Drug Use Research & Management Program
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Drug Evaluation: Tramadol

Date of Review: March 2017
Generic Name: tramadol
PDL Class: Opioids, short acting and long acting

End Date of Literature Search: 02/10/2017
Brand Name (Manufacturer): Ultram
Dossier Received: no

Purpose of Review: The purpose of this review is to establish the place in therapy of tramadol for the management of acute and chronic non-cancer pain relative to other opioid therapy. Additionally, this paper will describe the risk for misuse, abuse, diversion, and dependence of tramadol relative to other opioids, which may affect coverage decisions.

Research Questions:

- What is the comparative efficacy or effectiveness of tramadol compared to other opioids in reducing acute or chronic non-cancer pain and improving functional outcomes in adult and pediatric patients?
- What is the evidence for comparative harms, safety concerns (cognitive impairment, sedation, and respiratory depression), unintended effects (euphoria and withdrawal cravings) and risk of misuse, abuse, dependence, and diversion of tramadol compared to other opioids in adult and pediatric patients treated for chronic non-cancer pain?
- Are there subpopulations of patients based on age (e.g., pediatric patients), race, comorbidities (e.g., renal or hepatic impairment, history of opioid abuse, alcohol dependence, mental health conditions, or pre-initiation functional level), concomitant drug therapies (benzodiazepines or marijuana use), or socio-economic status (e.g., Medicaid) who may be at a higher risk for harms or risk for misuse, abuse, dependence, and diversion with tramadol use?

Conclusions:

- There is low quality evidence that tramadol is more effective than placebo in reduction of pain and improved function for the treatment of chronic pain, chronic low back pain, and osteoarthritis. For the treatment of chronic low back pain, tramadol was associated with moderate effects on pain versus placebo (standardized mean difference [SMD] -0.55; 95% CI -0.66 to -0.44, with a mean difference of 1 point or less on a 0-10 pain scale) and small effects on function (SMD -0.18; 95% CI -029 to -0.07, mean difference of approximately 1 on the Roland-Morris Disability Questionnaire [RDQ]), which is well below the level considered clinically important.
- There is very low quality evidence that there is no difference in pain relief between sustained release tramadol and transdermal buprenorphine in patients with musculoskeletal pain.
- For the treatment of post-operative pain in children and adolescents, there is low quality evidence from 4 trials demonstrating no clear difference in the need for rescue analgesia between tramadol and morphine (RR 1.25; 95% CI 0.83 to 1.89). An accurate risk-benefit analysis is difficult since adverse events were poorly reported.

Author:

- There is insufficient long-term evidence of the comparative efficacy or safety of tramadol compared to other opioid therapies.
- Although tramadol has lower affinity for the μ-opioid receptor, there is insufficient evidence that tramadol has a lower addiction risk than other opioid analgesics. One RCT comparing buprenorphine patches to tramadol found no indication for abuse or diversion in either treatment group. An additional study with many limitations suggested that tramadol had significantly lower rates of abuse and dependence compared to hydrocodone (2.7% vs. 4.9%).
- Common adverse events that occur more frequently with tramadol than placebo are nausea (22.2% vs. 8.0%), constipation (18% vs. 5.3%), dizziness (13.2% vs. 4.6%) and somnolence (13.2% vs. 3.8%). Unique safety concerns associated with tramadol use include an increase in the risk of seizures and serotonin syndrome when used with other serotonergic medications. Those who are ultra-rapid CYP2D6 metabolizers appear to be more susceptible to opioid effects from tramadol, including dependency and sedation.

Recommendations:

- Maintain tramadol in current opioid prior authorization policy.

Background:

In recent years, there has been a growing understanding of significant harms associated with opioids, particularly at high doses, including addiction, abuse, and overdose. Opioid overdose has steadily increased from 2000 to 2015, with 91 Americans dying every day from opioid overdose.[1] Furthermore, there is a lack of high-quality evidence that opioids improve pain or function for chronic pain. Prevention, assessment, and treatment of chronic pain are challenging for clinicians. Pain can limit the ability to perform certain activities, decrease work productivity and quality of life. 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. The contributing factors associated with overdose can be divided into those associated with the opioid itself (e.g., potency, dose, or duration of action) and factors specific to the patient (e.g., older age, adolescence, depression, substance use disorder, or history of overdose).[2] As a result of the increase in opioid overdose, the Center for Disease Control and Prevention (CDC) released guidelines for prescribing opioids for chronic pain.[3] The CDC guidelines prefer nonpharmacological therapy and non-opioid analgesic therapy before turning to opioids. The maximum recommended dose of opioids should not exceed 90 morphine equivalents.[3] However, tramadol is not included in the guideline recommendations. Tapentadol, another mu receptor agonist and SNRI, is included in dosing recommendations with the following information: "*morphine milligram equivalent is based on degree of* μ*-receptor activity, but it is unknown if this drug is associated with overdose in the same dose-dependent manner as observed with medications that are solely mu receptor agonists."* [3]

