Review Article

Comparative Efficacy and Safety of Long-Acting Oral Opioids for Chronic Non-Cancer Pain: A Systematic Review

Roger Chou, MD, Elizabeth Clark, MD, MPH, and Mark Helfand, MD, MPH
Departments of Medicine (R.C., M.H.) and Family Medicine (E.C.), Oregon Health & Science University; Oregon Evidence-Based Practice Center (R.C., M.H., E.C.); and Portland Veterans Affairs Medical Center (M.H.), Portland, Oregon, USA

Abstract
Opioids have been endorsed as appropriate treatment for refractory chronic non-cancer pain when used according to published guidelines. They are widely used for this indication. However, there appear to be gaps in our understanding of the efficacy and safety of individual long-acting opioids compared to each other or as a class compared to short-acting opioids. This systematic review summarizes and assesses the evidence for the comparative efficacy and safety of long-acting opioids in the management of chronic non-cancer pain. Randomized trials (for comparative efficacy and adverse events) and observational studies (for adverse events only) that included non-parenteral long-acting opioids were sought using electronic databases, handsearching reference lists, and soliciting pharmaceutical company submissions. Searches were performed through October 2002. The validity of each included study was assessed using a data abstraction form and predefined criteria. An overall grade was allocated for the body of evidence for each key question. A total of 16 randomized trials (comparative efficacy and adverse events), enrolling 1427 patients, and 8 observational studies (adverse events) of 1190 patients were included in this review. No randomized trial was rated good quality; observational studies were generally of poorer quality than the trials. There was insufficient evidence to prove that different long-acting opioids are associated with different efficacy or safety profiles. There was also insufficient evidence to determine whether long-acting opioids as a class are more effective or safer than short-acting opioids. A subgroup of three studies on long-acting versus short-acting oxycodone was more homogeneous and provided fair evidence that these formulations are equally effective for pain control. J Pain Symptom Manage 2003;26:1026–1048.

Key Words
Analgesics, opioid, pain, meta-analysis, fentanyl, morphine, oxycodone, codeine

Address reprint requests to: Roger Chou, MD, 9721 SW Morrison St., Portland, OR 97225, USA.

Accepted for publication: March 18, 2003.

Note: Evidence tables and appendices are available on the website http://www.oregonrx.org/Orgrx PDF/Opioid%20Review.htm (last updated April 2002) or from the authors (updated October 2002).

0885-3924/03/$–see front matter
doi:10.1016/j.jpainsymman.2003.03.003

Introduction

Chronic pain, typically defined as pain of at least 6 months' duration, is a common cause of major disability. It is estimated that 1 in 5 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 appropriate treatment for refractory chronic non-cancer pain in the general population as well as in older patients,[4] 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.[5] 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 over 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.[6]

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). The Oregon Health Plan refers to a collective series of laws enacted from 1989 through 1995 that sought to expand Medicaid coverage to low-income Oregonians by creating state-run insurance pools, enacting insurance reforms, using a federal waiver that allowed for Medicaid expansion, and excluding certain diagnoses and treatments from coverage. As part of this process for developing a PMPDP for the Oregon Health Plan, the Oregon Health Resources Commission (OHRC) required that an evidence-based review of the state's most expensive drug classes be performed. The 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.

Scope and Key Questions

The scope of the review and key questions were developed and refined with input from an OHRC 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 the PMPDP 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. "Short-acting" was defined as opioids administered more frequently than three times a day. Although "sustained-release" and "immediate-release" are other terms used to describe the onset and duration of action of certain opioid preparations, for this review we classified opioids on the basis of dosing frequency.

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 or most severe 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 remains arbitrary. 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.[7] 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 multiquestion assessment. 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, respiratory depression, nausea, vomiting, constipation, dizziness, somnolence, and confusion. These were the adverse events felt by the subcommittee to be the most common or 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.[8,9] 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.[10] 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.[11–13] 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 ("opioid rotation")—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.[14–17] In some cases, opioid rotation may be done to minimize adverse events.

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 October 2002, using updates on electronic databases after the initial searches.

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. Although studies of longer duration were preferred, we had no lower limit on the length of follow-up, but excluded "single-dose studies," which examine the effects of a single dose of medication rather than a course of treatment.

Searches identified 3495 citations: 1081 from the Cochrane Library, 1106 from Medline, 1205 from EMBASE, 42 from reference lists, and 60 from pharmaceutical company submissions. We identified 1226 clinical trials and excluded 1195 of these (see Appendix C for detailed search results). Nine hundred twenty-two 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-one 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.[18] Sixteen randomized controlled trials provided usable data and are included in evidence tables. We also reviewed eight observational studies that evaluated adverse event rates from long-acting opioids.

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 follow-up, method of outcome ascertainment (e.g., scales used), and results for each outcome. Although there is no clear consensus on "true" equianalgesic doses of opioid medications, equianalgesic doses were estimated using published tables.[19] We recorded intention-to-treat results if available and the trial did not report high overall loss to follow-up. In trials with crossover, because of the potential for differential withdrawal prior to crossover biasing subsequent results, outcomes for the first intervention were recorded if available. A second reviewer checked all data.

