Drug Use Research & Management Program
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Month/Year of Review: March 2014
PDL Classes: Long-Acting Opioid Analgesics

Date of Last Review: September 2013
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: FENTANYL ER TRANSDERMAL FILM (DURAGESIC®), MORPHINE SULFATE ER (MS CONTIN®)
- Non-preferred Agents: BUPRENORPHINE ER TRANSDERMAL FILM (BUTRANS®), HYDROMORPHONE ER (EXALGO®), LEVORPHANOL, METHADONE, MORPHINE SULFATE ER (AVINZA®, KADIAN®), MORPHINE SULFATE/NALTRESONE ER (EMBEDA®), OXYCODONE ER (OXYCONTIN®), OXYMORPHINE ER (OPANA ER®), TAPENTADOL ER (NUCYNTA®), TRAMDOL ER (ULTRAM ER®, CONZIP®)

Previous Conclusions Recommendations:

- There continues to be insufficient comparative evidence to establish differences in effectiveness among LAOs. Morphine and fentanyl have the most evidence of efficacy against placebo. Treatment guidelines consistently recommend morphine as first-line with fentanyl patches recommended for patients who cannot tolerate oral medications.
- There continues to be insufficient comparative evidence to establish differences in safety among the LAOs. All carry FDA Black Box warnings for increased risk of death and risk of abuse and misuse. However, methadone alone carries the warning of accumulation and was associated with more than 30% of opioid related deaths in Oregon.
- There is insufficient comparative evidence in subpopulations to differentiate drugs.
- Remove methadone from preferred status due to safety concerns.
- A form of morphine ER should remain a preferred option.
- There is insufficient evidence to establish difference in effectiveness or safety of tramadol ER versus the other LAOs.

PA Criteria: There is a maximum dose prior authorization (PA) required for doses greater than 120 morphine equivalent doses (MED) on all LAOs. Duplication of LAOs is not allowed except for cross-titration. Methadone carries an additional PA for initial doses above 20 mg per day when prescribed for pain. Methadone for addiction treatment is covered via professional claims (Appendix 1).

Research Questions:

- Is there any new comparative evidence on LOA's
- Is there any new comparative safety data of LOA's
- Are there subpopulations of patients for which one medication or formulation is more effective or associated with fewer adverse effects?

Methods:

The DERP Scan was used to identify any new comparative research that has emerged since the last P&T review.[1]

Conclusions and Recommendations:

- There is insufficient comparative evidence to establish differences in effectiveness of hydrocodone ER (Zohydro® ER) versus the other LAOs.
- There is insufficient comparative evidence to establish differences in safety of hydrocodone ER versus other LAOs.
- There is insufficient comparative evidence in subpopulations to differentiate hydrocodone ER from the other LAOs.
- Maintain hydrocodone ER as non-preferred and evaluate comparative costs in executive session.

New Formulations:

Hydrocodone bitartrate ER oral capsule (Zohydro® ER) was FDA approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in October 2013.[1] Because of the risks of addiction, abuse, and misuse, and the extended-release formulation, it should be reserved for use in patients for whom alternative treatment options (non-opioids or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate.[2] Hydrocodone ER is a Schedule II controlled substance and the first FDA-approved single-entity (not combined with an analgesic such as acetaminophen) and extended-release hydrocodone product. It will be part of the ER/LA Opioid analgesics Risk Evaluation and Mitigation Strategy (REMS).

The efficacy of hydrocodone ER is based on one randomized, double-blind, placebo-controlled unpublished study of patients with chronic low back pain (n=302).[3] Subjects were eligible if they had moderate to severe chronic low back pain present for at least several hours a day for a minimum of 3 months, required around-the-clock opioid therapy, were taking opioids for at least 5 days/week for the past 4 weeks at the equivalent of at least an average daily dose of 45 mg oral morphine equivalents per day, and had an average clinic pain score of 4 or greater on the numerical rating scale. Subjects with a history of illicit substance or alcohol abuse in the past 5 years or history of opioid abuse were excluded. The primary efficacy endpoint was change from baseline in average pain intensity on the 11-point scale as recorded in an electronic diary compared to placebo. There was high attrition through the study; although the primary efficacy analysis was done in the intention to treat population. The change from baseline in average daily pain score was 0.48 in the hydrocodone group and 0.96 in the placebo group (p=0.008). The specific results for the secondary endpoints were not provided in the FDA review document.[3] This study remains unpublished and cannot be adequately assessed for quality and risk of bias.

Discontinuations due to adverse events occurred in about 10% of patients in both groups in the titration phase, with the most common adverse events being nausea, somnolence, constipation, vomiting, and headache.[3] They occurred in 6.4% of patients during the treatment phase and 10.6% in the placebo group. The most common adverse events were consistent with the opioid class of drugs and include constipation, nausea, somnolence, fatigue, headache, and dizziness.

