Drug Class Review
on Long-Acting Opioid Analgesics

FINAL REPORT

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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] as appropriate treatment for refractory chronic non-cancer pain in the general population as well as 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]

In 2001, the Oregon Legislature passed Senate Bill 819, which mandated the development of a Practitioner-Managed Prescription Drug Plan (PMPDP) for the Oregon Health Plan (OHP). As part of this process, it required that an evidence-based review of the state's most expensive drug classes be performed. The Oregon Health Resources Commission (OHRC) requested a review of the long-acting opioid drug class specifically in persons with chronic non-cancer pain. The OHRC requested information about 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.

Regular six-month updates for this report are scheduled. Update #1 was submitted in September 2003, based on searches performed in March 2003. Update #2, presented here, was completed in February 2004 from searches performed in November 2003. Changes to the report made for update #1 have been incorporated into the text. New changes for update #2 are highlighted in the text and tables of this report. A new table summarizing main efficacy results of trials of long-acting opioids (Table 1.3) was also added. At the time the update was conducted, the FDA had approved no new long-acting nonparenteral opioids. The next update searches will be performed in May 2004.

Scope and Key Questions

The scope of the review and key questions were developed and refined with input from an OHC subcommittee comprised of statewide experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). In consultation with the subcommittee, we selected the following key questions to guide the 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, 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?
    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, 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?
    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. Senate Bill 819 specifically excludes cancer patients and patients with HIV from this process, and they were not part of this review.

Drugs. We included oral or transdermal long-acting opioids. "Long-acting" was defined as opioids administered twice a day or less frequently. Long-acting opioids that we identified were transdermal fentanyl and oral oxycodone, morphine, methadone, levorphanol, codeine and dihydrocodeine.

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.[8] 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 another 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 subcommittee selected the following adverse events for our review: abuse, addiction, nausea, vomiting, constipation, dizziness, somnolence, and confusion. These were the adverse events felt by the subcommittee 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 a particular adverse effect. In some studies, only "serious" adverse events or adverse events "thought related to treatment medication" are reported. Many studies do not define these terms.

The subcommittee specifically requested that we examine 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.[9, 10] 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 in its arms: withdrawals were due to adverse events in patients on long-acting oxycodone, but due to inadequate pain control in the patients on placebo.[11] High withdrawal rates probably indicate some combination of poor tolerability and ineffectiveness. An important subset is withdrawal due to any adverse event (those who discontinue specifically because of adverse effects).

Study types. We included controlled clinical trials to evaluate efficacy. The validity of controlled trials depends on how they are designed. Randomized, properly blinded clinical trials are considered the highest level of evidence for assessing

efficacy.[12-14] Clinical trials that are not randomized or blinded, and those that have other methodologic 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 provided indirect comparative data.

To evaluate adverse event rates, we included clinical trials and observational cohort studies. 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. Observational studies designed to assess adverse event rates may include broader populations, carry out observations over a longer time period, utilize higher quality methodologic 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.[15-18]

METHODS

Literature Search

To identify articles relevant to each key question, we searched, in order, 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, the State of Oregon created and disseminated a submission protocol 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.

In March 2003, we performed Update #1 searches. We searched the Cochrane Library (2002, Issue 4), MEDLINE (through March 2003), and EMBASE (through March 2003). We also received dossiers from two manufacturers (Janssen for transdermal fentanyl and Purdue for long-acting oxycodone).

We conducted Update #2 searches of the Cochrane Library (through third quarter, 2003), MEDLINE (through November week 2 2003), and Embase (through fourth quarter, 2003) in November 2003. We used the same search strategy as was used for the original report. The electronic searches were supplemented with hand searches of the current issues of relevant journals, and reference lists. Pharmaceutical manufacturers

were invited to submit update dossiers, including citations, using a protocol issued by the State of Oregon (http://www.ohppr.state.or.us/index.htm). These submissions were reviewed to identify new citations not previously submitted. All citations were imported into an electronic database (EndNote 6.0).

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 the subcommittee. 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 one of the long-acting opioids listed above 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 that reported adverse event rates for one of the long-acting opioids listed above.

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.

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 (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.[19] Sixteen randomized controlled trials provided usable data and are included in evidence tables.

In update search # 1(March 2003), we identified a total of 646 new citations: 499 from the Cochrane Library, 66 from MEDLINE, 70 from EMBASE, and 11 from manufacturer submissions (2 from Purdue and 9 from Janssen). We also found updated results from the Drug Abuse Warning Network (DAWN) published by the U. S. Department of Health and Human Services[20] and a review of deaths related to methadone

in Oregon published by the Office of Communicable Disease and Epidemiology, Oregon Department of Human Services.[21]

From these citations, we identified one head-to-head clinical trial[22] and two observational studies[23, 24] on safety that met inclusion criteria. We also reviewed updated results of the DAWN network[20] and from the Oregon Department of Human Services[21] regarding adverse events from long-acting opioids.

In electronic update searches performed in November 2003, we found 176 new citations. Twenty-one were from the Cochrane Central Register of Controlled Trials, 57 from Medline, and 98 from Embase. Thirteen additional citations came from hand searches or reference lists. We also received dossiers from two pharmaceutical companies (Purdue for controlled-release oxycodone and Janssen for transdermal fentanyl) with 19 citations not otherwise identified. Of the citations found, 5 reported results from clinical trials and met initial screening criteria for inclusion. 29 other trials were excluded at the title and abstract review stage for the following reasons: 12 did not evaluate an included patient population, 14 did not evaluate an included intervention, 2 were available as abstract only, and 1 was non-English language. Of the citations that met initial screening criteria for inclusion, one met inclusion criteria after the full paper was reviewed. Four trials were excluded at this stage: 1 because it was available as an abstract only,[25] 1 because it administered the opioid three times daily (we had defined a long-acting opioid as one that was administered twice daily or less frequently),[26] and 2 because they evaluated a medication not available in the United States (transdermal buprenorphine).[27, 28] No head-to-head trials were included. One placebo-controlled trial of long-acting oxycodone in patients with diabetic neuropathy met inclusion criteria.[29]

We identified one observational study reporting methadone-related deaths in Hennepin County, Minnesota.[30] Although we identified no large, high-quality observational studies evaluating adverse events from long-acting opioids that met inclusion criteria, we reviewed one small observational study on long term effects of oral sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain[31] and one small series of torsades de pointes associated with very high doses of methadone.[32] We also reviewed a report from the federal General Accounting Office on factors that may have contributed to the abuse and diversion of long-acting oxycodone (oxycontin).[33]

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.[34] 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 biasing subsequent results, outcomes for the first intervention were recorded if available. All data were checked by a second reviewer.

