Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Update: Opioid Analgesics

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

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

Purpose for Class Update:
The purpose of this update is to propose new drug policies for short- and long-acting opioid analgesics that align with guidance from the U.S. Centers for Disease Control and Prevention (CDC) and the prioritized list of health services established by the Oregon Health Plan (OHP) Health Evidence Review Commission (HERC). The focus of the review will be on evidence for short-acting opioids (SAO) published since this class was last presented to the Oregon Drug Use Review / Pharmacy and Therapeutics (P&T) Committee in May 2015. The long-acting opioid class was recently reviewed by the P&T Committee in May 2016;[1] however, new approvals by the U.S. Food and Drug Administration (FDA) of long-acting opioid products since May 2016 will also be reviewed.

Research Questions:
1. What is the comparative efficacy or effectiveness of different SAOs in reducing pain and improving functional outcomes (e.g., disability) in adult patients being treated for acute or chronic non-cancer pain?
2. What are the comparative harms (including addiction and abuse) of different SAOs in adult patients being treated for acute or 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 acute or chronic non-cancer pain for which one SAO is more effective or associated with less harm?

Conclusions:
- Updated evidence for SAO comes from one systematic review of opioids for chronic low back pain,[2] one systematic review that compared NSAIDs to opioids for acute soft tissue injuries,[3] one systematic review of hydromorphone for neuropathic pain,[4] and 2 systematic reviews that studied tramadol with or without acetaminophen.[5,6] In general, systematic reviews that specifically limited their research to SAO analgesics were not found. Two randomized controlled clinical trials assessed SAO agents in the Emergency Department (ED) setting.[7,8]
- There is insufficient comparative evidence to know if SAOs differ in their analgesic effect for acute or chronic non-cancer pain when given at equivalent doses. Increasing the dose of an opioid, or combining an opioid with a simple analgesic such as acetaminophen, modestly improves analgesia in chronic pain but it is unclear if these improvements are clinically important.
- There is low quality but consistent evidence of no difference in functional improvement or pain relief from acute soft tissue injuries between NSAID therapy and opioid therapy with or without acetaminophen.

- There is insufficient comparative evidence to know if SAOs differ in harms, such risk for abuse, diversion, addiction, or respiratory depression when administered at equipotent doses, regardless of whether the formulation has abuse-deterrent properties or not.
- There is insufficient evidence to know if specific subpopulations may benefit more from one SAO over another.
- Evidence for use of a new extended-release capsule formulation of oxycodone and naltrexone (Troxyca ER) is based on one short-term, placebo-controlled trial in patients with chronic low back pain that showed modest pain reduction of unclear clinical importance.[9]

Recommendations:

- No further review or research needed at this time. After review comparative SAO costs in the executive session, no changes to PDL status in the drug class were made.
- Maintain non-preferred status for Troxyca ER (oxycodone/naltrexone) extended-release capsules.
- Approve the proposed clinical prior authorization (PA) criteria for short- and long-acting opioid analgesics in **Appendix 4**. Previous prior authorization criteria for opioid analgesics approved by the P&T Committee in May 2016 are in **Appendix 5**.
    - Patients with a terminal diagnosis or cancer diagnosis are exempt from PA.
    - All non-preferred SAO products and preferred SAO products prescribed for more than 7 days are subject to clinical PA criteria.
    - All long-acting opioid analgesics are subject to clinical PA criteria.
    - Update quantity limits for new drug approvals.
- Oregon Health Authority to work with the Pharmacy Benefits Manager (HPE) on timing of implementation of new drug policies.

Previous Conclusions and Recommendations:

- Update current prior authorization criteria for excessive dose limits on opioid/non-narcotic combination products.
- Propoxyphene products and combination products containing 500 mg of acetaminophen were removed, and the maximum recommended daily aspirin dose was decreased from 8 g/day to 4 g/day.

Background:

More than 30% of persons within the U.S. have some form of acute or chronic pain.[10] An estimated 20% of patients who present to physician offices with non-cancer pain symptoms or pain-related diagnoses (acute or chronic) receive an opioid prescription.[11] Opioid analgesics are now the most commonly prescribed class of medications in the U.S.[10] Per capita prescriptions for opioid analgesics increased 7.3% from 2007 to 2012, with the largest increases occurring in family practice, general practice and internal medicine compared to other specialties.[11] About 65% of opioid prescriptions dispensed from retail pharmacies are for short-term (<3 weeks) therapy.[10] However, approximately 3-4% of the U.S. adult population receives long-term opioid therapy, which accounts for an estimated 9.6-11.5 million adults.[11] There is a clear lack of consensus among prescribers, however, as stark differences in opioid prescribing patterns exist between states that cannot be explained by underlying health status.[11]

Prevention, assessment, and treatment of chronic pain are challenging for clinicians. Pain might go unrecognized, and patients of racial and ethnic minority groups, women, elderly, persons with cognitive impairment, patients with cancer, and patients at the end of life, can be at risk for inadequate pain treatment.[11] There are clinical, psychological and social consequences associated with chronic pain. For example, pain can limit the ability to perform certain activities, and can result in decreased work productivity, reduced quality of life, and stigma. However, there are also serious harms associated with opioid use. Opioid analgesics are widely diverted and improperly used, which has resulted in a national epidemic of opioid-related deaths.[10] From 1999 to 2014, more than 165,000

people died from overdose related to opioids in the U.S, and increasing rates of overdose deaths during that time correlated with increasing rates of opioid prescribing.[11] In addition, more than 420,000 ED visits were related to misuse or abuse of opioids in 2011, the last year with available data for ED visits.[11] Increased diagnoses of opioid use disorder, which is distinct from opioid dependence or tolerance which inevitably results with repeated administration of an opioid, has shown that opioid misuse and abuse causes significant impairment and distress in an increasing number of opioid users in the U.S.

The major source of diverted opioids is from physician prescriptions.[10] Such consequences emphasize the importance of appropriate and compassionate care with careful consideration of the benefits and risks of treatment options.[11] Many clinicians, however, admit that they are not confident about how to prescribe opioids safely, how to detect emerging addiction, or even how discuss these issues with their patients.[10] Addiction to opioids is unpredictable and is not limited to a few high-risk individuals even when risk mitigation strategies are used.[12] The CDC issued guidance in 2016 for prescribing opioids for chronic pain to help address some of these issues.[11] The guidance is based on a systematic review of studies over the past 20 years, expert opinion and stakeholder review in order to inform recommendations for primary care clinicians who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care.[11] Pain management involves a full range of therapeutic options. However, it is difficult to estimate the number of patients who could potentially benefit from long-term opioid therapy. Evidence supports short-term efficacy (less than 12 weeks) of opioids for relieving pain and improving function in non-cancer nociceptive and neuropathic pain,[11] although the effects in some pain conditions such as low back pain are modest and may not be clinically meaningful for most patients.[2] Evidence for long-term efficacy of opioids, however, is lacking despite well documented risks for long-term opioid therapy.[11]

In 2016, the Oregon Health Plan (OHP) Health Evidence Review Commission (HERC) established Guideline Note 60 in the Prioritized List of Health Services based on evidence for low back pain.[13] Low back pain is the leading cause of disability worldwide and is the leading reason for prescribing opioids in the primary care setting.[12] Low back pain can be managed with several nonpharmacological measures which can be supplemented with analgesics like acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs).[2] However, many patients with chronic low back pain are prescribed opioid analgesics despite their lack of long-term efficacy, their well-documented harms, and modest, if clinically insignificant, short-term pain relief.[2] The HERC clinical guideline note establishes restrictions for opioid prescribing for conditions of the back and spine in OHP patients:[13]

For <u>acute</u> injury, acute flare of chronic pain, or after surgery:

