

# Drug Class Review on Long-Acting Opioid Analgesics

Update #6: Preliminary Scan Report #2

April 2010



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

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## OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

## Date of Last Update Report

April 2008 (searches through September 2007)

## Date of Last Preliminary Update Scan

July 2009

## Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Oregon Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative efficacy of different long-acting opioids in reducing pain and improving functional outcomes in adult patients being treated for chronic non-cancer pain?
  - a. In head-to-head comparisons, have one or more long-acting opioid been shown to be superior to other long-acting opioids in reducing pain and improving functional outcomes when used for treatment of adults with chronic non-cancer pain?
  - b. In trials comparing long-acting opioids to other types of drugs or to placebo, is there a pattern to suggest that one long-acting opioid is more effective than another?

- c. Have long-acting opioids been shown to be superior to short-acting opioids in reducing pain and improving functional outcomes when used for treatment of adults with chronic non-cancer pain?
2. What are the comparative incidence and nature of adverse effects (including addiction and abuse) of long-acting opioid medications in adult patients being treated for chronic non-cancer pain?
  - a. In head-to-head comparisons, have one or more long-acting opioid been shown to be associated with fewer adverse events compared to other long-acting opioids when used for treatment of adults with chronic non-cancer pain?
  - b. In trials comparing long-acting opioids to other types of drugs or to placebo, is there a pattern to suggest that one long-acting opioid is associated with fewer adverse events than another?
  - c. Have long-acting opioids been shown to have fewer adverse events than short-acting opioids when used for treatment of adults with chronic non-cancer pain?
3. Are there subpopulations of patients (specifically by race, age, sex, or type of pain) with chronic non-cancer pain for which one long-acting opioid is more effective or associated with fewer adverse effects?

## **Inclusion Criteria**

### Populations

Adult (greater than 18 years old) patients with chronic non-cancer pain. We defined chronic non-cancer pain as continuous or recurring pain of at least 6 months' duration. Cancer patients and patients with HIV were excluded from this review.

### Interventions

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

### Outcomes

The main efficacy measures were pain intensity, pain relief, and function. There is no single accepted standard regarding how to measure these outcomes.

### Study types

We included controlled clinical trials to evaluate efficacy. To evaluate adverse event rates, we included clinical trials and observational cohort studies designed to assess adverse events between different long-acting opioids.

## METHODS

### Literature Search

To identify relevant citations, we searched Ovid MEDLINE (June 2009 to March Week 4 2010) using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/Safety/MedWatch/SafetyInformation/default.htm>) and Health Canada (<http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php>) web sites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X1) and duplicate citations were removed.

### Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

## RESULTS

### Overview

Searches resulted in 244 citations. Of those, there are 3 new potentially relevant trials (see Appendix A). One (Wilsey) measured abuse potential of long- vs short-acting opioids, one (Gould) was a secondary analysis of a placebo-controlled trial of oxymorphone extended release in patients with low back pain, and one compared opioid therapy to conventional therapy without opioids in elderly women with osteoarthritis pain (Corsinovi).

Seven potentially relevant trials were identified in the previous preliminary update scan. These are summarized in Table 1.

**Table 1. Potentially relevant trials identified in previous update scan**

Author, year	Comparators	Condition
<b>Head to head (secondary analysis of a trial)</b>		
Kalso, 2007	Transdermal fentanyl vs. SR oral morphine	Low back pain
<b>Active control trials</b>		
Gatti, 2009	CR Oxycodone vs. Pregabalin	Neuropathic pain
Hale, 2007	ER Oxycodone vs. OROS Hydromorphone	Osteoarthritis pain

Lowenstein, 2009	Oxycodone PR vs Oxycodone PR/Naloxone	Improvement in constipation in patients with chronic pain
Simpson, 2008	Oxycodone PR vs Oxycodone PR/Naloxone	Improvement in constipation in patients with noncancer pain
<b>Placebo-controlled trial</b>		
Ma, 2008	CR Oxycodone vs placebo	Acute pain in chronic neck pain patients
<b>One group trial</b>		
Panjabi, 2008	ER Morphine	Chronic pain

## New Drugs

Embeda™ (Morphine sulfate and naltrexone hydrochloride) was FDA-approved in August 2009 for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. A literature search was conducted including terms for the new drug. Five citations were identified, but none met inclusion criteria.