Quality Assessment

We assessed quality of trials based on the predefined criteria listed in Appendix B, which were submitted to the Health Resources Commission in December 2001. 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).[12, 13] Trials that had a fatal flaw in one or more categories were rated poor-quality; trials that met all criteria were rated good-quality; the remainder 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.

After assignment of quality ratings by the initial reviewer, quality ratings were independently assigned by a second reviewer. Overall quality rating and quality rating scores (for studies on adverse event assessment) were compared between reviewers. If overall quality ratings differed, the two reviewers would come to consensus with a third reviewer prior to assigning a final quality rating.

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 the subcommittee is 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

Trials Included in Original Report:

We identified 17 (16 for the original report and 1 for update #1) randomized trials (1,427 patients enrolled) that evaluated long-acting opioids in chronic non-cancer pain populations (Table 1.1). Recent non-systematic reviews on adverse events from opioids have identified only two trials each.[2, 7] We did not find a relevant systematic review for any of the key questions.

Only two of the 16 trials reviewed in the original report compared one long-acting opioid to another.[35, 36] One of these trials[35] compared transdermal fentanyl to long-acting morphine; the other[36] compared a once-daily morphine preparation to a twice-daily morphine preparation. Seven trials compared a long-acting opioid to a short-acting opioid,[37-43] and seven compared a long-acting opioid to a non-opioid or placebo.[11, 44-49] Seven trials used a crossover design.[35, 39, 40, 44, 46, 47, 49] We identified trials on long-acting oxycodone,[11, 38, 40, 43, 49] long-acting morphine,[35, 36, 41, 45-47] long-acting dihydrocodeine,[39, 42] long-acting codeine,[37, 44, 48] and transdermal fentanyl.[35] We did not identify any trials on levorphanol or methadone. One trial[50] cited in reference lists[2, 44] 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[46] to 295[36] evaluable enrollees, with an average of 79 enrollees. Five of the trials focused on osteoarthritis,[11, 36, 38, 42, 48] five on back pain,[37, 39-41, 43] two on neuropathic pain,[45, 49] one on phantom limb pain,[46] and three on heterogenous chronic non-cancer pain.[35, 44, 47]

All of the trials were of relatively short duration, ranging from 5 days[37] to 16 weeks.[41] 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 55.

Assigned quality ratings did not differ between reviewers for trials assessing efficacy or for trials assessing adverse events. Of the fifteen trials addressing adverse event rates, assigned scores were identical for twelve and differed by one point for three.[39, 42, 47] For none of these did the difference in point scores result in re-classification of overall quality rating for adverse event assessment.

Additional Trials Included in Updates:

One additional small (n=18) head-to-head crossover trial (4 weeks per intervention) of transdermal fentanyl versus long-acting oral morphine in patients with chronic pancreatitis was identified for update #1.[22]

One short-term (6 weeks) trial of controlled-release oxycodone (twice daily, average titrated dose 42 mg/day) compared to placebo in 159 patients with diabetic neuropathy was identified for update #2.[29]

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?

Three 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).[22, 35, 36] One trial[35] compared transdermal fentanyl to long-acting morphine twice a day. Another trial[36] compared a once-daily morphine preparation to a twice-daily morphine preparation. The third trial[22] compared transdermal fentanyl to long-acting morphine twice a day in patients with chronic pancreatitis. Main results from these trials are summarized in Table 1.3.

The study 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 [35]. This study was rated poor-quality because of several major methodologic flaws (Evidence Table 1.1). The most important areas of concern were that neither patients nor investigators were blinded, and many of the trial participants were on one of the study drugs prior to entry. Blinding is particularly important in studies using subjective measures. This may have been an even greater factor in this trial, in which 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.

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, though raw numbers were not reported. A 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.

How similar was the study sample to the population of interest to the ORC subcommittee? As discussed above, the subjects can best be described as patients who 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 Oregon practitioners: "in *unselected patients* who have chronic pain requiring treatment with opioids, is transdermal fentanyl more effective than long-acting morphine?"

Other aspects of the trial make its external validity difficult to assess. Exclusion criteria were not specified, and 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.

The study that compared a once-daily morphine preparation to a twice-daily morphine preparation[36] 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 no evaluation of the blinding, no comparison of persons who completed the study, 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 morphine treatment groups were better than placebo for most measures of efficacy. Withdrawal rates were similar in all active treatment groups.

External validity of this trial was difficult to assess because the numbers of patients screened and eligible for entry were not reported, the length of follow-up for each drug regimen was only 4 weeks, and duration of pain and previous narcotic use in evaluated patients was not reported.

A small (n=18) head-to-head trial of transdermal fentanyl vs. oral morphine in patients with chronic pancreatitis was identified during the update process in March 2003.[22] It found no significant differences between these two medications for patient preference, pain control, or quality of life (Evidence Table 1.1). This was an open-label study rated fair-quality and may not be applicable to the general population of patients with chronic non-cancer pain, since it only included patients with a relatively uncommon specific condition.

No head-to-head trials meeting inclusion criteria were found for update #2. One head-to-head trial comparing transdermal fentanyl and sustained-release morphine in 680 patients with chronic low back pain was only available in abstract form and was excluded.[25] There was insufficient data in the abstract to assess study quality. It found that transdermal fentanyl and sustained-release morphine provided comparable relief from low back pain. Transdermal fentanyl was associated with significantly less

constipation, and superior relief at rest and at night. Safety profiles were reported as similar.

Summary

In summary, three randomized trials provide the only direct evidence of the comparative efficacy of different long-acting opioids in chronic non-cancer pain. A poor-quality randomized trial comparing transdermal fentanyl to twice-daily morphine found conflicting evidence regarding efficacy. Although improved pain control was seen after treatment with transdermal fentanyl, increased withdrawals were also seen on this medication. Several important methodologic 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. 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. There are no data directly comparing fentanyl or long-acting morphine to any other long-acting preparation.

No head-to-head trials of long-acting opioids meeting inclusion criteria were identified for update #2.

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?

We identified 14 fair-quality trials (876 patient enrolled) that gave indirect evidence regarding the comparative efficacy of long-acting opioids. Seven studies compared long-acting opioids to short-acting opioids,[37-43] and seven studies compared long-acting opioids to non-opioids or placebos.[11, 44-49] These trials exhibited a high degree of heterogeneity with respect to study designs, patient populations, interventions, and outcomes measured (Table 1.1). All studies were rated fair-quality (see Evidence Tables 1.2 and 1.3) and had at least one of the following methodologic 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,[49] phantom limb pain,[46] osteoarthritis,[11, 38, 42, 48] back pain,[37, 39-41, 43] and miscellaneous chronic non-cancer pain.[44, 47] Three trials evaluated long-acting codeine,[37, 44, 48] two long-acting dihydrocodeine,[39, 42] four long-acting morphine,[41, 45-47] and five long-acting oxycodone.[11, 38, 40, 43, 49] The average equipotent opioid dose received varied greatly and in two trials was not reported.[39, 42] 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 and rescue

drug use (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 five trials on oxycodone, one used a visual analogue scale, [49] three others used two different (0-3[11, 40] or 0-4[38]) categorical scales, and one did not report pain intensity as an outcome.[43] 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 used were sleep quality (1-5 scale[38] or 0-10 scale,[11]) nighttime rescue medication use,[37] hours of sleep,[41] average nights awakened by sleep,[42] and visual analogue scales (1-100) for trouble falling asleep and needing medication to sleep.[48] 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.