Quality Assessment

We assessed quality of trials based on the predefined criteria listed in Appendix B. We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; 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 Center for Reviews and Dissemination (UK).[11,12] Trials that had a fatal flaw in one or more categories were rated poor-quality; trials that met all criteria were rated good-quality; the remainder was rated fair-quality. As the "fair-quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *unlikely* to be valid, while others are *probably* or *likely to be* valid. A "poor-quality" trial is not valid—the results are at least as likely to reflect flaws in the study design rather than true differences between the compared drugs. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events.

Appendix D shows the criteria we used to rate clinical trials and 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 came to consensus 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.

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

Results

Overview of Included Trials

We identified 16 randomized trials (1427 patients enrolled) that evaluated long-acting opioids in chronic non-cancer pain populations (Table 1). Recent non-systematic reviews on adverse events from opioids have identified only two trials each.[2,6] We did not find a relevant systematic review for any of the key questions.

Only two of the 16 trials compared one long-acting opioid to another.[20,21] One of these trials[20] compared transdermal fentanyl to long-acting morphine; the other[21] compared a once-daily morphine preparation to a twice-daily morphine preparation. Seven trials compared a long-acting opioid to a short-acting opioid,[22–28] and seven compared a long-acting opioid to a non-opioid or placebo.[10,29–34] Seven trials used a crossover design.[20,24,25,29,31,32,34] We identified trials on long-acting oxycodone,[10,23,25,28,34] long-acting morphine,[20,21,26,30–32] long-acting dihydrocodeine,[24,27] long-acting codeine,[22,29,33] and transdermal fentanyl.[20] We did not identify any trials on levorphanol or methadone. One small trial[35] with a high rate of withdrawal (14/20) cited in reference lists[2,29] could not be located despite searches for journal, title, and author.

The trials ranged in size from 12[31] to 295[21] evaluable enrollees, with an average of 79 enrollees. Five of the trials focused on osteoarthritis,[10,21,23,27,33] five on back pain,[22,24–26,28] two on neuropathic pain,[30,34] one on phantom limb pain,[31] and three on heterogeneous chronic non-cancer pain.[20,29,32]

All of the trials were of relatively short duration, ranging from 5 days[22] to 16 weeks.[26] 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. Race was rarely reported. Sex had a slight predominance (slightly greater than 50%) towards women. The average age of enrollees was 55.

Assigned quality ratings did not differ between reviewers.

Key Question Outcomes

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?

Two trials directly compared the efficacy of one long-acting opioid to another in chronic pain of non-cancer origin.[20,21] One trial[20] compared transdermal fentanyl to long-acting morphine twice a day. The other trial[21] compared a once-daily morphine preparation to a twice-daily morphine preparation.

The study that compared transdermal fentanyl to oral long-acting morphine used a crossover design in a population of 256 heterogeneous chronic pain patients with an average duration of 9 years pain.[20] This study was rated poor quality because of several major

Table 1
Overview of All Long-Acting Opioid Trials

Author, Year	Long-Acting Opioid	Study Type	Pain Type	Duration	Sample Size	Average Dose (mg/day)	Pain Intensity Score	Scale	Rescue Drug	Average Rescue Drug Usage
Long-acting vs. long-acting trials										
Allan 2001	A: Transdermal fentanyl	Crossover	Miscellaneous	4 weeks[a]	212	NR	A: 57.8	0–100 VAS	Not specified	29.4 mg/day
	B: Oral morphine (twice daily)						B: 62.9			23.6 mg/day
Caldwell 2002	A: Morphine (once daily a.m.)	RCT	Osteoarthritis	4 weeks	295	A: 30 mg	A: 313	0–500 VAS	Not permitted	N/A
	B: Morphine (once daily p.m.)					B: 30 mg	B: 326			
	C: Morphine (twice daily)					C: 30 mg	C: 322			
Long-acting vs. placebo or non-opioid trials										
Arkinstall 1995	Codeine (vs. placebo)	Crossover	Miscellaneous	7 days[a]	46	353	35	0–100 VAS	Tylenol with codeine	3.6 tabs/day
Peloso 2000	Codeine (vs. placebo)	RCT	Osteoarthritis	4 weeks	103	159	32.5	0–100 VAS	Tylenol	4.2 tabs/day
Harke 2001	Morphine (vs. carbamazepine)	RCT	Neuropathic pain	8 days	38	83	6.9[b]	0–10 VAS	Not permitted	N/A
Huse 2001	Morphine (vs. placebo)	Crossover	Phantom limb pain	4 weeks[a]	12	115	3.62	0–10 VAS	Aspirin + paracetamol	NR
Moulin 1996	Morphine (vs. benztropine)	Crossover	Miscellaneous	6 weeks[a]	61	83.4	45	0–100 VAS	Paracetamol	3.5 tabs/day
Roth 2000	Oxycodone (vs. placebo)	RCT	Osteoarthritis	2 weeks	133	40	1.6	0–3 Cat.	Not permitted	N/A
Watson 1998	Oxycodone (vs. placebo)	Crossover	Postherpetic neuralgia	4 weeks[a]	50	45	35	0–100 VAS	Not permitted	N/A
Long-acting vs. short-acting trials										
Caldwell 1999	Oxycodone (vs. SA oxycodone + acetaminophen)	RCT	Osteoarthritis	4 weeks	107	40	1.3	0–4 Cat.	Not permitted	N/A
Hale 1999	Oxycodone (vs. SA oxycodone)	Crossover	Back pain	6 days[a]	47	40	1.2	0–3 Cat.	SA Oxycodone 5–10 mg PRN	0.6 tabs/day
Salzman 1998	Oxycodone (vs. SA oxycodone)	RCT	Back pain	10 days	57	40	1.1	0–3 Cat.	SA Oxycodone 5–10 mg PRN	NR
Hale 1997	Codeine (vs. acteminophen + SA codeine)	RCT	Back pain	5 days	83	200	1.6	0–4 Cat.	Acetaminophen	4.0 tabs/day
Gostick 1989	Dihydrocodeine (vs. SA dihydrocodeine)	Crossover	Back pain	2 weeks[a]	61	NR	1.75	Not provided	Paracetamol	1.54 tabs/day
Lloyd 1992	Dihydrocodeine (vs. dextropropoxyphene + paracetamol)	RCT	Osteoarthritis	2 weeks	86	NR	39.2	0–100 VAS	Not permitted	N/A
Jamison 1998	LA Morphine + SA oxycodone (vs. SA oxycodone)	RCT	Back pain	16 weeks	36	41	54.9	0–100 VAS	Not permitted	N/A