1) *During the first 6 weeks after the acute injury, flare or surgery, opioid treatment is included on these lines ONLY*
    a. *When each prescription is limited to 7 days of treatment, AND*
    b. *For short acting opioids only, AND*
    c. *When one or more alternative first line pharmacologic therapies such as NSAIDs, acetaminophen, and muscle relaxers have been tried and found not effective or are contraindicated, AND*
    d. *When prescribed with a plan to keep active (home or prescribed exercise regime) and with consideration of additional therapies such as spinal manipulation, physical therapy, yoga, or acupuncture, AND*
    e. *There is documented lack of current or prior opioid misuse or abuse.*
2) *Treatment with opioids after 6 weeks, up to 90 days, requires the following:*
    a. *Documented evidence of improvement of function of at least thirty percent as compared to baseline based on a validated tools (e.g. Oswestry, Neck Disability Index, SF-MPQ, and MSPQ);*
    b. *Must be prescribed in conjunction with therapies such as spinal manipulation, physical therapy, yoga, or acupuncture;*
    c. *Verification that the patient is not high risk for opioid misuse or abuse. Such verification may involve:*
        i. *Documented verification from the state's prescription monitoring program database that the controlled substance history is consistent with the prescribing record*

ii. *Use of a validated screening instrument to verify the absence of a current substance use disorder (excluding nicotine) or a history of prior opioid misuse or abuse*

iii. *Administration of a baseline urine drug test to verify the absence of illicit drugs and non-prescribed opioids;*

d. *Each prescription must be limited to 7 days of treatment and for short acting opioids only.*

3) *Further opioid treatment after 90 days may be considered ONLY when there is a significant change in status, such as a clinically significant verifiable new injury or surgery. In such cases, use of opioids is limited to a maximum of an additional 7 days. In exceptional cases, use up to 28 days may be covered, subject to the criteria in #2 above.*

For patients with chronic pain from diagnoses on these lines currently treated with long term opioid therapy, opioids must be tapered off using an individual treatment plan developed by January 1, 2017 with a quit date no later than January 1, 2018. Taper plans must include nonpharmacological treatment strategies for managing the patient's pain based on Guideline Note 56 NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE. If a patient has developed dependence and/or addiction related to their opioids, treatment is available on Line 4 SUBSTANCE USE DISORDER.[13]

There is no simple or single change in prescribing that can alleviate risk for opioid diversion, overdose and addiction since these risks are largely independent and governed by different factors.[10] The contributing factors associated with overdose can be divided into those associated with the opioid itself (potency, dose, duration of action) and factors specific to the patient (e.g., older age, adolescence, depression, substance use disorder, history of overdose). However, several common strategies can mitigate these risks: 1) use of screening tools to identify patients with a substance-use disorder (e.g., Opioid Risk Tool; the Screener and Opioid Assessment for Patients with Pain [SOAPP], version 1.0; SOAPP-Revised; or the Brief Risk Interview); 2) use of data from the Prescription Drug Monitoring Program (PDMP); 3) use of urine drug screening; and 4) doctor-patient agreement on opioid adherence.[10]

Routine use of opioid analgesia for pain management should be practiced only with the awareness of opioid abuse and the role that prescription opioids have in contributing to opioid abuse.[12] Information on potential misuse and abuse of prescription opioid analgesics can help prescribers such as primary care physicians and dentists strike a balance between alleviating pain for patients and ensuring safe prescribing.[14] Prescription drug monitoring programs (PDMP) are statewide databases that accrue information from pharmacies on dispensed prescriptions of controlled substances. All states except Missouri have implemented the PDMP as a tool to curb high-risk prescribing behaviors (i.e., multiple prescriptions from multiple prescribers) and abuse of controlled substances like opioid analgesics.[15] Prescribers, pharmacists, law enforcement agencies, and medical licensure boards may access their state PDMP for information on controlled substance prescribing.[14] National data over a 10-year period have shown that implementation of a PDMP has been associated with a sustained reduction of more than 30% in rates of opioid prescribing and a slight increase in prescribing of non-opioid analgesics.[14] The PDMPs have also been associated with an average reduction of 1.12 opioid-related overdose deaths per 100,000 population in their first year after implementation, with more robust programs associated with greater reductions in opioid-related overdose deaths.[15]

Pain research is needed to improve the practice of opioid prescribing.[10] Areas of uncertainty include how to differentiate the unique properties of acute and chronic pain and how to describe the process by which acute pain transitions into chronic pain.[10] In addition, research is needed to identify new, potent non-opioid analgesics and other pain treatment strategies.[10] In general, opioids have shown modest efficacy in pain reduction. Pain intensity measurements used in the trials included the visual analog scale (VAS; scale, 0-100 or 0-10) and numerical rating scale (NRS; scale, 0-10).[2] The NRS and VAS are highly correlated and can be interpreted equally.[2] For acute pain, the minimum clinically important difference (MCID) in the 11-point VAS is 1.4 (95% CI, 1.2 to 1.6).[16] Similar MCID values have been shown with 100-point scales.[17] The proposed MCID thresholds for chronic pain and low back pain are about 2.0 points on the 0 to 10-point scale or 20 points on the 0 to 100-point scale.[2] The impact of opioids on disability is also frequently studied in clinical trials of low back pain. Measurements commonly used include the Oswestry Disability Index scores (range, 0-100) and the Roland-Morris Disability Questionnaire (RMDQ) scores (range, 0-24).[2] The

Oswestry Disability Index and RMDQ tools are also highly correlated and share similar properties.[2] Similarly, a 10-point difference in 0-100 scales for chronic disability is considered a "minimal" difference and 20-point differences are considered to be "clinically important".[2]

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 U.S. Food and Drug Administration (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.

All FDA approvals identified since the long-acting opioid class update was reviewed and presented to the DUR/P&T Committee in May 2016 will also be included under "New Formulations or Indications".

New Systematic Reviews:
<u>Opioids for Low Back Pain</u>
A recently published systematic review with meta-analysis assessed the association between use of opioid analgesics and clinical efficacy, tolerability, and dose-dependent effects in patients with chronic low back pain.[2] Eligible studies included RCTs that studied single ingredient or combination opioid analgesics in patients with nonspecific acute or chronic low back pain (i.e., low back pain where a cause had not been identified).[2] Studies were included if they reported pain, disability or adverse event (AE) outcomes.[2] Both placebo-controlled RCTs and RCTs that compared 2 opioids or different doses of the same drug were eligible for inclusion.[2] Pain and disability outcomes were converted to a common 0 to 100 scale (0 = no pain or disability; 100 = worst possible pain or disability).[2] Pain intensity measurements used in the trials included the VAS and NRS.[2] The NRS was converted to the same 0-100 scale as in the VAS because of the high correlation between the tools.[2] The disability measurements used to calculate pooled effects were Oswestry Disability Index scores (range, 0-100) and Roland-Morris Disability Questionnaire (RMDQ) scores (range, 0-24).[2] The RMDQ was also converted to the same 0-100 scale as in the Oswestry Disability Index because of the high correlation between the tools and the fact that they share similar properties.[2] Results were presented in mean differences (MD).[2] A 10-point difference in 0-100 scales for pain and disability was considered a "minimal" difference and a 20-point difference was considered to be "clinically important" which is consistent with thresholds for MCIDs for chronic pain and low back pain literature.[2] The investigators considered differences less than 10 points (out of 100) on the pain or disability scales to be unnoticeable by most patients.[2] Short-term pain relief (follow-up <3 months) was the primary outcome.[2] Intermediate-term (≥3 months to <12 months) and long-term (≥12 months) pain relief was also evaluated if data were available.[2] Grading of recommendations assessment, development, and evaluation (GRADE) criteria were used to evaluate the evidence.