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%[40] to 53%.[11] For long-acting morphine, the withdrawal rate ranged from 0%[46] to 30%.[47] Similar wide ranges for withdrawal rates were seen for the studies on long-acting dihydrocodeine and long-acting codeine. The wide range of withdrawal rates 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.

One placebo-controlled trial identified for update #2 met inclusion criteria (Tables 1.1 and 1.2, Evidence Tables 1.2 and 1.3).[29] It was a short-term (6 weeks) study of controlled-release oxycodone (twice daily, average titrated dose 42 mg/day) compared to placebo in 159 patients with diabetic neuropathy. This trial was rated good quality for evaluation of efficacy. It found that controlled-release oxycodone was more effective than placebo for overall average daily pain intensity (4.1 for oxycodone versus 5.3 for placebo) using a 0 (no pain) to 10 (worst pain) scale (Table 1.3).

Several trials that were excluded may be of interest to subcommittee members. One study, a short-term (8 weeks) trial of different strengths of levorphanol in 81 patients with chronic neuropathic pain, was excluded because it administered the medication three times daily ("long-acting opioid" was defined in the original report as an opioid administered twice daily or less frequently).[26] This study found that higher doses of levorphanol were more effective in reducing the intensity of neuropathic pain than lower doses. Two short-term (15 and 6 day) trials of transdermal buprenorphine were excluded because this formulation is not currently approved in the United States.[27, 28] Furthermore, they primarily evaluated patients with cancer pain (77% and 55%) and did not report

results in patients with non-cancer pain separately. Neither study appeared to be good quality. One study[27] 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, but the other[28] found no statistically significant difference. A meta-analysis of three studies of transdermal buprenorphine (including the two cited above) 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.[51] Statistical significance was not reported.

Summary

In summary, 14 fair-quality clinical trials of long-acting opioids versus other types of drugs or placebo provide no useful information regarding the comparative efficacy of long-acting opioids. The studies were of insufficient quality and too heterogeneous in terms of study designs, patient populations, interventions, and assessed outcomes to permit meaningful comparisons for most outcomes. Withdrawal rates, the single uniformly reported outcome, varied greatly for each long-acting opioid and did not suggest that one long-acting opioid is superior to the others.

The data regarding comparative efficacy of long-acting opioids are quite limited. Most opioids have not been compared directly in clinical trials. There are only two trials directly comparing one long-acting opioid with another. The indirect evidence from 14 other trials of long-acting opioids are too heterogeneous and of insufficiently high quality to determine relative efficacy for pain control, pain intensity, functional status, and withdrawal rates. There is insufficient evidence to suggest that one long-acting opioid is more effective than any other in chronic non-cancer pain patients. Reviewed trials were characterized by lack of high quality and marked heterogeneity in terms of design, patient population, assessed outcomes, interventions, and results. We therefore did not perform meta-analysis on any sub-group of trials.

One additional (15th) trial, rated good quality, met inclusion criteria and was reviewed for update #2. It did not significantly change the above summary.

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?

We identified seven randomized clinical trials (568 patients enrolled), all rated fair-quality, that 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.[38, 40, 43] One of these studies[40] re-randomized patients who had enrolled in a previous trial.[43] Two studies evaluated long-acting dihydrocodeine,[39, 42] one evaluated long-acting codeine,[37] and one evaluated long-acting morphine.[41] 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,[41] long-acting dihydrocodeine,[42] and long-acting codeine[37] had features that might invalidate these results. In the trials on long-acting morphine[41] and long-acting codeine,[37] 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,[42] significant differences in pain relief were only seen when the long-acting dihydrocodeine group was compared to itself at different points in time, but no significant differences were found when the long-acting opioid was compared directly to the short-acting opioid. Functional outcomes were inconsistently examined or used heterogeneous measurement 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.[38, 40, 43] One of these trials[40] investigated a re-randomized population of patients studied in a previous trial[43] 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[38] 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.

Summary

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

No additional trials meeting inclusion criteria for this key question were identified for update #2.

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

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

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

As discussed earlier, only three randomized trials (two reviewed in the original report and one in update #1) directly compared two long-acting opioids. One of these trials[35] compared two different long-acting opioids (transdermal fentanyl and long-acting morphine) and another[36] compared once-daily versus twice-daily preparations of oral morphine. Neither study assessed rates of addiction or abuse. No deaths were reported in either study. The last 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.[22] 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 trial which compared transdermal fentanyl with long-acting oral morphine was rated poor-quality for adverse event assessment (Evidence Table 2.1).[35] This trial failed to adequately meet six 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%, $p<0.001$) only as assessed by a bowel function questionnaire, and not 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.

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).[36] This trial failed to adequately meet five out of the 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 treated patients were 37-45%, with withdrawal rates due to adverse events ranging from 23-25%.

No additional trials meeting inclusion criteria for this key question were identified for update #2.

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?

Randomized Trials. We reviewed 13 fair- or poor-quality randomized trials (994 patients enrolled) that gave indirect evidence regarding the 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).[37-43] Six others[11, 44, 46-49] compared a long-acting opioid with placebo (Evidence Table 2.3). One trial of long-acting morphine versus carbamazepine for neuropathic pain[45] was excluded because accurate adverse event rates could not be abstracted from the graphs in the article.

With regard to adverse event assessment, all 13 studies had at least two important methodologic 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).

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%[38] to 50%[43] in five trials (Table 2.1). Withdrawal rates due to adverse events ranged from 4%[40] to 32%[11] 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).

A placebo-controlled trial of long-acting oxycodone in patients with diabetic neuropathy was rated fair-quality (adverse events not pre-specified or defined, inadequate description of adverse event assessment technique, no analysis of confounders) for adverse event assessment. As expected, adverse events were more common in the controlled-release oxycodone group, with 32% (26/82) patients on controlled-release oxycodone and 13% (10/77) on placebo reporting adverse events that resulted in dose limits or discontinuation. Rates for other common adverse events fell within ranges for other trials of long-acting oxycodone and other long-acting opioids (Table 2.1) and didn't provide additional information about comparative safety.

