Oregon Health Resources Commission

Long-acting OPIOID Analgesics for Non-cancer Pain

Update #4, July 2006

This report is the fourth update of the initial Opioid Subcommittee Report of June 2002. All new revisions are highlighted.

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Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan. The statute specifically directs the Health Resources Commission (HRC) to advise the Department of Human Services on this Plan.

In January of 2002 the HRC appointed a subcommittee to perform an evidence-based review of the use of long-acting opioids for non-cancer pain. Members of the subcommittee consisted of physicians, pharmacists, nurse practitioners, other health care professionals, consumers and advocates. The subcommittee had six meetings, two of which were general sessions of orientation and evidence-based analysis education. All meetings were held in public with appropriate notice provided.

Subcommittee members worked with Oregon Health and Science University's Evidence-based Practice Center (OHSU-EPC) to develop and finalize key questions for drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities.

Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each full study was assessed for quality according to predetermined criteria.

The OHSU-EPC report titled "*Drug Class Review on Opioid Analgesics for Non-cancer Pain*" was completed the week of April 1, 2002, circulated to subcommittee members and posted on the web. The subcommittee met on April 10, 2002, to review the document. By consensus, the subcommittee members agreed to adopt the report. Time was allotted for public comment, questions and testimony. The subcommittee's meeting on April 24, 2002 was specifically scheduled to allow additional time for public testimony. All available sources of information; the EPC report, which includes information submitted by pharmaceutical manufacturers, and public testimony were considered. The conclusions drawn by the Opioid Subcommittee comprise the body of this report. Although cancer pain was not the purview of the subcommittee, the report, *Management of Cancer Pain Summary*[1] funded by the Agency for Healthcare Research and Quality (AHRQ) and published January 2001, was also reviewed. The Opioid Subcommittee notes that the evidence analysis for cancer pain showed similar conclusions to those outlined below for non-cancer pain.

[1] Management of Cancer Pain. Summary, Evidence Report/Technology Assessment: Number 35. AHRQ Publication No. 01-E033, January 2001. Agency for Healthcare Research and Quality, Rockville, MD. *http://www.ahrq.gov/clinic/epcsums/canpainsum.htm*

The HRC appointed a standing update committee to perform evidence-based reviews of the June 2002 *Long-Acting OPIOID Analgesics for Non-cancer Pain Subcommittee Report* every year based on new information or changes in the FDA package inserts. This report is the fourth update of the initial June 2002 Opioid Subcommittee Report. All new revisions are highlighted.

Members of the Standing Update Committee consisted of one HRC member, one Oregon State University (OSU) pharmacist, one OHPR physician, two subcommittee physicians, one OHSU-EPC physician, one nurse practitioner, and one PharmD.

The OHSU EPC's Preliminary *Drug Class Review on Opioid Analgesics for Chronic Non-Cancer Pain Forth Update Report* was completed April 2006, circulated to the Standing Update Committee members and posted on the OHPR website at http://www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

The Standing Update Committee met once on July 11, 2006 and reviewed the preliminary document and any additional evidence. By consensus, the committee members agreed to adopt the EPC's Drug Class Review on Opioid Analgesics for Chronic Non-Cancer Pain Final Report #4. Time was allotted for public comment, questions, written and oral testimony. All available sources of information from the EPC's report that included information submitted by pharmaceutical manufacturers and public testimony were considered.

The Update Committee presented its finding to the HRC and the revisions were approved at its meeting on September 8, 2006.

This report is prepared to facilitate the HRC in providing recommendations to OMAP for the plan drug list (PDL). This update report does not recite or characterize all the evidence that was discussed by the OHSU-EPC, the Standing Update Committee, or the HRC. For further information provided during the committee process readers are encouraged to review the source materials on the website.

The Standing Update Committee of the HRC, working together with the EPC, OMAP, and the OSU College of Pharmacy, will continue to monitor medical evidence for new developments in this drug class. Every year emerging pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PDL will be made. Significant new evidence for pharmaceuticals already on the PDL will be assessed and Federal Drug Administration (FDA) changes in indications and safety recommendations will be evaluated. The OPIOID Subcommittee Report will be amended if indicated. Substantive changes will be brought to the attention of the HRC, who may choose to approve the report, or reconvene the OPIOID Subcommittee.

