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# Class Update: Long-acting Opioids

**Date of Review:** May 2016 **Date of Last Review:** March 2015

**Current Status of PDL Class:**
See **Appendix 1**.

**Purpose for Class Update:**
To evaluate current policies on long-acting opioids (LAOs) that are consistent with recent high-quality systematic reviews and updated clinical practice guidelines.

**Research Questions:**
1. What is the comparative efficacy or effectiveness of different LAOs in reducing pain and improving functional outcomes in adult patients being treated for chronic non-cancer pain?
2. What are the comparative harms (including addiction and abuse) of different LAOs in adult patients being treated for chronic non-cancer pain? Do harms differ between drugs with and without abuse-deterrent mechanisms or between drugs with different abuse-deterrent mechanisms?
3. Are there subpopulations of patients (specifically by race, age, sex, socio-economic status, type of pain, or comorbidities) with chronic non-cancer pain for which one LAO is more effective or associated with fewer harms?

**Conclusions:**
- Since the LAOs were last reviewed, there have been 2 high-quality systematic reviews and 2 clinical practice guidelines published.
- The Washington State Agency Medical Directors Group (AMDG), whose recommendations have previously informed opioid-related prior authorization (PA) criteria for the Oregon Health Plan (OHP) fee-for-service (FFS) population, have recently updated their guidelines.[1] The group recommends frequent utilization of prescription drug monitoring programs (PDMP), random urine analyses, and patient-directed goals for patients chronic LAOs.[1] The group continues to recommend against daily opioid doses of 120 mg morphine milligram equivalents (MME) or greater unless evaluated by a pain specialist and provided with a prescription for naloxone.[1] The group continues to reinforce that there are insufficient data to support long-term prescribing of LAOs in chronic noncancer pain.[1] The LAOs should be avoided in patients with comorbid mental health disorders, patients with family history or personal history of substance abuse disorder, or patients on benzodiazepines or sedative hypnotics.[1]
- The Centers for Disease Control and Prevention (CDC) have recently published guidelines for opioid use.[2] Overall, the CDC's recommendations are similar to the AMDG except the CDC recommends against prescribing daily opioid doses that exceed 90 mg MME and prescribing naloxone for any patient who receives a prescription for an opioid that exceeds 50 mg per day MME.[2] The CDC recognizes that daily opioid doses that exceed 100 mg MME do not offer

additional analgesia but patients at these doses are 9-times more likely to overdose compared to doses of 20 mg per day MME.[2] Doses between 50 and 100 mg per day MME are 2.2 to 4.6-times higher risk of overdose compared to doses less than 20 mg per day MME.[2]

- The Drug Effectiveness Review Project (DERP) at Oregon Health & Science University (OHSU) deemed that there is still insufficient evidence of efficacy and effectiveness in terms of improvement in pain, functional improvement, and quality of life to support the use of one LAO over another.[3]
- Comparative evidence of harms between LAOs, including outcomes related to addiction and abuse potential, continue to be insufficient.[3]
- There is insufficient comparative evidence to determine if there are differences in effectiveness or harms between LAOs for different subpopulations based on socio-economic status, type of pain or associated comorbidities.[3]

**Recommendations:**

- No changes to the Oregon Health Plan (OHP) Preferred Drug List (PDL) are recommended based on clinical evidence alone. After review of comparative drug costs in the executive session no changes to the current PDL were made.
- Modify current clinical prior authorization (PA) criteria for high dose opioids to include all opioids and opioid-combination products (see **Appendix 4**). Primary changes include a maximum MME of 90 mg per day without a naloxone prescription, and prescriber utilization of the Oregon Prescription Drug Monitoring Program (PDMP) and assessment of pain and functional status at least every 3 months. Patients currently on doses that exceed 90 mg per day MME will be given 12 months to taper the dose to 90 mg per day MME or less.
- Discontinue PAs for methadone, opioid/non-opioid fixed dose combination products, and short-acting fentanyl products. These drugs will be incorporated into the one aforementioned PA. The U.S. Food and Drug Administration (FDA) already requires a Risk Evaluation and Mitigation Strategy (REMS) program to be in place for all short-acting fentanyl products. All prescribers, patients and pharmacies must be enrolled in the program to closely monitor for safety, misuse and abuse of the products.
- Continue current codeine PA to restrict use in pediatric patients.

**Previous Conclusions:**

- There is low quality evidence that long term use of opioid therapy was associated with increased risk of abuse, overdose, fracture, myocardial infarction and markers of sexual dysfunction. There is insufficient evidence to evaluate benefits and harms of long-term opioid therapy in high risk patients or other subgroups.
- There is low quality evidence of no clinically meaningful change in pain with hydrocodone ER compared to placebo, as rated on an 11-point pain-intensity numeric rating scale (difference in mean change from baseline -0.53; 95% CI -0.88 to -0.18, p= 0.0016).
- There is low quality evidence of no clinically meaningful change in pain with oxycodone/naloxone ER compared to placebo, as rated on an 11-point pain intensity numeric rating scale (4.2 versus 3.7; 95% CI 0.1 to 0.8; p= 0.006).
- There is low quality evidence of no clinically meaningful change in pain with morphine/naltrexone ER compared to placebo, as rated on the Brief Pain Inventory scale (-0.2 vs 0.3; p= 0.0455).
- There is insufficient evidence to establish differences in effectiveness of hydrocodone ER, oxycodone/naloxone ER, or morphine/naltrexone ER versus other LAOs.
- There is insufficient evidence to establish differences in safety of hydrocodone ER, oxycodone/naloxone ER, or morphine/naltrexone ER versus other LAOs.
- There is insufficient comparative evidence in subpopulations to differentiate hydrocodone ER, oxycodone/naloxone ER, or morphine/naltrexone ER from other LAOs.
- There is insufficient evidence to determine whether an abuse-deterrent formulation of any LAO decreases the abuse or misuse of these drugs.

**Previous Recommendations:**

- Maintain hydrocodone ER, oxycodone/naloxone ER, and morphine/naltrexone ER as non-preferred.
- No changes made to the PDL after comparing costs of other LAOs in the executive session.

**Background:**

The use of prescription opioids for the treatment of chronic pain, defined as pain lasting longer than 3 months or past the time of normal tissue healing, is a growing epidemic in the United States. Opioid and non-opioid analgesics have been developed and marketed to improve pain, function and quality of life in patients who suffer from chronic pain. It is estimated that 20% of patients presenting with noncancer pain symptoms receive an opioid prescription, despite limited evidence supporting long-term benefits of opioid therapy.[5] The prevalence of opioid use disorder and opioid-related hospitalizations and deaths have increased significantly in recent years. A 2012-2013 survey estimated that 212,000 Oregonians were using prescription pain relievers for non-medicinal purposes.[6] It is estimated that 1 in 5 patients on chronic opioid analgesic therapy will develop opioid use disorder as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V).[1] In Oregon, hospitalizations due to opioids have increased 285% from 2.6 per 100,000 in 2000 to 10.0 per 100,000 in 2013 and unintentional opioid-related overdose remains one of the leading causes of injury mortality in the state.[6,7] A 2013 Oregon Health Authority (OHA) report found that of the 423 unintentional deaths due to poisoning, 38% were associated with prescription opioids.[6] A study in U.S. Veterans found that patients prescribed LAOs were 2.5-times more likely to experience an unintentional overdose than those prescribed short-acting opioids (SAOs).[8] Opioid use has become a major public health concern at national and state levels. Recently, the CDC has acknowledged the risks associated with opioid use and provided guidance for use of opioid analgesics for chronic noncancer pain.

New guidance places heavy emphasis on the use non-pharmacologic and non-opioid therapy prior to the initiation of opioid analgesics, which reflects the limited evidence of benefits with prolonged opioid use and the well identified risks associated with continued opioid use. In an effort to reduce risks associated with opioid use, supportive measures have been added to guidance documents such as patient directed therapy management goals, utilization of prescription drug monitoring databases, and prescribing of naloxone for high opioid dosages.

**Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

**New Systematic Reviews:**

Long-Acting Opioid Analgesics: An OHSU Drug Effectiveness Review Project (DERP)

The DERP updated a systematic review of LAO analgesics in September 2015.[3] The purpose of the review was to compare the effectiveness and harms between LAOs and between LAOs and SAOs in adults with chronic noncancer pain.[3] Twenty-five head-to-head studies evaluating LAO use for chronic noncancer pain were identified. Eighteen of the 25 trials directly compared a LAO to another LAO. For the purpose of this review, evidence from 7 RCTs and 1 observational study published since the last DERP review will be discussed in detail. With the exception of 1 small RCT, patients at high risk for drug or substance abuse were excluded from trials, thus limiting the evidence of harms in terms of addiction and abuse potential. All studies were eligible for inclusion, regardless of sample size or study duration. The review rated the strength of evidence (high, moderate, low, and insufficient) based on 4 key domains: risk of bias (including study design and aggregate quality), consistency, directness, and precision of the evidence.[3]

There were two 12-week studies with moderate-strength evidence that demonstrated tapentadol ER 100 to 250 mg twice daily had a greater likelihood of reducing pain than patients taking oxycodone CR 20 to 50 mg twice daily in patients with osteoarthritis of the knee.[3] In one study, more patients on tapentadol ER were likely to experience a 30% or greater improvement in pain intensity (43.0% compared to placebo) than those on oxycodone CR (24.9% compared to placebo)( RR of 1.73, 95% CI 1.39 to 2.16).[3] Similarly, more patients on tapentadol ER were likely to obtain 50% or greater improvement in pain intensity (32.0% compared to placebo) than those on oxycodone CR (17.3% compared to placebo) (RR 1.85, 95% CI 1.40 to 2.45).[3] A similarly designed study in patients with low back pain produced low-quality evidence that tapentadol ER was found to have no benefit over oxycodone CR in pain relief.[3] The other trial included patients with low back pain and hip and knee osteoarthritis but had poor quality design.[3] The study found no statistical difference in pain reduction on an 11-point pain numeric rating scale (NRS).[3] Pooled safety analyses of these trials produced moderate-strength evidence favoring the use of tapentadol ER over oxycodone CR.[3] Lower study withdrawal rates due to adverse effects were seen in the tapentadol ER group (20% vs. 39%, RR 0.52, 95% CI 0.47 to 0.59).[3] Of the adverse events reported, gastrointestinal (GI) events were observed less frequently with tapentadol ER vs oxycodone CR (47% vs. 65%, respectively; RR 0.73, 95% CI 0.68 to 0.78).[3] The greatest difference in adverse effects seen was with vomiting (8% for tapentadol ER vs. 20% for oxycodone CR; RR 0.39, 95% CI 0.32 to 0.48), followed by nausea (20% for tapentadol ER vs. 36% for oxycodone CR; RR 0.55, 95% CI 0.49 to 0.62) and constipation (20% for tapentadol ER vs 34% for oxycodone CR; RR 0.58, 95% CI 0.51 to 0.65).[3] Somnolence and dizziness was also reported less frequently in the tapentadol ER group.[3]

The other 3 trials published since the last review did not find conclusive evidence to support the use of one LAO over another.[3] One poor quality study found no difference in pain relief with transdermal buprenorphine compared to transdermal fentanyl at 3, 6, and 12 months.[3] Fifty percent of patients on buprenorphine experienced a 3-point reduction on an 11-point visual analogue scale (VAS) at 3 months compared to 43% in the fentanyl arm.[3] No safety data was reported in this trial.[3] Low-strength evidence from one 20-week trial found no differences in effectiveness or harms between patients with back, arthritic, and neuropathic pain treated with hydromorphone Osmotic Release Oral System (OROS) 8 mg to 32 mg once daily and oxycodone sustained release (SR) 10 mg to 40 mg twice daily ($p$=0.348).[3] The third trial was the only trial to include patients with opioid use disorder but was poor quality due to dissimilar baseline characteristics and high-level attrition.[3] The trial found no differences on an 11-point pain relief scale between buprenorphine 4-16 mg plus naloxone 1-4 mg daily (87.4% pain reduction from baseline) and methadone 10 to 60 mg daily (88.6 % pain reduction from baseline).[3] In addition, there were no significant differences in safety and abuse outcomes.[3]

A retrospective cohort study of U.S. Veterans (n = 108,492) treated with methadone or LA morphine for back, joint, or limb pain provided low-strength evidence for lower mortality risk with methadone use.[3] The average daily dose of morphine LA was 67.5 mg and the average daily dose of methadone was 25.4 mg.[3] The highest risk of death was during the first 30 days of drug exposure (1.2% in the methadone cohort and 3.7% in the morphine LA cohort).[3] It should be noted that most patients on methadone were younger with fewer medical comorbidities, but had more psychiatric comorbidities than the morphine cohort.[3]

In efficacy and effectiveness analyses, tapentadol ER showed favorable outcomes in pain reduction.[3] However, no studies found evidence of superiority for one LAO over another in terms of functional improvement or quality of life.[3] From the last DERP report, there are no clear or consistent differences in harms between LA oxycodone and LA oxymorphone, morphine ER and LA oxycodone, ER (once-daily) and SR (twice-daily) formulations of morphine, hydromorphone ER and LA oxycodone, or morphine/naltrexone and morphine ER.[3] Head-to-head evidence for other comparisons (race, age, sex, socio-economic status type of pain, or comorbidities) of LAOs was low-strength or insufficient, primarily due to few trials of any one comparison, small sample sizes and methodological shortcomings of included studies.[3]

Tapentadol for Chronic Musculoskeletal Pain in Adults

A Cochrane systematic review was preformed to determine the efficacy, safety, and tolerability of tapentadol ER use in moderate-to-severe chronic musculoskeletal pain.[4] Thirty-seven articles (7 studies) were identified. Five reports (3 studies) were excluded due to trial design. Four moderate quality parallel-designed RCTs met inclusion criteria.[4] All 4 trials compared FDA approved tapendadol ER at doses of 100 to 500 mg daily to oxycodone CR, and 3 of the 4 trials additionally included placebo arms.[4] Two separate meta-analyses were performed for each control; however for the purpose of the class update, the outcomes of the oxycodone CR comparison arm will be discussed. Limitations of this meta-analysis include modest differences between interventions in efficacy outcomes between trials, high heterogeneity within comparisons and outcomes, large participation withdrawal rates, and the use of last-observation-carried-forward due to lack of data access.[4]

All 4 trials reported data on change in pain intensity from baseline.[4] Tapentadol ER demonstrated modest and perhaps clinically insignificant pain reduction and when compared to oxycodone CR.[4] On an 11-point NRS, tapentadol ER reduced pain by 0.24 points from baseline when compared to oxycodone CR (95% CI, -0.43 to -0.05) and a 0.56 point reduction when compared to placebo (95% CI, -0.92 to -0.20).[4] However, 2 of the 4 trials analyzed patients meeting at least 50% pain relief and found no significant difference between tapentadol ER and oxycodone CR (29.6% vs. 20.2%, respectively; RR 1.46; 95% CI, 0.92 to 2.32).[4]

Quality of life outcomes were assessed in 2 trials using standardized EuroQol-5 Dimension (EQ-5D) and the Western Ontario and McMaster Universities (WOMAC) scoring systems. The EQ-5D addresses 5 domains (mobility, self-care, usual activity, pain/discomfort, and anxiety or depression) on a scale of 0 to 1.[9] Tapentadol ER was associated with a higher increase in EQ-5D index (mean change 0.2, least squares mean difference (LSMD) vs. placebo, 0.05; 95% CI, 0.02 to 0.09) when compared to oxycodone CR (mean change 0.1, LSMD vs. placebo, -0.01; 95% CI, -0.05 to 0.02) (mean difference (MD) 0.1; 95% CI, 0.07 to 0.13).[4] It is unclear what a clinically meaningful difference would be. WOMAC is a standardized questionnaire comprised of 24 questions evaluating pain, physical function, and stiffness in osteoarthritis patients. It was unclear which WOMAC scale was used or what value would detect a clinically meaningful difference in pain. However, the 2 trials found no difference in the pain subscale (MD -0.03; 95% CI, -0.23 to 0.17) between tapentadol ER (LSMD vs. placebo -0.27; 95% CI, -0.422 to -0.126) and oxycodone CR (LSMD vs. placebo -1.05; 95% CI, -0.338 to 0.000).[4]

