxycodone,[12, 24, 38, 55, 57, 60, 66] long-acting morphine,[39-41, 52, 53, 58, 62-64] long-acting dihydrocodeine,[56, 59] long-acting codeine,[54, 61, 65] long-acting oxymorphone,[38] transdermal fentanyl,[39, 52] levorphanol,[22] and methadone.[25] No trials of long-acting hydromorphone met inclusion criteria. One trial[67] cited in reference lists[2, 61] 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[63] to 680[39] evaluable enrollees, with an average of 110 enrollees. Five of the trials focused on osteoarthritis,[12, 53, 55, 59, 65] seven on back pain,[38, 39, 54, 56-58, 60] seven on neuropathic pain,[22-25, 40, 62, 66] one on phantom limb pain,[63], one on chronic pancreatitis pain,[21] and four on heterogenous chronic non-cancer pain.[41, 52, 61, 64]

Nearly all of the trials were of relatively short duration, ranging from 5 days[54] to 16 weeks.[58] The one exception was a head-to-head trial of transdermal fentanyl versus oral long-acting morphine that was 13 months in duration.[39] 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. Gender had a slight predominance (slightly greater than 50%) towards females. The average age of enrollees was in the 50's.

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.[56, 59, 64] None of the difference in point scores result in re-classification 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.[46, 47] Neither attempted to assess the comparative efficacy of different long-acting opioids, or the efficacy of long-acting compared to 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.[46] Mean post-treatment pain intensity scores were 14 units lower (0 to100 scale) on opioids compared to placebo. Nausea, constipation, drowsiness, 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.[47] About 80% of patients experienced at least one adverse

event, with constipation, nausea, and somnolence being most common. There was insufficient data to assess tolerance and addiction.

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

Five randomized trials provide the only direct evidence of the comparative efficacy of different long-acting opioids in chronic non-cancer pain. The largest (680 subjects) and longest duration (13 months) randomized trial found that transdermal fentanyl and twice-daily morphine were similar in efficacy for patients with chronic low back pain who had not been previously on regular strong opioids.[39] This trial was rated fair quality because it was open-label and did not report intention-to-treat results for some outcomes. A poor-quality randomized trial comparing the same two drugs in a mixed pain population found conflicting evidence regarding efficacy.[52] Although improved pain control was seen after treatment with transdermal fentanyl, increased withdrawals were also seen on this medication. Several important methodological problems were identified, making these results difficult to interpret. A fair-quality randomized trial comparing once-daily morphine to twice-daily morphine found similar efficacy, with the only difference that one of seven measures of sleep quality showed improved efficacy for once-daily morphine given in the morning.[53] A small (n=18), fair-quality, open-label trial of transdermal fentanyl vs. oral morphine in patients with chronic pancreatitis found no significant differences between these two medications for patient preference, pain control, or quality of life.[21] There are no trials directly comparing transdermal fentanyl or oral long-acting morphine to any other long-acting preparation. One fair-quality, blinded trial of long-acting oxymorphone (which is not yet available in the U.S.) versus long-acting oxycodone found no differences for efficacy.[38] 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.[68]

Evidence review

Five trials directly compared the efficacy of one long-acting opioid to another in chronic pain of non-cancer origin (Tables 1.1 and 1.2, Evidence Table 1.1).[21, 38, 39, 52, 53] Three trials[21, 39, 52] compared transdermal fentanyl to long-acting morphine twice a day. Another trial[53] compared a once-daily morphine preparation to a twice-daily morphine preparation. The fifth trial compared long-acting oxymorphone to long-acting oxycodone in patients with low back pain.[38] Four[21, 38, 52, 53] of the five trials were four weeks or less in duration. Main results from these trials are summarized in Table 1.3.

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.[39] 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 analogue scores, for example, the study only reported results for 608 out of 680 randomized subjects. In addition, even though this trial only enrolled 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 were not reported.

This trial found that, after 13 months of treatment, pain relief (VAS); the proportion of patients reporting severe pain at rest, on movement, during the day, or at night (ITT 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 mcg/hr in the transdermal fentanyl group and to 140 mg/day in the oral morphine group. More patients in the sustained release morphine group completed the study compared to the transdermal fentanyl group (53% vs. 48%). The difference could be attributed to more withdrawals because of adverse events in the transdermal fentanyl group (37% vs. 31%).

The second trial that compared transdermal fentanyl 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 [52]. 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.

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

Certain aspects of this trial 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 dosage

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 question it addresses is, "do 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?" The study 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 versus oral morphine in patients with chronic pancreatitis found no significant differences for patient preference, pain control, or quality of life (Evidence Table 1.1).[21] 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 relatively uncommon, specific condition.

The study that compared a once-daily morphine preparation to a twice-daily morphine preparation[53] used a randomized, double blinded design and compared a once-daily morphine preparation to a twice-daily preparation in a population of 295 osteoarthritis patients. 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 follow-up for each drug regimen was only 4 weeks, and duration of pain and previous narcotic use in evaluated patients was not reported.

The fifth trial compared long-acting oxymorphone (not yet available in the U.S.) and long-acting oxycodone in patients with low back pain.[38] It was rated fair quality because randomization methods were not adequately described, high withdrawal rates, and because intention-to-treat analyses were not performed. In addition, the external validity of this trial was compromised because only about 70% of patients who entered the dose titration phase were eventually entered into the 18-day intervention phase. This trial 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.

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

One meta-analysis of transdermal fentanyl compared to long-acting morphine was excluded because it included studies available only as abstracts or from the drug company sponsor and did not provide enough information to judge their quality.[48] In addition, it pooled data across two randomized trials and two uncontrolled studies. Transdermal fentanyl and long-acting morphine were associated with similar pain relief at 28 days.

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

2 good-quality and 18 fair-quality clinical trials of long-acting opioids versus short-acting opioids, placebo, or non-opioids provided no useful indirect evidence for determining the comparative efficacy of long-acting opioids. Clinical trials found superior efficacy for long-acting oxycodone (4 trials[12, 23, 24, 66]), long-acting morphine (5 trials[40, 41, 62-64]), long-acting codeine (2 trials[61, 65]), and methadone (1 trial[25]) compared to placebo. One trial comparing high-strength levorphanol to low-strength levorphanol (used as an active control) for neuropathic pain found the higher strength more effective for pain intensity and relief.[22] The studies were generally of insufficient quality and too heterogeneous in terms of study designs, patient populations, interventions, and assessed outcomes to permit meaningful comparisons for important outcomes. 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.

Evidence review

We identified 2 good-quality[23, 40] and 18 fair-quality trials (1287 patients enrolled) that gave indirect evidence regarding the comparative efficacy of long-acting opioids. Seven studies compared long-acting opioids to short-acting opioids,[54-60] twelve studies compared long-acting opioids to non-opioids or placebos,[12, 23-25, 40, 41, 61-66] and one trial[22] compared high-strength with low-strength levorphanol (low-strength levorphanol considered an active control). Three trials used other 'active' placebos (benztropine[24, 64] or lorazepam[40]). The trials exhibited a high degree of heterogeneity with respect to study designs, patient populations, interventions, and outcomes measured (Table 1.1). The two good-quality trials were both in patients with neuropathic pain.[23, 40] One was a short-term (6 weeks) study that found that controlled-release oxycodone (average titrated dose 42 mg/day) was more effective than placebo for overall average daily pain intensity in 159 patients with diabetic neuropathy (4.1 for oxycodone versus 5.3 for placebo) using a 0 (no pain) to 10 (worst pain) scale.[23] The other was a four-arm, multiple crossover trial (each intervention for five weeks) comparing long-acting morphine (average titrated dose 45 mg/day), gabapentin, the combination of long-acting morphine and gabapentin, and low-dose lorazepam (used as an active placebo) for neuropathic pain.[40] It found that long-acting morphine was

superior to placebo for mean pain intensity (3.70 for morphine versus 4.49 for placebo on 0 to 10 scale), the 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. 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. Main results of these trials are summarized in Table 1.3.

The trials evaluated patients with a variety of chronic non-cancer pain conditions, including post-herpetic neuralgia,[66], diabetic neuropathy,[23, 24] various neuropathic pain conditions,[22, 25, 40] phantom limb pain,[63] osteoarthritis,[12, 55, 59, 65] back pain,[54, 56-58, 60] and miscellaneous chronic non-cancer pain.[41, 61, 64] Three trials evaluated long-acting codeine,[54, 61, 65] two long-acting dihydrocodeine,[56, 59] six long-acting morphine,[40, 41, 58, 62-64] seven long-acting oxycodone,[12, 23, 24, 55, 57, 60, 66] one levorphanol,[22] and one methadone.[25] The average opioid dose varied greatly and in two trials was not reported.[56, 59] The duration of followup ranged from 5 days to 16 weeks, and a wide range of outcomes and measures were employed. The most common outcomes assessed were pain intensity, rescue drug use, and withdrawals (Table 1.1). The studies used different pain intensity measures, the most common being visual analogue scales.

For most outcomes of clinical efficacy, the scales used varied too much across trials to draw meaningful comparisons between different long-acting opioids. For pain intensity, for example, of seven trials on oxycodone, two used a 0-100 visual analogue scale, [24, 66] and one used a 0-10 visual analogue scale,[23]; others used different (0-3[12, 57] or 0-4[55]) categorical scales, and one did not report pain intensity as an outcome.[60] For the outcomes pain intensity, pain relief, and functional outcome, there did not appear to be a pattern favoring one long-acting opioid over another.

Functional outcomes assessment also varied widely between studies. For sleep, the most widely reported functional outcome, measurement tools included sleep quality (1-5 scale[55] or 0-10 scale,[12, 23]) nighttime rescue medication use,[54] hours of sleep,[58] average nights awakened by sleep,[59], the Pain and Sleep Questionnaire,[24] the Brief Pain Inventory Sleep score,[40] and visual analogue scales (1-100) for trouble falling asleep and needing medication to sleep.[65] 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 marked heterogeneity in measurement scales.

Included trials markedly differed in terms of use of crossover, having 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.[25] 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-strength superior

to low-strength levorphanol for pain intensity and relief in patients with neuropathic pain are not comparable to results from trials using a non-opioid control or true placebo.[22]

Withdrawal rates were reported in all studies and also did not exhibit a pattern favoring one long-acting opioid versus other long-acting opioids (Table 1.2). For long-acting oxycodone, the withdrawal rate ranged from 4%[57] to 53%.[12] For long-acting morphine, the withdrawal rate ranged from 0%[63] to 30%.[64] Wide ranges for withdrawal rates were also seen for the trials on long-acting dihydrocodeine and long-acting codeine. 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, or other factors.

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 United States.[43, 69, 70] 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[69] found that 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 to placebo, one[70] found no statistically significant difference, and the third[43] 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/hour) and 46% with the highest dose (70 μg/hour), compared to 23% with placebo.[71] Statistical significance was not reported. Randomized controlled trial of long-acting hydromorphone[72] (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.

Evidence review

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 1.4). Three studies compared long-acting oxycodone to short-acting oxycodone.[55, 57, 60] One of these studies[57] re-randomized patients who had enrolled in a previous trial.[60] Two studies evaluated long-acting dihydrocodeine,[56, 59] one evaluated long-acting codeine,[54] and one evaluated long-acting morphine.[58] 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 1.4). Three studies that found differences in efficacy favoring long-acting morphine,[58] long-acting dihydrocodeine,[59] and long-acting codeine[54] had features that might invalidate these results. In the trials of long-acting morphine[58] and long-acting codeine,[54] 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,[59] significant differences in pain relief were only seen 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 inconsistently examined 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.[55, 57, 60] One of these trials[57] investigated a re-randomized population of patients studied in a previous trial[60] 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[55] 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.

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.[11] 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 was insufficient data from five head-to-head trials of long-acting opioids to conclude that any long-acting opioid is safer overall compared to others. None of the trials was designed to specifically assess safety. One was rated fair quality for adverse event assessment[39] and two poor-quality.[52, 53] The other was too small (n=18)[21] to adequately compare adverse event rates. Withdrawal due to any adverse events, a marker for serious or intolerable adverse events, was higher for transdermal fentanyl compared to oral long-acting morphine in two trials that compared these drugs.[39, 52] However, rates of constipation were lower for transdermal fentanyl in both trials. 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.

Evidence review

As discussed earlier, only five randomized trials directly compared two long-acting opioids (Table 2.1). Three of these trials compared two different long-acting opioids (transdermal fentanyl versus long-acting oral morphine[39, 52] or long-acting oxymorphone versus long-acting oxycodone[38]) and another[53] 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 five head-to-head trial was a very small trial (n=18) study of transdermal fentanyl versus twice-daily oral morphine in patients with chronic pancreatitis.[21] 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.

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).[39] 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% vs. 65% favoring transdermal fentanyl, $p<0.05$).

Although this trial found that rates of constipation were lower for transdermal fentanyl versus 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 versus 20% in morphine group), nausea (37% in both groups), and constipation (11% versus 23%). The proportion of withdrawals due to other adverse events (such as skin reactions, somnolence, dry mouth, or others) 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).[52] 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 compared to long-acting morphine (29% vs. 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.

One trial compared long-acting oxymorphone to long-acting oxycodone in patients with low back pain and was rated poor-quality for adverse event assessment (Evidence Table 2.1).[38] It met three out of the seven predefined criteria for adverse event assessment. It found no significant differences between the two long-acting opioids for rate of any adverse event, withdrawal due to adverse events, constipation, or sedation. Other adverse events were not reported.

The trial which compared once-daily versus twice-daily preparations of oral morphine was also rated poor-quality for adverse events (Evidence Table 2.1).[53] This trial met three out of seven predefined criteria for adverse event assessment. Serious complications (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%) vs. twice-daily morphine (29%), but a lower rate of asthenia (1% vs. 9%). The overall withdrawal rates in patients randomized to any long-acting

morphine preparation were 37-45%, with withdrawal rates due to adverse events ranging from 23-25%.

One meta-analysis[48] was excluded because it only included 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 the effectiveness of opioid rotation in patients with chronic non-cancer pain for management of adverse events associated with long-acting opioids.

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

Evidence regarding adverse events from 19 clinical trials comparing a long-acting opioid to short-acting opioid, placebo, or non-opioid is too heterogeneous and of insufficient quality to determine comparative risk of common gastrointestinal and neurological adverse event rates, as well as withdrawal rates due to adverse events. Rates of abuse and addiction were not reported in these trials. Two fair-quality retrospective studies that both used data from California Medicaid patients found that long-acting oxycodone[29, 30] was associated with higher risks of constipation than transdermal fentanyl. One of these studies[30] also found that long-acting morphine and transdermal fentanyl were not associated with statistically significant differences in risk of constipation. Other observational studies on adverse event were of generally poorer quality than the clinical trials and did not provide additional reliable information regarding comparative adverse event rates. Epidemiologic data published by the State of Oregon found that the rise in methadone-associated deaths observed between 1999 and 2002 is proportionate to changes in prescribing patterns and do not provide additional evidence regarding the risk of methadone compared to other long-acting opioids. Updated data from the DAWN study suggest that emergency-room visit "mentions" for various opioids have all increased, and don't clearly show an increased risk from specific opioids.[31]

Randomized Trials. 19 fair- or poor-quality randomized trials (1100 patients enrolled) gave indirect evidence regarding comparative adverse event rates from long-acting opioids in patients with chronic non-cancer pain. Seven trials compared the rates of adverse events for a long-acting opioid with a short-acting opioid (Evidence Table 2.2).[54-60] Eleven trials[12, 23-25, 40, 41, 61, 63-66] compared a long-acting opioid with placebo (Evidence Table 2.3). One trial that compared morphine to placebo also randomized patients to either gabapentin alone or gabapentin plus morphine.[40] One trial compared high-strength to low-strength levorphanol.[22] One trial of long-

acting morphine versus carbamazepine for neuropathic pain[62] was excluded because accurate adverse event rates could not be abstracted from the graphs in the article.

With regard to adverse event assessment, all 19 studies had at least two important methodological flaws (Table 2.1). In addition, these trials had heterogeneous study designs, interventions, outcomes, and patient populations, making meaningful comparisons across studies difficult (Table 1.1). Included trials generally found a higher rate of adverse events with long-acting opioids compared to placebo or active placebo (benztropine[24, 64] and lorazepam[40]). In trials that assessed adverse events from different doses of a long-acting opioid,[12, 22] 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).[40] 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, for example, rates of nausea ranged from 15%[55] to 50%[60] in five trials (Table 2.1). Withdrawal rates due to adverse events ranged from 4%[57] to 32%[12] in these same studies. Given the uncertainty regarding the adverse event rates 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 2.1).

Observational Studies. We identified 13 cohort studies evaluating the safety of long-acting opioids in patients with non-cancer pain.[12, 26-30, 53, 61, 73-77] None were rated good-quality for adverse event assessment (Evidence Table 2.4).

Opioids assessed were long-acting codeine,[61] long-acting morphine,[28, 30, 53, 74, 77] transdermal fentanyl,[26, 27, 29, 30, 73, 76] methadone,[74, 75] and long-acting oxycodone.[12, 29, 30] Two studies evaluated the comparative risk of constipation from different long-acting opioids;[29, 30] 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[75] to 2095.[29] Eight were prospective cohort studies[12, 26-28, 53, 61, 73, 76] and five were retrospective cohorts.[29, 30, 74, 75, 77] The prospective cohort studies recruited all[12, 53, 61, 73] or some[76] of their patients from completed clinical trials. Three of the prospective cohorts[12, 53, 61] were open-label extensions of clinical trials included in this review.

Two large, fair-quality retrospective cohort studies of California Medicaid patients found that rates of a new diagnosis of constipation was significantly higher in patients prescribed long-acting oxycodone (adjusted odds ratios 2.55, 95% CI 1.33-4.89[29] and 1.78, 95% CI 1.05-3.03[30]) compared to transdermal fentanyl 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 to transdermal fentanyl and did not find a statistically significant difference (adjusted odds ratio 1.44, 95% CI 0.80-2.60).[30] 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.[39, 52]

Results of the other observational studies were not significantly different from those reported in clinical trials for common adverse events or withdrawal rates due to adverse events (Table 2.2). Some observational studies reported long-term outcomes and serious adverse events not reported in the trials. The largest (n=530) study[76] 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,[74, 75] 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.[12, 53, 61, 73] Rates ranged from 19% for transdermal fentanyl[73] to 54% for long-acting codeine.[61] 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.[28]

Other than in the 2 California Medicaid-based studies,[29, 30] 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,[12, 53, 61, 73, 76] 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.[74, 75, 77]

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.[78] No information on the numbers of prescriptions for methadone in the county, number of patients prescribed methadone, or on 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/day).[79] 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 (median 110 mg/day) of methadone found that 32% had QTc prolongation, but none had prolongation beyond the value (500 msecs) considered a definite risk for torsades de pointes.[80]

The ongoing Drug Abuse Warning Network (DAWN) study reports "mentions" of drug-related visits for various prescription and non-prescription opioids in emergency departments across the U.S.[81] Because this study does not report the underlying clinical condition of patients, however, and does not distinguish between long- or short-acting opioids or different modes of administration (intravenous vs. oral vs. 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 (e.g., the number of prescriptions or amount dispensed).[1] The most recent (from 1997 through 2002) analysis of the DAWN 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.[31] The DAWN methods have

recently undergone substantial revisions.[82] Data on emergency room mentions associated with different opioid medications using the new methodology will not be directly comparable to the older DAWN data when they become available.

Results published by the Office of Communicable Disease and Epidemiology on methadone deaths 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/100,000 persons between 1997 and 2001).[32] 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 a comparable abuse potential to morphine.

An evidence review on 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]

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 to short-acting opioids for all assessed adverse events. There was no data comparing rates of addiction or abuse with long-acting versus short-acting opioids.

Evidence review

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.[54-60] None of the studies were designed to assess rates of addiction or abuse.

In the single trial in this group rated fair-quality,[58] 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 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 2.1).

Across all trials, no pattern favoring either long-acting or short-acting opioids was evident for any of the reported adverse events (Table 2.3). In the three most comparable studies, which investigated roughly equivalent daily doses of oxycodone in short-acting and long-acting preparations,[55, 57, 60] 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[57, 60] that investigated the same (re-randomized) population.

Withdrawals due to adverse events were reported in five trials (Table 2.1). Three favored short-acting opioids,[54, 59, 60] one favored long-acting,[55] and one was equivocal.[57] 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.

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.[29] 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.

Evidence review

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-50's, though one study[66] evaluated patients with an average age of 70 years. Two trials[12, 55] performed very limited subgroup analysis on older patients; neither trial was a direct comparison of one long-acting opioid versus another and 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).[29] 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,[38, 39, 54, 56-58, 60] osteoarthritis, [12, 55, 59, 65] phantom limb pain,[63] and neuropathic pain.[22-25, 40, 62, 66] Only two trials were rated good-quality for assessment of clinical efficacy,[23, 40] and 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[25] and one trial of levorphanol[22] in adult patients with chronic non-cancer pain are available. Both of these trials used designs (methadone or placebo randomly administered only every other day and high- versus 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[39] longer than 6 months in duration.