[a]Duration per intervention of crossover trial.
[b]Maximum pain intensity prior to reactivation of spinal cord stimulation unit.
RCT = randomized controlled trial; VAS = visual analogue scale; PRN = as needed; SA = short-acting opioid preparation; NR = not reported.

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 clinician? 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 appears to address 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 clinicians: "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 length of follow-up for each drug regimen was only four weeks.

The study that compared a once-daily morphine preparation to a twice-daily morphine preparation[21] used a randomized, double-blinded design 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 four weeks, and duration of pain and previous opioid use in evaluated patients was not reported.

We found no trials directly comparing fentanyl or long-acting morphine to any other long-acting preparations.

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. These trials exhibited a high degree of heterogeneity with respect to study designs,

patient populations, interventions, and outcomes measured (Table 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 follow-up.

Three trials evaluated long-acting codeine,[22,29,33] two long-acting dihydrocodeine,[24,27] four long-acting morphine,[26,30–32] and five long-acting oxycodone.[10,23,25,28,34] The average equipotent opioid dose received varied greatly and in two trials was not reported.[24,27] The duration of follow-up 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). The studies used different pain intensity measures, the most common being VAS.

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 VAS,[34] three others used two different (0–3[10,25] or 0–4[23]) categorical scales, and one did not report pain intensity as an outcome.[28] 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[23] or 0–10 scale,[10]) nighttime rescue medication use,[22] hours of sleep,[26] average nights awakened by pain,[27] and VAS (1–100) for trouble falling asleep and needing medication to sleep.[33] 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. We were unable to perform meta-analysis on any subgroup of trials.

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 2). For long-acting oxycodone, the withdrawal rate ranged from 4%[25] to 53%.[10] For long-acting morphine, the withdrawal rate ranged from 0%[31] to 30%.[32] 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.

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?

A subgroup of 7 (568 patients enrolled) of the 14 trials reviewed for key question 1B directly compared the efficacy of long-acting opioids to short-acting opioids in patients with chronic non-cancer pain (Table 3). All were rated fair quality (Evidence Table 1.2). Three studies compared long-acting to short-acting oxycodone.[23,25,28] One of these studies[25] re-randomized patients who had enrolled in a previous trial.[28] Two studies evaluated long-acting dihydrocodeine,[24,27] one evaluated long-acting codeine,[22] and one evaluated long-acting morphine.[26] 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 3). Three studies that found differences in efficacy favoring long-acting morphine,[26] long-acting dihydrocodeine,[27] and long-acting codeine[22] had features that might invalidate these results. In the trials on long-acting morphine[26] and long-acting codeine,[22] the average daily doses of opioid in the long-acting arm were higher than the average daily doses given in the short-acting