Tapentadol ER was associated with less incidence of discontinuation of therapy due to adverse event (20%) when compared to oxycodone CR (38%) (NNH 6; 95% CI, 5 to 7 for 12 weeks).[4] However, patients on tapentadol ER were more likely to withdrawal from the study early due to lack of efficacy (RR 2.23; 95% CI, 1.45 to 3.42) and loss to follow-up (RR 1.73, 95% CI 1.04 to 2.89).[4] Actual withdrawal rates for each comparison were not provided. In adverse event outcome analyses, tapentadol ER was also associated with a lower risk of constipation and dizziness, but was associated with higher risk of dry mouth.[4] The clinical significance of these findings is not well defined due to study limitations. The review concluded that there is insufficient evidence to support tapentadol ER use in moderate-to-severe chronic musculoskeletal pain.[4]

**New Guidelines:**

Centers for Disease Control and Prevention: Guideline for Prescribing Opioids for Chronic Pain[2]

The CDC published new guideline recommendations for the use of opioids in the treatment of chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The CDC Advisory Committee has adopted the guideline evidence grading from the CDC Advisory Committee for Immunization Practices (ACIP) Grading of Recommendation Assessments, Development and Evaluation (GRADE) recommendations based on quality of evidence and applicability. Recommendations are based on a graded hierarchy of 4 types of evidence ranging from very confident to little confidence in the effect estimate (see **Table 1**). These recommendations are additionally categorized into applicability to patient population (Category A: applies to all patients and Category B: individual decision-making should apply).

Non-pharmacologic and non-opioid analgesic therapies are preferred for the management of chronic pain. **Table 2** summarizes specific recommendations from the CDC for opioid selection, dosage, duration, follow-up and discontinuation with supporting evidence. Lastly, **Table 3** summarizes the CDC recommendations for assessment of risk and harms with opioid use with supporting evidence.

**Table 1**. **Evidence Grade Recommendations**.[2]

| Evidence Grade | Body of Evidence | Implication |
|---|---|---|
| Type 1 evidence | RCTs or overwhelming evidence from observational studies | Indicates that once can be very confident that the true effect lies close to that of the estimate of the effect |
| Type 2 evidence | RCTs with important limitations, or exceptionally strong evidence from observational studies | True effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different |
| Type 3 evidence | Observational studies or RCTs with notable limitations | Confidence in the effect estimate is limited and the true effect might be substantially different from the estimate of the effect |
| Type 4 evidence | Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations | Indicates that one has very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of the effect |

**Table 2. Current CDC Recommendations for Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation.**[2]

| Recommendation | Supporting Evidence |
|---|---|
| Reserve LAO therapy for patients with severe chronic pain who have received SAO daily for at least 1 week.<br>Avoid the use of SAO in combination with LAO.<br><br>(Recommendation category: A, evidence type: 4) | Continuous, regularly-scheduled use of LAO has not demonstrated superiority in efficacy or safety when compared to SAO.<br>In the setting of LAO use in chronic pain management outside of active cancer pain, palliative care, or end-of-life care, there is insufficient safety data to support the use of SAO for breakthrough pain (expert opinion). |
| Prescribers should use caution when increasing dose of LAO ≥ 50 MME/day and should generally avoid doses ≥ 90 MME/day.<br><br>(Recommendation category: A, evidence type: 3) | One RCT showed 52 MME/day provided no further pain or functional benefit than 40 MME/day.<br>Doses of 50-99 MME/day were associated with increased risk of overdose by 1.9 to 4.6-fold when compared to doses of 1-19 MME/day; doses ≥100 MME/day were associated with 2.0-8.9-fold risk than doses of 1-19 MME/day. |
| Prescribers should evaluate benefits and harms of opioids within 1 to 4 weeks of initiation or dose escalation of opioid therapy. Follow-up should occur at least every 3 months for continuous therapy. If benefits do not outweigh harms, prescribers should work to reduce opioid dose and discontinue the opioid.<br><br>Note: shorter intervals (within 3 days) of follow up are recommended after methadone is initiated.<br><br>(Recommendation category: A, evidence type: 4) | Patients who do not experience pain relief with an opioid at 1 month are unlikely to experience pain relief with opioids at 6 months.<br>There is no evidence to support more frequent monitoring of effectiveness in chronic opioid therapy. However, there is a strong correlation between continuation of opioids past 3 months and opioid use disorder. |

Abbreviations: LAO = long-acting opioids; MME = morphine milligram equivalents; SAO = short-acting opioids

**Table 3. Current CDC Recommendations for Assessing Risk and Addressing Harms of Opioid Use.**[2]

| Recommendation | Supporting Evidence |
|---|---|
| Consider prescribing naloxone when high risk factors for opioid overdose are present (e.g., history of overdose, substance abuse disorder, or opioid dose ≥ 50 MME, concurrent use of benzodiazepines, etc.)<br><br>**(Recommendation category: A, evidence type: 4)** | Expert opinion. |
| Review PDMP data when starting opioid therapy and, at a minimum, every 3 months during opioid therapy.<br><br>(Recommendation category: A, evidence type: 4) | To date, the effectiveness of PDMP monitoring has not been studied. However, evidence suggests patients who receive opioid prescriptions from multiple providers or patients who receive high doses of an opioid are at higher risk for death due to opioid overdose. |
| Conduct a urine drug screen before the initiation of opioid therapy and at least annually throughout therapy.<br><br>(Recommendation category: B, evidence type: 4). | Expert opinion. Concurrent use of an opioid with other opioid or respiratory depressants (i.e., benzodiazepines) can increase risk for overdose. Urine drug screens can identify unreported medication use and can identify patients who may not take their opioids as prescribed, which may indicate diversion or difficulties with adverse effects. |
| Avoid prescribing opioids to patients receiving benzodiazepines whenever possible.<br><br>(Recommendation category: A, evidence type: 3). | Concurrent use of benzodiazepines and opioids are associated with increased risk of respiratory depression and death when compared to opioids alone. |
| Avoid methadone as first-line therapy for chronic pain.<br><br>(Recommendation not graded) | Variable and unpredictable pharmacokinetics increase risk of harm. |
| Use caution in prescribing transdermal fentanyl.<br>Prescribers of transdermal fentanyl must be familiar with the dosing titration and its absorption properties and be prepared to educate their patients about these risks.<br><br>(Recommendation not graded) | Both prescribers and patients often misunderstand the effects of dose titration or taper, which may lead to increased risk of harm. |

Abbreviations: LAO = long-acting opioids; MME = morphine milligram equivalents; PDMP = prescription drug monitoring program; SAO = short-acting opioids

Washington State Agency Medical Directors Group: Interagency Guideline on Prescribing Opioids for Pain[1]

The AMDG consists of state academic leaders, pain experts, and clinicians in Washington state that practice in primary care and specialty settings. The AMDG updated their 2010 guidelines in June 2015, which had focused on the safe and effective management of chronic non-cancer pain. The updated guideline was expanded to include: 1) opioid use in acute, subacute, and perioperative pain phases to prevent inappropriate chronic opioid analgesic therapy when other alternatives for treating pain may be equally effective and safer in the long-term; 2) opioid use in special populations (during pregnancy and neonatal abstinence syndrome, in children and adolescents, in older adults, and in cancer survivors); 3) tapering and opioid use disorder; and 4) opioid use disorder.

The AMDG evaluated recent systematic reviews that examined the effectiveness of opioids for chronic pain and found insufficient data to support broad prescribing of LAOs with only modest effectiveness and minimal functional improvement. Due to the lack of evidence to support chronic use of LAOs, the guideline primarily focused on strategies and recommendations to limit use of LOAs for chronic non-cancer pain (see **Table 4**).