In general, there was insufficient evidence to prove that one long-acting opioid is more effective or safer overall compared to others. The largest and highest-quality trial directly comparing long-acting opioids was rated fair-quality and didn't clearly demonstrate the superiority of transdermal fentanyl compared to oral long-acting morphine for either efficacy or overall safety.[39] It found that transdermal fentanyl and oral sustained-release morphine were similar for pain relief and other measures of efficacy. In addition, although transdermal fentanyl was associated with less constipation than oral morphine (31% vs. 48%), it was also associated with a higher (though not statistically significant) rate of withdrawal due to any adverse event (37% vs. 31%). Another trial that directly compared these two long-acting opioids was rated poor-quality and also gave inconclusive results.[52] The results were particularly difficult to interpret because the trial was open-label and included a large proportion of patients who were receiving one of the study drugs prior to enrollment. A third, small (n=18) fair-quality trial[21] found no significant differences between transdermal fentanyl and long-acting morphine in patients with the specific condition of chronic pancreatitis. A fair-quality trial[53] that directly compared once-daily versus twice-daily morphine also was inconclusive. Although this study found a slight improvement in overall quality of sleep for once-daily morphine given in the morning compared to twice-daily morphine, it also found significantly more constipation in the

once-daily morphine group (though less asthenia). Other measures of sleep quality and pain control were not significantly different. The fifth trial found no differences between long-acting oxymorphone or long-acting oxycodone for efficacy or safety.[38]

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.[29, 30] 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[55, 57, 60] 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 recent 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. Overview of all long-acting opioid trials

Author Year	Long acting opioid	Study type	Pain type	Duration	Sample size	Average dose (mg/day)	Pain intensity score	Scale	Rescue drug	Average rescue drug usage
Long-acting vs. long-acting trials										
Allan, 2005[39]	A: Transdermal fentanyl B: Oral morphine (twice daily)	RCT	Low back pain	13 months	683	A: 57 mcg/hr B: 140	Not reported	0-100 VAS	Not specified	Not reported ('did not differ')
Allan, 2001[52]	A: Transdermal fentanyl B: Oral morphine (twice daily)	RCT with crossover	Miscellaneous	4 weeks*	212	A: 57 mcg/hr B: 133	A: 57.8 B: 62.9	0-100 VAS	IR Morphine	29.4 mg/day 23.6 mg/day
Hale, 2005[38]	A: Oral oxymorphone (twice daily) B: Oral oxycodone (twice daily)	RCT	Low back pain	18 days	235	A: 79 mg B: 155 mg	Not reported	0-100 VAS	IR Morphine	13.8 mg/day 14.7 mg/day
Caldwell, 2002[53]	A: Morphine (once daily a.m.) B: Morphine (once daily p.m.) C: Morphine (twice daily)	RCT	Osteoarthritis	4 weeks	295	A: 30 mg B: 30 mg C: 30 mg	A: 313 B: 326 C: 322	0-500 VAS	Not permitted	N/A
Niemann, 2000[21]	A: Transdermal fentanyl B: Oral morphine (twice daily)	RCT with crossover	Chronic pancreatitis	4 weeks*	18	A: 56 mcg/hr B: 128	Not calcuable	5 point Cat.	IR Morphine	A: 30.7 mg B: 14.7 mg
Long-acting vs. short-acting, placebo or non-opioid trials										
Long-acting oxycodone										
Caldwell, 1999[55]	Oxycodone	RCT	Osteoarthritis	4 weeks	107	40	1.3	0-4 Cat.	Not permitted	N/A
Gimbel, 2003[23]	Oxycodone	RCT	Diabetic neuropathy	6 weeks	159	42	6.9	0-10 Cat.	Not permitted	N/A
Hale, 1999[57]	Oxycodone	RCT with crossover	Back pain	6 days*	47	40	1.2	0-3 Cat.	IR Oxycodone 5-10 mg PRN	0.6 tabs/day
Roth, 2000[12]	Oxycodone	RCT	Osteoarthritis	2 weeks	133	40	1.6	0-3 Cat.	Not permitted	N/A
Salzman, 1999[60]	Oxycodone	RCT	Back pain	10 days	57	40	1.1	0-3 Cat.	IR Oxycodone 5-10 mg PRN	NR
Watson, 2003[24]	Oxycodone	RCT with crossover	Diabetic polyneuropathy	4 weeks*	45	40	67	0-100 VAS	Acetaminophen 325-650 mg q 6 hrs	NR
Watson, 1998[66]	Oxycodone	RCT with crossover	Postherpic neuralgia	4 weeks*	50	45	35	0-100 VAS	Not permitted	N/A

Table 1.1. Overview of all long-acting opioid trials

Author Year	Long acting opioid	Study type	Pain type	Duration	Sample size	Average dose (mg/day)	Pain intensity score	Scale	Rescue drug	Average rescue drug usage
Other long-acting opioids										
Arkinstall, 1995[61]	Codeine	RCT with crossover	Miscellaneous	7 days*	46	353	35	0-100 VAS	Tylenol with codeine	3.6 tabs/day
Hale 1997[54]	Codeine	RCT	Back pain	5 days	83	200	1.6	0-4 Cat.	Acetaminophen	4.0 tabs/day
Peloso, 2000[65]	Codeine	RCT	Osteoarthritis	4 weeks	103	159	32.5	0-100 VAS	Tylenol	4.2 tabs/day
Lloyd, 1992[59]	Dihydrocodeine	RCT	Osteoarthritis	2 weeks	86	NR	39.2	0-100 VAS	Not permitted	N/A
Gostick 1989[56]	Dihydrocodeine	RCT with crossover	Back pain	2 weeks*	61	NR	1.75	Not provided	Paracetamol	1.54 tabs/day
Rowbotham 2003[!22]	Levorphanol	RCT	Neuropathic pain	4 weeks	81	9[!]	65	0-100 VAS	Not specified	Not reported
Morley, 2003[25]	Methadone	RCT	Neuropathic pain	2 phases of 20 days each**	19	Phase I: 10 Phase II: 10	NR	0-100 VAS	Not specified	Not reported
Gilron, 2005[40]	Morphine	RCT with crossover	Neuropathic pain	5 weeks*	57	45	3.7	0-10 VAS	Non-opioids	Not reported
Harke, 2001[62]	Morphine	RCT	Neuropathic pain	8 days	38	83	6.9†	0-10 VAS	Not permitted	N/A
Huse, 2001[63]	Morphine	RCT with crossover	Phantom limb pain	4 weeks*	12	115	3.62	0-10 VAS	Aspirin + paracetamol	NR
Jamison, 1998[58]	Morphine	RCT	Back pain	16 weeks	36	41	54.9	0-100 VAS	Permitted but not specified	NR
Maier, 2002[41]	Morphine	RCT with crossover	Various pain conditions	1 week*	49	100	5.1	0-10 scale	Step II opioids permitted	NR
Moulin, 1996[64]	Morphine	RCT with crossover	Miscellaneous	6 weeks*	61	83.4	45	0-100 VAS	Paracetamol	3.5 tabs/day

* Duration per intervention of crossover trial

**Each phase consisted of 10 days of randomly assigned methadone or placebo, alternating with 10 days of neither

† Maximum pain intensity prior to reactivation of spinal cord stimulation unit

! Data for high-dose levorphanol arm (low-dose levorphanol used as control)

RCT= randomized controlled trial; VAS=visual analogue scale; PRN=as needed; IR=immediate release opioid preparation; NR=not reported

Table 1.2. Withdrawal rates

Author Year	Long acting opioid	Pain type	Duration	Sample size	Overall withdrawal rates	Pre-randomization titration withdrawal	Withdrawal rates per drug	Inadequate pain control	Adverse effects	Other
Long-acting vs. long-acting trials										
Allan, 2005[39]	A: Transdermal fentanyl B: Oral morphine (twice daily)	Low back pain	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)	Miscellaneous	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	Low back pain	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
Caldwell, 2002[53]	A: Morphine (once daily a.m.) B: Morphine (once daily p.m.) C: Morphine (twice daily) D: Placebo	Osteoarthritis	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)	Chronic pancreatitis	4 weeks*	18	6%	N/A	A: 6% (1/18) B: 0% (0/18)	Not clear	Not clear	N/A

* Duration per intervention of crossover trial
**Withdrawal on day of or after receiving methadone or placebo
† $p<0.05$
RCT= randomized controlled trial; VAS=visual analogue scale; PRN=as needed; IR=immediate release opioid preparation; NR=not reported

Table 1.2. Withdrawal rates

Author Year	Long acting opioid	Pain type	Duration	Sample size	Overall withdrawal rates	Pre-randomization titration withdrawal	Withdrawal rates per drug	Inadequate pain control	Adverse effects	Other
Long-acting vs. short-acting, placebo or non-opioid trials										
Long-acting oxycodone										
Caldwell, 1999[55]	Oxycodone	Osteoarthritis	4 weeks	107	34%	22% (36/176) Adv. Ef 10% (17/167) Ineff. Tx 4% (7/167) Other	*LA Oxycodone:* 21%† (7/34)	3†	3	1
							IR Oxycodone: 30% (11/37)	4	5	2
							Placebo: 50% (18/36)	13	3	2
Gimbel, 2003[23]	Oxycodone	Diabetic neuropathy	6 weeks	159	28%	Not reported	Overall: 28% (44/159)	1	7	12
							By intervention, not clear	11	4	12
Hale, 1999[57]	Oxycodone	Back pain	6 days*	47	6%	See Salzman	*LA Oxycodone:* 4% (2/47)	0	2	0
							IR Oxycodone: 2% (1/47)	0	1	1
Roth, 2000[12]	Oxycodone	Osteoarthritis	2 weeks	133	53%	N/A	*LA Oxycodone 20mg:* 42% (19/44)	5†	14†	0
							LA Oxycodone 10mg: 50% (24/44)	12	12	0
							Placebo: 60% (27/45)	22	2	3
Salzman, 1999[60]	Oxycodone	Back pain	10 days	57	18%	N/A	*LA Oxycodone:* 20% (6/30)	NR	6	NR
							IR Oxycodone: 7% (2/27)		2	
							Adv. Eff. Only + 2 others NOS			
Watson, 2003[24]	Oxycodone	Diabetic neuropathy	4 weeks*	45	20%	N/A	*LA Oxycodone: 22% (10/45)*	1	7	2
							Placebo: 24% (11/45)	7	1	3
Watson, 1998[66]	Oxycodone	Postherpic neuralgia	4 weeks*	50	22%	N/A	*LA Oxycodone:* 12% (6/50)	0	5	1
							Placebo: 10% (5/50)	1	3	1

* Duration per intervention of crossover trial
**Withdrawal on day of or after receiving methadone or placebo
† p<0.05
RCT= randomized controlled trial; VAS=visual analogue scale; PRN=as needed; IR=immediate release opioid preparation; NR=not reported

Table 1.2. Withdrawal rates

Author Year	Long acting opioid	Pain type	Duration	Sample size	Overall withdrawal rates	Pre-randomization titration withdrawal	Withdrawal rates per drug	Inadequate pain control	Adverse effects	Other
Other long-acting opioids										
Arkinstall, 1995[61]	Codeine	Miscellaneous	7 days*	46	28%	N/A	*Codeine:* 19% (9/46) *Placebo:* 9% (4/46)	1 0	7† 1	1 3
Hale, 1997[54]	Codeine	Back pain	5 days	83	22%	N/A	*LA Codeine:* 32%† (17/53) *IR Codeine:* 12% (6/51)	1 1	15† 5	1 0
Peloso, 2000[65]	Codeine	Osteoarthritis	4 weeks	103	36%	N/A	*40% (20/51) Codeine* *33% (17/52) Placebo*	1 5	15† 5	1 0
Gostick 1989[56]	Dihydrocodeine	Back pain	2 weeks*	61	26%	N/A	NR	NR	NR	NR
Lloyd, 1992[59]	Dihydrocodeine	Osteoarthritis	2 weeks	86	34%	N/A	*Dihydrocodeine:* 47%† (20/43) *Dextropropoxyphene + paracetamol:* 21% (9/43)	1 2	17† 4	2 3
Rowbotham, 2003[22]	Levorphanol	Neuropathic pain	4 weeks	81	27%	N/A	*Not reported by drug; 31% (25/81) overall*	3 overall	15 (high-dose) 3 (low-dose)	4 overall
Morley, 2003[25]	Methadone	Neuropathic pain	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

* Duration per intervention of crossover trial
**Withdrawal on day of or after receiving methadone or placebo
† p<0.05
RCT= randomized controlled trial; VAS=visual analogue scale; PRN=as needed; IR=immediate release opioid preparation; NR=not reported

Table 1.2. Withdrawal rates

Author Year	Long acting opioid	Pain type	Duration	Sample size	Overall withdrawal rates	Pre-randomization titration withdrawal	Withdrawal rates per drug	Inadequate pain control	Adverse effects	Other
Other long-acting opioids										
Gilron, 2005[40]	Morphine	Neuropathic pain	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[62]	Morphine	Neuropathic pain	8 days	38	8%	N/A	*Morphine:* 5% (1/19) *Placebo:* 11% (2/19)	NR	NR	1 2
Huse, 2001[63]	Morphine	Phantom limb pain	4 weeks*	12	0%	N/A	*Morphine:* 0% (0/12) *Placebo:* 0% (0/12)	NR	N/A	N/A
Jamison, 1998[58]	Morphine	Back pain	16 weeks	36	0%	N/A	*LA Morphine+IR Oxy.:* 9% (1/11) *IR Oxycodone:* 15% (2/13)	NA	1 2	NA
Maier, 2002[41]	Morphine	Miscellaneous	1 week*	49	6%	N/A	*Morphine:* 12% (3/25) *Placebo:* 0% (0/23)	None reported	3 0	NR
Moulin, 1996[64]	Morphine	Miscellaneous	6 weeks*	61	30%	*Morphine:* 48%† (15/31) *Benztropine:* 13% (4/30)	3 others (not specified)	NR	NR	NR

* Duration per intervention of crossover trial
**Withdrawal on day of or after receiving methadone or placebo
† $p<0.05$
RCT= randomized controlled trial; VAS=visual analogue scale; PRN=as needed; IR=immediate release opioid preparation; NR=not reported

Table 1.3. Main efficacy results, head-to-head and placebo-controlled trials of long-acting opioids for chronic non-cancer pain

Medications	Trial Quality rating	Population Number enrolled	Main outcomes
Head-to-head trials			
A: Transdermal fentanyl B: Long-acting morphine (twice daily)	Allan 2005[39] **FAIR**	Low back pain requiring strong opioids, in patients not receiving regular strong opioids at study entry 683	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).
A: Transdermal fentanyl B: Long-acting morphine (twice daily)	Allan 2001[52] **POOR**	Non-cancer pain requiring continuous opioids 256	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).
A: Long-acting oxymorphone (twice daily) B: Long-acting oxycodone (twice daily) C: Placebo	Hale 2005[38] **FAIR**	Low back pain on stable doses of opioids 235	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.
A: Once-daily morphine in a.m. B: Once-daily morphine in p.m. C: Twice-daily morphine D: Placebo	Caldwell 2002[53] **FAIR**	Osteoarthritis with moderately severe pain and insufficient response to non-opioids 295	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).
A: Transdermal fentanyl B: Long-acting morphine (twice daily)	Niemann 2000[21] **FAIR**	Opioid treated chronic pancreatitis 18	No significant differences between treatments for preference or global pain control using unspecified methods, or quality of life using SF-36.

*Results reported for 20 mg bid dose intervention
VAS=visual analogue scale

Table 1.3. Main efficacy results, head-to-head and placebo-controlled trials of long-acting opioids for chronic non-cancer pain

Medications	Trial Quality rating	Population Number enrolled	Main outcomes
Long-acting opioid vs. placebo			
Long-acting codeine			
Long-acting codeine	Arkinstall 1995[29] **FAIR**	Chronic non-malignant pain of at least moderate intensity 46	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.
Long-acting codeine	Peloso 2000[65] **FAIR**	>35 years old with primary osteoarthritis requiring analgesics for >3 months 103	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			
Levorphanol	Rowbotham 2003[22] **FAIR**	Various neuropathic pain 81	High-strength levorphanol superior to low-strength (comparator) for pain intensity using 0-100 VAS; no differences for pain relief using 0-5 categorical scale, mood disturbance/cognitive impairment using Profile of Mood States or Symbol-Digit Modalities Test, or quality of life using Multidimensional Pain Inventory
Methadone			
Methadone	Morley 2003[25] **FAIR**	Various neuropathic pain 19	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

*Results reported for 20 mg bid dose intervention
VAS=visual analogue scale

Table 1.3. Main efficacy results, head-to-head and placebo-controlled trials of long-acting opioids for chronic non-cancer pain

Medications	Trial Quality rating	Population Number enrolled	Main outcomes
Long-acting morphine			
Long-acting morphine	Gilron 2005[40] **GOOD**	Moderate or greater pain from diabetic neuropathy or postherpetic neuralgia for at least 3 months 57	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.
Long-acting morphine	Harke 2001[62] **FAIR**	Neuropathic pain patients treated successfully with spinal cord stimulation who agreed to forego spinal cord stimulation and completed another trial 38	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.
Long-acting morphine	Huse 2001[63] **FAIR**	Unilateral amputees with phantom limb pain at least 3 out of 10 12	Long-acting morphine superior to placebo for pain intensity using 0-10 VAS and for proportion of treatment responders (greater than 50% reduction in pain).
Long-acting morphine	Maier 2002[41] **FAIR**	Various noncancer pain unresponsive to pre-specified treatments 47	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)
Long-acting morphine	Moulin 1996[64] **FAIR**	Moderate or greater stable non-malignant pain for at least 6 months unresponsive to non-opioids 61	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.

*Results reported for 20 mg bid dose intervention
VAS=visual analogue scale

Table 1.3. Main efficacy results, head-to-head and placebo-controlled trials of long-acting opioids for chronic non-cancer pain

Medications	Trial Quality rating	Population Number enrolled	Main outcomes
Long-acting oxycodone			
Long-acting oxycodone	Gimbel 2003[23] **GOOD**	Painful diabetic polyneuropathy documented by physical exam for >3 months 160	Long-acting oxycodone superior to placebo for pain intensity, pain right now, and worst pain using 0-10 numeric analogue 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.
Long-acting oxycodone	Roth 2000[12] **FAIR**	Osteoarthritis clinically and radiographically for >1 month 133	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)*
Long-acting oxycodone	Watson 2003[24] **FAIR**	Painful diabetic neuropathy 45	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
Long-acting oxycodone	Watson 1998[66] **FAIR**	Moderate or greater postherpetic neuralgia for >3 months 50	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.

*Results reported for 20 mg bid dose intervention
VAS=visual analogue scale

Table 1.4. Overview of randomized controlled trials of long acting vs short acting opioids†

Author Year	Pain type	Duration	Patients	Findings
Oxycodone				
Caldwell 1999[55]	Osteoarthritis	30 days	107	LA Oxycodone and IR Oxycodone plus Tylenol are equally effective for pain control and improvement of sleep.
Hale 1999[57]	Back pain	6 days*	47	LA Oxycodone and IR Oxycodone are equally effective for pain control.
Salzman 1999[60]	Back pain	10 days	57	LA Oxycodone and IR Oxycodone are equally effective when titrated for pain control.
Codeine				
Hale 1997[54]	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[56]	Back pain	2 weeks*	61	LA Dihydrocodeine and IR Dihydrocodeine are equally effective for pain control.
Lloyd 1992[59]	Osteoarthritis	2 weeks	86	LA Dihydrocodeine and IR Dihydrocodeine are equally effective for pain control when compared directly.
Morphine				
Jamison 1998[58]	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.

* Duration per intervention of crossover trial

† All trials are of FAIR quality

LA=long-acting opioid preparation; IR=immediate release/short-acting opioid preparation

Table 2.1. Study characteristics and adverse events, trials of long-acting opioids

Study	Interventions	Quality Rating *	Nausea	Vomiting	Constipation	Drowsiness or Somnolence	Dizziness	Confusion or Difficulty Concentrating	Withdrawal†
Head-to-head trials of one long-acting opioid versus another									
Allan, 2005[39]	A: Transdermal fentanyl	FAIR (4)	A: 54% (176/338)	A: 29% (97/338)	A: 52% (176/338)	A: 27% (92/338)	A: 25% (85/338)	Not reported	A: 37% (125/335)
	B: Long-acting morphine		B: 50% (169/338)	B: 26% (89/338)	B: 65% (220/338)	B: 30% (102/338)	B: 24% (81/338)		B: 31% (104/337)
Allan, 2001[52]	A: Transdermal fentanyl	POOR (2)	A: 26% (64/250)	A: 10% (25/250)	A: 16% (41/250)	A: 18% (45/250)	A: 11% (28/250)	Not reported	A: 11% (27/250)
	B: Long-acting morphine		B: 18% (44/238)	B: 10% (24/238)	B: 22% (52/238)	B: 14% (34/238)	B: 4% (9/238)		B: 4% (10/238)
Caldwell, 2002[53]	A: Once-daily morphine a.m.	POOR (3)	A: 21% (15/73)	A: 6% (4/73)	A: 49% (36/73)	A: 16% (12/73)	A: 10% (10/73)	Not reported	A: 23% (17/73)
	B: Once-daily morphine p.m.		B: 32% (23/73)	B: 16% (12/73)	B: 40% (29/73)	B: 12%(9/73)	B: 10% (10/73)		B: 25% (18/73)
	C: Twice-daily morphine		C: 26% (20/76)	C: 8% (6/76)	C: 29% (22/76)	C: 12% (9/76)	C: 12% (9/76)		C: 24% (18/76)
	D: Placebo		D: 10% (7/73)	D: 1% (1/73)	D: 4% (3/73)	D: 0%	D: 1% (1/73)		D: 7% (5/73)
Hale, 2005[38]	A: Long-acting oxymorphone	POOR (3)	NR	NR	A: 35% (39/110)	A: 17% (19/110)	NR	NR	A: 15% (25/166) titration, 2.5% (2/80) treatment
	B: Long-acting oxycodone				B: 29% (32/111)	B: 20% (22/111)			B: 16% (26/164) titration, 5.0% (4/80) treatment
	C: Placebo				C: 11% (12/108)	C: 2% (1/108)			C: 6.7% (5/75) treatment
Niemann, 2000[21]	A: Transdermal fentanyl	POOR (3)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	A: 6% (1/18)
	B: Long-acting morphine								B: 0%

Table 2.1. Study characteristics and adverse events, trials of long-acting opioids

Study	Interventions	Quality Rating *	Nausea	Vomiting	Constipation	Drowsiness or Somnolence	Dizziness	Confusion or Difficulty Concentrating	Withdrawal†
Long-acting opioid versus short-acting opioid, placebo, or non-opioid									
Long-acting oxycodone:									
Caldwell, 1999[55]	A: Long-acting oxycodone	POOR (3)	A: 15%(5/34)	A: 6%(2/34)	A: 71%(24/34)	A: 53%(18/34)	A: 12%(4/34)	Not reported	A: 6% (3/34)
	B: Short-acting oxycodone + acetaminophen		B: 38%(14/37)	B: 11%(4/37)	B: 54%(20/37)	B: 70%(26/37)	B: 24%(9/37)		B: 14% (5/37)
Gimbel, 2003[23]	A: Long-acting oxycodone	FAIR (4)	A: 36% (30/82)	A: 21% (17/82)	A: 42% (35/82)	A: 40% (33/82)	A: 32% (26/82)	Not reported	A: 9% (7/82)
	B: Placebo		B: 8% (6/77)	B: 3% (2/77)	B: 14% (11/77)	B: 1% (1/77)	B: 10% (8/77)		B: 5% (4/77)
Hale, 1999[57]	A: Long-acting oxycodone	POOR (3)	A: 16%(4/25)	A: 0%(0/25)	A: 32%(8/25)	A: 12%(3/25)	A: 16%(4/25)	Not reported	A: 4% (2/47)
	B: Immediate-release oxycodone		B: 41%(9/22)	B: 0%(0/22)	B: 45%(10/22)	B: 18%(4/22)	B: 9%(2/22)		B: 2% (1/47)
Roth, 2000[12]	A1: Long-acting oxycodone 20 mg bid	FAIR (5)	A1: 41%(18/44)	A1: 23%(10/44)	A1: 32%(14/44)	A1: 27%(12/44)	A1: 20%(9/44)	Not reported	A1: 32%(14/44)
	A2: Long-acting oxycodone 10 mg bid		A2: 27%(12/44)	A2: 11%(5/44)	A2: 23%(10/44)	A2: 25%(11/44)	A2: 30%(13/44)ß		A2: 27%(12/44)
	B: Placebo		B: 11%(5/45)	B: 7%(3/45)	B: 7%(3/45)	B: 4%(2/45)	B: 9%(4/45)		B: 4%(2/45)
Salzman, 1999[60]	A: Long-acting oxycodone	POOR (3)	A: 50%(15/30)	A: 20%(6/30)	A: 30%(9/30)	A: 27%(8/30)	A: 30%(9/30)	A: 3%(1/30)	A: 20% (6/30)
	B: Short-acting oxycodone		B: 33%(9/27)	B: 4%(1/27)	B: 37%(10/27)	B: 37%(10/27)	B: 22%(6/27)	B: 0%(0/27)	B: 7% (2/27)
Watson, 2003[24]	A: Long-acting oxycodone	POOR (3)	A: 36% (16/45)	A: 11% (5/45)	A: 29% (13/45)	A: 20% (9/45)	A: 16% (7/45)	Not reported	A: 16% (7/45)
	B: Benztropine		B: 18% (8/45)	B: 4% (2/45)	B: 9% (4/45)	B: 24% (11/45)	B: 7% (3/45)		B: 2% (1/45)
Watson, 1998[66]	A: Long-acting oxycodone	FAIR (4)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
	B: Placebo								

Table 2.1. Study characteristics and adverse events, trials of long-acting opioids