A total of 20 RCTs were included (n=7295 patients); 17 trials compared an opioid analgesic to placebo and 3 trials compared 2 opioid analgesics.[2] All but one trial evaluated patients with chronic low back pain and one head-to-head trial evaluated patients with subacute low back pain.[2] Subjects enrolled in 7 of the 13 trials

were ineligible to be randomized in their respective studies unless they responded favorably to the study opioid and tolerated the drug in the initial run-in phase of the trial.[2] There was moderate-quality evidence from 13 studies of chronic low back pain (n=3419) for short-term efficacy of questionable clinical importance for single-ingredient opioid analgesics on pain relief (MD -10.1; 95% CI, -12.8 to -7.4).[2] There was high-quality evidence from 6 studies (n=2605) for intermediate-term efficacy for single-ingredient opioid analgesics on pain relief (MD -8.1; 95% CI, -10.2 to -6.0).[2] Combination opioid analgesics (e.g., with acetaminophen) had moderate-quality evidence for intermediate-term efficacy on pain relief (MD -11.9; 95% CI, -19.3 to -4.4).[2] The effects of single-ingredient and combination opioids were minimal at approximately half the 20-point threshold for clinical importance, and in no case did the confidence intervals cross the 20-point clinically important threshold.[2] There were limited data on disability outcomes. Very low quality evidence from 2 short-term trials showed modest improvements by 4-6 points that were not clinically significant.[2]

The morphine milligram equivalent (MME) daily dose in these 13 studies ranged from 40.0 to 242.7 mg per day. A meta-regression model of these trials showed significant effects of the opioid dose on treatment effects, with a 12.0-point greater pain relief for every 10 MME per day increase in dose (p=0.046).[2] However, none of the doses recommended in the guidelines (40-120 MME/day) achieved clinical important pain relief in these trials.[2] In half of the trials, 50% of the patients enrolled withdrew early from the studies because of lack of pain relief.[2] Even in 7 trials where subjects were enrolled only if they tolerated and responded to medication in the run-in phase, early withdrawal ranged from 31.4% to 61.9% due to AEs and 3.3% to 29.6% withdrew early due to lack of efficacy.[2] Overall, the median rates of AEs were 49.1% for placebo (interquartile range [IQR] 44.0-55.0%) and 68.9% (IQR 55.0-85.0%) (risk ratio [RR] 1.3; p<0.01).[2] The most common AE reported were related to the central nervous system (headache, somnolence, dizziness), the gastrointestinal tract (constipation, nausea, vomiting) and autonomic events such as dry mouth.[2]

NSAIDs vs. Opioid Analgesics

The Cochrane Collaboration conducted a recent systematic review to assess the benefits and harms of NSAIDs with other oral analgesics, including opioid analgesics, for treatment of acute soft tissue injuries.[3] Sixteen RCTs that compared oral NSAID therapy to acetaminophen, or an opioid with or without acetaminophen in subjects with acute soft tissue injury that occurred within 48 hours of injury were included in the review.[3] Soft tissue injuries could be a sprain, strain or contusion of a joint, ligament, tendon or muscle.[3] Studies were excluded if they focused on back pain, cervical spine injury, repetitive strain injuries, delayed onset muscle soreness or primary inflammatory injuries (i.e., tendonitis or arthritis).[3] No restrictions were placed on age of subjects.[3] The primary outcome was pain which was assessed using categorical or VAS.[3] Secondary outcomes included swelling, function and AEs.[3] Quality of evidence was assessed using GRADE criteria.[3] Sixteen trials were included, 4 trials (n=958) of which compared NSAIDs with opioid therapy and 4 trials (n=240) that compared NSAIDs with opioid plus acetaminophen therapy.[3]

Most of the evidence that compared NSAID therapy to opioid therapy (without acetaminophen) focused on valdecoxib which was subsequently withdrawn from the market.[3] Pooled data from the remaining trials provided low quality evidence of no clinically important difference between NSAID therapy versus opioid therapy for acute soft tissue injuries when pain was measured using a VAS (0 to 100 mm) within 24 hours of therapy (MD 0.10 mm; 95% CI, -3.55 to 3.74 mm), at days 4 to 6 (MD -2.9 mm; 95% CI, -6.06 to 0.26 mm), and at day 7 (-6.50 mm; 95% CI, -9.31 to -3.69).[3] Little difference was found between the two groups in the number of patients with swelling at day 10 in one study (15/44 vs. 12/40; RR 1.14; 95% CI, 0.61 to 2.13).[3] However, return to function at or after day 7 was superior with NSAID therapy versus opioid therapy in pooled analysis (366/484 vs. 176/265, respectively; RR 1.13; 95% CI, 1.03 to 1.25; p=0.01) based on low quality evidence.[3] There were fewer gastrointestinal (GI) AEs with Cox-2 selective NSAID therapy versus opioid therapy (50/468 vs. 60/238, respectively; RR 0.42; 95% CI, 0.30 to 0.60) but no difference was seen with non-selective NSAID therapy versus opioid therapy (9/31 vs. 5/32, respectively; RR 1.86; 95% CI, 0.70 to 4.93; p=0.21) based on very low quality evidence with significant heterogeneity (I^2=87.3%).[3]

Most of the evidence that compared NSAID therapy to opioid plus acetaminophen therapy used propoxyphene combination drugs that are no longer available.[3] Overall, very low quality evidence suggests no difference in relief of pain (little to no pain) between NSAID therapy versus opioid plus acetaminophen therapy at day 1 (1/26 vs. 0/25, respectively; RR 2.89; 95% CI, 0.12 to 67.75; p=0.51), day 3 (12/75 vs. 8/74, respectively; RR 1.49; 95% CI, 0.65 to 3.40; p=0.34) or day 7 (49/68 vs. 47/70, respectively; RR 1.05; 95% CI, 0.88 to 1.25; p=0.41).[3] For assessment of function, little difference was found between the groups in the number of cured patients by day 7 (30/45 vs. 23/44; RR 1.28; 95% CI, 0.90 to 1.81; p=0.17).[3] In addition, there was no difference in GI AEs (0/70 vs. 4/71; RR 0.21; 95% CI, 0.03 to 1.74) based on low quality evidence.[3] The authors concluded that there is low quality but consistent evidence of no difference between NSAID therapy and opioid therapy with or without acetaminophen for pain associated with acute soft tissue injuries and return to normal function.[3]

Hydromorphone for Neuropathic Pain

The Cochrane Collaboration also conducted a systematic review to assess the efficacy of hydromorphone at reducing chronic neuropathic pain in adults, as well as the AEs associated with its use in this population.[4] Trials eligible for inclusion were double-blind RCTs of at least 2 weeks' duration that compared hydromorphone (any dose and formulation) with placebo or an active treatment for chronic neuropathic pain.[4] However, only 4 studies were identified and 3 of them were excluded leaving only one post-hoc analysis that assessed reduction in chronic neuropathic pain.[4] Thus, insufficient evidence is available for this population to support or refute the use of hydromorphone for chronic neuropathic pain.[4]

Tramadol and Tramadol/Acetaminophen

The Canadian Agency for Drugs and Technologies in Health (CADTH) conducted an updated abbreviated review for tramadol[5] and tramadol plus acetaminophen fixed-dose combination drugs[5,6] for the management of chronic and acute pain in adult patients. Tramadol has a relatively lower affinity for the mu-opioid receptor than other opioid analgesics.[5] Tramadol and its active metabolite bind to the mu-opioid receptors in the central nervous system and inhibit the ascending pain pathways, as well as inhibit the reuptake of norepinephrine and serotonin involved in the descending inhibitory pain pathway.[5] However, place in therapy for tramadol for management of pain is unclear. The first review assessed systematic reviews and RCTs published since 2012 that compared tramadol or tramadol combination products with placebo or active comparators.[5] The second review assessed RCTs published since 2014 that compared tramadol/acetaminophen fixed-dose combination products with active comparators for management of pain in adults.[5]

Four systematic reviews were identified as relevant to the fist review.[5] Three systematic reviews showed greater pain reduction with tramadol or tramadol combination when compared to placebo; however differences were statistically significant in only one systematic review that evaluated chronic low back pain (MD -0.55; 95% CI, -0.66 to -0.44). One systematic review for chronic low back pain did not find a statistically significant difference (MD -1.72; 95% CI, -3.45 to 0.01) and the third systematic review, which evaluated painful diabetic neuropathy, did not report statistical analyses (≥30% pain reduction: 56.2% vs. 37.9% for tramadol combination vs. placebo, respectively).[5] These systematic reviews found AEs to be more common with tramadol than placebo (RR 1.74; 95% CI, 1.20 to 2.52) and with tramadol/acetaminophen than placebo (nausea: 11.9% vs. 3.3%, dizziness: 6.3% vs. 1.3%, and somnolence: 6.3% vs. 1.3%).[5]