**Table 4. 2015 AMDG Recommendations.**[1]

| Recommendation | Supporting Evidence |
|---|---|
| Use extreme caution in prescribing LAOs in patients with comorbid mental health disorders; family or personal history of substance abuse disorder; concurrent use of benzodiazepines, sedative-hypnotics, or barbiturates; or medical health conditions that can increase sensitivity to opioid related side effects. | The lifetime prevalence of DSM-V prescription opioid abuse disorder is 21% in patients who receive LAOs.<br>There are increased and dose-dependent risks of opioid overdose and serious fractures with concurrent use of benzodiazepines, sedatives, or barbiturates. |
| Prescribe opioids in multiples of 7-day supply. | Reduce the incidence of the supply ending on a weekend. |
| Initiate proper bowel regimen when a LAO is prescribed. | Constipation is one of the most common side effects of opioid use. |
| Screen for risk of opioid misuse with validated tools (i.e., Opioid Risk Tool, SOAPP-R, DIRE, CAGE-AID) | Expert opinion. |
| Utilize state PDMP when prescribing opioids.<br><br>Low Risk — Monitor ≥ once annually<br>Moderate Risk — Monitor ≥ 2 times per year<br>High Risk or opioid doses >120 mg MME/day — Monitor ≥ 3-4 times per year | Expert opinion. |
| Perform random urine drug tests. | Expert opinion. Frequency should be determined by patients risk category, with similar frequency to PDMP recommendations. |
| Consult a pain management specialist for opioid doses >120 mg MME/day. If opioid doses must exceed 120 mg MME/day, consider prescribing naloxone. | Opioid doses that exceed 100 mg/day MME do not offer additional analgesia but are 9-times more likely to overdose compared to doses of 20 mg/day MME. Doses between 50 and 100 mg/day MME are 2.2 to 4.6-times higher risk of overdose compared to doses < 20 mg/day MME. |
| Avoid prescribing methadone unless necessary. | Methadone has been associated with increased risk of cardiac and respiratory deaths due to numerous drug-drug interactions, unpredictable pharmacokinetics, and risk of accumulation. |
| High risk patients on LAO therapy should be seen in person at least monthly to assess and address aberrant behavior. | Expert opinion. |
| Screen for depression and for anxiety using validated tools. If comorbid mental health conditions exist in the presence of pain, they need to be treated or the patient's pain will not improve regardless of opioid therapy. | Expert opinion. |
| Consider tapering off LAO if patient has been maintained on opioid therapy for ≥ 3 months and there is no sustained clinical meaningful improvement in function. | Expert opinion. Validation tools for screening and assessment are available through the guidelines. |

Abbreviations: DSM-V = The Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition; LAO = long-acting opioid; MME = morphine milligram equivalents; PDMP = prescription drug monitoring program.

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**New Safety Alerts:**
Tramadol: Drug Safety Communication – FDA Evaluating Risks of Using in Children Aged 17 and Younger (September 21, 2015)[10]

Ultra-rapid metabolizers are more likely to have higher-than-normal levels of active O-desmethyltramadol, placing these patients at higher risk respiratory depression. A recent case-report reported a 5-year-old with respiratory depression after taking a single dose of tramadol oral solution following tonsillectomy. On follow-up the child was found to be an ultra-rapid metabolizer and had high levels of active opioid. Currently tramadol is not FDA-approved for use in children despite its off-label use in recent studies. The current FDA recommendation is to consider prescribing alternative FDA-approved pain medicines in children.[10]

**New Formulations or Indications:**
Belbuca™ (buprenorphine) film
Buprenorphine buccal film was approved by the FDA in October 2015 for the treatment of severe chronic pain.[11] Buccal film formulations are available in 75, 150, 300, 450, 600, 750, and 900 mcg strips and recommended to be taken once daily or every 12 hours.[11] Buprenorphine film is not recommended for patients on MME doses exceeding 160 mg daily.[11] Three 12-week trials have been completed.[11] Only 2 of the 3 trials demonstrated statistically significant pain reduction on an 11-point NRS in patients with low back pain when compared to placebo.[11]

An open-label study enrolled 749 patients with chronic low back pain.[11] Over 8 weeks, buprenorphine film doses were titrated to 150 mcg every 12 hours and patients were able to continue to increase the dose in 150 mcg dose increments every 4-8 days for up to 6 weeks.[11] Patients who achieved pain relief were then randomized to continue at that dose or matched placebo.[11] Patients on buprenorphine film were more likely to have at least a '30% reduction in pain' score than those on placebo (62% and 47%, respectively).[11] Similarly, more patients on buprenorphine film were likely to have at least a '50% reduction in pain' score from baseline versus placebo (41% and 33%, respectively).[11] Twelve percent of patients on buprenorphine film discontinued therapy early due to either an adverse event (8%) or lack of therapeutic effect (4%).[11] In contrast, early discontinuation rates in the placebo group were 4% due to an adverse event and 11% due to lack of therapeutic effectiveness.[11] No statistical analyses of the data were found.

Another 12-week open-label trial enrolled 810 patients on chronic opioid therapy (30-160 MME mg/day) for chronic pain.[11] Patients previously on 30 to 89 MME mg daily were initiated on 150 mcg buprenorphine film every 12 hours while patients taking 90-160 MME mg daily were initiated on 300 mcg buprenorphine film every 12 hours.[11] Patients were eligible to increase the dose by 150 mcg every 12 hours after 4 days for up to 6 weeks.[11] A higher proportion of buprenorphine film patients (64%) had at least a '30% reduction in pain' score compared to placebo (31%), while 39% of buprenorphine film patients had at least a '50% reduction in pain' score from baseline compared to placebo (17%).[11] Ten percent of patients on buprenorphine film discontinued prematurely due to an adverse event (2%) or lack of therapeutic effect (8%) compared to 30% of patients on placebo who discontinued early, primarily due to lack of efficacy (25%) and adverse events (5%).[11]

MorphaBond™ (morphine sulfate extended-release) tablets

A new morphine sulfate ER tablet formulation (MorphaBond™) with 'abuse-deterrent' properties was approved by FDA in October 2015 for the management of chronic pain.[12] The recommended dosing schedule is every 12 hours.[12] There are no published clinical trials available.

Xartemis XR™ (oxycodone/acetaminophen (APAP) extended-release) tablets

A new oxycodone/APAP XR tablet formulation (Xartemis XR™) with intended abuse-deterrent properties was approved by the FDA in March 2015 for the management of acute pain severe enough to require opioid treatment for which alternative treatment options are inadequate.[13] Tablets are available as a single strength 7.5/325 mg formulation.[13] The recommended dosing is 2 tablets every 12 hours.[13] The FDA reviewed data that showed a reduction in pain intensity over a 48-hour period when compared to placebo in acute post-operative patients.[13] However, results of this trail have not been published.

**Randomized Controlled Trials:**

A total of 6 citations were manually reviewed from the literature search. After further review, 4 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 2 trials are briefly described in **Table 5**. Full abstracts are included in **Appendix 2**.

**Table 5**. **Description of Randomized Comparative Clinical Trials**.

| Study | Comparison | Population | Primary Outcome | Results |
|---|---|---|---|---|
| Leng, et al.[14]<br>MC, DB, AC, DD, NI, RCT<br><br>NCT01476774 | 1. Transdermal buprenorphine (5, 10, and 20 mcg/hour, maximum dose of 20 mcg/hour)<br>2. Tramadol SR (100 mg, maximum dosage of 400 mg/day) | Adults ≥18 years of age with moderate to severe musculoskeletal pain ≥4 weeks | Difference in VAS pain scores from baseline to treatment completion | Transdermal buprenorphine is non-inferior to tramadol SR. VAS scores decreased -3.30 ± 2.29 vs. -3.75 ± 2.15 (FAS) and -3.86 ± 2.0 vs. -4.28 ± 1.86 (PP) from baseline. Least squares mean difference was 0.45 (95% CI -0.02 to 0.91), which was within the ± 1.5 predefined threshold. |
| Verthein, et al.[15]<br>MC, OL, CO, R<br><br>NCT01079117 | 1. Slow-release oral morphine<br>2. Methadone<br>Flexible dose regimens were used | Opioid dependent adults ≥18 years of age | Self-reported mental symptoms, rated according to the SCL-27 | Slow-release oral morphine was associated with less overall severity of mental symptoms (ARR of 0.07, p = <0.01). |