Study	Interventions	Quality Rating *	Nausea	Vomiting	Constipation	Drowsiness or Somnolence	Dizziness	Confusion or Difficulty Concentrating	Withdrawal†
Long-acting codeine:									
Arkinstall¶ 1995[61]	A: Long-acting codeine	FAIR (4)	A: 33%ß	A: 14%	A: 21%	A: 16%	A: 21%	Not reported	A: 15% (7/46)
	B: Placebo		B: 12%	B: 3.8%	B: 10%	B: 5%	B: 14%		B: 2% (1/46)
Hale, 1997[54]	A: Long-acting codeine	POOR (2)	A: 31% (16/52)	A: 10% (5/52)	A: 19% (10/52)	A: 10% (5/52)	A: 17% (9/52)	Not reported	A: 13/53 (25%)
	B: Short-acting codeine		B: 18% (9/51)	B: 2% (1/51)	B: 16% (8/51)	B: 4% (2/51)	B: 4% (2/51)		B: 4/51 (8%)
Peloso, 2000[65]	A: Long-acting codeine	FAIR (4)	Not reported	Not reported	A: 49%(25/51)ß	A: 39%(20/51)	A: 33%(17/51)	Not reported	A: 29%(15/51)
	B: Placebo				B: 11%(6/52)	B: 10%(5/52)	B: 8%(4/52)		B: 8%(4/52)
Long-acting dihydrocodeine									
Gostick 1989[56]	A: Long-acting dihydrocodeine	POOR (3)	Not reported	Not reported	A: 55% (23/42)‡	Not reported	Not reported	Not reported	26% (16/61) overall, "no treatment differences"
	B: Short-acting dihydrocodeine				B: 48% (21/44)				
Lloyd§ 1992[59]	A: Long-acting dihydrocodeine	POOR (3)	A: 31%(12/39)	Not reported	A: 8%(3/39)	A: 26%(10/39)	Not reported	A: 10%(4/39)	A: 40%(17/43)
	B:Dextropropoxyphene + paracetamol		B: 10%(4/41)		B: 10%(4/41)	B: 15%(6/41)		B: 5%(2/41)	B: 9%(4/43)
Levorphanol									
Rowbotham 2003[22]	A: Levorphanol high-strength	FAIR (4)	Not reported	Not reported	Not reported	Not reported	A: 5% (2/43)	A: 12% (5/43)	31% overall, not reported by intervention
	B: Levophanol low-strength						B: 0% (0/38)	B: 0% (0/38)	
Methadone									
Morley 2003***[25]	A: Methadone	POOR (1)	A: 37% (7/19) for 10 mg/day; 47% (8/17) for 20 mg/day	A: 21% (4/19) phase I; 6% (1/17) phase II	A: 11% (2/19) phase I; 18% (3/17) phase II	A: 11% (2/19) phase I; 18% (3/17) phase II	A: 32% (6/19) phase I; 18% (3/17) phase II	Not reported	A: 5% (1/19) phase I; 18% (3/17) phase II
	B: Placebo		B: 21% (4/19) phase I; 24% (4/17) phase II	B: 5% (1/19) phase I; 6% (1/17) phase II	B: 5% (1/19) phase I; 6% (1/17) phase II	B: 11% (2/19) phase I; 12% (2/17) phase II	B: 0% (0/19) phase I; 6% (1/17) phase II		B: 0% (0/19) phase I; 18% (3/17) phase II

Table 2.1. Study characteristics and adverse events, trials of long-acting opioids

Study	Interventions	Quality Rating *	Nausea	Vomiting	Constipation	Drowsiness or Somnolence	Dizziness	Confusion or Difficulty Concentrating	Withdrawal†
Long-acting morphine:									
Gilron¶ 2005[40]	A: Long-acting morphine	FAIR (4)	A: 5%	0% in all arms	A: 39%	A: 16%	A: 0%	A: 2%	Not reported
	B: Gabapentin		B: 0%		B: 2%	B: 8%	B: 2%	B: 2%	
	C: Long-acting morphine + gabapentin		C: 7%		C: 21%	C: 21%	C: 0%	C: 7%	
	D: Placebo		D: 0%		D: 5%	D: 5%	D: 0%	D: 2%	
Huse‡‡ 2001[63]	A: Long-acting morphine	FAIR (4)	A: 0.74 cm	Not reported	A: 0.03 cmß	A: 2.21 cm	A: 1.27 cm	Not reported	Not reported
	B: Placebo		B: 0.4 cm		B: 0.02 cm	B: 1.33 cm	B: 0.71 cm		
Jamison¶ 1998[58]	A: Long-acting morphine + short-acting oxycodone	FAIR (5)	A: 31%	Not reported	A: 30%	A: 31%	A: 6%	A: 0%	A: 9% (1/11)
	B: Short-acting oxycodone		B: 14%		B: 18%	B: 14%	B: 19%	B: 1.4%	B: 15% (2/13)
Maier 2002[41]	A: Long-acting morphine	FAIR (3)	A: 23% (11/48)	A: 4% (2/48)	A: 19% (9/48)	A: 23% (11/48)	A: 20% (10/48)	NR	A: 12% (3/25)
	B: Placebo		B: 14% (6/48)	B: 4% (2/48)	B: 4% (2/48)	B: 2% (1/48)	B: 4% (2/48)		B: 0% (0/23)
Moulin 1996[64]	A: Long-acting morphine	FAIR (5)	A: 39%(18/46)ß	A: 39%(18/46)ß	A: 41% (19/46)ß	Not reported	A: 37%(17/46)	A: 9%(4/46)	A: 28%** (13/46)
	B: Benztropine		B: 7%(3/46)	B: 2%(1/46)	B: 4%(2/46)		B: 2%(1/46)	B: 15%(7/46)	B: 2%(1/46)

*Number of criteria out of seven adequately met

†Due to adverse events

¶Sample size not clear

ßp<0.05 for difference in rates

‡Constipation defined as bowel movement less frequently than every two days

§Results from end of first week of treatment because of high rate of withdrawals after first week

‡‡Results reported on 10 cm visual analog scale

**Dose-limiting side effects (not withdrawal rate), p=0.003 for difference in rates

***Adverse events reported on day of or day after taking methadone or placebo

Table 2.2. Study characteristics and adverse events, cohort studies of long-acting opioids

Study	Long-acting opioids studied	Quality rating*	Nausea	Vomiting	Constipation	Drowsiness or somnolence	Dizziness	Confusion or difficulty concentrating	Withdrawal†	Long-term use
Arkinstall 1995[61]	Long-acting codeine	POOR (2)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	54% (15/28)
Bach 1991[77]	Long-acting morphine (twice-daily)	POOR (0)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Caldwell 2002[53]	Long-acting morphine (once-daily)	POOR (2)	16% (29/181)	6% (11/181)	35% (63/181)	13% (23/181)	9% (16/181)	Not reported	33% (60/181)	48% (86/181)
Dellemijn 1998[73]	Transdermal fentanyl	POOR (2)	92%	54%	36%	58%	53%	<20%	Not reported	19% (9/48)
Dunbar 1996[74]	Methadone	POOR (0)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
	Long-acting morphine		Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Franco 2002[27]	Transdermal fentanyl	POOR (1)	22% (51/236)	15% (36/236)	15% (36/236)	22% (53/236)	25% (59/236)	Not reported	Not reported	53% (126/236)
Green 1996[75]	Methadone	POOR (0)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Milligan 2001[76]	Transdermal fentanyl	POOR (1)	9% (48/530)	8% (42/530)	Not reported	Not reported	Not reported	Not reported	25% (130/530)	57% (301/532)
Ringe 2002[26]	Transdermal fentanyl	POOR (0)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	20% (13/64)	77% (49/64)
Roth 2000[12]	Long-acting oxycodone	FAIR (4)	24% (25/106)	Not reported	52% (55/106)	30% (32/106)	Not reported	Not reported	30% (32/106)	43% (46/106)

* (Number of criteria out of seven adequately met)

† Due to adverse events

Table 2.3. Comparative results for adverse events, trials of long-acting opioid versus short-acting opioid

Study	Nausea	Vomiting	Constipation	Drowsiness or somnolence	Dizziness	Confusion	Withdrawal*
Long-acting oxycodone:							
Caldwell 1999[55]	Favors long-acting	Favors long-acting	Favors short-acting	Favors long-acting	Favors long-acting	Not reported	Favors long-acting
Hale** 1999[57]	Favors long-acting	No difference	Favors long-acting	Favors short-acting	Favors short-acting	Not reported	No difference
Salzman** 1998[60]	Favors short-acting	Favors short-acting	Favors long-acting	Favors long-acting	Favors short-acting	No difference	Favors short-acting
Other long-acting opioids:							
Gostick 1989[56]	Not reported	Not reported	Favors long-acting	Not reported	Not reported	Not reported	Not reported
Hale*** 1997[54]	Favors short-acting	Favors short-acting	No difference	Favors short-acting	Favors short-acting	Not reported	Favors short-acting
Jamison*** 1998[58]	Favors short-acting	Not reported	Favors short-acting	Favors short-acting	Favors long-acting	No difference	No difference
Lloyd 1992[59]	Favors short-acting	Not reported	No difference	Favors short-acting	Not reported	Favors short-acting	Favors short-acting

*Due to adverse event

**Studied same population

***Lower dose of opioid used in short-acting arm

Table 3. Summary of evidence

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	Most long-acting opioids have not been compared directly in clinical trials. Five trials directly compared one long-acting opioid to another. Three trials (two fair quality, one poor-quality) directly compared transdermal fentanyl to oral long-acting morphine. In the largest (n=683) fair quality trial of patients with chronic low back pain, there were no significant differences for pain relief or other measures of efficacy. A very small (n=18), fair-quality trial in patients with chronic pancreatitis found no differences in efficacy. One fair-quality study comparing different long-acting formulations (once- or twice-daily) and administration times (a.m. or p.m.) of morphine, found no significant differences in pain control and a significant difference for only one of seven measures of sleep quality using once-daily morphine in the a.m. There is insufficient evidence from head-to-head comparison studies to suggest that one long-acting opioid is superior to another in terms of efficacy in adult patients with chronic non-cancer pain. 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	Twenty trials compare long-acting opioids to other types of drugs or to placebo. The longest trial was 16 weeks. The trials are too heterogeneous and of insufficiently high quality to compare the efficacy of long acting opioids. There is insufficient evidence to suggest that one long-acting opioid is superior to another in terms of efficacy in adult patients with chronic non-cancer pain. One fair-quality trial found that methadone was 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, transdermal fentanyl, long-acting morphine, long-acting codeine, and long-acting dihydrocodeine have all been evaluated in two or more clinical trials.
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	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 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. There is fair evidence from three more homogeneous trials to suggest that long-acting oxycodone and short-acting oyxcodone are equally effective for pain control in adult patients with chronic non-cancer pain.

Table 3. Summary of evidence

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	Most long-acting opioids have not been compared directly in clinical trials. Of five head-to-head trials, none were rated good quality for adverse event assessment (1 fair quality, 4 poor quality). In the single fair-quality trial, transdermal fentanyl was associated with less constipation as assessed by a bowel function questionnaire than oral long-acting morphine (31% vs. 48%), but also a trend towards a higher rate of withdrawals due to any adverse event (37% vs. 31%). A similar pattern was observed in a poor-quality trial that compared these two drugs. There was insufficient evidence from head-to-head trials to suggest an overall adverse event or safety advantage for one long-acting opioid compared to any other.
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	Nineteen trials compare long-acting opioids to other types of drugs or placebo. These trials are too heterogeneous and of insufficiently high quality to determine relative risk of assessed adverse events. Rates of abuse and addiction were not reported in trials. Two fair-quality retrospective cohort studies found that transdermal fentanyl was associated with a lower risk of constipation than long-acting oxycodone. 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 found no clear increase in risk associated with any opioid, and do not provide specific data on long-acting opioid preparations. Epidemiologic data from the state of Oregon suggests that increases in methadone-associated deaths are proportionate to changes in prescribing patterns. There is insufficient evidence 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. 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.

Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author Year	Type of study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up (%) Analyzed
Allan 2005[39]	Randomized, open-label controlled trial Multicenter Clinic type and number not specified	A: Transdermal fentanyl (titrated from 25 mcg/hr) (Mean dose 57 mcg/h) B: Long acting morphine (titrated from 30 mg q 12 hrs) (Mean dose 140 mg) 13 months	Adults with chronic low back pain requiring regular strong opioids	Receipt of more than 4 doses of strong opioids in a week in the 4 weeks before the study, high risk of ventilatory depression or intolerance to study drugs, prior alcohol or substance abuse, presence of other chronic pain disorders, or life-limiting illness	Short acting analgesics permitted	Not reported Not reported 683 enrolled	342 (50%) 608

VAS = visual analogue scale; BID=twice daily; Q AM=every morning; Q PM=every evening

Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Allan 2005[39]	Avg. 54.0 years 61% female Race: not reported 35% nociceptive 4% neuropathic 46% nociceptive and neuropathic 3% nociceptive with psychologic factors 4% neuropathic with psychologic factors 83% mechanical low back pain 8% inflammatory 39% trauma/surgery 1% metabolic 3% other Prior opioid use not reported Pain duration average 124.7 months	**Pain relief** VAS (0-100) assessed at baseline and every week **Bowel function** PAC-SYM baseline, day 15, day 29, and monthly **Quality of Life** (SF-36) baseline, day 29, then monthly or 3-monthly **Back pain at rest, on movement, during day, and at night** scale not specified **Glocal assessment** investigator assessment on 3-point scale (deteriorated, unchanged, improved) **Rescue medication use** **Work status** number of days lost to work	FAIR: Allocation performed centrally. Groups similar at baseline, but baseline pain scores not reported. Eligibility criteria specified. Outcome assessors, care providers, and patients not blinded. High overall loss to follow-up: 50% completed trial. No intention-to-treat analysis for primary outcome (pain relief) (analyzed 608 of 683 randomized patients). Follow-up 56 weeks.

VAS = visual analogue scale; BID=twice daily; Q AM=every morning; Q PM=every evening

Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Allan 2005[39]	Fentanyl (A) vs. Long acting morphine (B) **Pain score** (mean, 0-100 VAS) at 56 weeks (N=608): 56.0 (A) vs. 55.8 (B) **Severe pain at rest (per protocol analyses, n=248 and 162)** 22/248 (9%) (A) vs. 20/162 (12%) (B), p=0.030 (no significant differences in ITT analysis, but data not provided) **Severe pain on movement (per protocol)** 70/248 (28%) (A) vs. 43/162 (27%) (B), p=0.61 **Severe pain during the day (per protocol)** 48/248 (19%) (A) vs. 40/162 (25%) (B), p=0.385 **Severe pain at night (per protocol)** 25/248 (10%) (A) vs. 26/162 (16%) (B), p=0.003 (no significant differences in ITT analysis, but data not provided) **Rescue strong opioids use** 154/296 (52%) (A) vs. 154/291 (53%) (B) **Quality of life (SF-36)** No differences between interventions **Loss of working days** No differences between interventions	Number screened not reported. Number eligible not reported. Clinic setting not described. Baseline or previous opioid use not reported.	Janssen Pharmaceutica. One author employed by Janssen.	Not blinded. ITT results not reported for several outcomes.

VAS = visual analogue scale; BID=twice daily; Q AM=every morning; Q PM=every evening

Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author Year	Type of study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up (%) Analyzed
Allan 2001[52]	Randomized open-label controlled trial Crossover International Multicenter (35) Pain clinics	A: Transdermal fentanyl (titrated) (Mean dose 57.3 mcg/h) B: Long acting morphine (titrated) (Mean dose 133.1 mg/day) 4 weeks initial intervention followed by 4 week crossover	Patients with chronic non-cancer pain requiring continuous treatment with potent opioids	Includes pain not responding to opioids, life threatening disease, skin disease precluding use of transdermal system, other significant medical or psychiatric illness, possible pregnancy or lactation	Immediate release morphine	Not reported Not reported 256	60 (23%) 212

VAS = visual analogue scale; BID=twice daily; Q AM=every morning; Q PM=every evening

Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Allan 2001[52]	Avg. 51.4 years 47% female 98% white 26% neuropathic 50% nociceptive 24% combined neuropathic and nociceptive 76% (194/256) on Morphine prior to study Pain duration average 9 years	**Patient Preference** assessed at end of trial or at time of withdrawal **Pain Intensity** VAS (0-100, 100 excruciating) assessed at baseline and end of each treatment period **Pain Control** categorical scale (scale not specified), assessed at each visit (timing of visits not specified) and at end of each treatment period. **Quality of Life** (SF-36) assessed at baseline and end of each treatment period **Rescue Drug Use**: mean mg/day **Global Efficacy** categorical scale (scale not specified), timing of assessment not reported	POOR: Treatment allocation done using central randomization minimization technique. Groups similar at baseline. Eligibility criteria specified. Outcome assessors, care providers, and patients not blinded. 196/256 completed trial. No comparison of groups completing trial provided. High overall and differential withdrawal rates: 38 (16%) (A) vs. 22 (9%) (B). Follow-up 8 weeks total, 4 weeks per intervention. Results reported such that it is not possible to evaluate each half of the crossover trial independently.

VAS = visual analogue scale; BID=twice daily; Q AM=every morning; Q PM=every evening

Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Allan 2001[52]	Fentanyl (A) vs. Long acting morphine (B) **Patient Preference**: "Preferred" or "Very Much Preferred" 138/212 (65%) A vs. 59/212 (28%) B (p<0.001) No difference in results between pain types. Better pain control main reason **Pain Intensity Score** (mean): 57.8 (A) vs. 62.9 (B) (p<0.001) **Pain Control** "Good" or "Very Good": 35% (A) vs. 23% (B) (p=0.002) **Quality of Life** (mean SF-36 scores) Summary score for physical functioning: 28.6 (A) vs. 27.4 (B) (p=0.004) Summary score for mental health: 44.4 (A) vs. 43.1 (B) (p=0.030) **Rescue Drug Use** (mean): 29.4 mg (A) vs. 23.6 mg (B) (p<0.001) **Global Efficacy (patient)** "Good" or "Very Good": 60% (A) vs. 36% (B) (p<0.001)	Number screened not reported. Number eligible not reported. Exclusion criteria not reported. High percent of enrollees on morphine prior to study. Difficult to assess external validity.	Janssen-Cilaj (Fentanyl) provided grant. No authors employed.	Not blinded, its main outcome measure is patient preference, and 76% of enrollees had been on Morphine prior to study. High withdrawal rate. Unable to accurately assess external validity. Post-hoc sub-group analysis excluding 24 patients reporting "bad" or "very bad" score on pre-trial morphine found that 69% expressed a "strong" or "very strong" preference for fentanyl.

VAS = visual analogue scale; BID=twice daily; Q AM=every morning; Q PM=every evening

Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author Year	Type of study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up (%) Analyzed
Caldwell 2002[53]	Randomized double blinded controlled trial USA Multicenter Clinic type and number not specified	A. Long acting morphine Q AM B. Long acting morphine Q PM C. Long acting morphine BID D. Placebo Mean dose 30 mg/day 4 weeks	40 years or older, osteoarthritis of hip or knee, prior suboptimal response to NSAIDS and acetaminophen or previous use of intermittent narcotics; baseline VAS 40 or more	Serious concomitant disease, history of or imminent joint surgery, weight <100 lbs., recent steroids, opioid treatment for >3 months, opioids allergy	Not permitted	Not reported Not reported 295	111 (37%) 295

VAS = visual analogue scale; BID=twice daily; Q AM=every morning; Q PM=every evening

Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Caldwell 2002[53]	Avg. 62.4 years 63% female 85% white 100% osteoarthritis (no further details reported) Pain duration not reported	**Pain intensity index joint** VAS (0-500, 500 extreme pain) assessed at baseline and weekly; difference from baseline reported **Pain intensity overall arthritis pain** VAS(1-100, 100 extreme pain) assessed at baseline and weekly; difference from baseline reported **Physical function** VAS (0-1700, 1700 extreme functional difficulty) assessed at baseline and weekly; difference from baseline reported **Stiffness index** VAS (0-200, 200 extreme stiffness) assessed at baseline and weekly; difference from baseline reported **Sleep duration** 12 point scale (1-12 hours) assessed at baseline and weekly; difference from baseline reported in hours **Sleep measures** including trouble falling asleep due to pain, need for sleep medication, awakening during the night	FAIR: Method of randomization not reported. Method of treatment allocation not reported. Groups similar at baseline. Comparison of prior opioid use not provided. Eligibility criteria specified. Trial double-blind using matched placebo pills. Blinding not evaluated. Intention to treat analysis provided. It is not clear how missing data are handled. 111/295 completed trial. No comparison of groups completing trial provided. Loss to follow up not differential. 4 weeks follow-up.

VAS = visual analogue scale; BID=twice daily; Q AM=every morning; Q PM=every evening

Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Caldwell 2002[53]	Long acting Morphine qam (A) vs. Long acting Morphine qpm (B) vs. Long acting Morphine bid (C) vs. placebo (D) **Pain intensity index joint:** -17.2 (A) vs -20.1 (B) vs. -18.4 (C) vs -6.48 (D) (treatment groups significantly different from placebo) **Pain intensity overall arthritis pain:** -25.8 (A) vs -21.9 (B) vs -22.3 (C) vs -13.7 (D) (not significantly different) **Physical function:** -207 (A) vs -204 (B) vs -181 (C) vs -96.7 (D) (not significantly different) **Stiffness index:** -23.6 (A) vs -23.5 (B) vs -20.5 (C) vs -15.7 (D) (not significantly different) **Increased sleep duration (hrs):** 0.6 (A) vs 0.25 (B) vs 0.3 (C) vs 0.2 (D) (not significantly different) **Improved overall quality of sleep:** 12 (A) vs 10 (B) vs 5 (C) vs 2 (D) (significantly different from placebo; A also significantly different from D) **Less trouble falling asleep:** -18 (A) vs -12 (B) vs -16 (C) vs -5 (D) (A and C significantly different from placebo) **Less need for sleep medication:** -13 (A) vs -6 (B) vs -5 (C) vs -1 (D) (A significantly different from placebo)	Number screened not reported. Number eligible not reported. Exclusion criteria provided. Osteoarthritis pain patients.	Funding source not reported.	Out of multiple sleep measures, one found a significant different between long acting morphine A and long acting morphine C

VAS = visual analogue scale; BID=twice daily; Q AM=every morning; Q PM=every evening

Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author Year	Type of study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up (%) Analyzed
Hale 2005[38]	Randomized double-blinded controlled trial USA Multicenter Clinic type and number not specified	A: Long acting oxymorphone (titrated) (Mean dose 79.4 mg/day) B: Long acting oxycodone (titrated) (Mean dose 155 mg/day) C: Placebo 18 days	18 to 75 years, moderate to severe low back pain for at least 15 days per month for past 2 months, stable dose of opioids for at least 3 days prior to enrollment	Fibromyalgia, multiple specified causes for back pain, malignancy, infection, neurologic dysfunction, psychiatric conditions, concomitant illness, history of drug or alcohol dependence, hypersensitivity to opioids, back surgery within 2 months or nerve/plexus block within 4 weeks, active or pending litigation	Immediate release morphine 15 mg q 4-6 hrs for first 4 days, then limited to 30 mg/day (mean 25 mg in active treatment groups for first four days, then mean 14 mg/day)	420 screened 330 underwent randomized titration 235 enrolled in stable dose intervention phase	96 (41%) 213
Niemann 2000[21]	Randomized open-label controlled crossover trial Denmark Multicenter Outpatient clinics	A: Transdermal fentanyl (titrated) (Mean dose 55.6 mcg/hr) B: Long acting morphine (titrated) (Mean dose 128.3 mg/day) 4 weeks initial intervention followed by 4 week crossover	Patients with opioid treated painful chronic pancreatitis	Not specified	Immediate release morphine tablets of 10 mg (mean dose not reported)	Not reported Not reported 18 enrolled	1/18 (5.6%) 18

VAS = visual analogue scale; BID=twice daily; Q AM=every morning; Q PM=every evening

Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Hale 2005[38]	Median age=46 years 47% female Race not reported Median duration of low back pain 8 years "Most common" etiologies: degenerative disc disease, disc herniation, fracture, spondylosis, and spinal stenosis	Pain intensity on VAS (0 to 100) at baseline and at 18 days and by 4 point categorical scale (0=none to 3=severe) Pain relief on VAS (0=no relief to 100=complete relief) Brief pain inventory Global evaluation on 5-point categorical scale (poor to excellent) Interference with normal activities on 100 point scale (0=no interference to 10=complete interference)	FAIR: Adequate randomization and treatment allocation. Groups reported as similar at baseline but data not clearly reported. Prior opioid use not reported. Clear eligilbility criteria. Blinded. No intention-to-treat analysis. 41% did not complete trial. No comparison of groups completing and not completing trial provided. 18 days follow-up.
Niemann 2000[21]	Median age=47 years 33.3% female Race not reported Median duration of chronic abdominal pain=9 years Etiology of chronic pancreatitis Alcohol abuse=17(94.4%) Sjogren's syndrome=1(5.6%)	Preference recorded at end of study (assessment method not reported, categorical scale used) Global pain control assessment of last two weeks of trial periods compared to last month prior to study entry (assessment method not reported, categorical scale used) Quality of life assessed using SF-36 questionnaire at end of each 4-week period Side effects assessed using unspecified questionnaire at weeks 1, 2, and 4 of each trial period	FAIR: Method of randomization not reported. Method of treatment allocation not reported. Groups similar at baseline. Prior opioid use provided. Minimal eligibility criteria specified. Open trial. Intention to treat analysis provided. It is not clear how missing data are handled. 17/18 completed trial. No comparison of groups completing trial provided. No loss to follow up. 4 weeks follow-up.