Tramadol is an opioid medication that produces analgesic effects through a dual mechanism of action. Tramadol is pharmacologically similar to other opioids but has a lower affinity for μ-opioid receptors and also acts as a weak inhibitor of the neuronal reuptake of norepinephrine and serotonin.[4] It has been suggested that tramadol has a lower potential of abuse and dependence due to its relatively low affinity for μ-opioid receptor. The affinity for the μ-opioid receptor is 4000-fold less than that of morphine; however, tramadol has still been shown to cause significant withdrawal syndrome and can include both opioid and SNRI-associated withdrawal symptoms.[5] When initially approved in 1994, it was classified as a non-scheduled drug and was not regulated by the Drug Enforcement Administration (DEA). Preliminary data had demonstrated a low potential for abuse, and it was already being used extensively in Europe.[5] Following approval, post-marketing surveillance found that there were approximately 2 to 3 cases per 100,000 per month of drug abuse or diversion with tramadol, and data demonstrated that higher doses of tramadol resulted in reinforcement and abuse potential in opioid abusers.[6] In 2014, the DEA officially scheduled tramadol as a Schedule IV substance in the US.[7] The DEA reviewed available data and concluded that there is strong evidence tramadol and propoxyphene are similar in their abuse potential pattern and appropriate to schedule tramadol as such. Furthermore, they cited that tramadol produces similar pharmacological effects as other opioids, including analgesia and respiratory depression.[7] As tramadol also inhibits reuptake of serotonin and norepinephrine, additional safety concerns

need to be accounted for, including the risk of serotonin syndrome and an increased risk of seizures.[4,5] The most common adverse reactions with tramadol include nausea, dizziness, and vomiting. At therapeutic doses, tramadol does not cause clinically relevant respiratory depression.

Although tramadol is not FDA approved for children 17 years or younger, it is commonly used off-label because many think it is safer and less potent than other opioids. [8] In 2015, the Food and Drug Administration (FDA) released a drug safety communication to further investigate the use of tramadol in children, because of the rare but serious risk of slowed or difficult breathing in those thought to be ultra-rapid metabolizers.[8] The risk may be increased in children treated for pain after tonsillectomy or adenoidectomy surgery.

In general, tramadol has shown modest efficacy in pain reduction. Pain intensity measurements used in trials include the visual analogue scale (VAS scale, 0-100 or 0-10) and the numerical rating scale (NRS; 0-10). For acute pain, the minimum clinically important difference in the 10-point VAS is 1.4; (95% CI 1.2 to 1.6). The proposed thresholds for a meaningful difference in chronic pain are about 2.0 points on the 0 to 10 point scale or 20 points on the 0-100 point scale. The impact on disability is a key clinical outcome. Scales used to measure function include the Oswestry Disability Index (ODI) and the Roland Morris Disability Questionnaire (RDQ). Improvements greater than 20 points on the ODI and 5 points on the RDQ are considered clinical important differences.[9]

Table 1. Pharmacology and Pharmacokinetic Properties.[10]

Parameter	
Mechanism of Action	Binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin
Oral Bioavailability	75%
Distribution and Protein Binding	Volume of distribution 2.6 L/kg in males and 2.9 L/kg in females; protein binding 20%
Elimination	30% excreted in the urine as unchanged drug; 60% excreted as metabolites
Half-Life	6.7 hours
Metabolism	CYP2D6, CYP3A4

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 2**, 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.

Systematic Reviews:

An Agency for Healthcare Research and Quality systematic review appraised the evidence on the comparative benefits and harms of noninvasive treatments for low back pain and included systematic reviews and RCTs comparing pharmacological treatments, including opioids and tramadol.[9] For chronic low back pain, the authors found moderate quality evidence that both opioids and tramadol were more effective in pain relief and function than placebo or sham.[9] Tramadol was associated with moderate effects on pain versus placebo (Standardized Mean Difference (SMD) -0.55; 95% Confidence Interval -0.66 to -0.44, with a mean difference of 1 point or less on a 0-10 pain scale). Compared to placebo, opioids were associated with small effects (SMD -0.43; 95% CI -0.52 to -0.33 for a mean difference of approximately 1 point on a 0-10 pain scale).[9] Effects on function were small for tramadol (SMD -0.18; 95% CI -0.29 to -0.07, mean difference of approximately 1 on the Roland-Morris Disability Questionnaire [RDQ]) and opioids (SMD -0.26; 95% CI -0.37 to -0.15, mean difference of approximately 1 on the RDQ) compared to placebo.[9] The RDQ is a measurement used to assess the impact of opioids on disability and ranges from 0-24. Two trials compared tramadol (50 mg three times daily) to celecoxib 200 mg twice daily. One trial found a small advantage for celecoxib on the percent of patients with a reduction in pain scores of at least 30% (66% responder vs. 57% for tramadol).[9] The second trial found no significant difference between the two therapies. No trials directly compared tramadol to other opioids. Trials were not designed to assess long-term harms or the risk for overdose, abuse, or addiction.