This report and the OHSU-EPC's update final report are all available on the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website:

www.oregonrx.org. Information regarding the HRC and its subcommittee policy and process can be found on the OHPR website:

http://www.ohpr.state.or.us/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

More information, copies of the report, or minutes and tapes of the meetings can be requested from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from OHSU Center for Evidence-based Policy by contacting:

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2611 SW 3rd Avenue, MQ 280
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Phone: 503-494-7239
littleal@ohsu.edu

There will be a charge for copying and handling in providing documents both from OHPR and OHSU Center for Evidence-based Policy.

Critical Policy:

- *Senate Bill 819*
  - "The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price."
- *Health Resources Commission*
  - "Clinical outcomes are the most important indicators of comparative effectiveness";
  - "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Inclusion Criteria:

- *Scope*
  - Adult patients with (a) any non-cancer pain syndrome requiring chronic use of long-acting opioid medications (b) acute non-surgical/non-obstetric low back pain. Exclude: Cancer pain, acute pain other than low back pain.

Definition of long-acting opioids for chronic pain (used three times daily or less often)

Generic	***Brand***
Morphine Sulfate SA	Oramorph SR
	MS Contin
	Kadian
	Avinza
Oxycodone	OxyContin
Oxymorphone	NA in US
Methadone	Dolophine
	Methadose
Fentanyl (transdermal)	Duragesic
Levorphanol	Levo-Dromoran
Hydromorphone	Palladone (NA in US)
Codeine	NA in US

Key Questions:

1. What is the comparative efficacy of different long-acting opioid medications in reducing pain and improving functional outcomes in adult patients being treated for chronic non-cancer pain?

2. What is 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?

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?

New Findings Update #4, July 2006:

1. Using the same search strategy as was used in the original long-acting opioids report, the EPC found 581 new citations through September 2005, but only 4 citations met all the inclusion criteria. The EPC received dossiers from Janssen, Purdue Pharma manufacturers, and Organon Pharmaceuticals but they contained no evidence-based trials not otherwise identified.

2. Since the 3rd update, extended release Hydromorphone was withdrawn from the market after the manufacturer provided data to the FDA showing that drinking alcohol could result in rapid release of the Hydromorphone.[2]

3. FDA changes in labeling in the 3rd review include a **BOXED WARNING** for fentanyl patches (Duragesic). Duragesic contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. Duragesic is indicated for management of persistent, moderate to severe chronic pain that requires continuous, around-the-clock opioid administration for an extended period of time. Because serious or life-threatening hypoventilation could occur, Duragesic (fentanyl transdermal system) is contraindicated in patients who are not opioid-tolerant.

4. One trial compared transdermal fentanyl and oral twice daily morphine in patients with chronic low back pain.[3]

5. Another trial compared long-acting oxymorphone and long-acting oxycodone in patients with low back pain.[4]

6. Another placebo-controlled trial evaluated long-acting morphine in patients with various pain conditions.[5]

7. Another trial compared morphine, gabapentin, placebo and the combination of morphine and gabapentin in patients with neuropathic pain.[6]

[2] FDA, FDA asks Purdue Pharma to withdraw Palladone for safety reasons. *FDA News* July 13, 2005;P05-42.
[3] Allan L, Richarz U, Simpson K et al. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naïve patients with chronic low back pain. *Spine* 2005;30:2484-2490.
[4] Hale ME, Dvergsten C, Gibel J. Efficacy and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. *J Pain.* 2005;6(1):21-28.
[5] Maier C, Hildebrandt J. Klinger R, Henrich-Eberl C, et al. Morphine responsiveness, efficacy and tolerability in patients with chronic non-tumor associated pain – results of a double-blind placebo-controlled trial (MONTAS) *Pain* 2002;;97(3):223-233.

Amended Summary of Results

1. WHAT IS THE COMPARATIVE EFFICACY OF DIFFERENT LONG-ACTING OPIOID MEDICATIONS 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?

Five randomized trials provide direct evidence of the comparative efficacy of different long-acting opioids in chronic non-cancer pain. Three randomized trial compared transdermal Fentanyl to long-acting morphine. Results were conflicting with improved pain control with Fentanyl but also increased adverse reactions to Fentanyl. The fourth fair-quality randomized trial compared once-daily morphine to twice-daily morphine and found similar efficacy. The fifth fair quality study compared long-acting oxymorphone (not yet available in the US) to long-acting oxycodone in patients with low back pain and found no differences for efficacy.[7]

One additional small (n=18) head-to-head crossover trial (4 weeks per intervention) of transdermal fentanyl vs. long-acting oral morphine in patients with chronic pancreatitis was identified from the EPC's first update. One short-term (6 weeks) trial of controlled-release oxycodone (twice daily, average titrated dose 42 mg/day) compared to placebo in 159 patients with diabetic neuropathy was identified for update # 2.