VAS = visual analogue scale; BID=twice daily; Q AM=every morning; Q PM=every evening

Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Hale 2005[38]	Long-acting oxymorphone (n=71) (A) vs. long-acting oxycodone (n=75) (B) vs. placebo (n=67) (C) **Pain Intensity** Mean difference from baseline vs. placebo (VAS): -18.2 vs. -18.6 **Pain Intensity** Categorical scale: Proportion rating pain intensity "none" or "mild" similar for A and B vs. C **Pain Relief** 56.8 vs. 54.1 vs. 39.1 **Pain Intereference** A and B similar and superior to C for general activity, mood, normal work, relations with other people, and enjoyment of life (no difference for sleep and walking ability) **Global Assessment** "Good", "very good", or "excellent':59% vs. 63% vs. 27% **Discontinuation due to treatment failure (treatment phase)** 20% vs. 16% vs. 57% **Discontinuation due to treatment failure (dose titration phase)** 7/166 (4.2%) vs. 4/164 (2.4%) **Rescue medication use** 13.8 vs. 14.7 mg/day after first 4 days	High number of patients screened and enrolled in titration phase not enrolled into randomized phase	Endo Pharmaceuticals Inc and Penwest Pharmaceuticals Co	Results of first randomization to long acting oxymorphone versus long acting oxycodone (titration phase) not reported. Not clear how patients re-randomized to treatment phase.
Niemann 2000[21]	Fentanyl (A) vs. Long acting morphine (B) **Patient Preference** (n=17): "Preference" or "Strong Preference" 8(47%) A vs. 7(41.2%) B (NS) **Pain Control** "Good" or "Very Good"(n=18): 8(44.4%) (A) vs. 6(33.3%) (B) (NS) **Quality of Life**: A vs B (NS) in physical functioning, general health, role physical, pain intensity, social functioning, mental health, and side effects summary median scores	Number screened not reported. Number eligible not reported. Exclusion criteria not provided. Chronic pancreatitis pain patients.	Janssen Research Foundation	Open-label design. Chronic pancreatitis pain patients. A and B equivalent in pain control; but supramaximal doses of A used, as well as higher doses of rescue morphine IR in the A group

VAS = visual analogue scale; BID=twice daily; Q AM=every morning; Q PM=every evening

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Type of study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled
Caldwell 1999[55]	Randomized trial US Multicenter (9) Rheumatology clinics	A: Long acting oxycodone (titrated) B: Slow acting oxycodone (titrated) + Acetaminophen C: Placebo Mean dose of oxycodone 40 mg/day 30 days	Adult osteoarthritis patients with moderate to severe daily pain despite regular NSAID use at stable doses and if greater than 1 month of frequent or persistent pain. Osteoarthritis determined using predefined clinical and radiographic criteria.	Involvement in litigation related to pain Intraarticular steroid injection within 6 weeks if injection involved joint being evaluated Contraindication to narcotic use Active cancer, severe organ dysfunction History of substance abuse Also excluded if withdrew during titration phase	Not permitted	Not reported Not reported 167
Gostick 1989[56]	Randomized trial Crossover Canada Multicenter Number and types of clinics not specified	A: Long acting dihydrocodeine (titrated, 60-120 mg BID) B: Short acting dihydrocodeine (titrated, 30-60 mg QID) Average dose not reported 2 weeks initial intervention with 2 weeks crossover	Chronic back pain due to osteoarthritis of weight bearing joints or chronic back pain	Pregnancy, lactation, contraindication to study medication	Paracetamol 500 mg, up to 8/day	Not reported Not reported 61

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Withdrawals or lost to follow-up Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Caldwell 1999[55]	36 (34%) 107 60 patients withdrew during titration phase, prior to randomization	Avg. 58 years 68% female 88% white 32%>65 years old 100% osteoarthritis back/neck 49% knee 37% 60% (101/167) on unidentified narcotics prior to study and discontinued at time of enrollment Pain duration average not reported.	**Pain intensity** in target joint (0-4, categorical, none-severe) collected globally at baseline, at end of 4 week titration phase, and at 2 and 4 weeks in RCT. Also collected in diary for 3 days preceding the end of the titration and RCT phases. **Quality of sleep** (1-5, categorical, poor-excellent) collected in a similar fashion as pain intensity.	FAIR: Randomization method not described. Treatment allocation by central randomization technique. At beginning groups similar in gender, age, global pain intensity scores & diary scores. Comparison of prior narcotic use not provided. Global quality of sleep score better at baseline for those randomized to long acting Oxycodone than short acting Oxy (p = 0.0068). Compared with those who did not complete titration phase, only significant difference was more women not randomized. Blinding performed, not evaluated. Intention to treat analysis provided. Differential loss to follow up due to withdrawal. Control group received usual care.
Gostick 1989[56]	16 (26%) 42	Avg. 52 years 56% female Race not reported Ostheoarthritis 45% Chronic back pain 55% Pain duration not reported	**Pain intensity:** Scale not described. Mean and Maximum scores collected daily **Rescue drug use:** average number of doses used per day **Global efficacy:** Scale not described. **Preference:** Percent preferring each treatment arm at end of study.	Fair: Randomization method not reported. Treatment allocation method not reported. Groups similar at baseline. No differential loss to follow up, therefore likely to be similar at end of trial, though data not supplied. Intention to treat not provided (analyses of 42/61 randomized patients). Blinding of patients and assessors done using identical placebo tablets. Blinding not assessed. Crossover design. Groups received similar care. 2 week follow up per arm.

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Caldwell 1999[55]	Long acting Oxycodone (A) vs. short acting Oxycodone + acetaminophen (B) vs. Placebo (C) **Pain intensity**: 1.3 (A), 1.3 (B), 2.0 (C) ($p < 0.05$, A vs. C) ($p < 0.05$, B vs. C), (NS, A vs. B). (Estimated from graph) **Mean Pain Intensity Increase:** 0.44 (A), 0.49 (B), 1.0 (C) ($p < 0.004$, A vs. C) ($p < 0.004$, B vs C) (NS, A vs. B) **Sleep quality**: 3.9 (A), 3.2 (B), 2.6 (C), ($p = 0.0382$ (A vs B) however, were significantly different from each other at baseline, $p < 0.05$ (A vs C), $p < 0.05$ (B vs. C)).	Number screened not reported. Number eligible not reported. Exclusion criteria provided. Osteoarthritis pain patients. High percent of enrollees on narcotics prior to study. Difficult to assess external validity.	Purdue Pharma (Long acting Oxycodone) sponsored this study. 1 author employed by Purdue.	Patients enrolled but not randomized were equal to those randomized except for % female in which greater women were not randomized.
Gostick 1989[56]	Long acting Dihydrocodeine (A) vs.short acting Dihydrocodeine (B) **Pain intensity (daily average):** 1.75 (A) vs. 1.80 (B); (p NS) **Pain intensity (maximum):** 2.48 (A) vs. 2.33 (B); (p NS) **Rescue drug use:** 1.54 (A) vs. 1.61 (B); (p NS) **Global efficacy:** no difference **Preference**: no difference	Number screened not reported. Number eligible not reported. Exclusion criteria provided. Difficult to assess external validity.	Not specified. One author employed by Napp Pharmecutical, maker of long acting dihydrocodeine.	

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Type of study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled
Hale 1997[54]	Randomized trial US 1 or 2 Centers	A: Long acting codeine (fixed) + acetaminophen B: Short acting codeine (titrated) + acetaminophen Mean dose opioid 200 mg/day (A) 71 mg/day (B) 5 days	Patients with chronic low back pain deemed by investigators to be in need of opioid or fixed combination codeine analgesics for control of stable mild to moderately severe pain	18 years and older; no medical contraindication to the use of codeine or acetaminophen	Acetaminophen 325 mg every four hours as needed (group A) or Acetaminophen 325 + codeine 30 mg every four hours as needed (group B)	Not reported Not reported 104
Hale 1999[57]	Randomized trial Crossover US Multicenter (5) Rheumatology clinics and others	A: Long acting oxycodone B: Short acting oxycodone Mean dose 40 mg/day 4-7 days followed by crossover	Patients at least 18 years old with stable, chronic moderate-to-severe low back pain caused by nonmalignant conditions, on maximum doses of nonopioid analgesics, with or without opioids.	History of substance abuse Involved in litigation regarding back pain condition. Able to achieved stable analgesia within 10 days during titration phase.	Short acting oxycodone 5-10mg/dose as needed	Not reported Not reported 57

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Withdrawals or lost to follow-up Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Hale 1997[54]	23 (22%) 82	Avg. 52 years 54% female Race not reported Back pain due to Arthritis (33%) mechanical injury (45%) Prior opioid use mentioned but not reported in detail. Pain duration not reported.	**Pain intensity** recorded at baseline and four times a day (0-3 categorical, no pain-severe) **Rescue medication use:** number of doses used.	FAIR: Randomization method not reported. Treatment allocation method not reported. Groups similar at baseline except baseline pain scores higher in group A. RCT blinded. Large overall withdrawal rate (23/104, 22%). Intention to treat not provided (82/104 analyzed). Attrition reported. Crossover and contamination not permitted. Groups received same care, except for type of rescue medication given: group A receieved acetaminophen only while group B received acetaminophen plus codeine. Follow up for 5 days.
Hale 1999[57]	3 (6%) 47 10 patients withdrew during titration phase. All randomized patients were included in analysis.	Avg. 55 years 51% female Race not reported Back pain due to: 1) intervertebral disc disease 2) osteoarthritis. 88% (50/57) were on unspecified narcotics prior to study Pain duration not reported	**Pain intensity** recorded in daily diary (0-3, categorical, none-severe) in morning, afternoon, evening, bedtime **Rescue drug use**: doses used per day	FAIR: Randomization method not reported. Treatment allocation method not reported. Groups reported to be similar at baseline though data not provided. RCT blinded but success not evaluated. Intention to treat not provided but is calculable. Unclear if maintained similar groups. Attrition reported. Crossovers and contamination not permitted. No differential loss to follow-up. Groups received same care. Follow up for 6 days.

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Hale 1997[54]	Long acting Codeine + Acetaminophen (A) vs. short acting Codeine + Acetaminophen (B) **Pain intensity:** Daily Pain Intensity Differences Scores: 4.25 (A) vs. 2.0 (B) (p = 0.008) Pain Score Variation: increases 2.0 vs 4.0 (p = 0.032) decreases 2.2 vs. 4.6 (p = 0.006) **Rescue medication use:** Night: 3.0 vs. 4.0 (p=0.032) Day: 1.01 vs. 1.53 (p = 0.018)	`	Purdue Frederick sponsored study. 1 author (corresponding) employed by Purdue.	Groups received different rescue medications. Not clear if rescue medication was blinded as well.
Hale 1999[57]	Long acting Oxycodone (A) vs. short acting Oxycodone (B) **Overall Pain intensity**: 1.2 (A) vs 1.1 (B) (not significantly different). **Mean Pain Intensity**: Slight (A) vs. Slight (B) (not significantly different). **Rescue drug use**: 0.6 doses per day on average (no difference between treatment groups).	Number screened not reported. Number eligible not reported. Exclusion criteria provided. Low back pain pain patients. External validity difficult to assess.	Purdue Pharma sponsored study. 4 authors employed by Purdue.	Titration study results reported in Saltzman. Titration phase randomized but not blinded to short acting or long acting Oxycodone. No information provided about the numbers in each group.

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Type of study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled
Jamison 1998[58]	Randomized trial US Single center Pain clinic	A: Long acting morphine + short-acting oxycodone + NSAID B: Short-acting oxycodone + NSAID C: Naproxen Mean dose A: 41.1 mg morphine equivalent/day Mean dose B: Not reported, max 20 mg oxycodone/day Mean dose C: Not reported, max 1000 mg/day 16 weeks	Chronic back pain >6 months duration, age 25 to 65 years, average pain intensiy >40 on scale of 0 to 100, unsuccessful response to traditional pain treatment	Cancer, acute osteomyelitis or acute bone disease, spinal stenosis and neurogenci claudication, nonambulatory, significant psychiatric history, pregnancy, treatment for drug or alcohol abuse, clinically unstable systemic illness, acute herniated disc within 3 months	Permitted, not specified	48 screened Not reported 36 enrolled
Lloyd 1992[59]	Randomized trial UK multicenter general practice clinics	A: Long acting dihydrocodeine B: Short acting dextropropoxyphene + paracetamol Average dose not reported 2 weeks	Severe hip osteoarthritis diagnosed by xray, hip replacement a future possibility 18 years or older, on dihydrocodeine and/or NSAIDs or expected to benefit from this therapy	COPD, known allergy to study medicine, use of MAOIs within 2 weeks of study, history of alcohol or drug abuse, severe cardiac, hepatic, or renal insufficiency, hypothyroidism, pregnancy, lactation, irregular bowel habits, or current pain medication regimen >240 mg of dihydrocodiene or 8 dextropropoxy-phene/paracetamol per day.	Not permitted	Not reported Not reported 86

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Withdrawals or lost to follow-up Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Jamison 1998[58]	1 (3%) 36	Avg. 43 years 57% female Race not reported 39% failed back syndrome 25% myofascial pain syndrome 19% degenerative spine disease 14% radiculopathy 3% discogenic back pain Prior opioid use not reported Average pain duration 79 months	**Pain Intensity:** timing not specified, Comprehensive Pain Evaluation Questionnaire **Functional status:** baseline and at end of treatment (SF-36) **Symptom checklist:** baseline and at end of treatment (Symptom Checklist-90) **Weekly activity record** at baseline and once a month **Medication diary** weekly **Overall helpfulness** during titration and at end of study (categorical scale, 0= no help, 10=extremely helpful)	FAIR: Randomization method not described, nor was method of treatment allocation. Open-label. Baseline characteristics for different intervention groups not reported. Appears to be intention-to-treat analysis.
Lloyd 1992[59]	29 (34%) 60	Avg. 66 years 71% female Race not reported Severe osteoarthritis of the hips Prior opioid use not reported Pain duration average 17 months	**Pain intensity**: 4 times per day (Visual Analogue Scale, 0-100, 0 = no pain) **Night time awakening** due to pain every morning **Pain with passive movement** assessed by investigators at baseline, and each week (categorical scale, 0-4, no pain - severe).	FAIR: Randomization method not described, nor was method of treatment allocation. Groups appear similar at baseline, but differential loss to follow-up occurred and no information provided about the remaining participants. Study reported to be double blind, but no description of method is provided. It is not clear how missing data are handled, though the report says that all measures were fully analyzed to maximize the available data.

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Jamison 1998[58]	Long acting Morphine + short acting Oxycodone (A) vs. short acting Oxycodone (B) **Average pain (means, 0-100 VAS):** 54.9 vs. 59.8 **Current pain (means, 0-100 VAS):** 51.3 vs. 55.3 **Highest pain (means, 0-100 VAS):** 71.4 vs. 75.5 **Anxiety (means):** 11.2 vs. 15.0 **Depression (means):** 10.8 vs. 16.4 **Irritability (means):** 17.7 vs. 20.5 **Level of activity (means, 0-100 scale):** 49.3 vs. 49.3 **Hours of sleep (means):** 5.9 vs. 5.9	Number eligible not reported. Number on previous narcotics not reported. Difficult to assess external validity.	Roxane Laboratories sponsored study (maker of long-acting morphine and short-acting oxycodone). Not clear if authors employed by Roxane.	Nonequivalent dose of opioids given. Most statistical comparisons involved comparisons across all three groups (including naproxen only arm).
Lloyd 1992[59]	Long acting Oxycodone (A) vs. short acting Oxycodone (B) **Maximum daily pain score (means)**: Week 1: 58.3 (A) vs. 48.6 (B) (NS), Week 2: 49.8 (A) vs. 49.2 (B) (NS); (A) scores significantly different week 1 vs. week 2 (p = 0.05) **Mean daily pain score**: Week 1: 50.1 (A) vs. 38.2 (B) (NS), Week 2: 39.2 (A) vs. 39.8 (B) (NS); (A) week 1 vs. week 2 score significantly different (p = 0.02) **Average nights wakened by pain per week**: NS, although (B) group improved wakening from week 1 to week 2 (p = 0.05). **Pain on passive movement**: (A) group improved pain from wk 1 to wk 3. (p = 0.02). For both treatments more patients improved than worsened.	Number screened not reported. Number eligible not reported. Number on previous narcotics not reported. Osteoarthritis pain. Difficult to assess external validity.	Not reported. However 5th author appears to be an employee of Napp Laboratories (maker of long acting dihydrocodone) and is the correspondence author.	Authors conclude that A improves pain control better than B because A pain control significantly improved at week 3 vs week 1 for treatment group A but not for treatment group B. However, direct week-to-week comparison of these two treatments shows not significant difference in level of pain intensity.

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Type of study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled
Salzman 1999[60]	Randomized trial US Multicenter (5) Rheumatology clinics and others	A: Long acting Oxycodone (titrated) B: Short acting Oxycodone (titrated) Titration comparison Mean dose A: 104 mg/day Mean dose B: 113 mg/day 10 days	18 years or older, chronic stable moderate to severe back pain despite analgesic therapy with or without opioids.	Contraindication to opioid history of substance abuse Unable to discontinue non-study narcotic Current oxycodone dose >80 mg/day Titration to 80 mg without achieving pain control.	Short acting oxycodone 5-10 mg/day every 4 hrs. as needed	Not reported Not reported 57

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Withdrawals or lost to follow-up Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Salzman 1999[60]	10 (18%) 57	Avg. 56 years 54% Female 87% White 13% Hispanic Intervertebral disc disease, nerve root entrapment, spondylolisthesis, osteoarthritis, and other non-malignant conditions 84% (48/57) Pain duration not reported	**Pain Intensity**: daily diary, categorical scale (0-3, none-severe) **Study Medication Use**: daily diary, amount used **Rescue Drug Use**: daily diary, amount used **Achievement of Stable Pain Control**: Stable pain control considered achieved if pain intensity rated as 1.5 or less for 48 hours with no more than 2 doses of rescue medication **Time to Stable Pain Control**: Days	FAIR: Method of randomization not discussed, nor was method of treatment allocation. Intention to treat calculation analysis not performed for primary pain outcome. Groups comparable at baseline, including prior use of opioids. Differential loss to follow up present. No analysis provided of groups that completed study vs. those who dropped out.

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Salzman 1999[60]	Long acting Oxycodone (A) vs. short acting Oxycodone (B) **Pain Intensity**: Not significantly different at baseline. **Mean decrease in pain intensity**: 1.1 units (A) vs. 1.3 units (B) (NS) **Acheivment of stable analgesia**: 87% (26) (A) vs. 96% (26) (B) (p = 0.36) 5/47 patients did not achieve stable analgesia: 1 titrated to maximum dose of short acting without control (80 mg); 4 experienced adverse side effects (3 long acting, 1 short acting) **Time to stable pain control**: 2.7 days (A) vs. 3.0 days (B) (p = 0.90). **Mean number of dose adjustments**: 1.1 adjustments (A) vs. 1.7 adjustments (B) (p = 0.58)	Number screened not reported. Number eligible not reported. High percent of enrollees on narcotics prior to study. Back pain. Difficult to assess external validity.	Purdue Pharma sponsored study. 2 authors employees of Purdue. Role not otherwise reported.	This paper reported results of two RCTs, one looking at patients with cancer, the other looking at patients with back pain of non-malignant origin. The presented results are from the non-cancer RCT. This study is the 10 day titration phase that preceded the study reported by Hale.