The Embeda™ product label contains this boxed warning:

- EMBEDA capsules contain pellets of morphine sulfate, an opioid receptor agonist with a sequestered core of naltrexone hydrochloride, an opioid receptor antagonist, and is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.
- EMBEDA is to be swallowed whole or the contents of the capsules sprinkled on apple sauce. The pellets in the capsules are not to be crushed, dissolved, or chewed. Misuse or abuse of EMBEDA by tampering with the formulation, crushing or chewing the pellets, causes the rapid release and absorption of both morphine and naltrexone. The resulting morphine dose may be fatal, particularly in opioid-naïve individuals. In opioid-tolerant individuals, the absorption of naltrexone may increase the risk of precipitating withdrawal.
- EMBEDA is NOT intended for use as a prn analgesic.
- EMBEDA 100 mg/4mg capsules ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY
- Patients should not consume alcoholic beverages or use prescription or non-prescription medications containing alcohol while on EMBEDA therapy.

FDA's Risk Evaluation and Mitigation Strategy (REMS) for Embeda™ is attached in Appendix B.

## New Indications

No new indications for included drugs were identified.

## New Safety Alerts

February 10, 2009 — The US Food and Drug Administration (FDA) announced that it has contacted the manufacturers of opioid pain medications, including fentanyl,

morphine, and oxycodone, requiring them to have a risk evaluation and mitigation strategy (REMS) to ensure that the benefits of these drugs outweigh the risks. Updated information on the REMS is available at:

<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>

March 2010: Health Canada issued changes to the Dose Conversion Guidelines in the Dosage and Administration section of the Canadian Product Monographs for Fentanyl Transdermal System. The content of the guidelines is provided below:

The manufacturers of Fentanyl Transdermal Systems (FTS) in collaboration with Health Canada wish to provide you with important new information regarding changes to the Dose Conversion Guidelines (Table 1.1) in the Dosage and Administration section of the Canadian Product Monographs for Fentanyl Transdermal System.

- A 1:3 parenteral to oral morphine dose ratio replaces the previous 1:2 parenteral to oral morphine
- The conversion doses of IV/IM morphine to Fentanyl Transdermal Systems for the 75, 87 and 100 mcg/hour patch strengths were revised to 'not applicable' to reflect the insufficiency of data available for guidance.
- The revised Dose Conversion Guidelines are provided below for your information and should be retained for future use. Changes have been highlighted for ease of reference.

### Dosage Conversion Guidelines for Fentanyl Transdermal Systems

**Table 1.1 <sup>1</sup>: Dose Conversion Guidelines**

To be used to convert from current opioid analgesic to the Fentanyl Transdermal Systems (FTS)

Current Analgesic	Daily Dosage (mg/d)						
Oral morphine	60-134	135-179	180-224	225-269	270-314	315-359	360-404
<b>IM/IV morphine (based on a 1:3 IM/IV:PO ratio)</b>	<b>20-44</b>	<b>45-60</b>	<b>61-75</b>	<b>76-90</b>	<b>NA<sup>2</sup></b>	<b>NA<sup>2</sup></b>	<b>NA<sup>2</sup></b>
Oral oxycodone	30-66	67-90	91-112	113-134	135-157	158-179	180-202
Oral codeine	150-447	448-597	598-747	748-897	898-1047	1048-1197	1198-1347
Oral hydromorphone	8-16	17-22	23-28	29-33	34-39	40-45	46-51
IV hydromorphone <sup>3</sup>	4.0-8.4	8.5-11.4	11.5-14.4	14.5-16.5	16.6-19.5	19.6-22.5	22.6-25.5
	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓
<b>Recommended Fentanyl Transdermal System (FTS) Dose</b>	<b>25 mcg/h</b>	<b>37 mcg/h</b>	<b>50 mcg/h</b>	<b>62 mcg/h</b>	<b>75 mcg/h</b>	<b>87 mcg/h</b>	<b>100 mcg/h</b>