Observational Studies. We identified ten observational studies (eight reviewed in the original report) evaluating the risk of long-acting opioids in 1490 patients with non-cancer pain.[11, 23, 24, 36, 44, 52-56] All were rated poor-quality for adverse event assessment except one,[11] which was rated fair (Evidence Table 2.4). For six of the eight studies reviewed for the original report, independently assigned quality rating scores were identical between two reviewers. For two studies, quality rating scores differed by one[57] or two[11] point; in neither case did this difference result in a change in overall quality rating. The single study rated fair-quality[11] met only four out of seven predefined quality assessment criteria. The most important areas of concern in this study were high overall loss to followup (60/106) and the failure to specify or define adverse events in advance.

No identified study was population-based. Opioids assessed were long-acting codeine,[44] long-acting morphine (once daily[36] or twice-daily[56]), transdermal fentanyl,[23, 24, 52, 55] methadone,[54] and long-acting oxycodone.[11] One study assessed both methadone and long-acting morphine.[53] The number of patients on long-acting opioids in these studies ranged from 11[54] to 530.[55] Seven were prospective cohort studies[11, 23, 24, 36, 44, 52, 55] and three were retrospective cohorts.[53, 54, 56] The prospective cohort studies recruited all[11, 36, 44, 52] or some[55] of their patients from completed clinical trials. Three of the prospective cohorts[11, 36, 44] were open-label extensions of clinical trials included in this review.

Results of the observational studies were not significantly different from those reported in clinical trials for gastrointestinal adverse events, neurological adverse events, and withdrawal rates due to adverse events (Table 2.2). The study rated fair-quality,[11] for example, reported a rate of 31% (32/103) of withdrawal due to adverse events, which fell within the range for trials of long-acting oxycodone.

Some observational studies reported long-term outcomes and serious adverse events not reported in the trials. The largest (n=530) study[55] 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,[53, 54] but they were retrospective studies with small samples (n=11 and 20) and no inception cohort. Four studies reported rates of long-term use, which could be a long-term measure of tolerability or clinical efficacy.[11, 36, 44, 52] Rates ranged from 19% for transdermal fentanyl[52] to 54% for long-acting codeine.[44]

The patients enrolled did not appear to be less selected than those in the controlled trials. In the prospective cohort studies, at least some participants were recruited from completed clinical trials,[11, 36, 44, 52, 55] resulting in an even more highly selected population than the original trials. In the retrospective studies, no inception cohort was identified and the population appeared to represent a "convenience" sample of patients for whom data was readily available.[53, 54, 56]

No meaningful conclusions regarding comparative adverse event risk of long-acting opioids can be drawn from these cohort studies.

In addition to cohort studies, for update #1 we also reviewed results from the ongoing national DAWN study (through 2001) and from epidemiologic data in the state of Oregon regarding methadone-related deaths.[20, 21] The DAWN study reports "mentions" of drug-related visits for various prescription and non-prescription opioids in emergency departments across the U.S. This study reported increased numbers of oxycodone, hydrocodone, and methadone mentions between 1994 and 2001. 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), which the DAWN report does not provide. A previously published paper using data from this same study did not find evidence that emergency department mentions of various opioid analgesics were disproportionate to estimates in changes in prescribing patterns.[1]

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).[21] Approximately 28% of the deaths occurred in patients being treated for chronic pain.

We reviewed several observational studies for update #2. A case series of methadone-related deaths in Hennepin County, Minnesota, reported data from 96 medical examiner investigated deaths from 1992 to 2002 in which methadone was detected.[30] Of these 96 deaths, 15% were in chronic pain patients, and about half of this group died from

overdose. No information on the numbers of prescriptions for methadone in the county, number of patients prescribed methadone, or on other long-acting opioids was provided. Another small (n=17) case series reported episodes of torsades de pointes associated with very high doses of methadone (mean about 400 mg/day).[32] About half of the cases occurred in patients being treated for chronic pain. Rates of this complication could not be estimated from the study.

A small (n=28) observational study on the long-term (12 months) effects of sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain was rated poor quality because it used the 10 patients who dropped out of the study as its control, and 7 out of the 18 patients on long-acting morphine were lost to follow-up at 12 months.[31] This study found that sustained release morphine was not associated with decreased neuropsychological performance assessed with a battery of neuropsychologic tests.

We also reviewed a report from the federal General Accounting Office investigated factors that may have contributed to long-acting oxycodone abuse and diversion.[33] It did not provide information about rates of abuse, or assess rates of abuse and diversion of long-acting oxycodone 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.

Summary

The data regarding comparative adverse event rates of long-acting opioids are quite limited. Most opioids have not been compared directly in clinical trials. There are only three trials (rated poor-quality for adverse event assessment) that directly compared long-acting opioids. One of these trials compared two different long-acting opioids, and the other compared once-daily versus twice-daily preparations of morphine. The third was a very small (n=18) trial of patients with chronic pancreatitis and did not provide usable information about comparative safety. The indirect evidence from 13 other trials are too heterogeneous and of insufficient quality to determine relative 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. 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. Recent 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. Data from the DAWN study also suggest that changes in emergency-room visit "mentions" for various opioids were roughly proportionate to estimates in changes in prescribing patterns.

One placebo-controlled trial and small observational studies reviewed for update #2 provided inadequate data to make additional judgments about comparative risks of long-acting opioids.

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?

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 outlined in Evidence Table 1.2.[37-43] None of the studies were designed to assess rates of addiction or abuse.

In the single trial in this group rated fair-quality,[41] adverse events were not prespecified or defined and patients and investigators were not blinded. Furthermore, patients in one arm of this trial were given higher doses of opioids than the other. Adverse events would be expected to be more common in the group receiving higher doses, the result 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,[38, 40, 43] 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[40, 43] 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,[37, 42, 43] one favored long-acting,[38] and one was equivocal.[40] 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 population.

No additional trials meeting inclusion criteria for this key question were identified for update #2.

Summary

In summary, for all assessed adverse events, there is no convincing evidence to suggest lower adverse event rates with long-acting opioids as a class compared to short-acting opioids.

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?

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 55 years, and one study[49] evaluated patients with an average age of 70 years. Two trials[11, 38] 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.

Several specific types of chronic non-cancer pain patients were studied in some of the reviewed trials. These categories included back pain,[37, 39-41, 43] osteoarthritis, [11, 38, 42, 48] phantom limb pain,[46] neuropathic pain,[45] and post-herpetic neuralgia.[49] None of these trials are direct comparisons of one long-acting opioid with another. All were rated fair-quality for general methodology 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.

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. 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.

No additional trials meeting inclusion criteria for this key question were identified for update #2.

SUMMARY

Results for each of the key questions are summarized in Table 3. It is important to note that we identified no trials investigating methadone or levorphanol in adult patients with chronic non-cancer pain. The results refer to studies that investigated transdermal fentanyl and long-acting oral oxycodone, morphine, codeine, and dihydrocodeine.