References:

1. Thakurta S. Drug Effectiveness Review Project. Drug Class Review: Long-acting Opioid Analgescis. Preliminary Scan Report 2. December 2013.
2. Zohydro ER prescribing information. Zogenix, Inc. October 2013
3. Food and Drug Administration. Center for Drug Evaluation and Research. Summary Review: Application Number: 202880Orig1s000. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202880Orig1s000SumR.pdf

Appendix 1: Prior Authorization Criteria

Opioid Analgesics – High Dose

Goal(s):

- Limit the use of high dose opioid therapy to above-the-line diagnoses that are supported by the medical literature
- Limit the use of non-preferred products
- Promote the safe use of opioids.
  - Opioids have been associated with an increasing proportion of deaths in Oregon and the US.
  - Opioid deaths in Oregon are often associated with concurrent use of other drugs (e.g. other opioids, benzodiazepines, skeletal muscle relaxants)
  - Opioid deaths in Oregon are often associated with patients with a history of drug abuse.
  - Buprenorphine, Fentanyl and Methadone carry FDA Black Box Warnings and have been associated with adverse cardiac effects associated with QTc prolongation and/or life-threatening hypoventilation.
    - This risk is increased with concurrent use of other drugs prolonging the QTc interval or other drugs affecting metabolism of methadone or fentanyl.
  - See Oregon DUR Board newsletter at:
    - http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/newsletter/articles/volume11/durv11i2.pdf
    - http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/newsletter/articles/volume5/durv5i5.pdf

Initiative:

Long and Short Acting Opioid quantity and dose limits: preferred agents, approved indications, and dose limits.

Length of Authorization:

Up to 6 months

Covered Alternatives:

A list of preferred opioids is available at www.orpdl.org

Requires a PA:

- All non-preferred opioids and preferred opioids exceeding the dose threshold in the table below, not to exceed a Morphine Equivalent Dose (MED) of 120mg per day.
- Patient with terminal diagnosis, hospice, and metastatic neoplasm (ICD9 = 190xx – 199xx) are exempt from the PA requirements.

-Approved Prior Authorizations may be subject to quantity limits

Dosing Threshold adapted from Washington State Agency Medical Directors Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain 2010 (www.agencymeddirectors.wa.gov)

Opioid	Dose threshold	Recommended starting dose for opioid-naïve patients	Considerations
Buprenorphine Transdermal	20mcg/hour (q 7 days)	5mcg/hr patch q 7 days	May increase dose q72 hours patients up to a max of 20mcg/hr q 7 days. Doses >20mcg/hr q7days increase risk of QTc prolongation.
Fentanyl Transdermal	50mcg/hour (q 72 hr)	Use only in opioid-tolerant patients who have been taking ≥ 60mg MED daily for a week or longer	
Hydromorphone	30mg per 24 hours	2mg q 4–6 hours	
Methadone	40mg per 24 hours	2.5-5mg BID – TID	Methadone is difficult to titrate due to its half-life variability. It may take a long time to reach a stable level in the body. Methadone dose should not be increased more frequently than every 7 days. Do not use as PRN or combine with other long-acting (LA) opioids.

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Morphine	120mg per 24 hours	Immediate-release: 10mg q 4 hours Sustained-release: 15mg q 12 hours	Adjust dose for renal impairment.
Oxycodone	80mg per 24 hours	Immediate-release: 5mg q 4–6 hours Sustained Release: 10mg q 12 hours	See individual product labeling for maximum dosing of combination products. Avoid concurrent use of any OTC products containing acetaminophen (maximum dose = 4000mg/day x <10day or 2500mg/day for 10 days or more)
Oxymorphone	40mg per 24 hours	Immediate-release: 5–10mg q 4–6 hours Sustained Release: 10mg q 12 hours	**Use with extreme caution due to potential fatal interaction with alcohol or medications containing alcohol**.

Dosing Threshold for select short acting opioids		
Opioid	**Dose threshold**	**Considerations**
Codeine	800mg/day	
Hydrocodone	120mg/day	Dosing limits based on combinations (e.g. acetaminophen, ibuprofen) may lower the maximum daily dose

Common indications OHP does not cover:*	**ICD9 Codes**
Disorders of soft tissue (including Fibromyalgia)	*729.0-729.2, 729.31-729.39, 729.4-729.9, V53.02*
Acute and chronic disorders of spine without one of the following neurologic impairments: a. Reflex loss b. Dermatomal muscle weakness c. Dermatomal sensory loss d. EMG or NCV evidence of nerve root impingement e. Cauda equina syndrome f. Neurogenic bowel or bladder See Prioritized List of Health Services Guideline Notes 37 and 41	*721-724, except 723.3 739, 839.2, 847*