For active comparisons, one systematic review included an RCT which compared tramadol with celecoxib and found that improvement in pain intensity was numerically greater with tramadol compared with celecoxib (63.2% vs. 49.9%) but AEs were numerically greater with tramadol compared with celecoxib (30.4% vs. 14.4%).[5] One systematic review of 2 head-to-head RCTs that assessed pain intensity showed tramadol statistically significantly reduced pain versus celecoxib (RR 0.82; 95% CI, 0.76 to 0.90).[5]

Four RCTs compared tramadol plus acetaminophen fixed-dose combination therapy with placebo.[5] These reviews reported on pain assessment (mostly chronic low back pain) using a variety of tools and formats.[5] Tools included global pain change, pain relief success rate, VAS scores, total pain relief scores (TOTPAR), and

sum of pain intensity difference (SPID).[5] There were generally greater improvements with the tramadol combination groups compared with placebo but the results were not always statistically significant.[5] Adverse events were higher in the tramadol combination groups compared to placebo groups.[5]

Three RCTs were identified that assessed the clinical effectiveness of tramadol plus acetaminophen fixed-dose combinations against active controls for the management of pain in adult patients.[5,6] One RCT identified compared tramadol plus acetaminophen and an NSAID as maintenance therapy in patients with knee osteoarthritis pain inadequately controlled by the NSAID.[5] All patients were treated with 4 weeks of add-on tramadol/acetaminophen and then randomized to tramadol/acetaminophen or NSAID.[5] Pain as assessed by NRS was not statistically significantly different between tramadol/acetaminophen versus NSAID (4.55 vs. 3.89, respectively; p=NS (p-values not provided)).[5] Prevalence and types of AEs were not significantly different between tramadol/acetaminophen vs. NSAID (nausea: 8.5% vs. 12.0%, dizziness: 8.5% vs. 8.0%, and constipation: 4.3% vs. 2.0%, respectively).[5] Another RCT found tramadol plus acetaminophen to be equally effective as paracetamol and codeine plus meprobamate at relieving pain after third molar extraction.[6] The third RCT investigated the use of tramadol and acetaminophen versus NSAID therapy in patients with low back pain and depression.[6] This study found that patients in the tramadol/acetaminophen group reported statistically significant less depression and lower pain scores on the NRS, but no statistically significant difference in scores in the Oswestry Disability Index, Pain Disability Assessment Scale, or Pain Catastrophizing Scale when compared to the NSAID group.[6] There was no significant difference in treatment-related AEs between the 2 groups.[6]

New Guidelines:
The Centers for Disease Control and Prevention (CDC) guideline for prescribing opioids for chronic non-cancer pain was published in 2016[11] and was previously reviewed in our class update for long-acting opioid analgesics.[1,11] The CDC systematically gathered 2 decades of the best scientific evidence combined with expert opinion and stakeholder review and found no evidence to support long-term use of opioid analgesics for chronic pain. The CDC systematic review and guideline is available in different formats.[11,18] Tools to help prescribers implement the guideline are also available at http://www.cdc.gov/drugoverdose/prescribing/resources.html.

New Safety Alerts:
The FDA issued a safety alert in August 2016 on the growing combined use of opioid analgesics with benzodiazepines or other drugs that suppress the central nervous system (CNS) which has resulted in numerous cases of respiratory depression and death.[19] In an effort to decrease the concurrent use of opioids and benzodiazepines, the FDA has added Boxed Warnings to the drug labeling of prescription opioid pain and cough medicines, and benzodiazepines.[19] Providers should limit prescribing opioid analgesics with benzodiazepines or other CNS depressants to patients for whom alternative treatment options are inadequate.[19] If these drugs must be prescribed concurrently, the dose and duration of each drug should be limited to the minimum possible.[19] Prescribing of prescription opioid cough medicines for patients on benzodiazepines or other CNS depressants, including alcohol, should be avoided.[19]

The FDA issued a safety alert in March 2016 regarding new safety warnings for opioid analgesics.[20] Specific warnings in labeling refer to opioid interactions with antidepressants and migraine medications that can increase the risk for serotonin syndrome. Warnings for increased risk of rare, but serious cases of adrenal gland cortisol suppression with opioid use and decreased sex hormone levels associated with long-term opioid use have also been added to drug labeling.[20]

New Formulations or Indications:

Troxyca ER (oxycodone/naltrexone extended-release [ER] capsule) was approved by the FDA in August 2016 for the management of chronic pain by healthcare providers knowledgeable in use of potent opioids.[21] Approval of oxycodone/naltrexone ER is based on one 12-week, double-blind RCT in opioid-naïve (n=162) and opioid-tolerant (n=119) patients with moderate-to-severe chronic low back pain.[9] Prior to the trial, there was an open-label phase where all enrolled patients were titrated to 20 to 160 mg of oxycodone/naltrexone every 12 hours.[9] Only patients with controlled pain (NRS ≤4) were eligible to be randomized to continue on oxycodone/naltrexone ER or to placebo after tapering off oxycodone/naltrexone.[9] A total of 281 of the 410 originally enrolled patients were eligible for randomization to oxycodone/naltrexone ER (n=147) or placebo (n=134).[9] Ninety-three patients did not complete the 12-week trial: 27% of patients withdrew early from the oxycodone/naltrexone group and 40% of patients withdrew early from the placebo group.[9] The primary end point of this study was defined as the mean change in weekly average 11-point NRS pain scores (based on patient diary entries) from baseline at randomization to the weeks 11 and 12.[9] The mean weekly NRS pain score at randomization baseline was 3.1 for placebo patients and 3.0 for oxycodone/naltrexone ER patients.[9] There was a statistically significant difference in mean change in the weekly average pain intensity NRS scores at weeks 11 and 12 from baseline between patients treated with oxycodone/naltrexone ER (least squares mean [LSM] +0.60; 95% CI, 0.27 to 0.93) compared to placebo (LSM +1.23; 95% CI, 0.87 to 1.58) (LSM Difference -0.62; 95% CI, -1.11 to -0.14; p=0.0114).[9] The differences observed are below accepted thresholds for clinical importance.

Randomized Controlled Trials:

A total of 41 citations were manually reviewed from the literature search. After manual review, 39 citations were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 2 trials are briefly described in the table below. Full abstracts are included in **Appendix 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Friedman, et al.[7] DB, SC, RCT	1. Naproxen 500 mg BID + Placebo 1-2 tablets Q8h (10-day supply) 2. Naproxen 500 mg BID + cyclobenzaprine 5 mg 1-2 tablets Q8h (10-day supply) 3. Naproxen 500 mg BID + oxycodone/APAP 5/325 mg 1-2 tablets Q8h (10-day supply)	Adults age 21-64 years w/ ED visit for LBP	Improvement on the RMDQ (scale 0-24) between ED discharge and the 7-day telephone follow-up (5-point improvement considered clinically significant).	1. naproxen + placebo: +9.8 (98.3% CI, 7.9 to 11.17) 2. naproxen + cyclobenzaprine: +10.1 (98.3% CI, 7.9 to 12.3) 3. naproxen + oxycodone/APAP: +11.1 (98.3% CI, 9.0 to 13.2) Mean Between Group Differences: - Cyclobenzaprine vs. placebo: 0.3 (98.3% CI, -2.6 to 3.2; p=0.77) - Oxycodone/APAP vs. placebo: 1.3 (98.3% CI, -1.5 to 4.1; p=0.28) - Oxycodone/APAP vs. cyclobenzaprine: 0.9 (98.3% CI, -2.1 to 3.9; p=0.45)
Chang, et al.[8] DB, SC, RCT n=120	1. oxycodone/APAP 5/325 mg 1 tablet Q4h PRN pain (3-day supply) 2. hydrocodone/APAP 5/325 mg 1 tablet Q4h PRN pain (3-day supply)	Adults age 21-64 years w/ ED visit for acute musculoskeletal extremity pain (including hip or shoulder joints)	Difference in improvement in mean NRS pain scores* at approximately 24 hours post-discharge, measured at 2 hours following the most recent ingestion of the study drug relative to the time of phone contact. *Difference of 1.4 points considered to be clinically significant	Mean change NRS scores from baseline: Oxycodone/APAP: 4.4 NRS units Hydrocodone/APAP: 4.0 NRS units Mean Between Group Difference: - 0.4 NRS units (95% CI, -0.2 to 1.1)