Abbreviations: AC = active-controlled; ARR = absolute risk reduction; CO = crossover study; DB = double blind; DD = double-dummy; FAS = full analysis set; MC = multicenter; NI = non-inferiority; OL = open-label; PP = per protocol set; R = randomized; RCT = randomized clinical trial; SCL-27 = symptom checklist (instrument used to measure depressive, vegetative, and agoraphobic symptoms); SR = sustained-release; VAS = visual analog scale (10 cm horizontal line anchored with word descriptors at each end; 0 cm = no pain and 10 cm = pain as bad as it could possibly be)

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**Appendix 1:** Current Status on Preferred Drug List

| Route | Formulation | Brand | Generic | PDL |
|---|---|---|---|---|
| ORAL | TABLET ER | MORPHINE SULFATE ER | MORPHINE SULFATE | Y |
| ORAL | TABLET ER | MS CONTIN | MORPHINE SULFATE | Y |
| TRANSDERM | PATCH TD72 | DURAGESIC | FENTANYL | Y |
| TRANSDERM | PATCH TD72 | FENTANYL | FENTANYL | Y |
| ORAL | CAP ER PEL | KADIAN | MORPHINE SULFATE | N |
| ORAL | CAP ER PEL | MORPHINE SULFATE ER | MORPHINE SULFATE | N |
| ORAL | CAP ER PO | EMBEDA | MORPHINE SULFATE/NALTREXONE | N |
| ORAL | CPBP 17-83 | TRAMADOL HCL ER | TRAMADOL HCL | N |
| ORAL | CPBP 25-75 | TRAMADOL HCL ER | TRAMADOL HCL | N |
| ORAL | CPMP 24HR | MORPHINE SULFATE ER | MORPHINE SULFATE | N |
| ORAL | ORAL CONC | METHADONE HCL | METHADONE HCL | N |
| ORAL | ORAL CONC | METHADONE INTENSOL | METHADONE HCL | N |
| ORAL | ORAL CONC | METHADOSE | METHADONE HCL | N |
| ORAL | SOLUTION | METHADONE HCL | METHADONE HCL | N |
| ORAL | TAB ER 12H | NUCYNTA ER | TAPENTADOL HCL | N |
| ORAL | TAB ER 12H | OPANA ER | OXYMORPHONE HCL | N |
| ORAL | TAB ER 12H | OXYCODONE HCL ER | OXYCODONE HCL | N |
| ORAL | TAB ER 12H | OXYCONTIN | OXYCODONE HCL | N |
| ORAL | TAB ER 12H | OXYMORPHONE HCL ER | OXYMORPHONE HCL | N |
| ORAL | TAB ER 24H | EXALGO | HYDROMORPHONE HCL | N |
| ORAL | TAB ER 24H | HYDROMORPHONE ER | HYDROMORPHONE HCL | N |
| ORAL | TAB ER 24H | HYSINGLA ER | HYDROCODONE BITARTRATE | N |
| ORAL | TAB ER 24H | TRAMADOL HCL ER | TRAMADOL HCL | N |
| ORAL | TAB ER 24H | ULTRAM ER | TRAMADOL HCL | N |
| ORAL | TAB IR ERO | XARTEMIS XR | OXYCODONE HCL/ACETAMINOPHEN | N |
| ORAL | TABLET | DOLOPHINE HCL | METHADONE HCL | N |
| ORAL | TABLET | LEVORPHANOL TARTRATE | LEVORPHANOL TARTRATE | N |
| ORAL | TABLET | METHADONE HCL | METHADONE HCL | N |
| ORAL | TABLET SOL | DISKETS | METHADONE HCL | N |
| ORAL | TABLET SOL | METHADONE HCL | METHADONE HCL | N |
| ORAL | TABLET SOL | METHADOSE | METHADONE HCL | N |
| ORAL | TBMP 24HR | TRAMADOL HCL ER | TRAMADOL HCL | N |
| TRANSDERM | PATCH TD72 | FENTANYL | FENTANYL | N |
| TRANSDERM | PATCH TDWK | BUTRANS | BUPRENORPHINE | N |

**Appendix 2:** Abstracts of Clinical Trials

**Effectiveness and Safety of Transdermal Buprenorphine Versus Sustained-release Tramadol in Patients With Moderate to Severe Musculoskeletal Pain: An 8-Week, Randomized, Double-Blind, Double-Dummy, Multicenter, Active-controlled, Noninferiority Study**[14]

*Objectives*: The aim of this noninferiority study was to investigate clinical effectiveness and safety of buprenorphine transdermal system (BTDS) in patients with moderate to severe musculoskeletal pain inadequately controlled with nonsteroidal anti-inflammatory drugs, compared with sustained-release tramadol tablets. *Materials and Methods*: Eligible patients were randomized (1:1) to receive low-dose 7-day BTDS (5, 10, and 20 µg/h, maximum dosage of 20 µg/h) or sustained-release tramadol tablets (100 mg, maximum dosage of 400 mg/d) over an 8-week double-blind treatment period (3-week titration, 5-week maintenance). The primary endpoint was the difference in the VAS pain scores from baseline to treatment completion. Noninferiority was assumed if the treatment difference on the VAS scale was within ±1.5 cm, this threshold indicating a clinically meaningful result. *Results*: Two hundred eighty patients were randomized to BTDS (n=141) or to tramadol (n=139). Both treatments were associated with a significant reduction in pain by the end of the treatment. The least squares mean difference of the change from baseline in VAS scores between the BTDS and tramadol groups were 0.45 (95% CI, -0.02 to 0.91), which was within the ±1.5 cm predefined threshold, indicating that the effectiveness of BTDS was not inferior to the effectiveness of sustained-release tramadol tablets. The incidence of adverse events was comparable between the 2 treatment groups. *Conclusions*: Our results suggest that BTDS is a good therapeutic option for patients experiencing chronic musculoskeletal pain of moderate to severe intensity that is insufficiently controlled by nonsteroidal anti-inflammatory drugs.

**Mental Symptoms and Drug Use in Maintenance Treatment with Slow-Release Oral Morphine Compared to Methadone: Results of a Randomized Crossover Study**[15]

*Background:* Opioid maintenance treatment is the option of choice to stabilize opioid-dependent patients. Whilst efficacy of methadone and buprenorphine has been studied extensively, fewer data on slow-release oral morphine are available. *Aims:* This study analyzes the effects of slow-release oral morphine compared to methadone with regard to self-reported mental symptoms, drug use and satisfaction with treatment. *Methods:* The study was carried out as an open-label randomized crossover trial in 14 treatment sites in Switzerland and Germany. It comprised 2 crossover periods of 11 weeks each. For measuring mental symptoms, the Symptom Checklist-27 (SCL-27) was used. Drug and alcohol use was assessed by the number of consumption days, and treatment satisfaction by a visual analogue scale. *Results:* A total of 157 patients were included for the analyses (per-protocol sample). Statistically significantly better outcomes for morphine as compared to methadone treatment were found for overall severity of mental symptoms (SCL-27 Global Severity Index), as well as 5 of the 6 syndrome groups of the SCL-27, and for treatment satisfaction. There were no statistically significant differences with regard to drug or alcohol use between groups. *Conclusions:* This study supports positive effects of slow-release oral morphine compared to methadone on patient-reported outcomes such as mental symptoms and treatment satisfaction with comparable effects on concomitant drug use. Slow-release oral morphine represents a meaningful alternative to methadone for treatment of opioid dependence.

**Appendix 3:** Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 10, 2014
1 exp Morphine 35325
2 exp Fentanyl 13833
3 exp Tramadol 2415
4 exp Methadone 10875
5 tapentadol.mp. 227
6 exp Oxymorphone 451
7 exp Oxycodone 1555
8 exp Hydromorphone 1075
9 exp Hydrocodone 432
10 exp Levorphanol 599
11 exp Buprenorphine 4007
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 64623
13 exp Transdermal Patch 639
14 exp Administration, Topical 72672
15 long acting.mp. 19562
16 sustained release.mp. 10864
17 13 or 14 or 15 or 16 102603
18 2 and 17 1028
19 1 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 18 53472
20 limit 19 to yr="2015-Current" 733
21 limit 20 to (English language and humans) 520
22 limit 21 to (clinical conference or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)

# Opioid Analgesics

**Goals:**

- Restrict use of opioid analgesics to OHP-funded conditions with documented sustained improvement in pain and function and with routine monitoring for opioid misuse and abuse.
- Promote the safe use of opioid analgesics by restricting use of high doses that have not demonstrated improved benefit and are associated with greater risk for accidental opioid overdose and death.
- Limit the use of non-preferred opioid analgesic products.