In general, there was insufficient evidence to prove that different long-acting opioids are associated with different efficacy or adverse event rates. Only one poor-quality trial[35] directly compared different long-acting opioids (transdermal fentanyl and long-acting morphine) and gave inconclusive results. This trial may show that transdermal fentanyl is a reasonable second choice for patients who have inadequate pain relief on morphine, but does not answer the general question of which long-acting opioid is superior for the general population of patients with chronic non-cancer pain. Another fair-quality trial[36] that directly compared once-daily versus twice-daily morphine also gave inconclusive results. 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. A third, small (n=18) fair-quality trial[22] found no significant differences between transdermal fentanyl and long-acting morphine in patients with chronic pancreatitis. 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. The comparative efficacy and adverse event rates of 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[38, 40, 43] 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.

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

The results of update #1 did not significantly alter the conclusions of the original report.

The results of update #2 also do not significantly alter the conclusions of the original report. No additional head-to-head trials were identified. One new placebo-controlled trial found that long-acting oxycodone was superior to placebo for diabetic neuropathy. New data reviewed for update #2 were not helpful in making judgments about comparative harms. One new head-to-head trial has been presented in abstract form and full results may be available for the next update.[25]

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Table 1.1. Overview of all long-acting opioid studies

Author Year	Long acting narcotic	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 studies										
Allan 2001	A: Transdermal fentanyl B: Oral morphine (twice daily)	Crossover	Miscellaneous	4 weeks*	212	NR	A: 57.8 B: 62.9	0-100 VAS	Not specified	29.4 mg/day 23.6 mg/day
Caldwell 2002	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 2002	A: Transdermal fentanyl B: Oral morphine (twice daily)	Crossover	Chronic pancreatitis	4 weeks*	18	NR	Not calcuable	5 point Cat.	IR Morphine	A: 30.7 mg B: 14.7 mg
Long-acting vs. short-acting, placebo or non-narcotic studies										
Caldwell 1999	Oxycodone	RCT	Osteoarthritis	4 weeks	107	40	1.3	0-4 Cat.	Not permitted	N/A
Gimbel 2003	Oxycodone	RCT	Diabetic neuropathy	6 weeks	159	42	6.9	0-10 Cat.	Not permitted	N/A
Hale 1999	Oxycodone	Crossover	Back pain	6 days*	47	40	1.2	0-3 Cat.	IR Oxycodone 5-10 mg PRN	0.6 tabs/day
Roth 2000	Oxycodone	RCT	Osteoarthritis	2 weeks	133	40	1.6	0-3 Cat.	Not permitted	N/A
Salzman 1998	Oxycodone	RCT	Back pain	10 days	57	40	1.1	0-3 Cat.	IR Oxycodone 5-10 mg PRN	NR
Watson 1998	Oxycodone	Crossover	Postherpic neuralgia	4 weeks*	50	45	35	0-100 VAS	Not permitted	N/A

* Duration per intervention of crossover trial

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

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

Table 1.1. Overview of all long-acting opioid studies (continued)

Author Year	Long acting narcotic	Study type	Pain type	Duration	Sample size	Average dose (mg/day)	Pain intensity score	Scale	Rescue drug	Average rescue drug usage
Other medications										
Arkinstall 1995	Codeine	Crossover	Miscellaneous	7 days*	46	353	35	0-100 VAS	Tylenol with codeine	3.6 tabs/day
Hale 1992	Codeine	RCT	Back pain	5 days	83	200	1.6	0-4 Cat.	Acetaminophen	4.0 tabs/day
Peloso 2000	Codeine	RCT	Osteoarthritis	4 weeks	103	159	32.5	0-100 VAS	Tylenol	4.2 tabs/day
Lloyd 1992	Dihydrocodeine	RCT	Osteoarthritis	2 weeks	86	NR	39.2	0-100 VAS	Not permitted	N/A
Gostick 1989	Dihydrocodeine	Crossover	Back pain	2 weeks*	61	NR	1.75	Not provided	Paracetamol	1.54 tabs/day
Harke 2001	Morphine	RCT	Neuropathic pain	8 days	38	83	6.9†	0-10 VAS	Not permitted	N/A
Huse 2001	Morphine	Crossover	Phantom limb pain	4 weeks*	12	115	3.62	0-10 VAS	Aspirin + paracetamol	NR
Jamison 1998	Morphine	RCT	Back pain	16 weeks	36	41	54.9	0-100 VAS	Not permitted	N/A
Moulin 1996	Morphine	Crossover	Miscellaneous	6 weeks*	61	83.4	45	0-100 VAS	Paracetamol	3.5 tabs/day

* Duration per intervention of crossover trial

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

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 narcotic	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 studies										
Allan 2001	A: Transdermal fentanyl B: Morphine (twice daily)	Miscellaneous	4 weeks*	212	23%	N/A	A: 15%† (38/250) B: 9% (22/238)	N/A	"11%" "4%"	N/A
Caldwell 2002	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	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
Long-acting vs. short-acting, placebo or non-narcotic studies										
Caldwell 1999	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) *IR Oxycodone:* 30% (11/37) *Placebo:* 50% (18/36)	3† 4 13	3 5 3	1 2 2
Gimbel 2003	Oxycodone	Diabetic neuropathy	6 weeks	159	28%	Not reported	Overall: 28% (44/159) By intervention, not clear	1 11	7 4	12 12

* Duration per intervention of crossover trial

† $p<0.05$

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

Table 1.2. Withdrawal rates (continued)

Author Year	Long acting narcotic	Pain type	Duration	Sample size	Overall withdrawal rates	Pre-randomization titration withdrawal	Withdrawal rates per drug	Inadequate pain control	Adverse effects	Other
Hale 1999	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	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 1998	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 1998	Oxycodone	Postherpic neuralgia	4 weeks*	50	22%	N/A	*LA Oxycodone:* 12% (6/50)	0	5	1
							Placebo: 10% (5/50)	1	3	1
Other medications										
Arkinstall 1995	Codeine	Miscellaneous	7 days*	46	28%	N/A	*Codeine:* 19% (9/46)	1	7†	1
							Placebo: 9% (4/46)	0	1	3
Gostick 1989	Dihydrocodeine	Back pain	2 weeks*	61	26%	N/A	NR	NR	NR	NR

* Duration per intervention of crossover trial

† $p<0.05$

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

Table 1.2. Withdrawal rates (continued)