Abbreviations: APAP = acetaminophen; BID = twice daily; CI = confidence interval; DB = double-blind; ED = emergency department; LBP = lower back pain; mg = milligrams; NRS = numerical rating scale; Q4h = every 4 hours; Q8h = every 8 hours; RCT = randomized clinical trial; RMDQ = Roland-Morris Disability Questionnaire (functional impairment questionnaire designed for LBP); SC = single-center

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
NASAL	SPRAY	BUTORPHANOL TARTRATE	BUTORPHANOL TARTRATE	Y
ORAL	ORAL SUSP	CAPITAL W-CODEINE	ACETAMINOPHEN WITH CODEINE	Y
ORAL	SOLUTION	ACETAMINOPHEN-CODEINE	ACETAMINOPHEN WITH CODEINE	Y
ORAL	SOLUTION	HYCET	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	SOLUTION	HYDROCODONE-ACETAMINOPHEN	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	SOLUTION	LORTAB	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	SOLUTION	MORPHINE SULFATE	MORPHINE SULFATE	Y
ORAL	SOLUTION	OXYCODONE HCL	OXYCODONE HCL	Y
ORAL	TABLET	ACETAMINOPHEN-CODEINE	ACETAMINOPHEN WITH CODEINE	Y
ORAL	TABLET	CODEINE SULFATE	CODEINE SULFATE	Y
ORAL	TABLET	DILAUDID	HYDROMORPHONE HCL	Y
ORAL	TABLET	ENDOCET	OXYCODONE HCL/ACETAMINOPHEN	Y
ORAL	TABLET	HYDROCODONE-ACETAMINOPHEN	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	HYDROMORPHONE HCL	HYDROMORPHONE HCL	Y
ORAL	TABLET	LORCET	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	LORCET HD	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	LORCET PLUS	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	LORTAB	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	MORPHINE SULFATE	MORPHINE SULFATE	Y
ORAL	TABLET	NORCO	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	OXYCODONE HCL	OXYCODONE HCL	Y
ORAL	TABLET	OXYCODONE-ACETAMINOPHEN	OXYCODONE HCL/ACETAMINOPHEN	Y
ORAL	TABLET	PERCOCET	OXYCODONE HCL/ACETAMINOPHEN	Y
ORAL	TABLET	ROXICODONE	OXYCODONE HCL	Y
ORAL	TABLET	TRAMADOL HCL	TRAMADOL HCL	Y
ORAL	TABLET	TYLENOL-CODEINE NO.3	ACETAMINOPHEN WITH CODEINE	Y
ORAL	TABLET	TYLENOL-CODEINE NO.4	ACETAMINOPHEN WITH CODEINE	Y
ORAL	TABLET	ULTRAM	TRAMADOL HCL	Y
RECTAL	SUPP.RECT	BELLADONNA-OPIUM	OPIUM/BELLADONNA ALKALOIDS	Y
RECTAL	SUPP.RECT	HYDROMORPHONE HCL	HYDROMORPHONE HCL	Y
RECTAL	SUPP.RECT	MORPHINE SULFATE	MORPHINE SULFATE	Y
BUCCAL	LOZENGE HD	ACTIQ	FENTANYL CITRATE	N
BUCCAL	LOZENGE HD	FENTANYL CITRATE	FENTANYL CITRATE	N
BUCCAL	TABLET EFF	FENTORA	FENTANYL CITRATE	N
NASAL	SPRAY/PUMP	LAZANDA	FENTANYL CITRATE	N

ORAL	CAPSULE	ASA-BUTALB-CAFFEINE-CODEINE	CODEINE/BUTALBITAL/ASA/CAFFEIN	N
ORAL	CAPSULE	ASCOMP WITH CODEINE	CODEINE/BUTALBITAL/ASA/CAFFEIN	N
ORAL	CAPSULE	BUTALB-ACETAMINOPH-CAFF-CODEIN	BUTALBIT/ACETAMIN/CAFF/CODEINE	N
ORAL	CAPSULE	BUTALB-CAFF-ACETAMINOPH-CODEIN	BUTALBIT/ACETAMIN/CAFF/CODEINE	N
ORAL	CAPSULE	BUTALBITAL COMPOUND-CODEINE	CODEINE/BUTALBITAL/ASA/CAFFEIN	N
ORAL	CAPSULE	FIORICET WITH CODEINE	BUTALBIT/ACETAMIN/CAFF/CODEINE	N
ORAL	CAPSULE	FIORINAL WITH CODEINE #3	CODEINE/BUTALBITAL/ASA/CAFFEIN	N
ORAL	CAPSULE	OXYCODONE HCL	OXYCODONE HCL	N
ORAL	LIQUID	DILAUDID	HYDROMORPHONE HCL	N
ORAL	LIQUID	HYDROMORPHONE HCL	HYDROMORPHONE HCL	N
ORAL	ORAL CONC	OXYCODONE HCL	OXYCODONE HCL	N
ORAL	SOLUTION	MEPERIDINE HCL	MEPERIDINE HCL	N
ORAL	SOLUTION	OXYCODONE-ACETAMINOPHEN	OXYCODONE HCL/ACETAMINOPHEN	N
ORAL	SOLUTION	ZAMICET	HYDROCODONE/ACETAMINOPHEN	N
ORAL	SYRINGE	MORPHINE SULFATE	MORPHINE SULFATE	N
ORAL	TABLET	HYDROCODONE-ACETAMINOPHEN	HYDROCODONE/ACETAMINOPHEN	N
ORAL	TABLET	MEPERIDINE HCL	MEPERIDINE HCL	N
ORAL	TABLET	NUCYNTA	TAPENTADOL HCL	N
ORAL	TABLET	OPANA	OXYMORPHONE HCL	N
ORAL	TABLET	OXYMORPHONE HCL	OXYMORPHONE HCL	N
ORAL	TABLET	PENTAZOCINE-NALOXONE HCL	PENTAZOCINE HCL/NALOXONE HCL	N
ORAL	TABLET	PRIMLEV	OXYCODONE HCL/ACETAMINOPHEN	N
ORAL	TABLET	TRAMADOL HCL-ACETAMINOPHEN	TRAMADOL HCL/ACETAMINOPHEN	N
ORAL	TABLET	ULTRACET	TRAMADOL HCL/ACETAMINOPHEN	N
ORAL	TABLET	VICODIN	HYDROCODONE/ACETAMINOPHEN	N
ORAL	TABLET	VICODIN ES	HYDROCODONE/ACETAMINOPHEN	N
ORAL	TABLET	VICODIN HP	HYDROCODONE/ACETAMINOPHEN	N
ORAL	TABLET	XODOL 10-300	HYDROCODONE/ACETAMINOPHEN	N
ORAL	TABLET	XODOL 5-300	HYDROCODONE/ACETAMINOPHEN	N
ORAL	TABLET	XODOL 7.5-300	HYDROCODONE/ACETAMINOPHEN	N
SUBLINGUAL	SPRAY	SUBSYS	FENTANYL	N
SUBLINGUAL	TAB SUBL	ABSTRAL	FENTANYL CITRATE	N
ORAL	TABLET	HYDROCODONE-ACETAMINOPHEN	HYDROCODONE/ACETAMINOPHEN	N
ORAL	TABLET	HYDROCODONE-IBUPROFEN	HYDROCODONE/IBUPROFEN	N
ORAL	TABLET	IBUDONE	HYDROCODONE/IBUPROFEN	N
ORAL	TABLET	OXYCODONE HCL-IBUPROFEN	IBUPROFEN/OXYCODONE HCL	N
ORAL	TABLET	REPREXAIN	HYDROCODONE/IBUPROFEN	N
ORAL	TABLET	XYLON 10	HYDROCODONE/IBUPROFEN	N

Appendix 2: Abstracts of Clinical Trials

Benjamin Friedman, et al.
Naproxen With Cyclobenzaprine, Oxycodone/Acetaminophen, or Placebo for Treating Acute Low Back Pain: A Randomized Clinical Trial. *JAMA* 2015.