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed
Arkinstall 1995[61]	Randomized trial Crossover Canada Multicenter (4) Clinic types not identified	A: Long acting codeine B: Placebo Mean dose 273 mg/day 7 days initial intervention, followed by crossover	History of chronic non-malignant pain of at least moderate intensity	Hypersensitivity to study medications, intolerance of rescue meds, concomitant use of other opioids, headache, intractable nausea, vomiting, history of substance abuse	Acetaminophen + short acting codeine, 1-2 tabs every 4 hrs. as needed	Not reported Not reported 46	13 (28%) 30
Gilron 2005[40]	Randomized trial Multiple crossovers Canada Single center Pain clinic	A: Long acting morphine titrated up to 120 mg/day B: Gabapentin C: Long-acting morphine plus gabapentin D: Lorazepam (active placebo) Average dose of morphine 45.3 mg (A) and 34.4 mg (B) 5 weeks initial intervention, followed by crossovers to each of the other three interventions	Diabetic neuropathy or postherpetic neuralgia for three months of more, modeate pain, age 18 to 89	Hypersensitivity to study medications, another severe pain condition, serious mood disorder, history of serious drug or alcohol abuse, pregnancy, lactation, no primary care physician, significant comorbdities	Nonopioid drugs other than gabapentin permitted	86 screened Number eligible not clear 57	16 (28%) 54

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Arkinstall 1995[61]	Avg. 55.1 years 57% female Race not reported Rheumatologic pain 43% (13) (9 osteo, 2 rheum, 2 other) Back pain 30% (9) Fibromyalgia 13% (4) Other 13% (4) 10% on morphine, 100% on Tylenol with codeine Pain duration average 72 months	**Pain Intensity:** twice daily, visual analogue scale (0-100, none-excruciating) and categorical (0-4, none-excruciating) **Disability Index:** visual analogue scale (0-10, none-complete disability) for 7 measures totaled together **Rescue drug use:** average doses per day **Patient preference:** which arm preferred **Investigator preference:** which arm seemed to provide better control	FAIR: Randomization done by computer. Treatment allocation done by central pharmacist. No report of groups at baseline, thus unable to compare comparability or report if maintained similar groups. Attrition reported. Crossover trial, results of initial intervention not reported. Contamination was not allowed. Groups received similar care except for study drug. Follow up for 7 days per arm.
Gilron 2005[40]	Avg 60 (diabetic neuropathy) and 68 (PHN) years Female gender: 49% and 36% Non-white race: 3% and 0% Diabetic neuropathy 61% Postherpetic neuralgia: 39% Prior morphine or oxycodone: 9% and 5% Duration of pain: 4.5 and 4.6 years	**Pain intensity:** 0 (none) to 10 (worst pain imaginable) scale **Adverse events** Pain: McGill Pain Questionnaire (0 to 45) Pain-related interference: Brief Pain Inventory (0 to 10) Mood: Beck Depression Inventory (0 to 63) Health status: SF-36 (0 to 100) Mental status: Mini-mental status examination (0 to 30) Global pain relief: 6 point scale (pain worse to complete relief Administered at baseline and during each treatment period when on maximal dose	GOOD. Results adjusted for treatment carryover effects

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Arkinstall 1995[61]	Long acting codeine (A) vs. placebo (B) **Pain intensity**: 35 vs 49 (p = 0.0001) **Disability index**: 25.0 vs. 35.1 (p = 0.0001) **Rescue drug use**: 3.6 vs. 6.1 (p = 0.0001) **Patient preference**: 73% vs. 10% (p = 0.016) **Investigator preference**: 80% vs. 7% (p = 0.0014)	Number screened not reported. Number eligible not reported. 10% of enrollees on morphine prior to study. Heterogenous pain patients. Difficult to assess external validity.	Purdue Frederick provided a research grant. 3 authors employed by Purdue including the corresponding author.	Patients who wished to continue treatment with long acting codeine after the study were offered this option (28 of 30 accepted).
Gilron 2005[40]	Long-acting morphine (A) vs. gabapentin (B) vs. long-acting morphine + gabapentin (C) vs. placebo (D) Mean pain intensity (baseline 5.72 +/- 0.23): 3.70 +/- 0.34 vs. 4.15 +/- 0.33 vs. 3.06 +/- 0.33 vs. 4.49 +/- 0.34 (C superior to A, B, and D) Brief Pain Inventory, general activity (baseline 4.7): 3.1 vs. 3.0 vs. 2.9 vs. 4.5 SF-36 Physical functioning (baseline 51.7): 57.8 vs. 61.1 vs. 62.4 vs. 56.0 Beck Depression Inventory (baseline 10.3): 6.7 vs. 6.4 vs. 6.0 vs. 8.5	Neuropathic pain patients. Pain clinic based.	Canadian Institutes for Health Research provided funding; gabapentin provided by Pfizer and morphine by Aventis-Pharma	Results of initial intervention not reported. 44% of patients and 33% of research nurses correctly guessed morphine treatment.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed
Gimbel 2003[23]	Randomized trial US Multicenter Pain clinic	A: Long-acting oxycodone titrated up to 60 mg bid B: Placebo Average dose 29 mg/day 6 weeks intervention	Chronic (>3 months), at least moderately painful symmetric distal diabetic polyneuropathy documented by Einstein Focused Neurologic Assessment	Unstable or poorly controlled diabetes, chronic pain unrelated to diabetic neuropathy, substance or alcohol abuse within the last 10 years, creatinine >2.5, hepatic dysfunction >3 times the upper limit of normal, active cancer, hypersensitivity to opioids, rapidly escalating pain or recent neurologic deficit, more than 3 doses a day of short-acting opioids within 3 weeks of study, treatment with any long-acting opioid, autonomic neuropathy, need for elective surgery, pregnant or breast-feeding	Opioid rescue not allowed, nonopioid analgesics could only be taken at pre-study doses	Not reported Not reported 160	44 (28%) 159

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Gimbel 2003[23]	Avg 58.9 years 48% female 16% non-white All diabetic neuropathy Baseline pain intensity mean 7 (out of 10) 12% short-acting opioids (not specified) Pain duration not reported	Primary end points Pain Intensity: numeric analogue scale (0-10, none-high), daily diary Worst pain (0-10) Satisfaction: 1 (not) to 6 (totally satisfied) Sleep: 0 (poor) to 10 (excellent) Recorded daily Secondary end points Brief Pain Inventory, Rand Mental Health Inventory, Sickness Impact Profile, SF-36 Health Survey Administered on days 0 and 42, and on days 14 and 28 (Brief Pain Inventory only)	GOOD

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Gimbel 2003[23]	Long-acting oxycodone (A) vs. placebo (B) Average pain intensity (change from baseline): -2.0 vs. -1.0, p<0.001 Pain right now (change from baseline): -2.1 vs. -1.1, p=0.002 Worst pain (change from baseline): -2.4 vs. -1.3, p=0.001 Satisfaction with study drug (postbaseline value): 3.4 vs. 2.4, p<0.001 Sleep quality (change from baseline): 1.2 vs. 0.5, p=0.024 Brief Pain Inventory (change from baseline): 9 out of 14 scores significantly improved for A vs. B SF-36, Rand Mental Health Inventory: No significant differences Sickness Impact Profile: 1 of 16 subscales significantly improved for A vs. B	Number screened and eligible not reported. Specific to stable diabetic patients with moderately painful peripheral neuropathy. Pain clinic based.	Purdue Pharma provided funding and one of the authors employed by them.	

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed
Harke 2001[62]	Randomized trial Two phase study (morphine vs. placebo second phase) Germany Single center Pain clinic	A: Long acting morphine 60-90 mg/day B: Placebo 8 days	Neuropathic pain patients treated successfully with spinal cord stimulation (SCS) with reproducible pain off SCS who agreed to forgo SCS and who completed an RCT looking at carbamazapine vs. placebo.	Heart disease Allergies Current analgesic use Patients were not allowed to receive SCS treatment if MMPI positive for signs of strong psychological and affective components	Not permitted	43 38 38	3 (8%) 35
Huse 2001[63]	Randomized trial Crossover Germany 1 center Pain clinic	A: Long acting morphine (individually titrated) (70-300 mg/day) B: Placebo Average dose not reported 4 weeks initial intervention followed by crossover	Unilateral amputees with phantom limb pain with an intensity of at least 3 out of 10 between ages 18-75	Neurological and psychiatric disorders, the presence of severe illness, pregnancy or breast-feeding, women with insufficient contraceptive protection, and presence of morphine-specific risk factors (allergy, heightened brain pressure, hypotension with hypovolemia, hyperplasia of the prostate, biliary disease, obstructive or inflammatory bowel disease, pheochromocytoma, and hypothyreosis)	Aspirin and paracetamol up to 6 times per day as needed.	12 12 12	0 (0%) 12

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Harke 2001[62]	Avg. 55 years 51% female Race not reported (Please note these statistics are for the 43 pts. who entered the initial RCT.) Radiculitis 39% (17) Peripheral nerve damage 16%(7) Reflex sympathetic dystrophy 15% (7) Postherpetic neuralgia 14% (6) Phantom limb pain 7% (3) Diabetic neuropathy 7% (3) 61% weak opioids 28% strong opioids Pain duration average 13 months	**Pain intensity:** numeric analogue scale (0-10, none-high) recorded every 2 hours **Time to SCS reactivation:** days to reactivation of spinal cord stimulator (SCS)	FAIR: Randomization method not discussed. Treatment allocation concealment not reported. Treatment groups appear similar prior to the RCT conducted before the RCT of interest to this report, however, demographics are not reported for the specific RCT of interest. Unclear if outcome assessor blind. Point estimate and measure of variance provided for "partial responders" but not for total study groups. Results provided in unusual manner creating three groups of very small numbers.
Huse 2001[63]	Avg. 50.6 years 16% female Race not reported Phantom Limb Pain 2 upper limb 9 lower limb 1 both Prior opioid use not reported 16 years since amputation	**Pain intensity**: visual analogue scale (0-10, none at all-extreme) collected hourly. In addition, sensory and affective pain were also collected on a similar scale at the end of each treatment period. **Treatment responders**: defined as those who showed a greater than 50% reduction in pain; partial responders showed some reduction, nonresponders had no reduction	FAIR: Randomization method not reported. Treatment allocation concealment adequate. Baseline statistics of treatment groups not reported. Not clear how many people were initially recruited for study nor how many people were included in the calculations. Blinding technique used included identical medications. However, both patients and physicians were reliably able to predict when they were on MST.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Harke 2001[62]	Long acting morphine (A) vs. placebo (B) Responders (1 (A) vs. 0 (B)): **Maximum Pain Intensity**: 1 (A) vs. N/A (B) **Time to reactivation**: 13 days (A) vs. N/A (B) Partial Responders: (13 (A) vs. 11 (B)) **Maximum Pain Intensity**: 6.7 (A) vs. 6.1 (B) (p = 0.41) **Time to reactivation**: 53 hrs (A) vs. 43 hrs (B) (p = 0.32) Nonresponders: (6 (A) vs. 4 (B)) **Maximum Pain Intensity**: 8.3 (A) vs. 8.3 (B) **Time to reactivation**: 4.3 hrs (A) vs. 3.3 hrs (B)	Number screened reported. Number eligible reported. A fair number of enrollees on narcotics prior to this study. Neuropathic pain patients.	Not reported	The method used to report the results is unusual and makes interpretation difficult.
Huse 2001[63]	Long acting morphine (A) vs. placebo (B) **Pain intensity**: less during A than baseline 3.26 (A) vs. 4.65 baseline, general, p < 0.01 0.80 (A) vs. 1.49 baseline, affective, p < 0.01 0.71 (A) vs. 2.00 baseline, sensory, p < 0.001 less during A than B 3.26 (A) vs. 3.99 (B), general, p=0.036 0.80 (A) vs. 1.57 (B), affective p < 0.001 0.71 (A) vs. 1.73 (B), sensory p < 0.01 B not different than baseline 3.99 (B) vs. 4.65 baseline, general, p = 0.026 1.57 (B) vs. 1.49 baseline, affective, p NS 1.73 (B) vs. 2.00 baseline, sensory p NS **Treatment responders:** 42% (A) vs 8% (B) treatment responders (p< 0.05) 8% (A) vs. 8% (B) partial treatment responders (p NS) 50% (A) vs. 84% (B) nonresponders (p=0.08) No effect on psychological variables.	Number screened reported. Number eligible reported. No report of prior narcotic use. Highly specific pain population. Pain clinic based.	Mundipharma (maker of MST Morphine) and Deutsche Forschungs-gemeinschaft provided funding.	Authors tested whether enrollees and physicians knew which drug the patient was on and found that both were able to reliably predict active treatment, but did not find an association between treatment outcome expectancy and positive treatment effect.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed
Maier 2002[41]	Randomized trial Crossover Germany Multicenter (8) Pain clinic	A: Long acting morphine (20 mg/day titrated up to 180 mg/day) B: Placebo Median daily dose 100 and 103 mg/day 1 week intervention followed by crossover	Neuropathic pain, nociceptive pain from chronic pancreatitis or from vertebral lesions and pain >5 on Numerical Rating Scale despite pretreatment (not including potent opioids)	Significant pulmonary or other comorbidities and pregancy	Non-opioids and co-analgesics allowed; step II opioids also allowed	997 Not reported 49	12 (24%) 48 included in ITT analyses
Morley 2003[25]	Randomized trial U.K. 1 center Pain clinic	A: Methadone 5 mg bid or 10 mg bid B: Placebo Phase I: methadone 5 mg bid or placebo every other day, with no treatment in between, for 20 days Phase II: methadone 10 mg bid or placebo every other day, with no treatment in between, for 20 days	Age 18-80 years with neuropathic pain, who were able to understand the trial assessments	Pregnant or lactating, known hypersensitivity to opioids or a history of alcohol or drug abuse.	Not specified	Not reported 33 19	8 (42%) 11 completed both phases

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Maier 2002[41]	Avg. 52.3 years 54% female Race not reported 4 postherpetic neuralgia 11 neuralgia 12 radiculopathy or neuropathy 6 other neuropathic pain 12 low back pain 3 other nociceptive pain Prior opioid use not reported Average 9.5 (group I) and 7 years (group II) pain duration	**Pain intensity:** Numeric rating scale (0=none to 10=worst pain imaginable) **Tolerability of pain:** 7 point scale (no pain to not bearable) **Sleep quality:** Visual rating scale (1 to 5) **Physical fitness:** Numeric rating scale (0 to 10) **Pain disability index:** Numeric rating scale (0 to 10) **Mental state and mood:** Numeric rating scale (0 to 10) **Depression scale:** Scale not specified **Symptoms intensity:** 20 symptoms, scored 0 (no) to 3 (severe) and summed (0 to 60) **Side effects:** Visual rating scale 0 (none) to 3 (severe)	FAIR: Not clear if randomization adequate ("random generator") and allocational concealment not described. Baseline characteristics not reported to test randomization. High loss to follow-up in patients randomized to morphine first after crossover to placebo compared to patients on placebo first. Blinding technique not adequately described and >87% of patients and investigators able to recognize morphine.
Morley 2003[25]	Avg. 57.0 years 32% female Race not reported 3 post-herpetic neuralgia 4 diabetic polyneuropathy 2 post-stroke pain 3 sciatica or radiculopathy 7 other neuropathic pain 8/19 (42%) previously on opioid analgesic	**Pain Intensity**: Neuropathic Pain Scale (NPS) of Galer and Jensen completed after each phase and visual analogue scale (0-100, 100=worst) completed daily	FAIR: Not clear if randomization adequate (eight replications of a Latin Square Design) and allocation concealment not described. Baseline characteristics not reported to test randomization. Unusual study design where patients received methadone or placebo during each phase of the study, randomly, only every other day. High loss to follow-up prior to Phase II.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Maier 2002[41]	Morphine (A) vs. Placebo (B) **Responder (pain relief at least 50% or pain intensity <5 on 10 point scale, tolerability of pain 3 or lower 0 to 6 scale, and adverse effects tolerable or controlled by medication):** 11/25 (44%) vs. 0/23 (0%) after 1 week Other outcomes not reported prior to crossover	Small proportion of patients eligible for trial entered. Had to fail other treatments before enrollment.	Munidipharma GmbH provided funding.	Most patients and investigators knew when they were receiving morphine.
Morley 2003[25]	Methadone (A) vs. Placebo (B) **Mean intensity of relief (difference between methadone and placebo)**: 5.07 (p=0.064) for Phase I and 9.07 (p=0.015) for Phase II	Number screened not reported. High proportion of eligible patients declined to participate. Majority of patients on prior narcotics. Heterogeneous patients with neuropathy. Pain center based. Trial design different from clinical practice.	Stanley Thomas Johnson Foundation provided funding.	Patients reported improved pain relief with methadone on days methadone taken. Trial design not similar to clinical practice (methadone or placebo given on alternate days randomly, with no intervention on in-between days).

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed
Moulin 1996[64]	Randomized trial Crossover Canada 1 center Pain clinic	A: Long acting morphine (titrated) B: Benztropine (titrated) Mean daily dose 83 mg/day 6 weeks initial intervention followed by crossover	Age 18-70 referrals to pain clinic, stable non-malignant pain for at least 6 months, moderate or greater in intensity for last week, regional pain of a myofascial, musculoloskeletal or rheumatic nature, failure to respond to NSAIDs and at least one tricyclic anti-depressant	Women of childbearing age had to be on effective birth control. History of drug or alcohol abuse, history of psychosis or major depression, neuropathic pain syndromes including reflex sympathetic dystrophy, isolated headache syndromes, congestive heart failure, history of MI in past year, allergy to morphine or codeine, history of asthma, epilepsy, hepatic or renal disease, history of use of major opioid (oxycodone, morphine, hydromorphone), history of codeine use OK.	Paracetamol 500 mg every 4 hrs as needed	Not reported 103 61	18 (30%) 46

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Moulin 1996[64]	Avg. 40.4 years 59% female Race not reported 12.9 years average education 25% employed 23 head, neck, shoulder pain, 21 low back pain 9 hip, or knee pain 5 neck and back pain 1 TMJ and coccygial 85% injury related 60/61 on codeine prior to study Pain duration average 4.1 years	**Mean Pain Intensity**: visual analogue scale (0-10, 10=worst) completed weekly **Mean Pain Rating Index**: visual analogue scale (0-100, 100 worst) completed weekly **Mean Pain Relief**: visual analogue scale (0-10, 10=worst) completed weekly **Functional Status**: Pain Disability Index completed weekly (no other details provided) **Rescue drug use**: average daily number of rescue drug used per day completed daily	FAIR: Randomization method not described. Treatment allocation method not mentioned. Study groups compared in terms of demographics and previous narcotic usage. Blinding done using identical tablets. Study evaluated the success of blinding. It was not successful.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Moulin 1996[64]	Long acting morphine (A) vs. Benztropine (B) **Mean Pain Intensity:** 6.5 (A) vs. 7.5 (B) ($p < 0.01$) (values estimated from graph) **Mean Pain Rating Index**: 45 (A) vs. 45 (B) (p NS) (values estimated from graph) **Mean Pain Relief**: 2.75 (A) vs. 2.25 (B) (p NS) (values estimated from graph) **Functional Status**: no significant difference (values not provided) **Mean Daily Rescue Drug Use**: 3.5 (A) vs 3.9 (B) (p=0.40) The study found evidence of a carry-over effect between arms therefore only the results from first arm were reported.	Number screened not reported. Number eligible reported. Majority of patients on prior narcotics. Heterogenous pain patients. Pain center based.	Purdue Frederick provided funding. Medical Research Council of Canada provided funding.	According to the authors, benztropine has no analgesic properties but mimics many of the possible side-effects of morphine (sedation, lightheadedness, nausea, dry mouth, constipation, urinary hesitancy).

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed
Peloso 2000[65]	Randomized trial Canada Multicenter (4) Hospital based	A: Long acting codeine B: Placebo Average final dose 318 mg/day 4 weeks	Primary osteoarthritis pain, >35 years old, requiring use of acetaminophen, or other medication use for at least 3 months. Patients were required to DC previous medication and had to experience a flair in pain to be eligible.	Pregnancy; Known allergy to codeine, other opioid or acetaminophen; History of drug seeking behavior; Secondary OA; Steroid use in past 2 months; Intraarticular viscosupplementation in past 5 months; Grade 4 OA awaiting replacement.	Acetaminophen 650 three times a day as needed	Not reported Not reported 103	37 (36%) 66

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Peloso 2000[65]	Avg. 61.6 years 62% female Race not reported 88% (58) knee pain 48% (32) hip pain (some enrollees have both) 13% on Codeine prior to study Pain duration average 10 years	**Daily Pain Intensity**: visual analogue scale (0-500, 500=extreme pain) collected daily **Weekly Pain Intensity**: visual analogue scale (0-100, 100=extreme pain) collected weekly **Pain over last 24 hours**: visual analogue scale (0-100, none-extreme) **Stiffness**: visual analogue scale (0-100, none-extreme) **Physical Function**: visual analogue scale(1-1700, no limitations-extreme limitations) **Trouble falling asleep**: visual analogue scale (0-100, no problems-extreme difficulty) **Need Medication to sleep**: visual analogue scale (0-100, never-always) **Pain on awakening**: visual analogue scale (0-100, none-extreme) **Rescue drug use**: average daily drug use	FAIR: Randomization method not described. Treatment allocation method not mentioned. Groups similar at baseline, nicely presented and described. No differential loss to follow-up occurred. Blinding achieved through use of identical placebo tablets. No assessment of success of blinding.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Peloso 2000[65]	Long acting codeine (A) vs. placebo (B) **Average Daily Pain Intensity**: 145.4 (A) vs. 221.3 (B) (p = 0.0004) **Weekly Pain Intensity**: 29.4 (A) vs. 47.8 (B) (p = 0.0001) **Pain over last 24 h**: 32.5 (A) vs. 47.7 (B) (p = 0.0001) **Stiffness**: 66.2 (A) vs. 87.1 (B) (p=0.003) **Physical function**: 456.2 (A) vs. 687.5 (B) (p=0.0007) **Trouble Falling Asleep**: 11.2 (A) vs. 23.8 (B) (p = 0.022) **Need Medication to Sleep**: 9.3 (A) vs. 22.3 (B) (p = 0.0039) **Pain on Awakening**: 21.5 (A) vs. 30.9 (B) (p=0.02321) **Rescue drug use**: 4.2 (A) vs. 9.2 (B) (p=0.005) **Global assessment score**: 2.1 (A) vs. 0.9 (B) (p=0.0001)	Number screened not reported. Number eligible not reported. A minority of patients on prior narcotics. Osteoarthritis pain patients. Difficult to assess external validity	No mention of funding is made. Purdue Frederick (maker of long acting codeine) employs 2 of the authors.	