Author Year	Long acting narcotic	Pain type	Duration	Sample size	Overall withdrawal rates	Pre-randomization titration withdrawal	Withdrawal rates per drug	Inadequate pain control	Adverse effects	Other
Hale 1992	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
Harke 2001	Morphine	Neuropathic pain	8 days	38	8%	N/A	*Morphine:* 5% (1/19) *Placebo:* 11% (2/19)	NR	NR	1 2
Huse 2001	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	Morphine	Back pain	16 weeks	36	8%	N/A	*LA Morphine+IR Oxy.:* 6% (1/18) *IR Oxycodone:* 12% (2/18)	NR	1 2	NR
Lloyd 1992	Dihydrocodeine	Osteoarthritis	2 weeks	86	34%	N/A	*Dihydrocodeine:* 47%† (20/43) *Dextropropoxyphene + paracetamol:* 21% (9/43)	1 2	17† 4	2 3
Moulin 1996	Morphine	Miscellaneous	6 weeks*	61	30%	*Morphine:* 48%† (15/31) *Benztropine:* 13% (4/30)	3 others (not specified)	NR	NR	NR
Peloso 2000	Codeine	Osteoarthritis	4 weeks	103	36%	N/A	40% (20/51) Codeine 33% (17/52) Placebo	15 5	15† 5	10 0

* Duration per intervention of crossover trial

† $p<0.05$

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 2001 **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: Once-daily morphine in a.m. B: Once-daily morphine in p.m. C: Twice-daily morphine D: Placebo	Caldwell 2002 **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 **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.
Long-acting opioid vs. placebo			
Long-acting codeine			
Long-acting codeine	Arkinstall 1995 **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 **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.

*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 (continued)

Medications	Trial Quality rating	Population Number enrolled	Main outcomes
Long-acting morphine			
Long-acting morphine	Harke 2001 **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 reponders 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 **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	Moulin 1996 **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.
Long-acting oxycodone			
Long-acting oxycodone	Gimbel 2003 **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.

*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 (continued)

Medications	Trial Quality rating	Population Number enrolled	Main outcomes
Long-acting oxycodone	Roth 2000 **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 1998 **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	Osteoarthritis	30 days	107	LA Oxycodone and IR Oxycodone plus Tylenol are equally effective for pain control and improvement of sleep.
Hale 1999	Back pain	6 days*	47	LA Oxycodone and IR Oxycodone are equally effective for pain control.
Salzman 1998	Back pain	10 days	57	LA Oxycodone and IR Oxycodone are equally effective when titrated for pain control.
Codeine				
Hale 1992	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	Back pain	2 weeks*	61	LA Dihydrocodeine and IR Dihydrocodeine are equally effective for pain control.
Lloyd 1992	Osteoarthritis	2 weeks	86	LA Dihydrocodeine and IR Dihydrocodeine are equally effective for pain control when compared directly.
Morphine				
Jamison 1998	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 2001	A: Transdermal fentanyl	POOR (1)	A: 26% (32/124)	Not reported	A: 16%*** (20/124)	Not reported	Not reported	Not reported	A: 11% (14/124)
	B: Long-acting morphine		B: 18% (23/127)		B: 22%*** (28/127)				B: 4% (5/127)
Caldwell 2002	A: Once-daily morphine a.m.	POOR (2)	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)
Niemann 2000	A: Transdermal fentanyl	POOR (2)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	A: 6% (1/18)
	B: Long-acting morphine								B: 0%
Long-acting oxycodone:									
Caldwell 1999	A: Long-acting oxycodone	POOR (2)	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)

*Number of criteria out of seven adequately met

†Due to adverse events

¶Sample size not clear

ß$p<0.05$ 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

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†
Gimbel 2003	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	A: Long-acting oxycodone	POOR (2)	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	A1: Long-acting oxycodone 20 mg bid	FAIR (4)	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 1998	A: Long-acting oxycodone	POOR (2)	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 1998	A: Long-acting oxycodone	FAIR (3)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
	B: Placebo								

*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

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	A: Long-acting codeine	FAIR (3)	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	A: Long-acting codeine	POOR (1)	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	A: Long-acting codeine	FAIR (3)	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	A: Long-acting dihydrocodeine	POOR (2)	Not reported	Not reported	A: 55%(23/42)‡	Not reported	Not reported	Not reported	Not reported
	B: Short-acting dihydrocodeine				B: 49%(21/43)				
Lloyd§ 1992	A: Long-acting dihydrocodeine	POOR (2)	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)

*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

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:									
Huse‡‡ 2001	A: Long-acting morphine	FAIR (3)	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	A: Long-acting morphine + short-acting oxycodone	FAIR (5)	A: 31%	Not reported	A: 30%	A: 31%	A: 6%	A: 0%	Not reported
	B: Short-acting oxycodone		B: 14%		B: 18%	B: 14%	B: 19%	B: 1.4%	
Moulin 1996	A: Long-acting morphine	FAIR (4)	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

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	Long-acting codeine	POOR (2)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	54% (15/28)
Bach 2001	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	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	Transdermal fentanyl	POOR (2)	92%	56%	36%	58%	54%	<20%	Not reported	19% (9/48)
Dunbar 1996	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	Transdermal fentanyl	POOR (1)	22% (51/236)	15% (36/236)	15% (36/236)	22% (53/236)	25% (59/236)	Not reported	Not reported	53% (110/236)
Green 1996	Methadone	POOR (0)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Milligan 2001	Transdermal fentanyl	POOR (1)	9% (48/530)	8% (42/530)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Ringe 2002	Transdermal fentanyl	POOR (0)	Not reported separately	28% (18/64) nausea or vomiting	14% (9/64)	8% (5/64)	19% (12/64)	Not reported	20% (13/64)	77% (49/64)
Roth 2000	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	Favors long-acting	Favors long-acting	Favors short-acting	Favors long-acting	Favors long-acting	Not reported	Favors long-acting
Hale** 1999	Favors long-acting	No difference	Favors long-acting	Favors short-acting	Favors short-acting	Not reported	No difference
Salzman** 1998	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	Not reported	Not reported	Favors long-acting	Not reported	Not reported	Not reported	Not reported
Hale*** 1997	Favors short-acting	Favors short-acting	No difference	Favors short-acting	Favors short-acting	Not reported	Favors short-acting
Jamison*** 1998	Favors short-acting	Not reported	Favors short-acting	Favors short-acting	Favors long-acting	No difference	Not reported
Lloyd 1992	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. Three trials directly compared one long-acting opioid to another. One poor-quality study (lack of blinding, high proportion of patients on study drug prior to entry, high loss to follow-up) directly compared one long-acting opioid (transdermal fentanyl) to another (morphine). 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. One small (n=18), fair-quality head-to-head trial of transdermal fentanyl vs. long-acting oral morphine in patients with chronic pancreatitis found no differences in efficacy. 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 new head-to-head trials were found for update #2.
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	Fourteen trials compare long-acting opioids to other types of drugs or to placebo. They 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 good-quality trial of long-acting oxycodone versus placebo in patients with diabetic neuropathy was found for update #2. It found long-acting oxycodone superior to placebo for measures of pain relief and sleep quality, but did not provide additional evidence regarding comparative efficacy of different long-acting opioids.
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. Three of the trials compare long-acting oxycodone to short-acting oxycodone and were more homogeneous. None found differences in clinical efficacy. There is fair evidence to suggest that long-acting oxycodone and short-acting oyxcodone are equally effective for pain control in adult patients with chronic non-cancer pain. No new trials were found for update #2.