Table 2
Withdrawal Rates

Author, Year	Long-Acting Opioid	Overall Withdrawal Rates	Withdrawal Rates Per Drug	Inadequate Pain Control	Adverse Effects	Other
Long-acting vs. long-acting trials						
Allan 2001	A: Fentanyl transdermal	23%	A: 15% (38/250)	N/A	"11%"	N/A
	B: Morphine oral (twice daily)		B: 9% (22/238)		"4%"	
Caldwell 2002	A: Morphine (once daily a.m.)	38%	A: 37% (27/73)	9	17	1
	B: Morphine (once daily p.m.)		B: 45% (33/73)	12	18	3
	C: Morphine (twice daily)		C: 37% (28/76)	8	18	2
	D: Placebo		D: 32% (23/72)	14	5	4
Long-acting vs. placebo or non-opioid trials						
Arkinstall 1995	Codeine	28%	LA Codeine: 19% (9/46)	1	7	1
			Placebo: 9% (4/46)	0	1	3
Peloso 2000	Codeine	36%	LA Codeine: 40% (20/51)	1	15	4
			Placebo: 33% (17/52)	5	5	7
Harke 2001	Morphine	8%	LA Morphine: 5% (1/19)	NR	NR	1
			Placebo: 11% (2/19)			2
Huse 2001	Morphine	0%	LA Morphine: 0% (0/12)	NR	N/A	N/A
			Placebo: 0% (0/12)			
Moulin 1996	Morphine	30%	LA Morphine:	NR	NR	NR
Roth 2000	Oxycodone	53%	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
Watson 1998	Oxycodone	22%	LA Oxycodone: 12% (6/50)	0	5	1
			Placebo: 10% (5/50)	1	3	1
Long-acting vs. short-acting trials						
Caldwell 1999	Oxycodone	34%	LA Oxycodone: 21% (7/34)	3	3	1
			SA Oxycodone: 30% (11/37)	4	5	2
			Placebo: 50% (18/36)	13	3	2
Hale 1999	Oxycodone	6%	LA Oxycodone: 4% (2/47)	0	2	0
			SA Oxycodone: 2% (1/47)	0	1	1
Salzman 1998	Oxycodone	18%	LA Oxycodone: 20% (6/30)	NR	6	NR
			SA Oxycodone: 7% (2/27) (only adverse event withdrawals reported)	0	2	0
Hale 1992	Codeine	22%	LA Codeine: 32% (17/53)	1	15	1
			SA Codeine: 12% (6/51)	1	5	0
Gostick 1989	Dihydrocodeine	26%	NR	NR	NR	NR
Lloyd 1992	Dihydrocodeine	34%	LA Dihydrocodeine: 47% (20/43)	1	17	2
			Dextropropoxyphene + paracetamol: 21% (9/43)	2	4	3
Jamison 1998	Morphine	8%	LA Morphine + *SA Oxy.*: 6% (1/18)	NR	1	NR
			SA Oxycodone: 12% (2/18)	0	2	0

Table 3
Overview of Randomized Controlled Trials of Long-Acting vs. Short-Acting Opioids[a]

Author, Year	Pain Type	Duration	Patients	Findings
Oxycodone				
Caldwell 1999	Osteoarthritis	30 days	107	LA oxycodone and SA oxycodone plus Tylenol are equally effective for pain control and improvement of sleep.
Hale 1999	Back pain	6 days[b]	47	LA oxycodone and SA oxycodone are equally effective for pain control.
Salzman 1998	Back pain	10 days	57	LA oxycodone and SA oxycodone are equally effective when titrated for pain control.
Codeine				
Hale 1992	Back pain	5 days	83	LA codeine plus acetaminophen are more effective for pain control than SA codeine plus acetaminophen, but these drugs were not given at therapeutically equivalent doses.
Dihydrocodeine				
Gostick 1989	Back pain	2 weeks[b]	61	LA dihydrocodeine and SA dihydrocodeine are equally effective for pain control.
Lloyd 1992	Osteoarthritis	2 weeks	86	LA dihydrocodeine and SA dihydrocodeine are equally effective for pain control when compared directly.
Morphine				
Jamison 1998	Back pain	16 weeks	36	LA morphine plus SA oxycodone together are more effective for pain control than SA oxycodone, but these drugs were not given at therapeutically equivalent doses.

[a]All trials are of fair quality.
[b]Duration per intervention of crossover trial.
LA = long-acting opioid preparation; SA = short-acting opioid preparation.

group. In the other study,[27] 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.[23,25,28] One of these trials[25] investigated a re-randomized population of patients studied in a previous trial[28] 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[23] reported improved sleep quality with long-acting oxycodone, but baseline sleep scores were significantly better in patients randomized to this intervention, which could invalidate this finding.

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

A variety of long-acting opioids are used for treatment of chronic non-cancer pain. There continue to be concerns, however, regarding the risk of adverse events.[9] 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.[6]

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 two randomized trials directly compared two long-acting opioids. One of these trials[20] compared two different long-acting opioids (transdermal fentanyl and long-acting morphine) and the other[21] 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 trial which compared transdermal fentanyl with long-acting oral morphine was rated

poor-quality for adverse event assessment (Evidence Table 2.1).[20] This trial failed to adequately meet 6 out of the 7 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).[21] This trial failed to adequately meet 5 out of the 7 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%) versus twice-daily morphine (29%), but a lower rate of asthenia (1% vs. 9%). The overall withdrawal rates in treated patients were not significantly different between interventions and ranged from 37–45%, with withdrawal rates due to adverse events ranging from 23–25%.

