Drug Class Review on Long-Acting Opioid Analgesics for Chronic Non-Cancer Pain

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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 adult 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). 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.

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 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 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.[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—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]

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.

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

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.[19] 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).[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 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

We identified 16 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, 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 trial[35] cited in reference lists[2, 29] 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[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 heterogenous 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, 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.[24, 27, 32] For none of these did the difference in point scores result in re-classification of overall quality rating for adverse event assessment.

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 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 [20]. 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[21] 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.

In summary, two 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 one of seven measures of sleep quality showing improved efficacy for once-daily morphine given in the morning only. There are no data 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. Seven studies compared long-acting opioids to short-acting opioids,[22-28] and seven studies compared long-acting opioids to non-opioids or placebos.[10, 29-34] 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.

The trials evaluated patients with a variety of chronic non-cancer pain conditions, including post-herpetic neuralgia,[34] phantom limb pain,[31] osteoarthritis,[10, 23, 27, 33] back pain,[22, 24-26, 28] and miscellaneous chronic non-cancer pain.[29, 32] 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 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, [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 sleep,[27] and visual analogue scales (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.

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%[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.

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.

Summary

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.

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 1.3). Three studies compared long-acting oxycodone 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 1.3). 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 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.

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.

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 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).[21] 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%.

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).[22-28] Six others[10, 29, 31-34] compared a long-acting opioid with placebo (Evidence Table 2.3). 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.

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%[23] to 50%[28] in five trials (Table 2.1). 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 2.1).

Observational Studies

We identified eight 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 six of the eight studies, independently assigned quality rating scores were identical between two reviewers. For two studies, quality rating scores differed by one[41] or two[10] point; in neither case did this difference result in a change in overall quality rating. The single study rated fair-quality[10] 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,[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] The prospective cohort studies recruited all[10, 21, 29, 36] or some[39] of their patients from completed clinical trials. 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 2.2). 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.

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 two poor-qualitys trial directly comparing one 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 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. There is insufficient evidence to suggest that one long-acting opioid is superior in terms of adverse events than any other in chronic non-cancer pain patients.

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.[22-28] None of the studies were designed to assess rates of addiction or abuse.

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 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,[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 2.1). 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, for all assessed adverse events, 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 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[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 post-herpetic neuralgia.[34] 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.

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[20] 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[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 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.

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[23, 25, 28] 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.

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