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed
Roth 2000[12]	Randomized trial US Multicenter (7) Rheumatology clinics	A1: Long acting oxycodone 20 mg every 12 hours A2: Long acting oxycodone 10 mg every 12 hours B: Placebo 14 days	Patients with >1 month history of osteoarthritis clinically and radiographically	Severe organ dysfunction History of drug or alcohol abuse	Not permitted	Not reported Not reported 133	70 (53%) 133
Rowbotham 2003[22]	Randomized trial U.S.A. 1 center (1) Pain clinic	A: Levorphanol 0.75 mg up to 7 tabs tid B: Levorphanol 0.15 mg up to 7 tabs tid Mean doses 8.9 mg/day versus 2.7 mg/day 4 weeks intervention, with 4 weeks titration and 4 weeks taper	Adults with confirmed neuropathic pain due to defined conditions (peripheral neuropathy, focal nerve injury, postherpetic neuralgia, spinal cord injury, stroke or focal brain lesion, or multiple sclerosis)	Previous opioid therapy exceeding equivalent of 360 mg of codedin/day, allergy to levorphanol, another server pain problem, cognitive impairment, significant psychiatric illness, significant other medical condition, immunosuppression, current drug or alcohol abuse, history of opioid abuse	Not specified	Not reported 100 81	22 (27%) 81 (100%) analyzed

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Roth 2000[12]	Avg. 62 years 74% female Race not reported 46% back 31% knee 61% (81/133) on unspecified opioids prior to study Pain duration average 9 years	**Pain intensity**: categorical scale (0-3, none-severe) daily; a 20% reduction in pain considered successful. **Achievement of successful pain reduction**: % achieving 20% reduction in pain from baseline **Quality of sleep**: categorical (1-5, very poor-excellent) daily, reported as "improvement from baseline" **Brief Pain Inventory**: visual analogue scale (0-10, 10=extreme) at baseline and Q week to assess pain intensity and function, reported as "improvement from baseline"	FAIR: Randomization technique not reported. Treatment allocation concealment by pharmacist. Groups similar at baseline, but do not report % of persons in each group who took and discontinued narcotics. Time delay between discontinuation of previous narcotics and beginning of trial not specified. Eligibility criteria specified. Outcome assessors, care providers, and patients all blinded, though effectiveness of blinding not evaluated. Attrition reported. High overall loss to follow-up: 70/133 (53%) did not complete trial. No report on whether those completing trial were similar to those who did not. Groups received similar care. No differential loss to follow up, though reasons for loss from each treatment group are different.
Rowbotham 2003[22]	Avg. 65 vs. 64 years 51% female 12% non-white race 8 multiple sclerosis 5 spinal cord injury 10 post-stroke or focal brain lesion 26 post-herpetic neuralgia 32 peripheral neuropathy or focal peripheral nerve injury Mean duration of pain 86 vs. 75 months Previous opioid treatment 15% vs. 22%	**Pain Intensity**: visual analogue scale (0-100, 100=worst) daily **Pain Relief**: cateogical scale (0-5, 5 'complete' pain relief) **Mood Disturbance**: Profile of Mood States (65 items) **Effects of Pain on Quality of Life**: Multidimensional Pain Inventory (61 items) **Attention or Concentration**: Symbol-Digit Modalities Test **Agonist and Antagonist Activity**: Opiate-Agonist Effects Scale (16 items) and Opiate Withdrawal Scale (21 items)	FAIR: Methods of randomization and allocation concealment not described, blinding methods not described. High loss to follow-up, but all enrolled patients analyzed.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Roth 2000[12]	Long acting oxycodone 20 mg(A1) vs. Long acting oxycodone 10 mg (A2) vs. placebo (B) **Achievement of successful reduction in pain**: A1: Achieved at day 1 A2: Achieved at day 2 B: Never achieved **Mean Pain Intensity**: (estimated from graph) 1.6 (A1) vs. 1.9 (A2) vs. 2.2 (B) ($p < 0.05$, A1 vs. B) **Quality of Sleep**: A1 better than B ($p < 0.05$, A1 vs. B) **Brief Pain Inventory**: (values estimated from graph) Pain right now: A1 better than B ($p < 0.05$) Worst Pain: A1 better than B ($p < 0.05$) Average Pain: A1 better than B ($p < 0.05$) Mood: 3.1 (A1) vs. 1.7 (A2) vs. 0.7 (B) ($p < 0.05$, A1 vs. B) Sleep: 3.2 (A1) vs. 1.7 (A2) vs. 1.2 (B) ($p < 0.05$, A1 vs. B) Life Enjoyment: 2.6 (A1) vs. 1.7 (A2) vs. 0.6 (B) ($p < 0.05$, A1 vs. B)	Number screened not reported. Number eligible not reported. Majority on prior narcotics. Osteoarthritis pain patients. Rheumatology clinic based. Difficult to assess external validity.	Purdue Pharma (LA Codeine) provided funding. 1 author employed by Purdue (corresponding author). Role not otherwise specified.	Trial had open-label extension for up to 18 months for patients who wished to participate
Rowbotham 2003[22]	High-dose levorphanol (A) vs. low-dose levorphanol (B) Pain intensity reduction (percent improvement in VAS): 36% vs. 21% ($p=0.02$) Pain relief: No difference at week 8, categorical scale Mood disturbance and cognitive impairment: No differences in Profile of Mood States or Symbol-Digt Modalities Test Quality of Life: No differences in Multidimensional Pain Inventory	Number screened not reported. Some enrollees on prior opioids. Pain clinicbased.	National Institue on Drug Abuse and the National Institue of Neurological Disorders and Stroke	

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed
Watson 1998[66]	Randomized trial Crossover Canada 1 center (1) Pain clinic	A: Long acting oxycodone (titrated) B: Placebo Mean final dose 45 mg/day 4 weeks initial intervention followed by 4 week crossover	Patients referred to pain specialist with postherpetic neuralgia of at least 3 months duration and pain intensity of at least moderate for half or more of the day	Hypersensitivity to opioids; Intolerance to oxycodone; History of drug or alcohol abuse; Pain of significant alternate etiology	Not permitted	Not reported Not reported 50	11 (22%) 38
Watson 2003[24]	Randomized trial Crossover Canada 2 centers (2) Pain clinics	A: Long acting oxycodone (titrated from 10 mg q 12 hrs) B: Benztropine (active placebo) Mean final dose 40 mg/day 4 weeks initial intervention followed by 4 week crossover	Diabetes mellitus with stable control and with painful symmetrical distal sensory neuropathy	Intolerance to oxycodone, history of drug or alcohol abuse, significant pain of alternate etiology	Acetaminophen 325-650 mg q 6 hrs	204 55 45	9 (20%) 36

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Watson 1998[66]	Avg. 70 years 58% female Race not reported Postherpetic neuralgia 63% thoracic 26% trigeminal 5% cervical 3% other 45% on narcotis prior to study Pain duration average 31 months	**Pain Intensity**: visual analogue scale (0-100, 100=unbearable) and categorical scale (0-4, no pain-unbearable) recorded daily in a diary **Pain relief:** categorical scale (0-6, 0=pain worse-5=complete relief) collected daily in a diary **Steady Pain, Paroxysmal Pain, Allodynia:** each assessed weekly using pain intensity and pain relief scales. **Disability:** categorical scale (0-3, no disability-severe disability) assessed weekly **Treatment Effectiveness:** categorical scale (0-3, not effective-highly effective) assessed weekly **Affective state**: assessed weekly using POMS and BDI. **Preference:** Patients asked after trial which treatment arm preferred.	FAIR:Method of randomization not described. Treatment allocation appears to have been blind (blocked in sets of 4). Comparison of groups at baseline not provided, however, is crossover design in which enrollee serves as their own control. Blinding performed with identical placebo tablets. Adequacy of blinding not assessed. No differential loss to follow-up.
Watson 2003[24]	Avg. 70 years 47% female Race not reported Prior opioid use not reported 53% on non-opioid analgesics	**Pain intensity**: visual analogue scale (0-100, 100=worst pain) and categorical (0-4, 4=worst) scale **Pain relief**: 0-5 (5=worse) categorical scale **Pain-related disability**: Pain Disability Index **Health-related status**: Short-Form 36 **Impact of pain on sleep**: Pain and Sleep Questionnaire **Effectiveness and Preference**: Patients and investigators rated each at end	FAIR:Method of randomization and allocation concealment (blocked in sets of 4) appear blind. Comparison of groups at baseline not provided, however, is crossover design in which enrollee serves as their own control. Not clear how blinding performed with benztropine (active control) and testing of blinding showed 88% of investigators and 88% of patients identified oxycodone. High loss to follow-up, but not differential.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Watson 1998[66]	Long acting Oxycodone (A) vs. placebo (B) **Mean daily pain intensity**: 35 (A) vs. 54 (B) (p=0.0001) VAS 1.7 (A) vs. 2.3 (B) (p=0.0001) categorical **Pain relief**: 2.9 (A) vs. 1.9 (B) (p=0.0001) **Steady pain**: 34 (A) vs. 55 (B) (p=0.0001) VAS 1.6 (A) vs. 2.3 (p=0.0001) categorical **Allodynia:** 32 (A) vs. 50 (B) (p=0.0001) VAS 1.6 (A) vs. 2.0 (B) (p=0.0155) **Paroxysmal pain:** 22 (A) vs. 42 (B) (p=0.0001) VAS 1.2 (A) vs. 1.9 (B) (p=0.0002) categorical **Disability**: 0.3 (A) vs. 0.7 (B) (p=0.041) **Treatment effectiveness:** 1.8 (A) vs. 0.7 (B) (p=0.0001) **Affective state:** No differences. **Patient preference:** 67% (A) vs. 11% (B) (p=0.001)	Number screened reported. Number eligible not reported. A substantial number of enrollees were on narcotics prior to study. Postherpetic neuraliga. Pain clinic based.	Purdue Frederick provided a research grant. 1 authors is employed by of Purdue Frederick.	No report given of differences between study groups because patients served as their own controls. Analyzed for carry-over effect: none found.
Watson 2003[24]	Long-acting Oxycodone (A) vs. benztropine (B) **Pain intensity**: 21.8 (p=0.0001 vs. baseline) vs. 48.6 VAS 1.2 (p=0.0001 vs. baseline) vs. 2.0 categorical **Pain relief**: 1.7 vs. 2.8 (p<0.0005) categorical **Pain and disability**: 16.8 (p<0.05 vs. baseline) vs. 25.2 total Pain Disability Index **Patient Preference**: 88% preferred oxycodone (p=0.0001) **Patient rated at least moderately effective**: 95% for oxycodone	Number screened and eligible reported. Number previously on opioids not reported. Diabetic retinopathy. Pain clinic based.	Purdue Pharma provided funding. One author employed by Purdue Pharma.	No report given of differences between study groups because patients served as their own controls. Analyzed for carry-over effect: none found. Most investigators and patients could identify active intervention.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 2.1. Adverse events from opioids for non-cancer pain: randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Type of Study	Interventions (Dose, Duration)	Number Enrolled	Method of Adverse Event Assessment and Adverse Events Assessed	Quality Rating (Number of Criteria Out of Seven Met
Allan 2005[39]	Randomized	A: Transdermal fentanyl (titrated from 25 mcg/hr) (Mean dose 57 mcg/h) B: Long acting morphine (titrated from 30 mg q 12 hrs) (Mean dose 58 mg) 13 months	683	Constipation (normal, diarrheal, constipated) based on entries in patient diaries, bowel function questionnaire (PAC-SYM), use of laxatives and other supplemental medications; other adverse events recorded but methods not stated	FAIR. Selection did not appear biased. High overall and differential loss to follow-up; not clear how losses to follow-up handled in calculation of adverse event rates. Constipation pre-specified but not clearly defined. Adverse events measured by bowel function assessment but validity of instrument not clear. Patients and assessors not blinded to intervention. No statistical analysis of potential confounders. Adequate duration of follow-up (up to 13 months). (4)
Allan 2001[52]	Randomized Crossover	A: Transdermal fentanyl (titrated to mean dose 57.3 mcg/hr) B: Long-acting morphine (titrated to mean dose 133.1 mg/day) 4 weeks initial intervention followed by 4 weeks crossover	256	Any treatment-related adverse event, assessment methods not clear other than a bowel function questionnaire was performed	POOR. Selection did not appear biased. High overall and differential loss to follow-up. Adverse events not specified or defined. Ascertainment techniques inadequately described. Patients and assessors not blinded to intervention. No statistical analysis of potential confounders. Adequate duration of follow-up, 4 weeks of initial intervention followed by 4 weeks cross-over. (2)

Evidence Table 2.1. Adverse events from opioids for non-cancer pain: randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Rate and Number of Adverse Events	Comments
Allan 2005[39]	Transdermal fentanyl (n=338) vs. long-acting oral morphine (n=342) Any adverse event: 87% vs. 91% Constipation (ITT): 176/338 (52%) vs. 220/338 (65%) (p<0.05) Nausea: 54% vs. 50% Vomiting: 29% vs. 26% Somnolence: 17% vs. 30% Dizziness: 25% vs. 24% Fatigue: 17% vs. 14% Pruritus: 15% vs. 20% Application site reactions: 9% in transdermal fentanyl group Deaths: None Addiction: None reported Use of laxatives: 177/336 (53%) vs. 221/336 (66%) (p<0.001) Use of antiemetics/anticholingergics: 38% vs. 36% Use of antihistamines: 21% vs. 12% (p=0.002) Withdrawal due to adverse events: 125/335 (37%) vs. 104/337 (31%) (p=0.098)	Most common reasons for discontinuations due to adverse events: nausea (37% in both groups), vomiting (24% for transdermal fentanyl and 20% for long-acting oral morphine), and constipation (11% vs. 23%).
Allan 2001[52]	Transdermal fentanyl (n=250) vs. long-acting oral morphine (n=238) Rates of adverse events reported for entire trial: Overall: 74% vs. 70% Nausea: 26% vs. 18% Constipation: 16% vs. 22% Constipation by bowel function questionnaire: 29% vs. 48%, p<0.001 "Serious" (not defined): 2.8% vs. 3.8% Deaths: None Withdrawals due to adverse event (all patients): 11% vs. 4% Withdrawals due to adverse event (patients not previously on fentanyl or morphine): 11% (7/66) vs. 9.8% (6/66)	Adverse events not reported for initial 4 week intervention period. Differential withdrawal rates during initial intervention period may have led to biases during crossover period. 76% of patients on long-term morphine prior to trial. Not clear how analgesic requirements determined at beginning of trial; mean doses of opioid analgesics during trial not reported.

Evidence Table 2.1. Adverse events from opioids for non-cancer pain: randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Type of Study	Interventions (Dose, Duration)	Number Enrolled	Method of Adverse Event Assessment and Adverse Events Assessed	Quality Rating (Number of Criteria Out of Seven Met
Caldwell 2002[53]	Randomized	A: Once-daily morphine (30 mg) in a.m. B: Once-daily morphine (30 mg) in p.m. C: Twice daily morphine (15 mg bid) D: Placebo 4 weeks	295	Any treatment-related adverse event, assessment methods not clear	POOR. Selection did not appear biased. High overall loss to follow-up. Adverse events not specified or defined. Ascertainment techniques inadequately described. Patients and assessors blinded to intervention. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 4 weeks. (3)

Evidence Table 2.1. Adverse events from opioids for non-cancer pain: randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Rate and Number of Adverse Events	Comments
Caldwell 2002[53]	Once-daily morphine in a.m. (n=73) vs. once-daily morphine in p.m. (n=73) vs. twice-daily morphine (n=76) vs. placebo (n=73), adverse events reported in >5% of any treatment group (significant differences reported between active treatment groups): Constipation: 49% vs. 40% vs. 29% vs. 4% (p<0.05 twice-daily morphine vs. once-daily morphine in a.m.) Nausea: 21% vs. 32% vs. 26% vs. 10% Somnolence: 16% vs. 12% vs. 12% vs. 0% Dizziness: 10% vs. 10% vs. 12% vs. 1% Vomiting: 6% vs. 16% vs. 8% vs. 1% (p<0.05 once-daily morphine in a.m. vs. once-daily morphine in p.m.) Headache: 6% vs. 4% vs. 7% vs. 6% Pruritus: 6% vs. 10% vs. 3% vs. 0% Asthenia: 1% vs. 6% vs. 9% vs. 0% (p<0.05 twice-daily morphine vs. once-daily morphine in a.m.) Dry mouth: 6% vs. 4% vs. 3% vs. 1% Pain: 3% vs. 4% vs. 5% vs. 1% Diarrhea: 0% vs. 4% vs. 1% vs. 6% Withdrawal (overall): 37% vs. 45% vs. 37% vs. 32% Withdrawal (adverse events): 23% vs. 25% vs. 24% vs. 7% Withdrawal (lack of efficacy): 12% vs. 16% vs. 11% vs. 19% "Serious" (not defined): 6 overall	42% of patients were on opioids prior to trial; specific opioids or doses not reported. High withdrawal rates; not clear how withdrawn patients accounted for in adverse event rates. "Serious" adverse events not defined and rate in different treatment groups not reported.

Evidence Table 2.2. Adverse events from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Type of Study	Interventions (Dose, Duration)	Number Enrolled	Method of Adverse Event Assessment and Adverse Events Assessed
Caldwell 1999[55]	Randomized	A: Long-acting oxycodone + acetaminophen (titrated) B: Short-acting oxycodone (titrated) C: Placebo Mean dose of oxycodone 40 mg/day 30 days of intervention	167 (107) 60 patients withdrew during titration phase, prior to randomization	Any adverse event at least possibly related to study medication, spontaneously reported by patients
Gostick 1989[56]	Randomized Crossover	A: Long acting dihydrocodeine (titrated, 60-120 mg BID) B: Short acting dihydrocodeine (titrated, 30-60 mg QID) Average dose not reported 2 weeks initial intervention with 2 weeks crossover	61	Methods not reported
Hale 1997[54]	Randomized	A: Long-acting codeine (fixed) plus acetaminophen B: Short-acting codeine (titrated) plus acetaminophen Mean doses 200 mg in group A, 71 mg group B 5 days	104	Any adverse event reported by >5% of either treatment group

Evidence Table 2.2. Adverse events from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Quality Rating (Number of Criteria Out of Seven Met)	Rate and Number of Adverse Events	Comments
Caldwell 1999[55]	POOR. Low overall and differential loss to follow-up. Adverse events not specified or defined. Ascertainment techniques inadequately described and based only on patient self-report. Inadequate statistical analysis (elderly patients only). Adequate duration of follow-up, 30 days. (3)	Long-acting oxycodone vs. short-acting oxycodone vs. placebo (Significance reported for differences between active treatments groups) Somnolence: 18/34 (53%) vs. 26/37 (70%) vs. 13/36 (36%), NS Constipation: 24/34 (71%) vs. 20/37 (54%) vs. 16/36 (44%), NS Nausea: 5/34 (15%) vs. 14/37 (38%) vs. 13/36 (36%), p=0.03 Pruritus: 11/34 (32%) vs. 14/37 (38%) vs. 10/36 (28%), NS Dizziness: 4/34 (12%) vs. 9/37 (24%) 10/36 (28%), NS Dry mouth: 11/34 (32%) vs. 20/37 (54%) vs. 12/36 (36%), NS Vomiting: 2/34 (6%) vs. 4/37 (11%) vs. 0/36 (0%), NS Withdrawal due to adverse events: 3/34 (6%) vs. 5/37 (14%) vs. 3/36 (8%), NS	More males randomized to controlled-release oxycodone group, otherwise demographic characteristics comparable. Approximately 1/3 did not get randomized because of issues during titration phase on immediate-release codeine. Limited statistical analysis of adverse events in elderly vs. younger patients during titration phase. Elderly patients (>65) during titration phase less frequent headache (2% vs. 8%) and pruritus (21% vs. 35%); more frequent vomiting (19% vs. 11%); other adverse event rates reported "similar". P values not provided.
Gostick 1989[56]	POOR. High overall (19/61) withdrawal/loss to follow-up. Adverse events not specified or defined. Ascertainment technique not described. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 2 weeks each intervention. (2)	Long-acting dihydrocodeine vs. short-acting dihydrocodeine Bowel movement less frequently than once every two days: 23/42 (55%) vs. 21/44 (48%) Daily use of laxaztive: 1/41 (2.4%) vs. 3/42 (7.1%) Withdrawals due to adverse events: 16/61 (26%) overall, "no treatment differences" Other adverse events: Not reported ("no significant differences")	
Hale 1997[54]	POOR. High overall (22/104) and differential (15/53 vs. 5/51) loss to follow-up. Adverse events not specified or defined. Ascertainment technique not described. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 5 days. (2)	Long-acting codeine (fixed) plus acetaminophen vs. short-acting codeine (titrated) plus acetaminophen (rate of "serious" adverse events in brackets) Nausea: 16/52 (31%) [15%] vs. 9/51 (18%) [4%] Vomiting: 5/52 (10%) [8%] vs. 1/51 (2%) [2%] Constipation: 10/52 (19%) [2%] vs. 8/51 (16%) [0%] Dizziness: 9/52 (17%) [4%] vs. 2/51 (4%) [0%] Headache: 8/52 (15%) [0%] vs. 4/51 (8%) [4%] Somnolence: 5/52 (10%) [0%] vs. 2/51 (4%) [0%] Dyspepsia: 4/52 (8%) [4%] vs. 2/51 (4%) [2%] Dry mouth: 8/52 (15%) [0%] vs. 0/51 (0%) [0%] Pruritus: 3/52 (6%) [4%] vs. 2/51 (4%) [2%] Withdrawal due to adverse events: 13/53 (25%) vs. 4/51 (8%)	Two arms did not receive equivalent doses of codeine. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates. "Serious" adverse events not defined.

Evidence Table 2.2. Adverse events from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Type of Study	Interventions (Dose, Duration)	Number Enrolled	Method of Adverse Event Assessment and Adverse Events Assessed
Hale 1999[57]	Randomized Crossover	A: Long-acting oxycodone B: Short-acting oxycodone Mean dose 40 mg/day 4-7 days followed by crossover	57 (47) 10 patients withdrew during titration phase	Any adverse event at least possibly related to study medication, assessed at each contact, assessment methods not clear
Jamison 1998[58]	Randomized	A: Long acting morphine + short-acting oxycodone (titrated doses) + NSAID B: Short-acting oxycodone (fixed dose) + NSAID C: Naproxen Mean dose A: 41.1 mg morphine equivalent/day Mean dose B: Not reported, max 20 mg oxycodone/day Mean dose C: Not reported, max 1000 mg/day 16 weeks	36	Pre-specified set of adverse events assessed on 0 to 10 scale by weekly phone interview
Lloyd 1992[59]	Randomized	A: Long-acting dihydrocodeine (titrated) B: Dextropropxyphene + paracetamol (titrated) Average dose not reported 2 weeks	86	Any adverse event, assessed by patient diary

Evidence Table 2.2. Adverse events from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Quality Rating (Number of Criteria Out of Seven Met)	Rate and Number of Adverse Events	Comments
Hale 1999[57]	POOR. High overall loss to follow-up (11/47). Adverse events not specified or defined. Ascertainment technique inadequately described. Adverse events ascertained only by patient self-report. No statistical analysis of potential confounders. Duration of follow-up may be inadequate, ranged from 4-7 days for each intervention phase.(3)	Long-acting oxycodone vs. short-acting oxycodone (initial intervention) Nausea: 4/25 (16%) vs. 9/22 (41%), NS Constipation: 8/25 (32%) vs. 10/22 (45%), NS Dizziness: 4/25 (16%) vs. 2/22 (9%), NS Pruritus: 7/25 (28%) vs. 6/22 (27%), NS Somnolence: 3/25 (12%) vs. 4/22 (18%), NS Vomiting: 0/25 (0%) vs. 0/22 (0%), NS Headache: 2/25 (8%) vs. 2/22 (9%), NS Withdrawal due to adverse events (initial intervention + crossover phase): 2/47 (4%) vs. 1/47 (2%)	88% of patients (as reported by Salzman 1999) were on opioids prior to entry into trial, specific opioids used not reported. Rates of adverse events reported during second intervention (crossover) period were not significantly different between treatment groups. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.
Jamison 1998[58]	FAIR. All patients completed 16 week intervention phase. Adverse events pre-specified but not defined. Ascertainment technique adequately described. Patients and assessors not blinded to intervention.(5)	Long-acting morphine + short-acting oxycodone vs. short-acting oxycodone (proportion reported weekly, sample sizes not clear) Dry mouth: 35% vs. 26% Drowsiness: 37% vs. 22% Headache: 32% vs. 20% Constipation: 30% vs. 18% Nausea: 31% vs. 14% Itching: 15% vs. 15% Dizziness: 6% vs. 19% Muddled thinking: 0% vs. 1.4% Withdrawal due to adverse events: 1/11 (9.1%) vs. 2/13 (15%)	Higher adverse events in long-acting morphine + short-acting oxycodone arm, but they also received higher average doses of opioids.
Lloyd 1992[59]	POOR. High overall and differential loss to follow-up (19/43 vs. 7/43). Adverse events not specified or defined. Ascertainment technique inadequately described. Patients and assessors blinded to intervention. Inadequate statistical analysis (rates of adverse events vs. time since intervention). Duration of follow-up appears adequate, 2 weeks.(3)	Long-acting dihydrocodeine vs. dextropropoxyphene plus paracetamol (figures only reflect side effect rated moderate or severe, results only reported from end of week 1 because of high rate of withdrawal): Nausea: 12/39 (31%) vs. 4/41 (10%) Vomiting: 8/39 (21%) vs. 3/41 (7%) Constipation: 3/39 (8%) vs. 4/41 (10%) Drowsiness: 10/39 (26%) vs. 6/41 (15%) Difficulty concentrating: 4/39 (10%) vs. 2/41 (5%) Withdrawal due to adverse events: 17/43 (40%) vs. 4/43 (9%)	Higher dosage regimen not associated with increased rate of adverse events. High overall and differential withdrawal rate. Not clear how patients and assessors blinded to treatment regimen (not reported in study), medications given at different frequency. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.