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. Of the 14 trials reviewed for key question 1B, 13 (994 patients enrolled) reported adverse event rates from long-acting opioids in patients with chronic non-cancer pain. One trial of long-acting morphine versus carbamazepine for neuropathic pain[30] was excluded because accurate adverse event rates could not be abstracted from the graphs in the article.

All 13 trials were rated fair or poor quality for adverse event assessment and had at least important methodologic flaws (Table 4; Evidence Tables 2.2 and 2.3). In addition, these trials had heterogeneous study designs, interventions, outcomes, and patient populations, making meaningful comparisons across studies difficult (Table 1). None of these trials assessed rates of abuse or addiction, and all excluded patients at risk for these complications.

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%[23] to 50%[28] in 5 trials (Table 4). Withdrawal rates due to adverse events ranged from 4%[25] to 32%[10] 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 4).

Observational Studies. We identified 8 observational studies evaluating the risk of long-acting opioids in 1190 patients with non-cancer pain.[10,21,29,36–40] All were rated poor quality for adverse event assessment except one,[10] which was rated fair (Evidence Table 2.4). For 6 of the 8 studies, independently assigned quality rating scores were identical between two reviewers. For two studies, quality rating scores differed by one[41] or two[10] points; in neither case did this difference result in a change in overall quality rating. The single study rated fair quality[10] met only 4 out of 7 predefined quality assessment criteria. The most important areas of concern in this study were high overall loss to follow-up (60/106) and the failure to specify or define adverse events in advance.

Opioids assessed were long-acting codeine,[29] long-acting morphine (once-daily[21] or twice-daily[40]), transdermal fentanyl,[36,39] methadone,[38] and long-acting oxycodone.[10] One study assessed both methadone and long-acting morphine.[37] The number of patients on long-acting opioids in these studies ranged from 11[38] to 530.[39] Five were prospective cohort studies[10,21,29,36,39] and three were retrospective cohorts.[37,38,40] No identified study was population-based. Three of the prospective cohorts[10,21,29] 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 5). The study rated fair quality,[10] 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[39] 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,[37,38] 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.[10,21,29,36] Rates ranged from 19% for transdermal fentanyl[36] to 54% for long-acting codeine.[29]

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,[10,21,29,36,39] 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.[37,38,40]

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

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

A subgroup of 7 of the 13 randomized trials reviewed for key question 2B directly compared long-acting with short-acting opioids.[22–28]

In the single trial in this group rated fair quality,[26] 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 4).

Across all trials, no pattern favoring either long-acting or short-acting opioids was evident for any of the reported adverse events (Table 6). In the three most comparable studies, which investigated roughly equivalent daily doses of oxycodone in short-acting and long-acting preparations,[23,25,28] 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[25,28] that investigated the same (re-randomized) population.

Withdrawals due to adverse events were reported in five trials (Table 4). Three favored short-acting opioids,[22,27,28] one favored long-acting,[23] and one was equivocal.[25] 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.

In summary, there is no convincing evidence to suggest superior 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 or 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 sexes. There is almost no information regarding the comparative efficacy of long-acting opioids for specific subpopulations as characterized by race, sex, or age. 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%), but differential efficacy or adverse event rates according to sex were not evaluated. The average age of included patients was 55 years, and one study[34] evaluated patients with an average age of 70 years. Two trials[10,23] 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,[22,24–26,28] osteoarthritis,[10,23,27,33] phantom limb pain,[31] neuropathic pain,[30] and postherpetic neuralgia.[34] None of these trials are direct

Table 4
Study Characteristics and Adverse Events, Trials of Long-Acting Opioids

Study	Interventions	Quality Rating[a]	Nausea	Vomiting	Constipation	Drowsiness or Somnolence	Dizziness	Confusion or Difficulty Concentrating	Withdrawal[b]
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)
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: Short-acting 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)[c]		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								
Long-acting codeine									
Arkinstall[d] 1995	A: Long-acting codeine	FAIR (3)	A: 33%[c]	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: 25% (13/53)
	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: 8% (4/51)

(*continued*)

Table 4
Continued

Study	Interventions	Quality Rating[a]	Nausea	Vomiting	Constipation	Drowsiness or Somnolence	Dizziness	Confusion or Difficulty Concentrating	Withdrawal[b]
Peloso 2000	A: Long-acting codeine	FAIR (3)	Not reported	Not reported	A: 49% (25/51)[c]	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)[e]	Not reported	Not reported	Not reported	Not reported
	B: Short-acting dihydrocodeine				B: 49% (21/43)				
Lloyd[f] 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)	Not reported	B: 5% (2/41)	B: 9% (4/43)
Long-acting morphine									
Huse[g] 2001	A: Long-acting morphine	FAIR (3)	A: 0.74 cm	Not reported	A: 0.03 cm[c]	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[d] 1998	A: Long-acting morphine + short-acting oxycodone	FAIR (5)	A: 31%	Not reported	A: 30%	A: 31%	A: 6%	A: 1%	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)[c]	A: 39% (18/46)[c]	A: 41% (19/46)[c]	Not reported	A: 37% (17/46)	A: 9% (4/46)	A: 28%[h] (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)

[a]Number of criteria out of seven adequately met.
[b]Due to adverse events.
[c]$P < 0.05$ for difference in rates.
[d]Sample size not clear.
[e]Constipation defined as bowel movement less frequently than every two days.
[f]Results from end of first week of treatment because of high rate of withdrawals after first week.
[g]Results reported on 10 cm visual analog scale.
[h]Dose-limiting side effects (not withdrawal rate), $P = 0.003$ for difference in rates.