A recent good-quality review found no trials evaluating the effectiveness of opioid rotation compared to other approaches such as dose escalation in patients with chronic non-cancer pain.[8] It found that evidence to support the practice of opioid-switching was largely anecdotal or based on observational, uncontrolled studies.

By consensus, the Standing Update Committee agrees that there is no comparative evidence that supports a difference between long-acting opioids in reducing pain and improving functional outcomes.

[6] Gilron I, Bailey JM, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. *NEJM* 2005;352(13):1324-1334.

[8] Quigley C. Opioid switching to improve pain relief and drug tolerability. *Cochrane Database of Systematic Reviews.* 2004(3):CD004847.

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?

Twelve studies compared long-acting opioids to non-opioids or placebo. All trials were rated as fair quality. One trial compared high strength with low strength Levorphanol and considered the low strength an active control.

Placebo controlled trials found superior efficacy for long-acting oxycodone (4 trials), long acting morphine (5 trials), long-acting codeine (2 trials), and methadone (l trial); but the trials were so heterogeneous that they could not identify any one agent as being superior in efficacy or lower in adverse reactions.

One short-term (6 weeks) placebo-controlled trial of sustained release oxycodone in patients with diabetic neuropathy was rated good quality and found benefit from oxycodone when compared to placebo.

By consensus, the Standing Update Committee finds that there is no evidence that any long-acting opioid has been shown to be superior in comparing long-acting opioids to other types of drugs.

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?

Seven fair quality trials directly compared long-acting and short-acting agents. There is no evidence to suggest that long-acting agents are superior to short-acting agents. A fair quality study found a significant difference in terms of sleep scores. The finding might be invalidated by baseline differences in the treatment groups.

By consensus the Standing Update Committee finds that long-acting opioids may improve sleep compared to short-acting opioids. There is no comparison study measuring sleep scores between different long-acting opioids.

2. WHAT IS 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?

Two trials comparing transdermal fentanyl to oral long-acting morphine found that withdrawal due to any adverse events was higher for transdermal fentanyl; however, rates of constipation were higher for oral long-acting morphine.[9],[10] No trials evaluate the effectiveness of opioid rotation for management of opioid-induced adverse events in patients with chronic non-cancer.

> ***The Standing Update Committee agrees by consensus that there was insufficient evidence to support a consistent difference between long-acting opioids for adverse effects including addiction and abuse.***

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?

In the 19 fair to poor quality trials, meaningful comparisons were difficult to make and no pattern for any drug could be established regarding adverse effects. Rates of abuse and addiction were not reported.

Two fair-quality retrospective studies that both used data from California Medicaid patients found that long-acting oxycodone was associated with higher risks of constipation than transdermal fentanyl. One of these studies also found that long-acting morphine and transdermal fentanyl were not associated with statistically significant differences in risk of constipation. However there were significant baseline differences in populations that make interpretation of these results difficult. Both of these studies focused on a single adverse outcome (constipation.) Such a narrow focus makes it impossible to assess the overall balance of adverse events.

One fair placebo-controlled trial of sustained release oxycodone in patients with diabetic neuropathy didn't provide additional comparative evidence about long acting opioids for adverse events. Another poor small (N=28) observational study on the

[9] Allan L, Richarz U, Simpson K et al. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naïve patients with chronic low back pain. *Spine* 2005;30:2484-2490.
[10] Allan L, Hays H, Jensen NH, et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. *British Medical Journal* 2001;322(7295):1154-1158

long-term (12 months) effects of sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain found that sustained release morphine was not associated with decrease in performance.

An observational study on methadone-related deaths in Hennepin County, Minnesota, reported that 15% of the 96 medical examiner investigated deaths were in chronic pain patients, and that one half of these died from overdose, although the clinical significance could not be determined because the numbers of prescriptions for methadone in the county, number of patients prescribed methadone, or information on other long-acting opioids were not provided.