Table 3. Summary of evidence (continued)

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	POOR	Most long-acting opioids have not been compared directly in clinical trials. Three head-to-head trials were rated poor-quality for adverse event assessment, and no reliable conclusions could be drawn from their results. No new head-to-head trials were found for update #2.
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	Thirteen 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 and no reliable observational data are available. Cohort studies on adverse event were of generally poorer quality than the clinical trials. Surveillance data from emergency departments in the United States suggests that increases in emergency room visits with mentions of opioids is roughly proportionate to changes in prescribing patterns. 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. One new placebo-controlled trial of long-acting oxycodone for diabetic neuropathy was rated fair-quality for adverse event assessment. It provided insufficient data to make comparative judgments about safety. Small observational studies also were insufficient to change conclusions about comparative safety.
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	There is almost no 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. No new data was found for update #2.

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	Randomized trial Crossover International Multicenter (35) Pain clinics	A: Transdermal fentanyl (titrated) (Mean dose not reported) B: Long acting morphine (titrated) (Mean dose not reported) 4 weeks initial intervention followed by 4 week crossover	Patients with chronic non-cancer pain requiring continuous treatment with potent opioids	Not specified	Permitted Drug not specified	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 (continued)

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Allan 2001	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 specficied), 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	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 loss to follow up: 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 (continued)

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Allan 2001	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**: Higher overall scores on A; significantly higher for bodily pain, vitality, social functioning, mental health. **Rescue Drug Use** (mean): 29.4 mg (A) vs. 23.6 mg (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 overall and differential loss to follow up. Unable to accurately assess external validity.

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 (continued)

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	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 (continued)

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Caldwell 2002	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 (continued)

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Caldwell 2002	Long acting Morphine (A) vs. Long acting Morphine (B) vs. Long acting Morphine (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 (continued)

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
Niemann 2000	Randomized, open, crossover trial Denmark Multicenter Outpatient clinics	A: Transdermal fentanyl (titrated) (Mean dose not reported) B: Long acting morphine (titrated) (Mean dose not reported) 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	2/18(11.1%) 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 (continued)

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Niemann 2000	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) Global pain control assessment of last two weeks of trial periods compared to last month prior to study entry (assessment method not reported) Quality of life assessed using SF-36 questionnaire at end of each 4-week period Side effects assessed using unspecified questionnaire at end of each 4-week 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. 16/18 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 (continued)

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Niemann 2000	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	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	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 (continued)

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	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	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 but calculable. 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 (continued)

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Caldwell 1999	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	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 (continued)

Author Year	Type of study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled
Hale 1997	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	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 (continued)

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	23 83	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 but is caculable. 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	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 (continued)

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Hale 1997	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)	Number screened not reported. Number eligible not reported. Exclusion critera provided. Low back pain patients. External validity difficult to assess.	Purdue Frederick sponsored study. 1 author (corresponding) employed by Purdue.	Study compares long actingcodeine with placebo, however, groups received different rescue medications. Placebo group received acetaminophen plus codeine. It is not clear if rescue medication was blinded as well.
Hale 1999	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 (continued)

Author Year	Type of study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Rescue Drug	Screened Eligible Enrolled
Lloyd 1992	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
Salzman 1998	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 (continued)

Author Year	Withdrawals or lost to follow-up Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Lloyd 1992	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.
Salzman 1998	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. Treatment allocation not concealed and study not blind. Intention to treat calculation provided. Groups comparable at baseline, including use of narcotics. 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 (continued)

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Lloyd 1992	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.
Salzman 1998	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

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	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
Gimbel 2003	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 cacner, 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

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Arkinstall 1995	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. However, is crossover design, thus each enrollee serves as own control. Attrition reported. Crossover trial. Contamination was not allowed. Groups received similar care except for study drug. Follow up for 7 days per arm.
Gimbel 2003	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 (continued)

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Arkinstall 1995	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).
Gimbel 2003	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 (continued)

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	Randomized trial	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	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 (continued)

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Harke 2001	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	Avg. 50.6 years 16% female Race not reported Phantom Limb Pain 2 upper limb 9 lower limb 1 both Prior narcotic 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 (continued)

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Harke 2001	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)	Numer 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	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 (continued)

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	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 (continued)

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Moulin 1996	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 (continued)

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Moulin 1996	Long acting morphine (A) vs. Beztropine (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, beztropine 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 (continued)

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	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 (continued)

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Peloso 2000	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 (continued)

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Peloso 2000	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 (continued)

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	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

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 (continued)

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Roth 2000	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.

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 (continued)

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Roth 2000	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

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 (continued)

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	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

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 (continued)

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Watson 1998	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.

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 (continued)

Author Year	Outcomes	External Validity	Funding Source and Role	Other comments
Watson 1998	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.

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 2001	Randomized Crossover	A: Transdermal fentanyl (titrated) B: Long-acting morphine (titrated) Mean doses not reported 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. Not clear if selection of patients biased; number eligible in study equals number enrolled. 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. (1)

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 (continued)

Author, Year	Rate and Number of Adverse Events	Comments
Allan 2001	Transdermal fentanyl vs. long-acting oral morphine (Sample size for adverse events not clear, only rates reported) 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)	Not clear what sample sizes used to calculate adverse event rates. 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 (continued)

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	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. 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)

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 (continued)

Author, Year	Rate and Number of Adverse Events	Comments
Caldwell 2002	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): Consipation: 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 effects 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	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
Hale 1997	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 effects from opioids for chronic non-cancer pain randomized controlled trials comparing a long-acting opioid with a short-acting opioid (continued)

Author Year	Quality Rating (Number of Criteria Out of Seven Met)	Rate and Number of Adverse Events	Comments
Caldwell 1999	POOR. Not clear if selection of patients biased, number eligible not reported. 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. (2)	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.
Hale 1997	POOR. Not clear if selection of patients biased, number eligible not reported. 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. (1)	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 effects from opioids for chronic non-cancer pain randomized controlled trials comparing a long-acting opioid with a short-acting opioid (continued)

Author Year	Type of Study	Interventions (Dose, Duration)	Number Enrolled	Method of Adverse Event Assessment and Adverse Events Assessed
Hale 1999	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
Lloyd 1992	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 effects from opioids for chronic non-cancer pain randomized controlled trials comparing a long-acting opioid with a short-acting opioid (continued)