Importance: Low back pain (LBP) is responsible for more than 2.5 million visits to US emergency departments (EDs) annually. These patients are usually treated with nonsteroidal anti-inflammatory drugs, acetaminophen, opioids, or skeletal muscle relaxants, often in combination.
Objective: To compare functional outcomes and pain at 1 week and 3 months after an ED visit for acute LBP among patients randomized to a 10-day course of (1) naproxen + placebo; (2) naproxen + cyclobenzaprine; or (3) naproxen + oxycodone/acetaminophen.
Design, Setting, And Participants: This randomized, double-blind, 3-group study was conducted at one urban ED in the Bronx, New York City. Patients who presented with nontraumatic, nonradicular LBP of 2 weeks' duration or less were eligible for enrollment upon ED discharge if they had a score greater than 5 on the Roland-Morris Disability Questionnaire (RMDQ). The RMDQ is a 24-item questionnaire commonly used to measure LBP and related functional impairment on which 0 indicates no functional impairment and 24 indicates maximum impairment. Beginning in April 2012, a total of 2588 patients were approached for enrollment. Of the 323 deemed eligible for participation, 107 were randomized to receive placebo and 108 each to cyclobenzaprine and to oxycodone/acetaminophen. Follow-up was completed in December 2014.
Interventions: All participants were given 20 tablets of naproxen, 500 mg, to be taken twice a day. They were randomized to receive either 60 tablets of placebo; cyclobenzaprine, 5 mg; or oxycodone, 5 mg/acetaminophen, 325 mg. Participants were instructed to take 1 or 2 of these tablets every 8 hours, as needed for LBP. They also received a standardized 10-minute LBP educational session prior to discharge.
Main Outcomes and Measures: The primary outcome was improvement in RMDQ between ED discharge and 1 week later.
Results: Demographic characteristics were comparable among the 3 groups. At baseline, median RMDQ score in the placebo group was 20 (interquartile range [IQR], 17-21), in the cyclobenzaprine group 19 (IQR, 17-21), and in the oxycodone/acetaminophen group 20(IQR, 17-22).At 1-week follow-up, the mean RMDQ improvement was 9.8 in the placebo group, 10.1 in the cyclobenzaprine group, and 11.1 in the oxycodone/acetaminophen group. Between-group difference in mean RMDQ improvement for cyclobenzaprine vs placebo was 0.3 (98.3%CI, -2.6 to 3.2; p=0.77), for oxycodone/acetaminophen vs placebo, 1.3 (98.3%CI, -1.5 to 4.1; p=0.28), and for oxycodone/acetaminophen vs cyclobenzaprine, 0.9 (98.3% CI, -2.1 to 3.9; p=0.45).
Conclusions and Relevance: Among patients with acute, nontraumatic, nonradicular LBP presenting to the ED, adding cyclobenzaprine or oxycodone/acetaminophen to naproxen alone did not improve functional outcomes or pain at 1-week follow-up. These findings do not support use of these additional medications in this setting.

Andrew Chang, et al.
Comparative Analgesic Efficacy of Oxycodone/Acetaminophen Versus Hydrocodone/Acetaminophen for Short-term Pain Management in Adults Following ED Discharge. *Academic Emergency Medicine* 2015.

Objectives: The objective was to test the hypothesis that oxycodone/acetaminophen provides superior analgesia to hydrocodone/acetaminophen for the treatment of acute extremity pain following emergency department (ED) discharge.
Methods: This was a prospective, randomized, double-blind clinical trial of nonelderly adult ED patients with acute musculoskeletal extremity pain, randomly allocated at discharge to receive oxycodone/acetaminophen (5 mg/325 mg) or hydrocodone/acetaminophen (5 mg/325 mg). The primary outcome was the between-group difference in improvement in numerical rating scale (NRS) pain scores over a 2-hour period following the most recent ingestion of study drug, obtained during telephone contact 24 hours after ED discharge. Secondary outcomes included proportionate decrease in pain, comparative side-effect

profiles, and patient satisfaction.
Results: A total of 240 patients were enrolled. The final sample consisted of 220 patients, 107 randomly allocated to oxycodone/acetaminophen and 113 to hydrocodone/acetaminophen. At 24 hours after ED discharge, the mean NRS pain scores prior to the most recent dose of outpatient pain medication were 7.8 and 7.9 in the oxycodone/acetaminophen and hydrocodone/acetaminophen groups, respectively. The mean decreases in pain scores over 2 hours were 4.4 NRS units in the oxycodone/acetaminophen group versus 4.0 NRS units in the hydrocodone/acetaminophen group, for a difference of 0.4 NRS units (95% confidence interval = 0.2 to 1.1 NRS units). Satisfaction with the analgesics was similar.
Conclusions: This study design could not detect a clinically or statistically significant difference in analgesic efficacy between oxycodone/acetaminophen (5 mg/325 mg) and hydrocodone/acetaminophen (5 mg/325 mg) for treatment of acute musculoskeletal extremity pain in adults following ED discharge. Both opioids reduced pain scores by approximately 50%.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to August Week 5 2016

1 buprenorphine/ or butorphanol/ or codeine/ or fentanyl/ or hydrocodone/ or hydromorphone/ or meperidine/ or morphine/ or opium/ or oxycodone/ or oxymorphone/ or pentazocine/ or tramadol/ 30188

2 acute pain.mp. or exp Acute Pain/ 4959

3 short-acting.mp. 4274

4 immediate-release.mp. 2414

5 2 or 3 or 4 11541

6 1 and 5 914

7 limit 6 to (english language and humans and yr="2015 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews)) 41

Short-acting Opioid Analgesics

Goals:

- Restrict use of short-acting opioid analgesics for acute conditions funded by the OHP.
- Promote use of preferred short-acting opioid analgesics.

Length of Authorization:

7 to 30 days (except 12 months for end-of-life or cancer-related pain)

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:

- Non-preferred short-acting opioids and opioid combination products.
- All short-acting products prescribed for more than 7 days.

Note:

- 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 morphine milligram equivalents per day (MME/day) of Oral Opioid Products.

Opioid	90 MME/day Dose	Notes
Codeine	600 mg	Codeine is not recommended for pediatric use; codeine is a prodrug of morphine and is subject to different rates of metabolism placing certain populations at risk for overdose.
Hydrocodone	90 mg	
Hydromorphone	22.5 mg	
Meperidine	900 mg	Meperidine is not recommended for management of chronic pain due to potential accumulation of toxic metabolites.
Morphine	90 mg	
Oxycodone	60 mg	
Oxymorphone	30 mg	
Tapentadol	225 mg	
Tramadol	400 mg	400 mg/day is max dose and is not equivalent to 90 MME/day.