**Length of Authorization:**

**3 to 12 months** (criteria-specific)

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

**Requires a PA:**

- All non-preferred opioids and opioid combination products.
- Any opioid listed in Table 1 or opioid combination product that contains an opioid listed in Table 1 that exceeds 90 morphine milligram equivalents (MME) per day.
- Any opioid product listed in Table 2 that exceeds quantity limits.

Note:

- Preferred opioid products that do not exceed 90 MME per day are exempt from this PA.
- Patients on palliative care with a terminal diagnosis or with cancer-related pain (ICD10 C6900-C799; C800-C802) are exempt from this PA.
- This PA does not apply to pediatric use of codeine products, which is subject to separate clinical PA criteria.

**Table 1. Daily Dose Threshold (90 MME/day) of Opioid Products.**

| Opioid | Dose Threshold (90 MME/day) | Recommended starting dose for opioid-naïve patients | Considerations |
|---|---|---|---|
| Note: Any opioid exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing an opioid and monitor all patients regularly for the development of these behaviors or conditions. | | | |

| Opioid | Dose Threshold (90 MME/day) | Recommended starting dose for opioid-naïve patients | Considerations |
|---|---|---|---|
| **Codeine** | 600 mg/24 hours | 30 mg q 4-6 hours | Codeine is a prodrug of morphine. Metabolism and conversion to morphine is subject so multiple polymorphisms in different populations. Subsequently, persons may be hypersensitive to the analgesic and respiratory effects of codeine or may be resistant to the effects of codeine. Dosing limits based on combinations (e.g., acetaminophen) may further limit the maximum daily dose. |
| **Fentanyl (transdermal patch)** | 37.5 mcg/hour (q 72 hr) | 12.5 mcg/hour q 72 hours | Use only in opioid-tolerant patients who have been taking ≥60 MME daily for a ≥1 week. Deaths due to a fatal overdose of fentanyl have occurred when pets, children and adults were accidentally exposed to fentanyl transdermal patch. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure. |
| **Hydrocodone** | 90 mg/24 hours | IR:<br>5-10 mg q 4-6 hours<br>ER:<br>10 mg q 12 hours | Dosing limits based on combinations (e.g., acetaminophen) may further limit the maximum daily dose.<br>Use the ER formulation with extreme caution due to potentially fatal interaction with alcohol or medications containing alcohol. Accidental consumption of even 1 dose of the ER formulation, especially by children, can result in a fatal overdose. |
| **Hydromorphone** | 22.5 mg/24 hours | IR:<br>2 mg q 4–6 hours<br>ER<br>8 mg q 24 hours | Hydromorphone is a potent opioid. Accidental ingestion of even one dose of hydromorphone ER, especially by children, can result in a fatal overdose of hydromorphone. |
| **Methadone** | 20 mg/24 hours | 2.5-5 mg BID or TID | Methadone is a very effective and inexpensive opioid but should be reserved to prescribers very familiar with the complex pharmacokinetic and pharmacodynamics variability of this drug. Methadone exhibits a non-linear relationship due to its long half-life and accumulates with chronic dosing. Methadone also has complex interactions with several other drugs. The dose should not be increased more frequently than once every 7 days. |
| **Morphine** | 90 mg/24 hours | IR<br>10 mg q 4 hours<br>ER<br>15 mg q 12 hours | Co-ingestion of alcohol with morphine ER may result in increased plasma levels and a potentially fatal overdose of morphine. Accidental ingestion of even one dose of morphine, especially by children, can result in a fatal overdose of morphine. |

| | | | |
|---|---|---|---|
| **Oxycodone** | 60 mg/24 hours | IR:<br>5 mg q 4-6 hours<br><br>ER:<br>10 mg q12 hours | Accidental ingestion of even one dose of oxycodone ER, especially by children, can result in a fatal overdose of oxycodone. The concomitant use of oxycodone ER with all cytochrome P450 (CYP-450) 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used CYP3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving oxycodone ER and any CYP3A4 inhibitor or inducer.<br>Avoid concurrent use of any products containing acetaminophen (maximum combined APAP dose = 4000 mg/day for <10 days or 2500 mg/day for ≥10 days) |
| **Oxymorphone** | 30 mg/24 hours | IR:<br>5–10 mg q 4-6 hours<br><br>ER:<br>10 mg q 12 hours | Accidental ingestion of even 1 dose of oxymorphone ER, especially by children, can result in a fatal overdose of oxymorphone.<br>Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products that contain alcohol while taking oxymorphone ER. Co-ingestion of alcohol with oxymorphone ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone. |
| **Tapentadol** | 225 mg/24 hours | IR:<br>50 mg q 4-6 hours<br><br>ER:<br>50 mg q 12 hours | Accidental ingestion of even one dose of tapentadol ER, especially by children, can result in a fatal overdose of tapentadol.<br>Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products that contain alcohol while taking tapentadol ER. Co-ingestion of alcohol with tapentadol ER may result in increased plasma tapentadol levels and a potentially fatal overdose of tapentadol.<br>Tramadol also possesses SSRI-like properties and interacts with multiple drugs. Use with caution with other drugs that may increase risk of serotonin syndrome or decrease seizure threshold. |
| **Tramadol** | 400 mg/24 hours (IR)<br><br>300 mg/24 hours (ER) | IR:<br>50 mg q 4-6 hours<br><br>ER:<br>100 mg per 24 hours | The threshold is based on maximum daily dosing for the IR and ER formulations. The threshold is not equivalent to 90 MME per day.<br>Tramadol also possesses SSRI-like properties and interacts with multiple drugs. Use with caution with other drugs that may increase risk of serotonin syndrome or decrease seizure threshold. |

Abbreviations: ER = extended-release or sustained-release formulation(s); IR = immediate-release formulation(s); MME = morphine milligram equivalent.

## Table 2. Specific Opioid Products Subject to Quantity Limits per FDA-approved Labeling.

| Drug Product | Quantity Limit |
|---|---|
| AVINZA | 1 dose/day |
| BELBUCA | 1 dose/day |
| BUTRANS | 1 patch/7 days |
| EMBEDA | 2 doses/day |
| EXALGO | 1 dose/day |
| Fentanyl patch | 1 dose/72 hrs |

| Drug Product | Quantity Limit |
|---|---|
| HYSINGLA ER | 2 doses/day |
| KADIAN | 2 doses/day |
| MORPHABOND | 2 doses/day |
| NUCYNTA ER | 2 doses/day |
| OPANA ER | 2 doses/day |
| OXYCONTIN | 2 doses/day |
| XARTEMIS XR | 4 doses/day |

| Drug Product | Quantity Limit |
|---|---|
| XTAMPZA ER | 2 doses/day |
| ZOHYDRO ER | 2 doses/day |
| | |
| | |
| | |
| | |
| | |

| Approval Criteria | | |
|---|---|---|
| 1. What is the patient's diagnosis? | Record ICD10 | |
| 2. Is the request for renewal of current therapy? | **Yes:** Go to **Renewal Criteria** | **No:** Go to #3 |
| 3. Is the patient being treated for cancer-related pain (ICD10 G89.3) or under palliative care services (ICD10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying? | **Yes:** Go to #4 | **No:** Go to #6 |
| 4. Is the requested medication a preferred agent? | **Yes:** Approve for up to 12 months | **No:** Go to #5 |
| 5. Will the prescriber change to a preferred product?<br><br>Note:<br>Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy. Both oral and transdermal options are available. | **Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months. | **No:** Approve for up to 12 months |
| 6. Is the diagnosis funded by the OHP? | **Yes:** Go to #7 | **No:** Pass to RPh. Go to #15 |
| 7. Is the opioid prescription for pain associated with a back or spine condition or for migraine headache? | **Yes:** Pass to RPh. Go to #15 | **No:** Go to #8 |
| 8. Will the prescriber change to a preferred product, not to exceed 90 MME per day and not to exceed quantity limits in Table 2?<br><br>Note:<br>Preferred products that do not exceed 90 MME per day and do not exceed quantity limits in Table 2 do not require prior authorization. | **Yes:** Inform prescriber of covered alternatives in class. | **No:** Go to #9 |
| 9. Does the total daily opioid dose exceed 90 MME? | **Yes:** Pass to RPh. Go to #15 | **No:** Go to #10 |