Table 5
Study Characteristics and Adverse Events, Observational Studies of Long-Acting Opioids

Study	Long-Acting Opioids Studied	Quality Rating[a]	Nausea	Vomiting	Constipation	Drowsiness or Somnolence	Dizziness	Confusion or Difficulty Concentrating	Withdrawal[b]	Long-Term Use
Arkinstall 1995	Long-acting codeine	POOR (2)	NR	NR	NR	NR	NR	NR	NR	54% (15/28)
Bach 2001	Long-acting morphine (twice-daily)	POOR (0)	NR	NR	NR	NR	NR	NR	NR	NR
Caldwell 2002	Long-acting morphine (once-daily)	POOR (2)	16% (29/181)	6% (11/181)	35% (63/181)	13% (23/181)	9% (16/181)	NR	33% (60/181)	48% (86/181)
Dellemijn 1998	Transdermal fentanyl	POOR (2)	92%	56%	36%	58%	54%	<20%	NR	19% (9/48)
Dunbar 1996	Methadone	POOR (0)	NR	NR	NR	NR	NR	NR	NR	NR
	Long-acting morphine		NR	NR	NR	NR	NR	NR	NR	NR
Green 1996	Methadone	POOR (0)	NR	NR	NR	NR	NR	NR	NR	NR
Milligan 2001	Transdermal fentanyl	POOR (1)	9% (48/530)	8% (42/530)	NR	NR	NR	NR	NR	NR
Roth 2000	Long-acting oxycodone	FAIR (4)	24% (25/106)	NR	52% (55/106)	30% (32/106)	NR	NR	30% (32/106)	43% (46/106)

[a]Number of criteria out of seven adequately met.
[b]Due to adverse events.
NR = not reported.

Table 6
Comparative Results for Adverse Events, Trials of Long-Acting Opioid versus Short-Acting Opioid

Study	Nausea	Vomiting	Constipation	Drowsiness or Somnolence	Dizziness	Confusion	Withdrawal[a]
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[b] 1999	Favors long-acting	No difference	Favors long-acting	Favors short-acting	Favors short-acting	Not reported	No difference
Salzman[b] 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[c] 1997	Favors short-acting	Favors short-acting	No difference	Favors short-acting	Favors short-acting	Not reported	Favors short-acting
Lloyd 1992	Favors short-acting	Not reported	No difference	Favors short-acting	Not reported	Favors short-acting	Favors short-acting
Jamison[c] 1998	Favors short-acting	Not reported	Favors short-acting	Favors short-acting	Favors long-acting	No difference	Not reported

[a]Due to adverse event.
[b]Studied same population.
[c]Lower dose of opioid used in short-acting arm.

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.

It is not possible to draw reliable conclusions regarding comparative efficacy or adverse event rates for any subpopulation from these data.

Summary of Results

Results for each of the key questions are summarized in Table 7. 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[20] directly compared different long-acting opioids (transdermal fentanyl and long-acting morphine) and gave inconclusive results. This was the only trial we identified that evaluated transdermal fentanyl in patients with non-cancer pain. 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. It also did not provide convincing evidence that transdermal fentanyl is associated with less constipation than oral morphine, as has been consistently found in trials of cancer patients.[42] Another fair-quality trial[21] 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

Table 7
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. Two 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 compared different long-acting formulations (once- or twice-daily) of morphine, found no significant difference in pain control and a significant difference for one of seven measures of sleep quality using once-daily morphine in the a.m., but not p.m. There is insufficient evidence from head-to-head comparison studies to suggest that one long-acting opioid is superior to another in terms of efficacy in adult patients with chronic non-cancer pain.
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.
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.
Adverse Events		
2A. In head-to-head comparisons, has one or more long-acting opioid been shown to be associated with fewer adverse events compared to other long-acting opioids when used for treatment of adults with chronic non-cancer pain?	POOR	Most long-acting opioids have not been compared directly in clinical trials. One poor-quality trial (see above) directly compares one long-acting opioid with another and one fair-quality trial (see above) directly compares once-daily with twice-daily morphine. In the fair-quality trial, once-daily morphine was associated with a higher frequency of constipation and a lower frequency of asthenia compared to twice-daily morphine; other adverse event rates were not significantly different. 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.
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. Observational studies on adverse event were of generally poorer quality than the clinical trials. 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.
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.

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. 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. In general, insufficient data was provided in the included trials to accurately assess external validity.

There was also insufficient evidence from a subgroup of seven trials to determine whether long-acting opioids as a class are more effective or associated with fewer adverse events than short-acting opioids. Three trials investigating long-acting oxycodone versus short-acting oxycodone[23,25,28] were 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, addiction, and overdose (including respiratory depression) 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.