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD10	
2. Is the diagnosis funded by the OHP? Note: conditions such as fibromyalgia, TMJ, pelvic pain syndrome and tension headache are not funded by the OHP.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP. Note: Management of opioid dependence is funded by the OHP.
3. Is the requested medication a preferred agent?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber change to a preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #5
5. 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:** Approve for up to 12 months.	**No:** Go to #6
6. Is the prescription for a short-acting fentanyl product? Note: Short-acting transmucosal fentanyl products are designed for breakthrough cancer pain only. This PA does not apply to transdermal fentanyl patches.	**Yes:** Pass to RPh. Deny; medical appropriateness Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #7
7. Is the opioid prescribed for pain related to migraine or other type of headache? Note: there is limited or insufficient evidence for opioid use for many pain conditions, including migraine or other types of headache.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8

8. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber reviewed at least once in the past 3 months the scheduled substances the patient has recently been prescribed from other providers?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Did the patient's pain originate from acute injury, flare, or surgery that occurred in the last 6 weeks?	**Yes:** Go to #10	**No:** Go to #15
10. Has at least one non-opioid analgesic (e.g., NSAID, acetaminophen, and/or muscle relaxant) been tried and found to be ineffective or are contraindicated?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the opioid prescription for pain associated with a back or spine condition?	**Yes:** Go to #12	**No:** Approve for up to 30 days
12. Has the prescriber also developed a plan with the patient to stay active (home or prescribed exercise regimen) and with consideration of additional therapies such as spinal manipulation, physical therapy, yoga, or acupuncture?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is this the first opioid prescription the patient has received for this pain condition?	**Yes:** Approve for up to 7 days	**No:** Go to #14
14. Can the prescriber provide documentation of sustained improvement in function of at least 30% compared to baseline with prior use of opioid analgesics (e.g., validated tools to assess function include: Oswestry, Neck Disability Index, SF-MPQ, and MSPQ)?	**Yes:** Approve for up to 7 days	**No:** Pass to RPh. Deny; medical appropriateness.
15. Has the patient been prescribed opioid analgesics for more than 6 weeks?	**Yes:** Go to #16	**No:** Go to #10

16. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale.*	**Yes:** Document tool used to measure pain and/or function. Go to #17	**No:** Pass to RPh. May approve for up to 30 days one time. For future claims without documentation: deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.
17. Has the patient had a urinary drug screen (UDS) within the past year to verify absence of illicit drugs and non-prescribed opioids?	**Yes:** Go to #18	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.
18. Is the opioid prescription for pain associated with a back or spine condition?	**Yes:** Go to #19	**No:** Go to #20
19. Have any of the following therapies also been prescribed and utilized by the patient: spinal manipulation, physical therapy, yoga or acupuncture?	**Yes:** Document additional therapy. Approve for up to 7 days. <u>Note</u>: Risks outweigh benefits for back and spine conditions. OHP will not fund chronic use of opioids for back or spine conditions beginning 1/1/2018. Prescriber must develop a taper plan with the patient with a quit date before 1/1/2018. OHP funds treatment for patients who have become dependent or addicted to opioid analgesics.	**No:** Pass to RPh. Deny; medical appropriateness.

20. Does the total daily opioid dose exceed 90 MME (Table 1)?	**Yes:** Pass to RPh. May approve one time. For future claims: deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.	**No:** Approve for up to 30 days.

*The PEG is freely available to the public http://www.agencymeddirectors.wa.gov/Files/AssessmentTools/1-PEG%203%20item%20pain%20scale.pdf.
Citation of the original publication:
Krebs EE, Lorenz KA, Bair MJ, Damush TA, Wu J, Sutherland JM, Asch SM, Kroenke K. Development and initial validation of the PEG, a 3-item scale assessing pain intensity and interference. *Journal of General Internal Medicine*. 2009 Jun;24:733-738

Clinical Notes:

How to Discontinue Opioids.
Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)

Selecting the optimal timing and approach to tapering depends on multiple factors. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for patients on high dose opioids, as too rapid a taper may precipitate withdrawal symptoms or drug-seeking behavior. In addition, behavioral issues or physical withdrawal symptoms can be a major obstacle during an opioid taper. Patients who feel overwhelmed or desperate may try to convince the provider to abandon the taper. Although there are no methods for preventing behavioral issues during taper, strategies implemented at the beginning of chronic opioid therapy such as setting clear expectations and development of an exit strategy are most likely to prevent later behavioral problems if a taper becomes necessary.

1. Consider sequential tapers for patients who are on chronic benzodiazepines and opioids. Coordinate care with other prescribers (e.g. psychiatrist) as necessary. In general, taper off opioids first, then the benzodiazepines.
2. Do not use ultra-rapid detoxification or antagonist-induced withdrawal under heavy sedation or anesthesia (e.g. naloxone or naltrexone with propofol, methohexital, ketamine or midazolam).
3. Establish the rate of taper based on safety considerations:
    a. Immediate discontinuation if there is diversion or non-medical use,
    b. Rapid taper (over a 2 to 3 week period) if the patient has had a severe adverse outcome such as overdose or substance use disorder, or
    c. Slow taper for patients with no acute safety concerns. Start with a taper of ≤10% of the original dose per week and assess the patient's functional and pain status at each visit.
4. Adjust the rate, intensity, and duration of the taper according to the patient's response (e.g. emergence of opioid withdrawal symptoms (see Table below)).
5. Watch for signs of unmasked mental health disorders (e.g. depression, PTSD, panic disorder) during taper, especially in patients on prolonged or high dose opioids. Consult with specialists to facilitate a safe and effective taper. Use validated tools to assess conditions.
6. Consider the following factors when making a decision to continue, pause or discontinue the taper plan:
    a. Assess the patient behaviors that may be suggestive of a substance use disorder
    b. Address increased pain with use of non-opioid options.
    c. Evaluate patient for mental health disorders.
    d. If the dose was tapered due to safety risk, once the dose has been lowered to an acceptable level of risk with no addiction behavior(s) present, consider maintaining at the established lower dose if there is a clinically meaningful improvement in function, reduced pain and no serious adverse outcomes.
7. Do not reverse the taper; it must be unidirectional. The rate may be slowed or paused while monitoring for and managing withdrawal symptoms.

8. Increase the taper rate when opioid doses reach a low level (e.g. <15 mg/day MED), since formulations of opioids may not be available to allow smaller decreases.
9. Use non-benzodiazepine adjunctive agents to treat opioid abstinence syndrome (withdrawal) if needed. Unlike benzodiazepine withdrawal, opioid withdrawal symptoms are rarely medically serious, although they may be extremely unpleasant. Symptoms of mild opioid withdrawal may persist for 6 months after opioids have been discontinued (see Table below).
10. Refer to a crisis intervention system if a patient expresses serious suicidal ideation with plan or intent, or transfer to an emergency room where the patient can be closely monitored.
11. Do not start or resume opioids or benzodiazepines once they have been discontinued, as they may trigger drug cravings and a return to use.
12. Consider inpatient withdrawal management if the taper is poorly tolerated.

Symptoms and Treatment of Opioid Withdrawal.

Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)

Restlessness, sweating or tremors	Clonidine 0.1-0.2 mg orally every 6 hours or transdermal patch 0.1-0.2 mg weekly (If using the patch, oral medication may be needed for the first 72 hours) during taper. Monitor for significant hypotension and anticholinergic side effects.
Nausea	Anti-emetics such as ondansetron or prochlorperazine
Vomiting	Loperamide or anti-spasmodics such as dicyclomine
Muscle pain, neuropathic pain or myoclonus	NSAIDs, gabapentin or muscle relaxants such as cyclobenzaprine, tizanidine or methocarbamol
Insomnia	Sedating antidepressants (e.g. nortriptyline 25 mg at bedtime or mirtazapine 15 mg at bedtime or trazodone 50 mg at bedtime). Do not use benzodiazepines or sedative-hypnotics.

P&T Review: *11/16 (AG)*
Implementation: *TBD*

Long-acting Opioid Analgesics

Goals:

- Restrict use of long-acting opioid analgesics to OHP-funded conditions with documented sustained improvement in pain and function and with routine monitoring for opioid misuse and abuse.
- Restrict use of long-acting opioid analgesics for conditions of the back and/or spine due to evidence of increased risk vs. benefit.
- Promote the safe use of long-acting 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.

Length of Authorization:

90 days (except 12 months for end-of-life or cancer-related pain)

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 long-acting opioids and opioid combination products.

Note:

- 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 Morphine Milligram Equivalents per Day) of Opioid Products.