| | | |
|---|---|---|
| 10. Is the patient concurrently on other short- or long-acting opioids (patients are permitted to be on only one opioid product total at a time)? | **Yes:** Pass to RPh. Go to #15 | **No:** Go to #11 |
| 11. Does the prescription exceed quantity limits applied in Table 2 (if applicable)? | **Yes:** Pass to RPh. Go to #15 | **No:** Go to #12 |
| 12. Can the prescriber provide documentation of sustained improvement of both pain and function in the past 3 months compared to baseline (e.g., validated tools to assess function include: Oswestry, Neck Disability Index, SF-MPQ, and MSPQ)? | **Yes:** Go to #13 | **No:** Pass to RPh. Go to #15 |
| 13. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (PDMP) and has the prescriber verified at least once in the past 3 months that the patient has been prescribed analgesics by only a single prescribing practice or prescriber and has received those analgesics by only a single pharmacy? | **Yes:** Go to #14 | **No:** Pass to RPh. Go to #15 |
| 14. Has the patient had a urinary drug screen (UDS) within the past 1 year to verify absence of illicit drugs and non-prescribed opioids? | **Yes:** Approve for up to 3 months. Subsequent approvals will require:<br>• Verification of patient's opioid claims history in the Oregon PDMP at least every 3 months<br>• Documentation of sustained improvement in both baseline pain and function at least every 3 months<br>• Documented UDS at least every 12 months | **No:** Pass to RPh. Go to #15 |

| | | |
|---|---|---|
| 15. Is the request to initiate new opioid therapy or to increase the total daily MME dose? | **Yes:** Pass to RPh. Deny; medical appropriateness. | **No:** Pass to RPh. Approve for 3 months.<br><br>Note:<br>Documentation of progress towards meeting all criteria in this PA will be required for approval of subsequent claims. All future opioid claims are subject to **Renewal Criteria** 3 months from this index claim. |

| **Renewal Criteria** | | |
|---|---|---|
| 1. Has the patient had a urinary drug screen (UDS) within the past 1 year to verify absence of illicit drugs and non-prescribed opioids? | **Yes:** Go to #2 | **No:** Pass to RPh. Deny; medical appropriateness |
| 2. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (PDMP) and has the prescriber verified at least once in the past 3 months that the patient has been prescribed analgesics by only a single prescribing practice or prescriber and has received those analgesics by only a single pharmacy? | **Yes:** Go to #3 | **No:** Pass to RPh. Deny; medical appropriateness |
| 3. Can the prescriber provide documentation of sustained improvement of both pain and function in the past 3 months compared to baseline? | **Yes:** Go to #4 | **No:** Pass to RPh. Deny; medical appropriateness |

| Renewal Criteria | | |
|---|---|---|
| 4. Does the prescription exceed quantity limits applied in Table 2 (if applicable)? | **Yes:** Approve for up to 3 months if there is documentation of an individualized taper plan with progress to meet the quantity limits applied in Table 2. | **No:** Go to #5 if not applicable.<br><br>Without documentation, pass to RPh. Deny; medical appropriateness. |
| 5. Is the patient concurrently on other short- or long-acting opioids (patients are permitted to be on only one opioid product total at a time)? | **Yes:** Approve for up to 3 months if there is documentation of an individualized taper plan with progress to be managed on one short- or long-acting opioid only. | **No:** Go to #6 if not applicable.<br><br>Without documentation, pass to RPh. Deny; medical appropriateness. |
| 6. Does the total daily opioid dose exceed 90 MME? | **Yes:** Approve for up to 3 months if there is documentation of an individualized taper plan with progress toward meeting ≤90 MME per day. | **No:** Go to #7 if not applicable.<br><br>Without documentation, pass to RPh. Deny; medical appropriateness. |
| 7. Is the diagnosis funded by the OHP? | **Yes:** Approve for up to 3 months. Subsequent approvals will require:<br>• Verification of patient's opioid claims history in the Oregon PDMP at least every 3 months<br>• Documentation of sustained improvement in both baseline pain and function at least every 3 months<br>• Documented UDS at least every 12 months | **No:** Approve for up to 3 months if there is documentation of an individualized taper plan with progress toward tapering off opioid.<br><br>Without documentation, pass to RPh. Deny; medical appropriateness. |

# Opioid/non-narcotic Combinations and Excessive Dose Limits

**Goal(s):**

- Decrease risk for adverse events attributed to high doses of acetaminophen (APAP) or aspirin (ASA) when combined with an opioid product.
- Pay only for conditions funded on the OHP list of prioritized services.

**Requires PA:**

- Non-preferred drugs.
- Prescriptions exceeding FDA recommendations of 4000 mg/day of APAP or ASA.
- All codeine-containing products for patients under 13 years of age.
  Note:
  - Pharmacy may need to adjust day's supply entry.
  - Prescriber may choose a product with a higher ratio of narcotic to keep APAP or ASA within maximum limits or use a single-ingredient opioid.

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

| Approval Criteria | | |
|---|---|---|
| 1. What diagnosis is being treated? | Record ICD10 code | |
| 2. Does daily dose of APAP or ASA exceed the maximum daily dose? | **Yes:** Go to #3 | **No:** Instruct pharmacy to correct day's supply entry |
| 3. Is the diagnosis funded on the OHP list of prioritized services? | **Yes:** Pass to RPh. Deny; medical appropriateness<br><br>Review FDA maximum dose and provide alternatives. | **No:** Pass to RPh. Deny; not funded by the OHP<br><br>Review FDA maximum dose and provide alternatives |

Author: C. Strouse/A. Gibler

Date: May 2016

**Examples of products containing ASA:**

| Aspirin Combinations | | | |
|---|---|---|---|
| **Drug** | **Maximum quantity per day** | **Drug** | **Maximum quantity per day** |
| Codeine/ASA/Caffeine/ Butalbital 30/325/40/50 mg | 12 tablets | Oxycodone/ASA 4.8355/325 mg | 12 tablets |
| Codeine/ASA/Carisoprodol 16/325/200 mg | 12 tablets | Dihydrocodeine/ASA/Caffeine 16/356.4/30 mg | 11 capsules |

**Examples of products containing APAP:**

| Hydrocodone/APAP combinations | | | |
|---|---|---|---|
| **Drug** | **Maximum quantity per day** | **Drug** | **Maximum quantity per day** |
| Hydrocodone/APAP 5/300 mg | 13 tablets | Hydrocodone/APAP 2.5/108 mg per 5 mL | 185 mL |
| Hydrocodone/APAP 7.5/300 mg | 13 tablets | Hydrocodone/APAP 5/217 mg per 10 mL | 184 mL |
| Hydrocodone/APAP 10/300 mg | 13 tablets | Hydrocodone/APAP 7.5/325 mg per 15 mL | 184.5 mL |
| Hydrocodone/APAP 2.5/325 mg | 12 tablets | Hydrocodone/APAP 7.5/500 mg per 15 mL | 120 mL |
| Hydrocodone/APAP 5/325 mg | 12 tablets | Hydrocodone/APAP 10/325 mg per 15 mL | 184.5 mL |
| Hydrocodone/APAP 7.5/325 mg | 12 tablets | | |
| Hydrocodone/APAP 10/325 mg | 12 tablets | | |

| Oxycodone/APAP combinations | |
|---|---|
| Oxycodone/APAP 5/300 mg | 13 tablets |
| Oxycodone/APAP 7.5/300 mg | 13 tablets |
| Oxycodone/APAP 10/300 mg | 13 tablets |
| Oxycodone/APAP 2.5/325 mg | 12 tablets |
| Oxycodone/APAP 5/325 mg | 12 tablets |

| | |
|---|---|
| Oxycodone/APAP 7.5/325 mg | 12 tablets |
| Oxycodone/APAP 10/325 mg | 12 tablets |
| Oxycodone/APAP 5/325 per 5 mL | 61.5 mL |

| **Codeine/APAP combinations** | |
|---|---|
| Codeine/APAP 12/120 mg per 5 mL | 166.5 mL |
| Codeine /APAP 15/300 mg | 13 tablets |
| Codeine /APAP 30/300 mg | 13 tablets |
| Codeine /APAP 60/300 mg | 13 tablets |

| **Other Combinations** | |
|---|---|
| Tramadol/APAP 37.5/325 mg | 12 tablets |
| Dihydrocodeine/APAP/caffeine 16/320.5/30 mg | 12 tablets |

*P&T Review:* *5/16 (AG); 5/15; 2/06; 11/99; 2/99*
*Implementation:* *7/1/15; 9/30/05; 5/16/05; 12/1/03; 5/1/03*

# Methadone

**Goal(s):**

- Promote safe use of methadone upon initiation.