Evidence Table 2.2. Adverse events from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Type of Study	Interventions (Dose, Duration)	Number Enrolled	Method of Adverse Event Assessment and Adverse Events Assessed
Salzman 1999[60]	Randomized	A: Long-acting oxycodone (titrated) B: Short-acting oxycodone (titrated) Mean dose A: 104 mg/day Mean dose B: 113 mg/day Duration up to 10 days	57	Any adverse event reported by >10% of one treatment group and at least possibly related to study medication, assessed by daily patient diary

Evidence Table 2.2. Adverse events from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author Year	Quality Rating (Number of Criteria Out of Seven Met)	Rate and Number of Adverse Events	Comments
Salzman 1999[60]	POOR. High overall loss to follow-up (16/57). Adverse events not specified or defined. Ascertainment techniques adequately described. Patients and assessors not blinded, adverse events ascertained only by patient self-report. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 10 days. (3)	Long-acting oxycodone vs. short-acting oxycodone Somnolence: 8/30 (27%) vs. 10/27 (37%) Nausea: 15/30 (50%) vs. 9/27 (33%) Vomiting: 6/30 (20%) vs. 1/27 (4%) Postural hypotension: 0% vs 0% Constipation: 9/30 (30%) vs. 10/27 (37%) Pruritus: 9/30 (30%) vs. 7/27 (26%) Confusion: 1/30 (3%) vs. 0% Dry mouth: 0/30 (0%) vs. 3/27 (11%) Dizziness: 9/30 (30%) vs. 6/27 (22%) Nervousness: 0/30 (0%) vs. 2/27 (7%) Asthenia: 2/30 (7%) vs. 3/27 (11%) Headache: 4/30 (13%) vs. 7/27 (26%) Withdrawal due to adverse events: 6/30 (20%) vs. 2/27 (7%)	Open-label dose-titration study. Study results from 48 cancer patients not abstracted (n=48). 88% of patients previously on opioid analgesics, specific opioids not reported. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Type of Study	Interventions (Dose, Duration)	Number Enrolled	Method of Adverse Event Assessment and Adverse Events Assessed	Quality Rating (Number of Criteria Out of Seven Adequately Met)
Arkinstall 1995[61]	Randomized Crossover	A: Controlled-release codeine (titrated) B: Placebo Mean dose 273 mg 7 days initial intervention, followed by crossover	46	Any adverse event reported in >5% of any treatment group, patients recorded adverse events in diary, also spontaneously reported and investigator-observed adverse events at end of each 7 day phase	FAIR. High differential and overall loss to follow-up. Adverse events not specified or defined. Techniques to ascertain adverse events adequately described. Adverse events ascertained by patient self-report or investigator-observed. No statistical analysis of potential confounders. Adequate duration of follow-up, 7 days initial intervention followed by 7 days cross-over. (4)
Gilron 2005[40]	Randomized Multiple crossovers	A: Long-acting morphine (titrated) B: Gabapentin C: Long-acting morphine + gabapentin D: Placebo 5 weeks initial interventinon, followed by crossovers to each of the other 3 interventions	57	Any reported adverse event	FAIR. Adverse events not pre-specified or defined. Inadequate description of adverse event assessment technique. No analysis of confounders. (4)

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Rate and Number of Adverse Events	Comments
Arkinstall 1995[61]	Long-acting codeine vs. placebo (Sample size for reported rates not clear, only rates reported) Rates of adverse events reported for entire trial (initial intervention and crossover period): Constipation: 20.9% vs. 9.5%, NS Nausea: 33% vs. 12%, p=0.013 Dizziness: 21% vs. 14%, NS Dry mouth: 14% vs. 14%, NS Headache: 23% vs. 14%, NS Somnolence: 16% vs. 4.8%, NS Vomiting: 14% vs. 4.8%, NS Asthenia: 9.3% vs. 9.5%, NS Abdominal pain: 9.3% vs. 9.5%, NS Pruritus: 7.0% vs. 0%, NS Sweating: 0% vs. 4.8%, NS Withdrawal due to adverse events: 7/46 (15%) vs. 1/46 (2%)	Adverse events not reported for initial 1 week intervention period. Patients were on chronic long-term opioids prior to entry (though proportion of patients on prior opioids and specific opioids used not reported); withdrawal symptoms may have occurred in placebo group that could not be distinguished from adverse events. Not reported if differential loss to follow-up occurred in initial intervention period. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.
Gilron 2005[40]	Long-acting morphine vs. gabapentin vs. long-acting morphine + gabapentin vs. placebo Withdrawals (overall) during first intervention: 4/16 (25%) vs. 3/13 (23%) vs. 4/14 (29%) vs. 0/14 (0%) Constipation: 39% vs. 2% vs. 21% vs. 5% Sedation: 16% vs. 8% vs. 21% vs. 6% Dry mouth: 5% vs. 6% vs. 21% vs. 0% Cognituve dysfunction: 2% vs. 2% vs. 7% vs. 2% Nausea: 5% vs. 0% vs. 0% vs. 7%	Adverse events not reported for initial 5 week intervention period. Withdrawals due to adverse events not clear.

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Type of Study	Interventions (Dose, Duration)	Number Enrolled	Method of Adverse Event Assessment and Adverse Events Assessed	Quality Rating (Number of Criteria Out of Seven Adequately Met)
Gimbel 2003[23]	Randomized	A: Long-acting oxycodone titrated up to 60 mg bid B: Placebo Average dose 29 mg/day 6 weeks intervention	160	Investigator assessed for adverse events at each visit, and reported events graded for severity and probability of relationship to study drug	FAIR. Adverse events not pre-specified or defined. Inadequate description of adverse event assessment technique. No analysis of confounders. (4)
Huse 2001[63]	Randomized Crossover	A: Long-acting morphine (titrated) B: Placebo Final dose between 70 to 300 mg/day morphine 4 weeks initial intervention, followed by crossover	12	Any reported adverse event, recorded in daily patient diary	FAIR. No loss to follow-up. Adverse events not specified or defined. Ascertainment technique adequately described. Patients and assessors blinded to intervention. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 4 weeks initial intervention followed by 2 week washout then crossover. (4)
Maier 2002[41]	Randomized Crossover	A: Long-acting morphine (titrated) Placebo Median dose 100 and 103 mg/day 1 week initial intervention, followed by crossover	49	20 symptoms or complaints rated on 0 (none) to 3 (severe) scale; some central nervous system and gastrointestinal symptoms pre-specified	FAIR. Low proportion of eligible patients entered into trial. High and differential loss to follow-up according to randomization sequence. Some adverse events pre-specified. Ascertainment technique inadequately described. Blinding not successful. No statistical analysis of potential confounders. (3)

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Rate and Number of Adverse Events	Comments
Gimbel 2003[23]	Long-acting oxycodone vs. placebo Constipation: 35/82 (42%) vs. 11/77 (14%), p<0.001 Somnolence: 33/82 (40%) vs. 1/77 (1%), p<0.001 Nausea: 30/82 (36%) vs. 6/77 (8%), p<0.001 Dizziness: 26/82 (32%) vs. 8/77 (10%), p<0.001 Pruritus: 20/82 (24%) vs. 6/ 77 (8%), p=0.005 Vomiting: 17/82 (21%) vs. 2/77 (3%), p<0.001 Dry mouth: 13/82 (16%) vs. 2/77 (3%), p=0.005 Asthenia: 12/82 (15%) vs. 5/77 (7%), p=0.125 Headache: 9/82 (11%) vs. 18/77 (23%), p=0.055 Withdrawals (overall): 19/82 (23%) vs. 25/77 (32%) Withdrawals (adverse event): 7/82 (9%) vs. 4/77 (5%)	
Huse 2001[63]	Long-acting morphine vs. placebo (results for initial intervention not reported), 10 cm visual analogue scale (cm) Tiredness: 2.21 vs. 1.33, NS Dizziness: 1.27 vs. 0.71, NS Sweating: 1.32 vs. 0.93, NS Constipation: 0.03 vs. 0.02, p<0.05 Micturition difficulties: 0.01 vs. 0, NS Nausea: 0.74 vs. 0.4, NS Vertigo: 0.98 vs. 0.42, NS Itching: 0.92 vs. 0.55, NS Slowing of respiration: 0.73 vs. 0.55, NS Withdrawal due to adverse events not reported	Not clear how dose of morphine titrated during intervention.
Maier 2002[41]	Morphine vs. placebo Withdrawal due to adverse events (initial intervention): 3/25 (12%) vs. 0/23 (0%) Severe side effects: 28/48 (58%) vs. 10/45 (22%), any side effects 36% vs. 27% Severe gastrointestinal: 21/48 (44%) vs. 5/45 (11%) Severe constipation: 10/48 (20%) vs. 2/45 (4.5%), any constipation 19% vs. 4.5% Severe nausea: 8/48 (16%) vs. 2/45 (4.5%), any nausea 23% vs. 13.5% Severe sedation: 6/48 (12%) vs. 6/45 (13%), any sedation 23% vs. 2% Severe micturition problems: 5/48 (10%) vs. 1/45 (2%) Severe dizziness: 2/48 (4%) vs. 1/45 (2%), any dizziness 20.5% vs. 4.5%	Not clear how lost to follow-up handled in safety analysis. Only withdrawal due to adverse events reported prior to crossover.

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Type of Study	Interventions (Dose, Duration)	Number Enrolled	Method of Adverse Event Assessment and Adverse Events Assessed	Quality Rating (Number of Criteria Out of Seven Adequately Met)
Morley 2003[25]	Randomized	A: Methadone 5 mg bid (Phase I) or 10 mg bid (Phase II) B: Placebo	19	Not specified	POOR. High loss to follow-up. Adverse events not specified or defined. Ascertainment technique not described. Blinding methods unclear. No statistical analysis of potential confounders. Not clear if duration of follow-up adequate because of unusual study design (methadone or placebo randomly given only every other day). (1)
Moulin 1996[64]	Randomized Crossover	A: Long-acting morphine (titrated) B: Benztropine (titrated) Mean daily dose 83 mg/day morphine 6 week initial intervention, followed by crossover	61	Any reported adverse event, assessed by weekly or biweekly adverse effects questionnaire	FAIR. Selection of patients does not appear biased. High overall and differential loss to follow-up (11/61 vs. 4/61). Adverse events not specified or defined. Ascertainment technique adequately described. Patients and assessors blinded to intervention, adverse events questionnaire was used. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 6 weeks followed by 6 weeks crossover. (4)

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Rate and Number of Adverse Events	Comments
Morley 2003[25]	Methadone vs. placebo Withdrawal due to adverse event: 1/19 vs. 0/19 (phase I); 3/17 vs. 3/17 (phase II) Nausea: 7/19 vs. 4/19 (phase I); 8/17 vs. 4/17 (phase II) Vomiting: 4/19 vs. 1/19 (phase I); 1/17 vs. 1/17 (phase II) Somnolence: 2/19 vs. 2/19 (phase I); 3/17 vs. 2/17 (phase II) Dizziness: 6/19 vs. 0/19 (phase I); 3/17 vs. 1/17 (phase II) Constipation: 2/19 vs. 1/19 (phase I); 3/17 vs. 1/17 (phase II) Dry mouth: 0/19 vs. 1/19 (phase I); 0/17 vs. 0/17 (phase II) Adverse effects reported on day of or day after taking methadone vs. placebo	Not clear how lost to follow-up handled in safety analysis. Adverse events reported on day of or day after taking methadone or placebo.
Moulin 1996[64]	Long-acting morphine vs. benztropine (active placebo) (Adverse events reported for entire trial): Vomiting: 18/46 (39%) vs. 1/46 (2%), p=0.0002 Dizziness: 17/46 (37%) vs. 1/46 (2%), p=0.0004 Constipation: 19/46 (41%) vs. 2/46 (4%), p=0.0005 Poor appetite/nausea: 18/46 (39%) vs. 3/46 (7%), p=0.002 Abdominal pain: 10/46 (22%) vs. 2/46 (4%), p=0.04 Fatigue: 10/46 (22%) vs. 3/46 (7%), p=0.10 Dry skin/itching: 7/46 (15%) vs. 2/46 (4%), p=0.18 Dry mouth: 8/46 (17%) vs. 5/46 (11%), NS Diarrhea: 6/46 (13%) vs. 6/46 (13%), NS Blurred vision: 6/46 (13%) vs. 9/46 (20%), NS Sleeplessness: 6/46 (13%) vs. 8/46 (17%), NS Confusion: 4/46 (9%) vs. 7/46 (15%), NS Dose-limiting side effects: 13/46 (28%) vs. 1/46 (2%), p=0.003 Withdrawal due to adverse events not reported	Data not reported in such a way that adverse events in initial intervention period could be calculated. 60/61 study participants on codeine (average dose 126 mg) at time of study entry. Multidisciplinary pain management program offered to study participants. Differential loss to follow-up during titration phase may have biased results of crossover phase. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Type of Study	Interventions (Dose, Duration)	Number Enrolled	Method of Adverse Event Assessment and Adverse Events Assessed	Quality Rating (Number of Criteria Out of Seven Adequately Met)
Peloso 2000[65]	Randomized	A: Long-acting codeine (titrated) B: Placebo Average final codeine dose 318 mg/day 4 weeks active treatment	103	Any reported adverse event, assessed by weekly nondirected adverse events questionnaire	FAIR. Not clear if selection of patients biased, number eligible not reported. High overall loss to follow-up (37/103). Adverse events not specified or defined. Ascertainment technique adequately described. Patients and assessors blinded to intervention, adverse events questionnaire was used. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 4 weeks. (3)
Roth 2000[12]	Randomized	A1: Long-acting oxycodone 10 mg bid A2: Long-acting oxycodone 20 mg bid B: Placebo 14 days	133	Any adverse event reported in >10% of patients, assessed by spontaneous patient reported or observed by investigators at each weekly visit	FAIR. High overall loss to follow-up (70/133). Adverse events not specified or defined. Ascertainment techniques adequately described. Patients and assessors blinded. Adequate statistical analysis of potential confounders (dose relationship, age, gender). Duration of follow-up appears adequate, 14 days. (5)
Rowbotham 2003[22]	Randomized	A: Levorphanol 0.75 mg up to 7 tabs tid B: Levorphanol 0.15 mg up to 7 tabs tid Mean doses 8.9 mg/day versus 2.7 mg/day 4 weeks intervention, with 4 weeks titration and 4 weeks taper	81	Not specified. Reported withdrawal due to adverse events, and serious adverse events	FAIR. High overall loss to follow-up (25). Adverse events not specified or defined. Ascertainment techniques not described. Patients and investigators blinded. Analyzed underlying condition's effect on withdrawal due to adverse events. Duration of follow-up appears adequate, 4 weeks intervention in addition to titration and taper. (4)

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Rate and Number of Adverse Events	Comments
Peloso 2000[65]	Long-acting codeine vs. placebo (study reports adverse events for "all patients randomized to treatment", assume intention-to-treat analysis as only rates reported) Constipation: 25/51 (49%) vs. 6/52 (11%), p<0.01 Somnolence: 20/51 (39%) vs. 5/52 (10%), p<0.01 Dizziness: 17/51 (33%) vs. 4/52 (8%), p<0.01 Overall (any): 42/51 (82%) vs. 30/52 (58%), p<0.01 Nausea: not significantly different (rates not reported) Long-acting codeine only: Severe constipation 13/51 (26%), severe somnolence 8/51 (16%), severe dizziness 6/51 (12%), severe nausea 2/51 (4%) Withdrawal due to adverse events: 15/51 (29%) vs. 4/52 (8%), p not reported	Patients required to discontinue baseline medications upon study entry, including opioids. 7/52 in placebo and 7/51 in codeine group previously on codeine; other baseline opioid and analgesic use not reported. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.
Roth 2000[12]	Long-acting oxycodone 20 mg bid vs. long-acting oxycodone 10 mg bid vs. placebo: Nausea: 18/44 (41%) vs. 12/44 (27%) vs. 5/45 (11%) Constipation: 14/44 (32%) vs. 10/44 (23%) vs. 3/45 (7%) Somnolence: 12/44 (27%) vs. 11/44 (25%) vs. 2/45 (4%) Vomiting: 10/44 (23%) vs. 5/44 (11%) vs. 3/45 (7%) Dizziness: 9/44 (20%) vs. 13/44 (30%) vs. 4/45 (9%) Pruritus: 7/44 (16%) vs. 8/44 (18%) vs. 1/45 (2%) Headache: 5/44 (11%) vs. 4/44 (9%) vs. 3/45 (7%) Withdrawal due to adverse events: 14/44 (32%) vs. 12/44 (27%) vs. 2/45 (4%)	Trial had open-label extension for up to 18 months for patients who wished to participate. Older (>65 years) patients more likely to have somnolence, other adverse event rates not significantly different. No difference in adverse event rates between genders. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.
Rowbotham 2003[22]	High-dose levorphanol vs. low-dose levorphanol (sample sizes for adverse event assessment not clear): Withdrawal due to adverse event: 25/81 overall, not reported by intervention Death: 0/43 vs. 1/38 Serious events: None Increased in high-dose group: itchy skin, sweating, and skin clammy Anger, irritability or mood or personality change: 6/43 vs. 0/38 Weakness or confusion: 5/43 vs. 0/38 Dizziness: 2/43 vs. 0/38	

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Type of Study	Interventions (Dose, Duration)	Number Enrolled	Method of Adverse Event Assessment and Adverse Events Assessed	Quality Rating (Number of Criteria Out of Seven Adequately Met)
Watson 1998[66]	Randomized Crossover	A: Long-acting oxycodone (titrated) B: Placebo Mean final dose 45 mg/day 4 week intervention followed by 4 week crossover	50	Most frequently reported adverse event, assessed by weekly questionnaire	FAIR. Not clear if selection of patients biased, number eligible not clear. High overall loss to follow-up (11/50), with an additional patient unaccounted for. Adverse events not specified or defined. Ascertainment techniques adequately described. Patients and investigators blinded. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 4 weeks for each intervention period. (3)
Watson 2003[24]	Randomized Crossover	A: Long acting oxycodone (titrated from 10 mg q 12 hrs) B: Benztropine (active placebo) Mean final dose 40 mg/day 4 weeks initial intervention followed by 4 week crossover	45	Events spontaneously reported by patients and observed by investigators recorded at each visit.	POOR. 9/20 lost to follow-up. Adverse events not specified or defined. Ascertainment techniques not described. Doesn't appear blinded. No statistical analysis of confounders. Duration of follow-up appears adequate (4 weeks per intervention). (3)

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Rate and Number of Adverse Events	Comments
Watson 1998[66]	Long-acting oxycodone vs. placebo (sample sizes not clear): Any adverse event: 76% vs. 49%, p=0.0074 Constipation (5 patients), nausea (4 patients), sedation (3 patients) most commonly reported adverse events Withdrawal due to adverse events not reported	Trial reports 11 withdrawals, 1 enrolled patient not accounted for. 45% of patients on opioids prior to trial, all withdrawn at least 1 week before intervention began. Opioids previously used not specified. Sample size for adverse events not clear. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.
Watson 2003[24]	Long-acting oxycodone (A) vs. placebo (B) Withdrawal due to adverse events: 7/45 vs. 1/45 Serious adverse events: 0/45 vs. 3/45 Nausea: 16/45 vs. 8/45 (p=0.09) Vomiting: 5/45 vs. 2/45 (p=0.26) Somnolence: 9/45 vs. 11/45 (p=0.56) Constipation: 13/45 vs. 4/45 (p=0.02) Dizziness: 7/45 vs. 3/45 (p=0.16) Asthenia: 2/45 vs. 5/45 (p=0.26) Insomnia: 3/45 vs. 4/45 (p=0.71) Pruritus: 4/45 vs. 1/45 (p=0.18) Sweating: 4/45 vs. 1/45 (p=0.18)	Not clear how withdrawals handled in safety analysis.

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: cohort studies of long-acting opioids

Author Year	Type of Study, Setting	Medications evaluated (dose, duration)	Eligibility Criteria	Exclusion Criteria	Other pain medications used or allowed
Ackerman 2004[29]	Retrospective cohort U.S. Population-based (California Medicaid)	A: Transdermal fentanyl B: Long-acting oxycodone	California Medicaid patients prescribed transdermal fentanyl or long-acting oxycodone during 3 consecutive months	California Medicaid ineligible, <18 years old, prescribed other long-acting opioid, prescribed codeine, prescribed transdermal fentanyl or long-acting oxycodone after start date, or prescribed both medications	Short-acting opioids and tricyclics controlled in analyses
Arkinstall 1995[61]	Prospective cohort (open-label extension of randomized trial) Canada Multicenter Pain clinics	Long-acting codeine, titrated to adequate pain control Mean dose at end of trial 264 mg Average duration 132 days	Patients completing trial by Arkinstall 1996 requesting continued long-term treatment with controlled-release codeine	Same as trial by Arkinstall 1996	Acetaminophen + codeine (short-acting)
Bach 1991[77]	Retrospective cohort Denmark Single center Pain clinic	A: Long-acting morphine B: Buprenorphine (short-acting) Mean dose at end of intervention 1.2 mg buprenorphine and 80 mg morphine Average duration 58 days	Patients with chronic pain being treated with either sublingual buprenorphine or oral sustained release morphine	Not specified	Anti-inflammatory agents, tricyclic antidepressants, or anticonvulsants

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: cohort studies of long-acting opioids

Author Year	Number screened Number eligible Number enrolled	Number withdrawn or lost to follow-up Number analyzed	Population characteristics	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven met)
Ackerman 2004[29]	Not reported Not reported 2106	Not applicable	Transdermal fentanyl vs. long-acting oxycodone Age: 67 vs. 54 years Female: 74% vs. 65% Non-white race: 31% vs. 26% Cancer: 10% vs. 3.16% Low daily dose: 41% vs. 28%	First episode of constipation event (ICD-9 code) using inpatient and outpatient claims data	FAIR. Inception cohort and number unable to be assessed not reported. Not clear if assessors blinded. Adequate duration of follow-up, 90 days. (5)
Arkinstall 1995[61]	30 screened 30 eligible 28 enrolled	13/28 (46%) withdrawn or lost to follow-up Not clear how many patients included in analysis	Age, gender, race not reported; Diagnosis, duration of pain not reported recruited from trial by Arkinstall 1996	Any adverse event spontaneously reported or investigator-observed, timing not clear	POOR. Not clear if selection of patients biased; number eligible in randomized trial not clear. High overall loss to follow-up (13/28). Adverse events not specified or defined. Ascertainment techniques inadequately described (timing not clear). Assessors do not appear to have been blinded. No statistical analysis of potential confounders. Adequate duration of follow-up, 132 days. (1)
Bach 1991[77]	Unable to assess, no inception cohort	Unable to assess number withdrawn or lost to follow-up, no inception cohort 264 analyzed	avg. 70 years Gender and race not reported 56% of non-cancer pain patients had ischemic leg pain 44% other non-cancer pain Pain duration not reported	Any adverse event as assessed weekly at follow-up visits or telephone calls by pain clinic nurses	POOR. Not clear if selection of patients biased, not clear if consecutive series. Unable to assess loss to follow-up, no inception cohort. Adverse events not specified or defined. Ascertainment techniques inadequately described. Assessors do not appear to have been blinded. No statistical analysis of confounders. Duration of follow-up not reported. (0)

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: cohort studies of long-acting opioids

Author Year	External validity	Funding sources and role of funder	Rate and number of adverse events	Comments
Ackerman 2004[29]	Population adequately described. California Medicaid population. Approximately 25% on short-acting opioids.	Janssen (transdermal fentanyl) One author employed by funder, not reported if data held by funder	Long-acting oxycodone versus transdermal fentanyl: adjusted odds ratio 2.55 (95% CI 1.33-4.89) for constipation; 7.33 (1.98-27.13) in persons >65 years old	Many significant baseline differences between groups; analysis adjusted for dose, concomitant medications, comorbidities including cancer. Data appears to overlap with Staats 2004.
Arkinstall 1995[61]	Population adequately described. Highly selected population that completed previous randomized trial. Exclusion criteria specified in original trial, numbers excluded for specific criteria not reported. Patients were on opioids during prior trial.	Purdue (controlled release codeine) One author (corresponding author) employed by funder, not clear if data held by funder	Long-acting codeine: Adverse events "similar to rates reported in trial". Long-term use: 15/28 (54%), not clear how many discontinued medication due to adverse events.	Did not report rates of specific adverse events in long-term follow-up. Reasons for discontinuation of medication in long-term follow-up not reported.
Bach 1991[77]	Population not adequately described, unable to assess whether population similar to populations in whom the intervention would be applied. Unable to assess how many patients screened. Exclusion criteria not specified.	Not reported	Oral long-acting morphine vs. sublingual buprenorphine: Any adverse event: 33/114 (28.9%) vs. 19.3% (29/150) Individual adverse events not reported according to indication for treatment	Tabulated results exclude 189 patients with cancer pain. Individual side effects not reported for non-cancer pain patients. Not clear if mean doses of medications equipotent between long-acting morphine and buprenorphine.