<sup>1</sup> **Table 1.1 should not be used to convert from DURAGESIC and other FTS to other therapies because this conversion to DURAGESIC and other FTS is conservative. Use of Table 1.1 for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible (see DOSAGE AND ADMINISTRATION, *Safe Use of Tables 1.1, and 1.2*).**

<sup>2</sup> NA (not applicable) reflects insufficient data available for guidance. If needed, prescribers should make these conversions very carefully and conservatively.

<sup>3</sup> The conversion ratio of parenteral hydromorphone to oral hydromorphone of 1:2 is based on clinical experience in patients with chronic pain. Reference: [Parenteral Drug Therapy Manual](#), Vancouver General Hospital, Pharmaceutical Sciences Clinical Services. 2006.

## APPENDIX A. Potentially Relevant New Trials (N= 3)

Corsinovi, L., E. Martinelli, et al. (2009). "Efficacy of oxycodone/acetaminophen and codeine/acetaminophen vs. conventional therapy in elderly women with persistent, moderate to severe osteoarthritis-related pain." Archives of Gerontology & Geriatrics **49**(3): 378-82.

We aimed to evaluate the efficacy and safety of oxycodone/acetaminophen (O/A) and codeine/acetaminophen (C/A) vs. conventional therapy (CT) without opioids in older women suffering from osteoarthritis (OA)-related pain, sub-optimally responsive to prior conventional treatments. We performed a 6 week, randomized, single blind, controlled study in three nursing homes. We enrolled 154 women with painful OA. They were assigned to treatment with O/A (n=52) and C/A (n=52) vs. CT (n=50). We evaluated at baseline and at week 6: average pain in the last week (mean pain, MeP), pain at rest (RP), pain in movement (MP) (numeric rating scale, NRS); depressive symptoms (Beck Depression Inventory-II, BDI-II); functional status (activities of daily living, ADL) and cognitive status (mini mental state evaluation, MMSE). We considered the adverse events (AEs) in the study period. At week 6, MeP, RP and MP were significantly reduced in all three groups ( $p < 0.001$ ); compared to CT, O/A and C/A were associated with greater reductions in MeP ( $p < 0.001$  and  $p = 0.004$ , respectively), in RP ( $p = 0.028$  and  $p = 0.032$ , respectively) in MP ( $p < 0.001$  and  $p = 0.002$ , respectively) and with significant improvement in BDI-II score ( $p = 0.05$  and  $p = 0.04$ , respectively) and ADL value ( $p = 0.04$  and  $p = 0.05$ , respectively). AE rates did not differ between groups.

Gould, E. M., M. P. Jensen, et al. (2009). "The pain quality response profile of oxymorphone extended release in the treatment of low back pain." Clinical Journal of Pain **25**(2): 116-22.

**OBJECTIVE:** In controlled trials of analgesics, the primary outcome variable is most often a measure of global pain intensity. However, because pain is associated with a variety of pain sensations, the effects of analgesic treatments on different sensations could go undetected if specific pain qualities are not assessed. This study sought to evaluate the utility of assessing the multiple components of non-neuropathic pain in an analgesic clinical trial. **METHODS:** A secondary analysis was performed using data from a clinical trial involving 140 individuals with low back pain who were converted from prestudy opioids to an equianalgesic dose of an extended release (ER) formulation of oxymorphone (OPANA ER), which was then titrated to a stable dose [defined as visual analog scale  $\leq 40$  mm (0 to 100 mm) on 3 of 5 consecutive days and requiring  $\leq 2$  doses rescue medication]. Stabilized participants were then randomly assigned to continue with either oxymorphone ER or placebo for 12 weeks. A multidimensional measure of pain quality, the Pain Quality Assessment Scale (PQAS), was administered before titration, after titration, and after treatment with oxymorphone ER or placebo. **RESULTS:** Significant pretitration to posttitration decreases were observed in 17 of the 20 PQAS pain descriptor items and all 3 PQAS scales. The largest effects of oxymorphone ER were found on the PQAS intense, unpleasant, deep, aching, and sharp items and the PQAS Paroxysmal and Deep scales. **DISCUSSION:** The results indicate that