**Initiative:**

Prescribing Recommendations:

- Opioid-naïve or patients receiving codeine preparations: start at low dose and increase slowly.
  - 2.5 mg BID-TID; upward titration by 2.5 mg q8h no sooner than weekly
- Conversion from other opioids
  - Starting dose 2.5 mg-5 mg q8h; upward titration by 2.5 mg q8h no sooner than weekly
  - Use short-acting opioid for breakthrough pain until optimum dose reached.

**Length of Authorization:**

Up to 6 months

**Requires PA:**

- Patients initiated on methadone (i.e., no previous claim within 90 days) on a total daily dose of 20 mg or more.

| Approval Criteria | | |
|---|---|---|
| 8. What diagnosis is being treated? | Record ICD10 code | |
| 9. Has patient had a recent urinary drug screen (within the past 90 days)? | **Yes:** Go to #3 | **No:** Pass to RPh. Deny; medical appropriateness<br><br>Recommend UDS |

| Approval Criteria | | |
|---|---|---|
| 10. Has patient been continuously on opioids other than codeine over the past 90 days? | **Yes:** Go to #4<br><br>Document previous opioid therapy. | **No:** Pass to RPh. Deny; medical appropriateness<br><br>Opioid-naïve or patients receiving codeine preparations should start methadone @ 2.5 mg BID-TID; upward titration by 2.5 mg q8h no sooner than weekly. |
| 11. Was the total daily Morphine Equivalent Dose less than 200 mg?<br><br>Opioid Dose Calculator at: http://www.agencymeddirectors.wa.gov/Calculator/DoseCalculator.htm | **No:** Go to #5 | **Yes:** Pass to RPh. Deny; medical appropriateness<br><br>Recommend initiate methadone @ 2.5mg - 5 mg q8h; upward titration by 2.5 mg q8h no sooner than weekly and use short-acting opioids for break-through pain |
| 12. Is this patient terminal (<6 months) or admitted to hospice? | **Yes:** Approve for up to 6 months | **No:** Go to #6 |
| 13. Is patient being treated for oncology pain? | **Yes:** Approve for up to 6 months | **No:** Pass to RPh. Deny; medical appropriateness |

*P&T Review:* *5/16 (AG); 1/12; 5/11; 3/11*
*Implementation:* *4/9/12*

# Fentanyl Buccal, Intranasal and Sublingual Products

**Goals:**

The purpose of this prior authorization policy is to ensure that fentanyl for breakthrough pain is appropriately prescribed in accordance to FDA black box warnings:

- Short-acting fentanyl is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.
- Patients considered opioid-tolerant are those who are taking at least 60 mg/day morphine, 50 mcg/hour transdermal fentanyl, or an equianalgesic dose of another opioid for a week or longer.
- Because life-threatening respiratory depression can occur at any dose in patients not taking chronic opioids, transmucosal and buccal fentanyl is contraindicated in the management of acute or postoperative pain.
- This product must not be used in opioid-naïve patients. Short acting (SA) fentanyl is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable and skilled in the use of Schedule II opioids to treat cancer pain.
- When prescribing, do not convert patients from other fentanyl products on a mcg per mcg basis. Pharmacokinetic differences between products could cause fatal over-dose.
- Caution should be used when combining these agents with CYP3A4 inhibitors. Increases in fentanyl concentrations can cause fatal respiratory depression.
- Patients and their caregivers must be instructed that fentanyl products contain a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly.

**Length of Authorization:**

Up to 6 months (with quantity limit)

**Requires PA:**

- Non-preferred short-acting fentanyl buccal, intranasal and sublingual products

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

| Approval Criteria | | |
|---|---|---|
| 1. What is the diagnosis for which fentanyl is being requested? | Record ICD10 code. | |
| 2. Is the pain diagnosis above the line or below the line? (for DMAP, short acting fentanyl is not limited to cancer pain but must be severe chronic pain) | **Above the line:** go to #3. | **Below the line:** No, Pass to RPH; Deny, (Not Covered by the OHP). |
| 3. Is the prescriber an oncologist or pain specialist? | **Yes:** Go to #4. | **No:** Pass to RPH; Deny, (Medical Appropriateness), with message:<br><br>"The described use is not consistent with the FDA labeling which SA fentanyl be used only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain." |
| 4. Is client tolerant to opioids (**Check profile)**, defined as chronic long-acting opioid dose of:<br>• Morphine greater than 60 mg per day? OR<br>• Transdermal fentanyl 50 mcg per hour? OR<br>• Equianalgesic dose of another opioid for at least one week? | **Yes:** Go to #5. | **No:** Pass to RPH; Deny, (Medical Appropriateness), *with message:*<br><br>*"Your request was reviewed and denied because it is not consistent with the FDA labeling. A trial of immediate release morphine or oxycodone is recommended prior to use of SA fentanyl."* |
| 5. Has the client tried and failed immediate release morphine or oxycodone? OR is the client allergic, unable to swallow or intolerant to morphine and oxycodone? | **Yes:** Go to #6. | **No:** Pass to RPH; Deny, (Medical Appropriateness), *with message:*<br><br>*"Your request was reviewed and denied based on the following: A trial of immediate release morphine or oxycodone is recommended prior to use of SA fentanyl."* |

| Approval Criteria | | |
|---|---|---|
| 6. Is the quantity >4 doses per day? | **Yes:** Pass to RPH; Deny, (Medical Appropriateness), *with message:*<br><br>*"Your request for a quantity greater than 4 doses per day has been denied because it exceeds limits."* | **No:** Approve for up to 6 months with quantity limit of 4 lollipops/tablets per day (i.e. 120/30 days). |

*P&T Review:* *5/16 (AG); 5/15; 6/13; 3/10; 12/09, 9/05, 5/05*
*Implementation:* *1/1/14; 4/26/10; 1/1/10; 6/1/08; 4/1/08; 9/1/06*

# Codeine

**Goal(s):**

- Promote safe use of codeine in pediatric patients

**Length of Authorization:**

Up to 3 days

**Requires PA:**

- All codeine products for patients under 13 years of age
- All codeine *analgesic* products for patients aged 13 through 17 years

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

| Approval Criteria | | |
|---|---|---|
| 1. What diagnosis is being treated? | Record ICD10 code. | |
| 2. What is the age of the patient? | **Ages 0-12 years:** Pass to RPh. Deny; medical appropriateness | **Ages 13-17 years:** Go to #3 |
| 3. Is the prescription for an OHP-funded condition? | **Yes:** Go to #4 | **No:** Pass to RPh. Deny; not funded by the OHP |
| 4. Has the patient recently undergone tonsillectomy or adenoidectomy? | **Yes:** Pass to RPh. Deny; medical appropriateness | **No:** Go to #5 |
| 5. Does the dose exceed 240 mg per day? | **Yes:** Pass to RPh. Deny; medical appropriateness | **No:** Approve no more than 3-day supply |

*P&T Review:* *5/16 (AG/KK); 9/15; 7/15*
*Implementation:* *10/9/15*