A more recent case series of 104 methadone-treated patients on (median dose 110 mg/day) 44found that 32% had QTc prolongation as defined as > 430 msecs for males and 450 msecs for females (median 428 msec, 396-494), but none had prolongation beyond the value (500 msecs) considered a definite risk for *torsades de pointes*.[11]

The Oregon Health Services CD Summary[12], although not a peer reviewed journal, reported that the use of Methadone in Oregon had increased 5-fold from 1997-2001 with a concomitant 4-fold rise in Methadone caused deaths from 1999-2002. Approximately 1/3 of the patients were using Methadone for chronic pain, 1/3 for heroin addiction, and 1/3 were unknown. Polypharmacy may have contributed to the cause of death. The Oregon Drug Utilization Review (DUR) Newsletter[13] advised a conservative dosing schedule for methadone advising "start low and go slow."

The Substance Abuse and Mental Health Services Administration (SAMHSA) issued a report on methadone-associated mortality in 2004.[14] It concluded that observed increases in methadone-associated mortality in several states since the late 1990's appeared largely related to increased accessibility of methadone obtained outside of licensed opioid treatment programs. Methadone associated deaths were usually associated with other central nervous system depressant agents (such as benzodiazepines, alcohol, and other opioids). The report did not compare mortality rates for different long-acting opioids.

Updated data from the ongoing Drug Abuse Warning Network (DAWN) study suggest that emergency-room visit "mentions" for various opioids have all increased, yet there is no increased risk from specific opioids.

[11] Cruciani RA , Sekine R, Homel P, et al. Measurement of QTc in patients receiving chronic methadone therapy. *J Pain Symptom Manage.* Apr 2005;29(4):385-391.
[12] Methadone Deaths (and Distribution) on the Rise, CD Summary – An Epidemiology Publication of the Oregon Department of Human Services 52(14), July 15, 2003.
[13] Methadone Dosing and Conversion: Be Conservative, Oregon DUR Board Newsletter Volume 5, Issue 5, May 2003
[14] Center for Substance Abuse Treatment. *Methadone-associated mortality: report of a national assessment. SAMHSA Publication No. 04-3904*, May 8-9 2003.

The Standing Update Committee finds by consensus the evidence comparing long-acting opioids to each other does not document any long-acting opioid having fewer adverse effects, including abuse and addiction.

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?

The seven trials referenced in #1B reveal no pattern favoring long or short-acting opioids for any adverse events

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The Standing Update Committee agrees by consensus that there is no evidence to show that long-acting opioids have fewer adverse effects than short-acting opioids.

3. ARE THERE SUB-POPULATIONS (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 trials or observational studies were designed to evaluate opioids with respect to use in different races, ethnicity, age, or gender. One fair-quality observational study found that the risk of constipation was higher for long-acting oxycodone than transdermal fentanyl in patients older than 65 for all patients included in the study, but the validity of this ad hoc study comes into question because of the non-comparability at base-line of the population studied. The few trials evaluating types of chronic pain did not provide sufficient evidence to establish significant differences between long-acting opioids.

The Standing Update Committee agrees by consensus *that there is insufficient evidence to draw any conclusions about the comparative efficacy, incidence and nature of adverse effects including addiction and abuse of long- acting opioids by age or gender or by differing racial and ethnic populations.*

CONCLUSION

In a series of public meetings with the opportunity for public questions, comment and testimony, the Standing Update Committee of the Health Resources Commission reviewed the medical evidence comparing long-acting opioids for non–cancer pain. All available sources of information including OH&SU's Evidence-based Practice Center report, and additional information presented in public testimony were considered. Using all available sources of information, the update committee arrived at the following conclusions about the comparative effectiveness and safety of long-acting opioid analgesics as supported by analysis of the medical literature.

There is concern on the part of the Standing Update Committee that preliminary information on generic equivalency of fentanyl patches should be included in the next update. Also the Committee wishes to continue to monitor any morbidity or mortality attributable to switching from one long-acting opioid to another.

It is the decision of the Standing Update Committee that:

- ***There is insufficient evidence to draw any conclusions about the comparative efficacy of long-acting opioids.***
- ***There is insufficient evidence to draw conclusions about incidence and nature of adverse effects, including discontinuation rates and addiction and abuse of long-acting opioids***
- ***There is insufficient evidence to support differences in efficacy or adverse effects in sub-populations by race and ethnicity, age, gender, or type of pain in this class of drugs.***
- ***Even though evidence does not demonstrate a difference between long-acting opioids or between long-acting opioids when compared to other drugs, limitations of studies currently available for review preclude a confident conclusion that no differences exist. It is possible that better controlled studies may yet demonstrate such differences.***

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Health Resources Commission

The State of Oregon's Health Resources Commission is a volunteer Commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The Commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the Commission subject to approval by a majority of the Commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.