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: cohort studies of long-acting opioids

Author Year	Type of Study, Setting	Medications evaluated (dose, duration)	Eligibility Criteria	Exclusion Criteria	Other pain medications used or allowed
Caldwell 2002[53]	Prospective cohort US Multicenter Pain clinics	Once-daily morphine titrated to adequate pain relief Mean daily dose at end of intervention 49 mg morphine (max 120 mg/day) 26 weeks of treatment	Adults with clinical and radiographic evidence of osteoarthritis who had failed course of non-opioids for pain and completed a randomized double-blind trial of once-daily morphine, twice-daily morphine, or placebo.	Patients with serious comorbid conditions or conditions that might affect assessment of pain, weight <100 lbs, steroids within 1 month, intra-articular injections within six months, opioids therapy for >3 weeks prior to baseline, substance abuse, unable to tolerate opioid during randomized trial	Acetaminophen, topical analgesics, and non-steroidal anti-inflammatory agents
Dellemijn 1998[73]	Prospective cohort Netherlands Single center Pain clinic	Transdermal fentanyl titrated to adequate pain relief (max 100 micrograms/hr) Maximum tolerated dose at end of treatment 75 micrograms/hour (7 patients) 12 weeks of treatment, followed by tapering off transdermal fentanyl and substitution with fixed dose long-acting morphine (60 mg bid)	Adults with noncancer neuropathic pain who had completed a randomized double-blind trial with intravenous fentanyl plus diazepam or saline	Use of opioids or modified pain regimens during the 2 weeks before starting the study, contraindications to opioids, presence of multiple sites or other types of pain, intermittent neuropathic pain, and uncertainty about origin of pain	Continued other entry medications at baseline level.

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: cohort studies of long-acting opioids

Author Year	Number screened Number eligible Number enrolled	Number withdrawn or lost to follow-up Number analyzed	Population characteristics	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven met)
Caldwell 2002[53]	184 screened 184 eligible 181 enrolled	52% (86/181) discontinued or withdrew prematurely 181 analyzed for adverse events	Age, gender, race not reported Characteristics and duration of osteroarthris pain not reported for patients enrolling in open-label extension	Any adverse event, assessment methods not clear	POOR. Not clear if selection of patients biased, number eligible not reported. High overall loss to follow-up. Adverse events not specified or defined. Ascertainment techniques inadequately described. Patients and assessors blinded to intervention. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 4 weeks. (2)
Dellemijn 1998[73]	50 screened 50 eligible 48 enrolled	33% (16/48) discontinued or withdrew prematurely 4% (2/48) lost to follow-up 44 analyzed for adverse events	avg. 49 years 77% female Race not reported Neuropathic pain: 58% radiculopathy 19% post-traumatic neuralgia 6% post-herpetic neuralgia 4% phantom pain 6% central pain 6% postrhizotomy pain Pain duration not reported	Any adverse event, assessment methods not clear, severity graded on 0-100 VAS	POOR. Not clear if selection biased; number eligible in prior trial not reported. High overall loss to follow-up (18/48). Adverse events not specified or defined. Ascertainment techniques not described. Patients and assessors not blinded to treatment. Adequate duration of follow-up appears adequate, 12 weeks. (1)

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: cohort studies of long-acting opioids

Author Year	External validity	Funding sources and role of funder	Rate and number of adverse events	Comments
Caldwell 2002[53]	Population not adequately described, unable to assess whether population similar to patients in whom the intervention would be applied, Exclusion criteria reported for prior randomized trial, numbers excluded for specific criteria not reported. 28 patients had been on placebo during prior randomized trial.	Funding source not clear; one author employed by drug manufacturer of once-daily morphine (Elan Pharmaceutical)	Adverse events reported in >5% of patients taking once-daily morphine either in a.m. or p.m., n =181 Constipation: 35% Nausea: 16% Diarrhea: 13% Somnolence: 13% Dizziness: 9% Abdominal pain: 8% Pain: 8% Headache: 8% Infection: 7% Insomnia: 6% Peripheral edema: 6% Vomiting: 6% Dry mouth: 4% Accidental injury: 4%	High withdrawal and loss to follow-up rate, not clear how withdrawn patients accounted for in adverse event rates.
Dellemijn 1998[73]	Population adequately described. Number eligible and screened in prior trial not reported, unable to assess whether population similar to populations in whom the intervention would be applied. Exclusion criteria reported in prior trial, numbers excluded for specific criteria not reported.	Janssen (transdermal fentanyl) Author not employed by funder, not reported if data held by funder	Side effects on transdermal fentanyl occurring at any time (estimated from graph), n=44: Nausea: 92% Sweating: 68% Headache: 68% Fatigue: 58% Vomiting: 54% Dizziness: 53% Constipation: 36% Dyspnea: 36% Pruritus: 33% Dry mouth: 31% Insomnia: 28% Anorexia: 25% Anxiety: 18% Skin irritation: 18% Other adverse events reported in <20% Long-term use: 9/48 (19%) continued >2 years	High withdrawal and loss to follow-up rate, not clear how withdrawn patients accounted for in adverse event rates.

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: cohort studies of long-acting opioids

Author Year	Type of Study, Setting	Medications evaluated (dose, duration)	Eligibility Criteria	Exclusion Criteria	Other pain medications used or allowed
Dunbar 1996[74]	Retrospective cohort US Single Center Pain clinic	6/20 (30%) oxycodone alone 6/20 (30%) methadone alone 5/20 (25%) methadone and oxycodone 1/20 (5%) morphine SR + oxycodone 1/20 (5%) hydromorphone + oxycodong 1/20 (5%) morphine SR alone Doses not reported Pain duration not reported	Patients with chronic non-cancer pain and a prior history of substance abuse who were managed on opioids for any period of time	None	Not reported
Franco 2002[27]	Prospective cohort	Transdermal fentanyl Mean dose 42 mg/day 6 months	Patients of either gender aged 18 years or over presenting with chronic non-cancer pain susceptible to be treated with opioids and a mental status sufficient to be able to complete effectiveness tests; unsuccessful pain relief under current treatment with weak opioids at maximal doses (WHO) analgesic ladder to step 3 or previous treatment with morphine (in particular, when > 120 mg/day was required)	Previous treatment with fentanyl; history of alcohol abuse, drug dependence, or severe personality disorders according DSM-III-R criteria	Analgesics

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: cohort studies of long-acting opioids

Author Year	Number screened Number eligible Number enrolled	Number withdrawn or lost to follow-up Number analyzed	Population characteristics	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven met)
Dunbar 1996[74]	Unable to assess, no inception cohort	Unable to assess number withdrawn or lost to follow-up, no inception cohort 20 analyzed	35% peripheral neuropathy 20% chronic pancreatitis 10% failed back surgery 20% arachnoiditis 15% other Duration not reported	Prescription drug abuse assigned by physician reviewing data	POOR. Not clear if selection of patients biased, not clear if consecutive series. Unable to assess loss to follow-up, no inception cohort. Adverse events not specified or defined. Ascertainment technique not described. Assessors do not appear to have been blinded. No statistical analysis of confounders. Duration of follow-up not reported. (0)
Franco 2002[27]	Not reported Not reported 236 enrolled	110(46.6%) withdrawn 236 analyzed	avg. 66.2 years 31% female Race not reported 50.8% neuropathic pain Pain duration not reported	Incidence, nature, time of onset, duration and intensity were recorded using non-specific and specific questions related to expected adverse events. Intensity determined by patient subjective evaluation. Investigator determined relationship between the treatment and adverse events.	POOR. Not clear if selection of patients biased, number eligible not reported. High overall loss to follow-up. Adverse events not specified or defined. Ascertainment techniques inadequately described. Patients and assessors not blinded to intervention. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 6 months. (1)

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: cohort studies of long-acting opioids

Author Year	External validity	Funding sources and role of funder	Rate and number of adverse events	Comments
Dunbar 1996[74]	Population adequately described. Number eligible and screened not reported, unable to determine whether population similar to populations in whom the intervention would be applied. Exclusion criteria not specified.	Not reported	Abuse: Oxycodone alone 1/6 (16.7%); methadone alone 3/6 (50%); methadone + oxycodone 3/5(60%); long-acting morphine + oxycodone 0/1 (0%); hydromorphone + oxycodone 1/1 (100%); long-acting morphine 1/1 (100%)	Only study addressing risk of abuse in higher-risk population. Diagnosis of abuse not specified or defined and assigned by physician not blinded to patient's prior condition or current treatment. Inadequate detail regarding length of opioid treatment, dose, and severity of underlying pain. No inception cohort.
Franco 2002[27]	Population adequately described, unable to assess whether population similar to populations in whom the intervention would be applied. Unable to assess how many patients screened. Exclusion criteria specified.	Not reported	Transdermal fentanyl (n=236) Any adverse effect: 177(75%) Somnolence=53(22.5%) Nausea=51(21.6%) Vomiting=36(15.3%) Constipation=36(15.3%) Dizziness=59(25%) Irritability=12(5.1%) Urinary retention=10(4.2%) Sweating=22(9.3%) Local pruritus=9(3.8%)	High withdrawal rate

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: cohort studies of long-acting opioids

Author Year	Type of Study, Setting	Medications evaluated (dose, duration)	Eligibility Criteria	Exclusion Criteria	Other pain medications used or allowed
Green 1996[75]	Retrospective cohort	Methadone Mean dose not reported (range 30 to 120 mg/day) Duration not reported	Patients with chronic non-cancer pain on methadone	Not reported	Not reported
Milligan 2001[76]	Prospective cohort International Multicenter Pain clinics	Transdermal fentanyl (titrated) Mean final dose 90 micrograms/hr 12 months	Patients >18 years old with chronic nonmalignant pain >6 weeks requiring continuous treatment with a potent opioid	Allergy or hypersensitivity to opioids, life-threatening disease, skin condition precluding use of transdermal system, history of substance abuse, other significant disease	Immediate-release morphine for breakthrough pain

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: cohort studies of long-acting opioids

Author Year	Number screened Number eligible Number enrolled	Number withdrawn or lost to follow-up Number analyzed	Population characteristics	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven met)
Green 1996[75]	Unable to assess, no inception cohort	Unable to assess number withdrawn or lost to follow-up, no inception cohort 11 analyzed	avg. 56 years 27% female Race not reported 73% chronic back pain 18% neuropathy 9% chronic headaches Pain duration not reported	Any adverse event, assessment methods not clear	POOR. Not clear if selection of patients biased, not clear if consecutive series. No inception cohort, unable to assess loss to follow-up. Adverse events not specified or defined. Ascertainment technique not described. Assessors do not appear to have been blinded. No statistical analysis of potential confounders. Duration of follow-up not reported. (0)
Milligan 2001[76]	Screened unclear Eligible unclear 532 enrolled (Study reports number eligible = number enrolled)	62% (231/532); 226 withdrew, 5 lost to follow-up 530 analyzed for adverse events	avg. 51 years 52% female 99% white 51% neuropathic 69% nociceptive 70% somatic 7.5% visceral Pain duration average 8.8 years	Any adverse event possibly or definitely treatment-related, recorded monthly and at study discontinuation, assessment method not described	POOR. Not clear if selection of patients biased, number eligible not reported. High overall loss to follow-up. Adverse events not specified or defined. Ascertainment technique inadequately described. Patients and assessors not blinded. Inadequate statistical analysis (age only). Duration of follow-up appears adequate, 12 months. (1)

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: cohort studies of long-acting opioids

Author Year	External validity	Funding sources and role of funder	Rate and number of adverse events	Comments
Green 1996[75]	Population adequately described. No inception cohort, unable to determine whether population similar to populations in whom the intervention would be applied. Exclusion criteria not specified.	Not reported	Methadone: Any adverse effect: 6/11 (55%) Abuse: 1/11 (9%) Overdose on patient's methadone by family member or friend: 1/11 (9%) Sudden death: 1/11 (9%) Severe anorexia, sedation, and nausea: 1/11 (9%)	Small study, not clear how patients selected for methadone treatment or how selected for inclusion. No inception cohort.
Milligan 2001[76]	Population adequately described. Number of patients eligible and screened not reported, unable to determine whether population similar to populations in whom the intervention would be applied. Exclusion criteria specified, numbers excluded for specific criteria not reported.	Janssen (transdermal fentanyl) One author employed by Janssen, not reported if data held by funder.	Transdermal fentanyl: Severe nausea: 48/530 (9%) Severe vomiting: 42/530 (8%) Severe diaphoresis: 37/530 (7%) All serious adverse events: 146/530 (28%) Serious adverse events probably or possibly treatment related: 38/530 (7%) One or more adverse events considered possibly or definitely related to study medication: 387/530 (73%) and 170/530 (32%) Withdrawals due to adverse events: 130/530 (25%) Respiratory depression: 4/530 (1%) Drug abuse: 3/530 (0.6%) Addiction: None reported Deaths thought related to trial medication: 1/530 (0.2%)	103 patients had participated in trial by Allan. High overall withdrawal rate; not clear how withdrawn patients accounted for in adverse event rates. No significant difference in adverse event rates between older (>65) and younger patients, raw numbers not presented.

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: cohort studies of long-acting opioids

Author Year	Type of Study, Setting	Medications evaluated (dose, duration)	Eligibility Criteria	Exclusion Criteria	Other pain medications used or allowed
Ringe 2002[26]	Prospective cohort Germany Multicenter	Transdermal fentanyl (titrated) Mean dose not reported 42/64(65.6%) 25 mg/h 3/64(4.6%) 50 mg/h 17/64(25.6%) required unspecified up-titration Median observation duration=30 days	Patients with at least one osteoporotic vertebral fracture causing pain that required continuous administration of strong opioids	Osteoporotic fracture of the femoral neck or with osteoporosis caused by malignant diseases	Nonopioid analgesics Baseline=38/64(59%) Day 15=8/64(12.5%) Weak opioids Baseline=17/64(26.6%) Day 15=4/64(6.3%) Strong opioids Temporary=2/64(3.1%)
Roth 2000[12]	Prospective cohort (open-label extension of randomized trial) US Multicenter Rheumatology clinics	Long-acting oxycodone (titrated) Average dose 40 mg/day 6 month initial period with two optional 6 month extension periods	Patients completing clinical trial (Roth 2000) who wished to continue controlled-release oxycodone therapy	Severe organ dysfunction or history of drug or alcohol abuse	No rescue medications allowed
Staats 2004[30]	Retrospective cohort U.S. Population-based (California Medicaid)	A: Transdermal fentanyl B: Long-acting oxycodone C: Long-acting morphine	Random sample of California Medicaid patients, no prior constipation diagnosis, no long-acting opioid during previous 3 months, prescribed one of the included long-acting opioids during 3 consecutive months	Claims for two or more opioids of interest, use of other opioids other than codeine	Not specified

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: cohort studies of long-acting opioids

Author Year	Number screened Number eligible Number enrolled	Number withdrawn or lost to follow-up Number analyzed	Population characteristics	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven met)
Ringe 2002[26]	Screened unclear Eligible unclear 64 enrolled	15(23%) withdrew 64 analyzed	Mean age=71 years 86% female Race nr Primary osteoporosis=70% Secondary osteoporosis=30% Median duration of pain=14 days	All adverse events assessed by severity (mild, moderate, severe) and relationship to treatment (none, unlikely, possible or probable)	POOR. Not clear if selection of patients is biased. High overall loss to follow-up. Adverse events not specified or defined. Ascertainment technique inadequately described. Patients and assessors not blinded. No statistical analysis of confounders. Inadequate duration of treatment (30 days). (0)
Roth 2000[12]	133 screened 133 eligible 106 enrolled	60 withdrew 106 analyzed for adverse events	Not reported, population participated in study by Roth 2000	Any adverse event Spontaneously reported or observed by investigator at each visit (weekly to once every 8 weeks)	FAIR. Selection of patients does not appear biased. High overall loss to follow-up. Adverse events not specified or defined. Ascertainment technique adequately described. Patients and assessors not blinded. Inadequate statistical analysis (duration of treatment only). Duration of follow-up appears adequate, 6-18 months. (3)
Staats 2004[30]	Not reported Not reported 1836	Not applicable	Transdermal fentanyl vs. long-acting oxycodone vs. long-acting morphine Age: 66 vs. 54 vs. 56 years Female: 71% vs. 60% vs. 56% Non-white race: 34% vs. 30% vs. 40% Cancer: 38% vs. 15% vs. 38% Dose (morphine equivalent); 116 vs. 232 vs. 208	First episode of constipation event (ICD-9 code) using inpatient and outpatient claims data	FAIR. Inception cohort and number unable to be assessed not reported. Not clear if assessors blinded. Adequate duration of follow-up, 90 days. (5)

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: cohort studies of long-acting opioids

Author Year	External validity	Funding sources and role of funder	Rate and number of adverse events	Comments
Ringe 2002[26]	Population adequately described. Number eligible and screened not reported, unable to determine whether population similar to populations in whom the intervention would be applied. Limited exclusion criteria not specified.	Janssen-Cilag GmbH	Transdermal fentanyl: Patients with at least one adverse event: 25(39%) Withdrawal due to adverse events: 13(20.3%)	
Roth 2000[12]	Population adequately described. Highly selected population, patients completing randomized trial who wanted to continue open-label extension. Exclusion criteria specified, numbers excluded for specific criteria not reported. Patients on prior opioids during previous 14 day trial.	Purdue (sustained release oxycodone) One author employed by funding source, not reported if data held by funder	Long-acting oxycodone: Long-term use: 46/106 (43%) Withdrew due to adverse event: 32/106 (30%) Constipation: 55/106 (52%) Somnolence: 32/106 (30%) Nausea: 25/106 (24%) Pruritus: 21/106 (20%) Nervousness: 16/106 (15%) Headache: 14/106 (13%) Insomnia: 14/106 (13%) Hospitalization during observation period: 13/106 (12%), 5/106 (5%) possibly related to intervention	Varying periods of follow-up. Number enrolled (106) does not match numbers reported in duration of follow-up (114). Not clear how withdrawn patients accounted for in adverse event rates.
Staats 2004[30]	Population adequately described. California Medicaid population. High proportion with cancer, varied between intervention arms.	Janssen (transdermal fentanyl) One author employed by funder, not reported if data held by funder	Long-acting oxycodone and long-acting morphine versus transdermal fentanyl (comparator): adjusted odds ratio 1.78 (95% CI 1.05-3.03) and 1.44 (0.80-2.60) for constipation	Many significant baseline differences between groups; analysis adjusted for dose, concomitant medications, comorbidities including cancer. Data appears to overlap with Ackerman 2004.

Appendix A: Search Strategy

1 exp analgesics, opioid/ or "opioid analgesics".mp.
2 exp narcotics/ or "narcotics".mp.
3 1 or 2
4 (intractable pain or severe pain or chronic pain).mp.
5 3 and 4
6 limit 5 to human
7 limit 6 to english language
8 6 not 7
9 limit 8 to abstracts
10 7 or 9

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2005>
Search Strategy:
---
1 opioid analgesics.mp. (121)
2 narcotics.mp. (685)
3 analgesics, opioid.mp. (2546)
4 1 or 2 or 3 (3251)
5 pain.mp. (31978)
6 4 and 5 (2306)
7 limit 6 to yr="1898 - 1998" (1002)
8 limit 6 to yr="1999 - 2005" (1304)
9 from 8 keep 1-1304 (1304)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2005>
Search Strategy:
---
1 opioid analgesics.mp. (121)
2 narcotics.mp. (685)
3 analgesics, opioid.mp. (2546)
4 1 or 2 or 3 (3251)
5 pain.mp. (31978)
6 4 and 5 (2306)
7 limit 6 to yr="1898 - 1998" (1002)
8 from 7 keep 1-1002 (1002)

Database: Ovid MEDLINE(R) <1966 to September Week 3 2005>
Search Strategy:
---
1 opioid analgesics.mp. (785)
2 narcotics.mp. (12607)
3 analgesics, opioid.mp. (13544)
4 1 or 2 or 3 (25906)
5 pain.mp. (244418)
6 4 and 5 (10463)
7 opioid analgesics.mp. or exp Analgesics, Opioid/ (64576)
8 narcotics.mp. or exp NARCOTICS/ (64860)
9 7 or 8 (71918)
10 (intractable pain or severe pain or chronic pain).mp. (12690)
11 9 and 10 (1865)
12 limit 11 to human (1715)
13 limit 12 to english language (1472)
14 12 not 13 (243)
15 limit 14 to abstracts (185)
16 13 or 15 (1657)
17 ("20041119" or 2004112$ or 2004113$ or 200412$ or 2005$).ed. (516260)
18 16 and 17 (132)
19 from 18 keep 1-132 (132)

Database: Ovid MEDLINE(R) <1966 to September Week 3 2005>
Search Strategy:
---
1 opioid analgesics.mp. or exp Analgesics, Opioid/ (64576)
2 narcotics.mp. or exp NARCOTICS/ (64860)
3 1 or 2 (71918)
4 (intractable pain or severe pain or chronic pain).mp. (12690)
5 3 and 4 (1865)
6 limit 5 to human (1715)
7 limit 6 to english language (1472)
8 6 not 7 (243)
9 limit 8 to abstracts (185)
10 7 or 9 (1657)
11 hydromorphone.mp. or exp HYDROMORPHONE/ (922)
12 oxymorphone.mp. or exp OXYMORPHONE/ (353)
13 11 or 12 (983)
14 limit 13 to humans (598)
15 limit 14 to english language (570)
16 14 not 15 (28)
17 limit 16 to abstracts (11)
18 15 or 17 (581)
19 4 and 13 (64)
20 19 not 10 (10)
21 from 20 keep 1-10 (10)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2005>
Search Strategy:
---
1 opioid analgesics.mp. (121)
2 narcotics.mp. (685)
3 analgesics, opioid.mp. (2546)
4 1 or 2 or 3 (3251)
5 pain.mp. (31978)
6 4 and 5 (2306)
7 (hydromorphone or oxymorphone).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (183)
8 5 and 7 (93)
9 8 not 6 (45)
10 from 9 keep 1-45 (45)

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)	
Type of study (RCT, crossover, population-based, retrospective cohort, prospective cohort)	
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 follow-up 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)	

Appendix C. Quality abstraction tool for adverse events of opioids (continued)

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: Updated clinical trials search results