Opioid	90 MME/day	Notes
Codeine	600 mg	Codeine is not recommended for pediatric use; codeine is a prodrug of morphine and is subject to different rates of metabolism placing certain populations at risk for overdose.)
Fentanyl (transdermal patch)	37.5 mcg/hr	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	
Hydromorphone	22.5 mg	
Morphine	90 mg	
Oxycodone	60 mg	
Oxymorphone	30 mg	
Tapentadol	225 mg	
Tramadol	300 mg	300 mg/day is max dose and is not equivalent to 90 MME/day.
Methadone*	20 mg ***DO NOT USE unless very familiar with the complex pharmacokinetic and pharmacodynamics properties of methadone**. 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. Methadone is associated with an increased incidence of prolonged QTc interval, torsades de pointe and sudden cardiac death.	

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

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

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
TROXYCA ER	2 doses/day

Drug Product	Quantity Limit
XARTEMIS XR	4 doses/day
XTAMPZA ER	2 doses/day
ZOHYDRO ER	2 doses/day

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD10 code	
2. Is the diagnosis funded by the OHP? Note: Management of pain associated with *back or spine conditions with long-acting opioids* is not funded by the OHP*. Other conditions, such as fibromyalgia, TMJ, tension headache and pelvic pain syndrome are also not funded by the OHP.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP. Note: Management of opioid dependence is funded by the OHP.
3. Is the requested medication a preferred agent?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber change to a preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #5
5. 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:** Approve for up to 12 months	**No:** Go to #6
6. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 3 months that the patient has been prescribed opioid analgesics by only a single prescribing practice or prescriber?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the prescription for pain associated with migraine or other type of headache? Note: there is limited or insufficient evidence for opioid use for many pain conditions, including migraine or other types of headache.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8

8. Does the total daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #9
9. Is the patient concurrently on other short- or long-acting opioids (patients may receive a maximum of one opioid product regardless of formulation)? Note: There is insufficient evidence for use of concurrent opioid products (e.g., long-acting opioid with short-acting opioid).	**Yes:** Pass to RPh. Deny; medical appropriateness Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #10
10. Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale.**	**Yes:** Go to #12 Document tool used and score vs. baseline: _____	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.
12. 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 90 days.	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.

*See Guideline Note 60 within the Prioritized List of Health Services for conditions of coverage for pain associated with back or spine conditions: http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx

**The PEG is freely available to the public http://www.agencymeddirectors.wa.gov/Files/AssessmentTools/1-PEG%203%20item%20pain%20scale.pdf.

Citation of the original publication:

Krebs EE, Lorenz KA, Bair MJ, Damush TA, Wu J, Sutherland JM, Asch SM, Kroenke K. Development and initial validation of the PEG, a 3-item scale assessing pain intensity and interference. *Journal of General Internal Medicine*. 2009 Jun;24:733-738.

Clinical Notes:

How to Discontinue Opioids.

Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)

Selecting the optimal timing and approach to tapering depends on multiple factors. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for patients on high dose opioids, as too rapid a taper may precipitate withdrawal symptoms or drug-seeking behavior. In addition, behavioral issues or physical withdrawal symptoms can be a major obstacle during an opioid taper. Patients who feel overwhelmed or desperate may try to convince the provider to abandon the taper. Although there are no methods for preventing behavioral issues during taper, strategies implemented at the beginning of chronic opioid therapy such as setting clear expectations and development of an exit strategy are most likely to prevent later behavioral problems if a taper becomes necessary.

13. Consider sequential tapers for patients who are on chronic benzodiazepines and opioids. Coordinate care with other prescribers (e.g. psychiatrist) as necessary. In general, taper off opioids first, then the benzodiazepines.
14. Do not use ultra-rapid detoxification or antagonist-induced withdrawal under heavy sedation or anesthesia (e.g. naloxone or naltrexone with propofol, methohexital, ketamine or midazolam).
15. Establish the rate of taper based on safety considerations:
    a. Immediate discontinuation if there is diversion or non-medical use,
    b. Rapid taper (over a 2 to 3 week period) if the patient has had a severe adverse outcome such as overdose or substance use disorder, or
    c. Slow taper for patients with no acute safety concerns. Start with a taper of ≤10% of the original dose per week and assess the patient's functional and pain status at each visit.
16. Adjust the rate, intensity, and duration of the taper according to the patient's response (e.g. emergence of opioid withdrawal symptoms (see Table below)).
17. Watch for signs of unmasked mental health disorders (e.g. depression, PTSD, panic disorder) during taper, especially in patients on prolonged or high dose opioids. Consult with specialists to facilitate a safe and effective taper. Use validated tools to assess conditions.
18. Consider the following factors when making a decision to continue, pause or discontinue the taper plan:
    a. Assess the patient behaviors that may be suggestive of a substance use disorder
    b. Address increased pain with use of non-opioid options.
    c. Evaluate patient for mental health disorders.
    d. If the dose was tapered due to safety risk, once the dose has been lowered to an acceptable level of risk with no addiction behavior(s) present, consider maintaining at the established lower dose if there is a clinically meaningful improvement in function, reduced pain and no serious adverse outcomes.
19. Do not reverse the taper; it must be unidirectional. The rate may be slowed or paused while monitoring for and managing withdrawal symptoms.
20. Increase the taper rate when opioid doses reach a low level (e.g. <15 mg/day MED), since formulations of opioids may not be available to allow smaller decreases.
21. Use non-benzodiazepine adjunctive agents to treat opioid abstinence syndrome (withdrawal) if needed. Unlike benzodiazepine withdrawal, opioid withdrawal symptoms are rarely medically serious, although they may be extremely unpleasant. Symptoms of mild opioid withdrawal may persist for 6 months after opioids have been discontinued (see Table below).
22. Refer to a crisis intervention system if a patient expresses serious suicidal ideation with plan or intent, or transfer to an emergency room where the patient can be closely monitored.
23. Do not start or resume opioids or benzodiazepines once they have been discontinued, as they may trigger drug cravings and a return to use.
24. Consider inpatient withdrawal management if the taper is poorly tolerated.

Symptoms and Treatment of Opioid Withdrawal. Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)	
Restlessness, sweating or tremors	Clonidine 0.1-0.2 mg orally every 6 hours or transdermal patch 0.1-0.2 mg weekly (If using the patch, oral medication may be needed for the first 72 hours) during taper. Monitor for significant hypotension and anticholinergic side effects.
Nausea	Anti-emetics such as ondansetron or prochlorperazine
Vomiting	Loperamide or anti-spasmodics such as dicyclomine
Muscle pain, neuropathic pain or myoclonus	NSAIDs, gabapentin or muscle relaxants such as cyclobenzaprine, tizanidine or methocarbamol
Insomnia	Sedating antidepressants (e.g. nortriptyline 25 mg at bedtime or mirtazapine 15 mg at bedtime or trazodone 50 mg at bedtime). Do not use benzodiazepines or sedative-hypnotics.

P&T Review: *11/16 (AG); 05/16*
Implementation: *TBD*

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.			
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: 5-10 mg q 4-6 hours ER: 10 mg q 12 hours	Dosing limits based on combinations (e.g., acetaminophen) may further limit the maximum daily dose. 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: 2 mg q 4–6 hours ER 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 10 mg q 4 hours ER 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: 5 mg q 4-6 hours ER: 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. 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: 5–10 mg q 4-6 hours ER: 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. 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: 50 mg q 4-6 hours ER: 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. 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. 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) 300 mg/24 hours (ER)	IR: 50 mg q 4-6 hours ER: 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. 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 previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the requested medication a preferred agent?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber change to a preferred product? Note: 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.	**No:** Go to #5
5. 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:** Approve for up to 12 months	**No:** Go to #6
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? Note: 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: • Verification of patient's opioid claims history in the Oregon PDMP at least every 3 months • Documentation of sustained improvement in both baseline pain and function at least every 3 months • 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. Note: 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 (e.g., validated tools to assess function include: Oswestry, Neck Disability Index, SF-MPQ, and MSPQ)?	**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. 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. 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. 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: • Verification of patient's opioid claims history in the Oregon PDMP at least every 3 months • Documentation of sustained improvement in both baseline pain and function at least every 3 months • 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. Without documentation, pass to RPh. Deny; medical appropriateness.