Discussion

The current available literature does not provide enough evidence to guide the prescribing physician in choosing an initial long-acting opioid medication for patients with chronic non-cancer pain. The lack of high-quality evidence comparing long-acting opioids to one another and to short-acting opioids in patients with chronic non-cancer pain is concerning given the wide use of this class of medication in this population. Data are inadequate to determine whether long-acting opioid preparations, either compared to each other or to short-acting opioids, have different efficacy and safety profiles. Given the ever-rising costs of medications, it is likely that pressure will continue to increase to watch the bottom line. Without good quality evidence of comparative efficacy and safety, payers may be compelled to rely on cost as the only method of differentiating between medications in this drug class, or extrapolate from studies performed in other populations (e.g., cancer pain patients) that may not be applicable to the population in question.

Ideal studies to investigate comparative efficacy and safety would perform head-to-head comparisons of equianalgesic doses of long-acting opioids to other long-acting or short-acting opioids, be adequately blinded, use a predefined and systematic method for identifying adverse events, be of longer duration, and account for prior opioid use of enrollees. Large, population-based observational studies would help determine whether rare but serious adverse event rates (such as respiratory depression) differed between long-acting opioids. Particular attention to the risks of abuse and addiction would also be best obtained from high-quality cohort studies, as trials have typically excluded patients at high risk for these complications. Outcomes should be standardized or measured using a variety of visual analogue scales, categorical scales, and common multiquestion assessments, so that results can be meaningfully compared across studies. Another area that deserves careful study is the efficacy of opioid rotation in this group of patients. We hope this report helps to highlight remaining gaps in our understanding of this important class of medication and that studies to fill these gaps will be supported and undertaken.

Acknowledgments

The authors wish to acknowledge the Oregon Department of Human Resources for its funding support. They also wish to acknowledge the administrative support provided by Kathryn Pyle Krages, AMLS, MA, Susan Wingenfeld, Susan Carson, MPH, and Patty Davies, MS. Additional information regarding Oregon's Practitioner-Managed Prescription Drug Plan is available at http://www.ohpr.state.or.us.

References

1. Joranson DE, Ryan KM, Gilson AM, et al. Trends in medical use and abuse of opioid analgesics. JAMA 2000;283(13):1710–1714.

2. Strumpf M, Dertwinkel R, Wiebalck A, et al. Role of opioid analgesics in the treatment of chronic non-cancer pain. CNS Drugs 2000;14(2):147–155.

3. Anonymous. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. Clin J Pain 1997;13(1):6–8.

4. Anonymous. The management of chronic pain in older persons. AGS Panel on Chronic Pain in Older Persons. American Geriatrics Society. Geriatrics 1998;53(Suppl 3):S8–24.

5. Schug SA, Merry AF, Acland RH. Treatment principles for the use of opioids in pain of nonmalignant origin. Drugs 1991;42(2):228–239.

6. Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. J Pain Symptom Manage 1996;11(4):203–217.

7. McQuay HJ. Opioid use in chronic pain. Bandolier 2002; available at http://www.jr2.ox.ac.uk/bandolier/booth/painpag/wisdom/S31.html

8. Rinaldi RC, Steindler EM, Wilford BB, et al. Clarification and standardization of substance abuse terminology. JAMA 1988;259:555–557.

9. Savage SR. Opioid use in the management of chronic pain. Med Clin North Am 1999;83(3):761–786.

10. Roth SH, Fleischmann RM, Burch FX, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: placebo controlled trial and long-term evaluation. Arch Intern Med 2000;160:853–860.

11. Anonymous. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews CRD Report Number 4 (2nd edition). York, UK: NHS Centre for Reviews and Dissemination; 2001. Report No. 4 (2nd edition).

12. Harris RP, Helfand M, Woolf SH, et al. Current methods of the third U.S. Preventive Services Task Force. Am J Prev Med 2000;20(3S):21–35.

13. Mulrow CD, Oxman A. How to conduct a Cochrane systematic review. Version 3.0.2. In: San Antonio Cochrane Collaboration; 1997.

14. Quang-Cantagrel ND, Wallace MS, Magnuson SK. Opioid substitution to improve the effectiveness of chronic noncancer pain control: a chart review. Anesth Analg 2000;90(4):933–937.

15. Thomsen AB, Becker N, Eriksen J. Opioid rotation in chronic nonmalignant pain patients: a retrospective study. Acta Anaesthesiol Scand 1999; 43:918–923.

16. Bruera E, Pereira J, Watanabe S, et al. Opioid rotation in patients with cancer pain. Cancer 1996; 78(4):852–857.

17. de Stoutz ND, Bruera E, Suarez-Almazor M. Opioid rotation for toxicity reduction in terminal cancer patients. J Pain Symptom Manage 1995;10(5):378–384.

18. Raja SN, Haythornthwaite JA, Pappagallo M, et al. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2002;59:1015–1021.