Author Year	Quality Rating (Number of Criteria Out of Seven Met)	Rate and Number of Adverse Events	Comments
Hale 1999	POOR. Selection of patients does not appear biased. 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.(2)	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.
Lloyd 1992	POOR. Not clear if selection biased, number eligible not reported. 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.(2)	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 effects from opioids for chronic non-cancer pain randomized controlled trials comparing a long-acting opioid with a short-acting opioid (continued)

Author Year	Type of Study	Interventions (Dose, Duration)	Number Enrolled	Method of Adverse Event Assessment and Adverse Events Assessed
Salzman 1999	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 effects from opioids for chronic non-cancer pain randomized controlled trials comparing a long-acting opioid with a short-acting opioid (continued)

Author Year	Quality Rating (Number of Criteria Out of Seven Met)	Rate and Number of Adverse Events	Comments
Salzman 1999	POOR. Unclear if selection of patients biased, number eligible not reported. 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. (2)	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 effects from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with placebo

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	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. Not clear if selection of patients biased, number eligible not reported. 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. (3)
Gimbel 2003	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.

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

Author, Year	Rate and Number of Adverse Events	Comments
Arkinstall 1995	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.
Gimbel 2003	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%)	

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

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)
Huse 2001	Randomized Crossover	A: Long-acting morphine (titrated) B: Placebo Final dose between 70 to 300 mg/day morphine 4 weeks initial intevention, followed by crossover	12	Any reported adverse event, recorded in daily patient diary	FAIR. Not clear if selection of patients biased, number eligible not reported. No loss to follow-up. Adverse events not specified or defined. Ascertainment technique adequately described. Patients and assessors blinded to intervention. No statistical anlaysis of potential confounders. Duration of follow-up appears adequate, 4 weeks initial intervention followed by 2 week washout then crossover. (3)
Moulin 1996	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 effects from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with placebo (continued)

Author, Year	Rate and Number of Adverse Events	Comments
Huse 2001	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.
Moulin 1996	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 effects from opioids for chronic non-cancer pain: randomized controlled trials comparing a long-acting opioid with placebo (continued)

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	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	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. Not clear if selection of patients biased, number eligible equals number enrolled in study. 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. (4)

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

Author, Year	Rate and Number of Adverse Events	Comments
Peloso 2000	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	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 partcipate. 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.

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

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	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)

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

Author, Year	Rate and Number of Adverse Events	Comments
Watson 1998	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.

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	Number screened Number eligible Number enrolled
Arkinstall 1995	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)	30 screened 30 eligible 28 enrolled
Bach 2001	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	Unable to assess, no inception cohort

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

Author, Year	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)
Arkinstall 1995	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 2001	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
Arkinstall 1995	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 2001	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	Number screened Number eligible Number enrolled
Caldwell 2002	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 moprhine, 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	184 screened 184 eligible 181 enrolled

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

Author, Year	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	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)

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	Population not adequately described, unable to assess whether pouplation similar to patients ub wgin tge ubtervebtuib wiykd be aookued, 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% Abominal 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.

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	Number screened Number eligible Number enrolled
Dellemijn 1998	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.	50 screened 50 eligible 48 enrolled

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

Author, Year	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)
Dellemijn 1998	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	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
Dellemijn 1998	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: 56% Dizziness: 54% Constipation: 36% Dyspnea: 36% Pruritus: 33% Dry mouth: 31% Insomnia: 30% Anorexia: 29% Anxiety: 22% Skin irritation: 20% 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	Number screened Number eligible Number enrolled
Dunbar 1996	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	Unable to assess, no inception cohort

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

Author, Year	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	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)

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	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.

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	Number screened Number eligible Number enrolled
Franco 2002	Retrospective 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	Not reported Not reported 236 enrolled

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

Author, Year	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)
Franco 2002	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
Franco 2002	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	Number screened Number eligible Number enrolled
Green 1996	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	Unable to assess, no inception cohort

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

Author, Year	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	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)

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	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.

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	Number screened Number eligible Number enrolled
Milligan 2001	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	Screened unclear Eligible unclear 532 enrolled (Study reports number eligible = number enrolled)

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

Author, Year	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)
Milligan 2001	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
Milligan 2001	Populaton 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%) 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	Number screened Number eligible Number enrolled
Ringe 2002	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%)	Screened unclear Eligible unclear 64 enrolled

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

Author, Year	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	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)

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	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%) Nausea/vomiting=18(28%) Dizziness=12(19%) Constipation=9(14%) Epigastric pressure=6(9%) Sedation=5(8%) Headache=4(6%) Diarrhea=1(2%) Inappetence=1(2%) Lack of appetite=1(2%) Sleep disorder=1(2%)	

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	Number screened Number eligible Number enrolled
Roth 2000	Prospective cohort (open-labell 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	133 screened 133 eligible 106 enrolled

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

Author, Year	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)
Roth 2000	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)

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
Roth 2000	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.

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 2003>
Search Strategy:
---
1 opioid analgesics.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (94)
2 narcotics.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (572)
3 analgesics, opioid.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1962)
4 1 or 2 or 3 (2554)
5 pain.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (26369)
6 4 and 5 (1782)
7 limit 6 to yr=2003 (21)
8 from 7 keep 1-21 (21)

Database: MEDLINE <1996 to November Week 2 2003>
Search Strategy:
---
1 opioid analgesics.mp. or exp Analgesics, Opioid/ (16550)
2 narcotics.mp. or exp NARCOTICS/ (15224)
3 1 or 2 (18581)
4 (intractable pain or severe pain or chronic pain).mp. (4956)
5 3 and 4 (730)
6 limit 5 to human (663)
7 limit 6 to english language (578)
8 6 not 7 (85)
9 limit 8 to abstracts (73)

10 7 or 9 (651)
11 10 and (200303$ or 200304$ or 200305$ or 200306$ or 200307$ or 200308$ or 200309$ or 200210$ or 200311$).em. (71)
12 from 11 keep 1-71 (71)

Database: EMBASE Drugs & Pharmacology <1991 to 4th Quarter 2003>
Search Strategy:
---
1 exp Narcotic Analgesic Agent/ or opioid analgesics.mp. (58043)
2 exp Narcotic Agent/dt [Drug Therapy] (14511)
3 1 or 2 (58326)
4 intractable pain.mp. or exp Intractable Pain/ (346)
5 chronic pain.mp. or exp Chronic Pain/ (4033)
6 severe pain.mp. (1282)
7 4 or 5 or 6 (5468)
8 3 and 7 (2498)
9 limit 8 to human (2300)
10 limit 9 to english language (1874)
11 9 not 10 (426)
12 limit 11 to abstracts (289)
13 10 or 12 (2163)
14 limit 13 to latest update (108)
15 from 14 keep 1-108 (108)

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	

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: Clinical trials search results*