*Covered diagnoses are dependent on funding levels. A list of currently funded diagnoses can be found at http://www.oregon.gov/OHA/OHPR/HSC/current_prior.shtml

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD9	
2. Is the request for methadone >100mg?	Yes: Go to 3	No: Go to 5

3. Does the patient have any of the following QTc Risk Factors? • Family history of "long QTc syndrome", syncope, sudden death • Potassium depletion primary or secondary to drug use (i.e. diuretics) • Concurrent use of C34 inhibitors or QTc prolonging drugs (see table below) • Structural heart disease, arrhythmias, syncope	Yes: Go to 4	No: Go to 5
4. Is this new therapy (i.e. no previous prescription for the same drug last month)?	Yes: Pass to RPH; Deny, (Medical Appropriateness) Go over black box warning and offer alternatives (e.g. Fentanyl transdermal, morphine extended release).	No: Pass to RPH, Approve for 30-60 days to allow time to taper or transition to alternative. Direct to DUR Newsletter for assistance. Refer to Rx "Lock-in" Program for evaluation and monitoring.
5. Is the patient being treated for any of the following: a. Oncology pain (ICD-9 338.3) b. Terminal diagnosis (<6 months) c. Hospice care	**Yes**: Go to #6	**No**: Go to #8
6. Is the requested medication a preferred agent?	**Yes:** Approve for up to 6 months	**No**: Go to #7
7. Will the prescriber consider a change to a preferred product?	**Yes**: Inform provider of covered alternatives in class.	**No**: Approve for up to 6 months
8. Will the prescriber consider a change to a preferred product not to exceed 120mg MED?	**Yes**: Inform provider of covered alternatives in class.	**No:** Go to #9
9. Is the diagnosis covered by the OHP?	**Yes**: Go to #10	**No:** Pass to RPh, Deny (Not Covered by the OHP) May approve for 30-60 days to allow for tapering
10. Is this new therapy (i.e. no previous prescription for the same drug, same dose last month)?	**Yes**: Go to #11	**No**: Go To #12
11. Does the total daily opioid dose exceed 120mg MED?	**Yes: Pass to RPh, Deny** (Medical Appropriateness) In general, the total dose of opioid should not exceed 120mg MED Risks substantially increase at doses at or above 100mg MED. Alternatives: Preferred NSAIDs or LAOs @ doses < 120mg MED.	**No**: Go to #12

12. Has the patient had a recent urinary drug screen (within the past 90 days)?	**Yes**: Go to #13	No: Pass to RPH: Deny (Medical Appropriateness) Recommend Urine Drug Screen
13. Is the patient seeing a single prescribing practice & pharmacy for pain treatment (short and long acting opioids)?	**Yes**: Go To #14	**No:** Approve 30-90 days; Refer to Rx Lock-In program for evaluation. Further approvals pending RetroDUR / Medical Director review of case.
14. Does the total daily opioid dose exceed 120mg MED?	**Yes**: Go to #15	**No:** Go to #16
15. Can the prescriber provide documentation of sustained improvement in both function and pain AND is prescriber is aware of additional risk factors (e.g. concurrent benzodiazepines, skeletal muscle relaxants, other LAO or history of drug abuse)?	**Yes: Approve up to 6 months.** **Quantity Limits Apply, e.g.:** Avinza: 1 dose / day Butrans: 1 patch / week Embeda: 2 doses / day Exalgo: 1 dose / day Fentanyl: 1 patch / 72 hours Kadian: 2 doses / day Opana XR: 2 doses / day Oxycodone ER: 2 doses / day	**No:** Approve 30-90 days to allow for potential tapering of dose. Refer to Rx Lock-In program for evaluation. Further approvals pending RetroDUR / Medical Director review of case.
16. Is the patient concurrently on other long-acting opioids (e.g. fentanyl patches, methadone, or long-acting morphine, long-acting oxycodone, and long-acting oxymorphone)?	**Yes**: Go to #17	**No**: Approve for up to 6 months
17. Is the duplication due to tapering or switching products? The concurrent use of multiple long-acting opioids is not recommended unless tapering and switching products. Consider a higher daily dose of a single long-acting opioid combined with an immediate release product for breakthrough pain.	**Yes**: Approve for 30-90 days at which time duplication LAO therapy will no longer be approved.	**No: Deny** (Medical Appropriateness) **May approve for taper only.** Refer to Rx Lock-In program for evaluation. If necessary, inform prescriber of provider reconsideration process.

P&T or DUR Board Action: *2/23/12 (TDW), 11/17/11(KK); 12/3/09 (KS), 9/9/09(klk), 12/4/08klk, 3/19/09*
Revision(s): *6/21/12, 5/14/12; 1/1/12; 1/1/10*
Initiated: *7/1/09*