19. Levy MH. Pharmacologic treatment of cancer pain. N Engl J Med 1996;335:1124–1132.

20. Allan L, Hays H, Jensen NH, et al. Randomized crossover trial of transdermal fentanyl and sustained-release oral morphine for treating chronic non-cancer pain. BMJ 2001;322:1154–1158.

21. Caldwell JR, Rapoport RJ, Davis JC, et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. J Pain Symptom Manage 2002;23:279–291.

22. Hale M, Speight K, Harsanyi Z, et al. Efficacy of 12 hourly controlled-release codeine compared with as required dosing of acetaminophen plus codeine in patients with chronic low back pain. Pain Res Manage 1997;2:33–38.

23. Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled- release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal anti-inflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. J Rheumatol 1999;26:862–869.

24. Gostick N, Allen J, Cranfield R, et al. A comparison of the efficacy and adverse effects of controlled-release dihydrocodeine and immediate-release dihydrocodeine in the treatment of pain in osteoarthritis and chronic back pain. In: Twycross RG, ed. Proceedings of The Edinburgh Symposium on Pain Control and Medical Education; 1989:137–143.

25. Hale ME, Fleischmann R, Salzman R, et al. Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double blind evaluation in patients with chronic back pain. Clin J Pain 1999;15:179–183.

26. Jamison RN, Raymond SA, Slawsby EA, et al. Opioid therapy for chronic noncancer back pain. A randomized prospective study. Spine 1998;23:2591–2600.

27. Lloyd RS, Costello F, Eves MJ, et al. The efficacy and tolerability of controlled-release dihydrocodeine tablets and combination dextropropoxyphene/paracetamol tablets in patients with severe osteoarthritis of the hips. Curr Med Res Opin 1992;13:37–48.

28. Salzman RT, Roberts MS, Wild J, et al. Can a controlled release oral dose form of oxycodone be used as readily as an immediate-release form for the purpose of titrating to stable pain control? J Pain Symptom Manage 1999;18:271–279.

29. Arkinstall W, Sandler A, Goughnour B, et al. Efficacy of controlled-release codeine in chronic nonmalignant pain: a randomized, placebo controlled clinical trial. Pain 1995;62:169–178.

30. Harke H, Gretenkort P, Ladleif HU, et al. The response of neuropathic pain and pain in complex

regional pain syndrome I to carbamazepine and sustained-release morphine in patients pretreated with spinal cord stimulation: a double-blinded randomized study. Anesth Analg 2001;92:488–495.

31. Huse E, Larbig W, Flor H, et al. The effect of opioids on phantom limb pain and cortical reorganization. Pain 2001;90:47–55.

32. Moulin DE, Iezzi A, Amireh R, et al. Randomized trial of oral morphine for chronic noncancer pain. Lancet 1996;347:143–147.

33. Peloso PM, Bellamy N, Bensen W, et al. Double blind randomized placebo control trial of controlled-release codeine in the treatment of osteoarthritis of the hip or knee. J Rheumatol 2000;27(3):764–771.

34. Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain a randomized trial in postherpetic neuralgia. Neurology 1998;50:1837–1841.

35. Moran C. MST continuous tablets and pain control in severe rheumatoid arthritis. Br J Clin Res 1991;2:1–12.

36. Dellemijn PL, van Duijn H, Vanneste JA. Prolonged treatment with transdermal fentanyl in neuropathic pain. J Pain Symptom Manage 1998; 16:220–229.

37. Dunbar SA, Katz NP. Chronic opioid therapy for nonmalignant pain in patients with a history of substance abuse: report of 20 cases. J Pain Symptom Manage 1996;11:163–171.

38. Green J, Hickey S, Ansbacher S, et al. Methadone use in a small series of selected patients with chronic nonmalignant pain. Pain Digest 1996;6:3–6.

39. Milligan K, Lanteri-Minet M, Borchert K, et al. Evaluation of long-term efficacy and safety of transdermal fentanyl in the treatment of chronic noncancer pain. J Pain 2001;2:197–204.

40. Bach V, Kamp-Jensen M, Jensen NH, et al. Buprenorphine and sustained-release morphine: effect and side effects in chronic use. Pain Clin 1991;4: 87–93.

41. Arkinstall WW, Goughnour BR, White JA, et al. Control of severe pain with sustained-release morphine tablets vs. oral morphine solution. Can Med Assoc J 1989;140:653–661.

42. Haazen L, Noorduin H, Megens A, et al. The constipation-inducing potential of morphine and transdermal fentanyl. European J Pain 1999;3(Suppl. A):9–15.

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

Appendix B

Methods for Drug Class Reviews for Oregon Health Plan Practitioner-Managed Prescription Drug Plan Oregon Health & Science University Evidence-Based Practice Center December 14, 2001

Available at http://www.oregonrx.org/OrgrxPDF/Opioid%20Review.htm or from the authors.

Appendix C

Quality Abstraction Tool for Adverse Events of Opioids

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

EXTERNAL VALIDITY	
Adequate description of study population: 1: Study reports 2 or more demographic characteristic 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