oxymorphone ER has different effects on different pain qualities of low back pain. The responsiveness of the PQAS items and scales to the results of treatment with an effective and generally well-tolerated dose of an analgesic, and the ability of the PQAS items and scales to discriminate between an active analgesic and placebo, support their validity as outcome measures. The findings support the utility of using pain descriptor measures for (1) identifying the effects of pain treatments on different pain qualities and (2) targeting pain treatments to those patients who experience certain types of pain.

Wilsey, B. L., S. Fishman, et al. (2009). "Markers of abuse liability of short- vs long-acting opioids in chronic pain patients: a randomized cross-over trial." Pharmacology, Biochemistry & Behavior **94**(1): 98-107.

**BACKGROUND:** Abuse liability is thought to possibly be lower in long- than in short-acting opioids because lower peak serum levels may be less likely to induce psychoactive effects. **METHODS:** We compared patient responses to extended-release morphine, hydrocodone plus acetaminophen, and placebo in a randomized, double-blind crossover study using markers of abuse liability. Patients indicated their craving for drugs on 5 visual analog scales (VASs), completed the Addiction Research Center Inventory, and underwent cue reactivity testing. To perform the latter, subjects watched a video intended to produce a positive or a negative affect, after which a vial of medication was or was not presented (the cue) and then indicated their craving for drugs on 5 different VASs (the reactivity). **RESULTS:** Differences in Addiction Research Inventory scores were statistically significant but clinically unimportant. Neuropsychological test results were mixed and unrelated to the medications studied. Cue reactivity did not differ among conditions but was uniformly high. **CONCLUSIONS:** Using several markers of abuse liability, long-acting opioids do not have lower abuse potential than do short-acting opioids or placebo. Although cue reactivity did not differ among the conditions, uniformly high results in these patients suggest that it may have some value as a component of abuse liability testing.

## Appendix B. Risk Evaluation and Mitigation Strategy for Embeda™

### NDA 22-321 EMBEDA™ (morphine sulfate and naltrexone HCl) Extended-Release Capsules

#### RISK EVALUATION AND MITIGATION STRATEGY (REMS)

#### I. GOALS

- a. To inform patients and providers about the potential for abuse, misuse, overdose, and addiction of EMBEDA™.
- b. To inform patients and providers about the safe use of EMBEDA™.

#### II. REMS ELEMENTS

##### A. Medication Guide

In compliance with 21 CFR 208.24, the following measures will be instituted:

- A Medication Guide (see Section 1.14.1 of the NDA) will be dispensed with each EMBEDA™ prescription.
- Medication Guides will be included in the primary and secondary packaging of the commercial product.
- Two (2) Medication Guides will be included as an insert within each bottle of EMBEDA™.
- Additional Medication Guides (24) will be provided with each carton containing 12 bottles of EMBEDA™, partial cases will include two additional Medication Guides per bottle.
- The Medication Guide also will be available on the company website or through our toll-free medical information line.

##### B. Communication Plan

A communication plan will be implemented to healthcare providers and relevant institutions to support the implementation of this REMS:

1. Letters will be sent to the following audiences:
  - Physicians (pain specialists and primary care physicians)
  - Pharmacists
  - Information to medical associations
  - Information to pharmacy associations
  - Information to state medical and pharmacy boards

These communications will emphasize the key safety messages for EMBEDA™ and highlight the risks and the associated goals of the REMS. The Dear Healthcare Professional letter will include instructions to discuss the risks of EMBEDA™ with their patients and encourage them to read the Medication Guide. The Dear Pharmacist letter will include instructions to provide the Medication Guide with each prescription.