A rapid response report from Canadian Agency for Drugs and Technologies Health (CADTH) reviewed the clinical effectiveness of tramadol and tramadol plus acetaminophen for the management of pain in adults compared to placebo or active treatment.[11,12] Four RCTs were identified comparing tramadol to placebo, one RCT compared tramadol with buprenorphine and one RCT compared tramadol with NSAIDs. Additionally, three systematic reviews were identified that showed greater pain reduction with tramadol or a tramadol combination product when compared with placebo. However, differences were only statistically significant in one systematic review that evaluated chronic low back pain (MD -0.55; 95% CI -0.66 to -0.44).[11] 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 reductions: 56.2% vs. 37.9% for tramadol combination vs. placebo, respectively).[11] There was an increase in adverse events with tramadol compared to placebo (RR 1.74; 95% CI 1.20 to 2.52). Common adverse events that occurred more frequently with tramadol than placebo were nausea (22.2% vs. 8.0%), constipation (18% vs. 5.3%), dizziness (13.2% vs. 4.6%), and somnolence (13.2% vs. 3.8%).[11] In another systematic review, improvement in pain intensity was greater with tramadol compared to celecoxib (63.2% vs. 49.9%), but adverse events were higher compared to celecoxib as well (30.4% vs. 14.4%).[11] One RCT in patients with musculoskeletal pain found no difference in change in VAS score between sustained release tramadol and transdermal buprenorphine.[11] The authors concluded that greater pain reduction and more adverse events are associated with tramadol compared with placebo.[11] A single RCT suggests that efficacy and safety with tramadol and buprenorphine were comparable. One non-randomized study compared the use of tramadol plus acetaminophen to transdermal fentanyl for the control of postoperative pain following corrective eye surgery. Transdermal fentanyl was significantly better at reducing pain, but was also associated with an increase in adverse events.[12]

A Cochrane systematic review evaluated the analgesic effectiveness, effect on physical function, duration of benefit, and the safety of oral tramadol in people with osteoarthritis.[13] Three placebo-controlled studies (n=362) reported a reduction in pain intensity compared to placebo (8.5 units less on a scale from 0-100; 95% CI -12.05 to -4.9) and a reduction in the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score, representing an improvement in pain, stiffness, and function (reduction in score by -0.34; 95% CI -0.49 to -0.19 on a scale of 0 to 10).[13] The most common adverse events reported in these short term studies (up to 3 months) were nausea, vomiting, dizziness, constipation, somnolence, tiredness, and headache. Patients on tramadol were more likely to develop minor (RR 2.27; 95% CI 1.77 to 2.66) and major adverse events (RR 2.6; 95% CI 1.96 to 3.63) compared to placebo.[13] There is insufficient evidence comparing tramadol to other drugs in the treatment of osteoarthritis and insufficient long term efficacy or safety data.

Another Cochrane review compared opioids to placebo or other treatments for chronic low back pain.[14] Tramadol was included in 5 trials (n=1378) resulting in low quality evidence of a significant reduction in pain compared to placebo (SMD -0.55; 95% CI -0.66 to -0.44) with a moderate effect size.[14] There was moderate quality evidence of improved function compared to placebo (SMD -0.18; 95% CI -0.29 to -0.07) with a small effect size.[14] Other opioids, including morphine, hydromorphone, and oxycodone) were also found to be superior to placebo for pain (SMD -0.43; 95% CI -0.52 to -0.33) and function (SMD -0.26; 95% CI -0.37 to -0.15). [14] One RCT (n=1583) provided very low quality evidence of little pain relief with tramadol 50 mg four times a day compared to celecoxib (RR 0.82; 95% 0.76 to 0.90). There are no RCTs evaluating the long term (longer than 4 months) safety or effectiveness of opioid therapy for treatment of chronic low back pain. As studies were short term only, there was limited evidence evaluating severe adverse effects, and trials were not designed to assess risk of misuse, abuse, addiction, overdose, or death.

A Cochrane systematic review evaluated the effectiveness and side effect profile of tramadol for postoperative pain relief in children and adolescents undergoing surgical procedures.[15] Twenty RCTs including 1170 patients were included in the analysis. The overall risk of bias in the trials was unclear because allocation concealment and blinding of outcome assessors were poorly described. Low quality evidence from 5 trials found that the need for rescue analgesia in the postoperative care unit was reduced in children receiving tramadol compared to placebo (RR 0.40; 95% CI 0.20 to 0.78).[15] There was low quality evidence from 4 trials which found no clear difference in the need for rescue analgesia between tramadol and morphine (RR 1.25; 95% CI 0.83 to 1.89).[15] Other comparators included in the studies are not currently available in the United States. Trials which included patients with moderate to severe pain did not use a validated pain scale, and results cannot be interpreted. Generally, adverse events were poorly reported. Those treated with tramadol, compared with placebo, did not have reduced postoperative nausea and vomiting (RR 0.84; 95% CI 0.28 to 2.52). [15] The authors concluded that the overall strength of the evidence is low or very low due to small studies and methodological problems. Tramadol appears to be slightly more effective than placebo in reducing pain in the postoperative setting, but evidence for the comparison to other opioids remains uncertain. An accurate risk-benefit analysis is difficult since adverse events were poorly reported. [15]

Guidelines:

Guidelines for the noninvasive treatment of acute, subacute, and chronic low back pain were published from the American College of Physicians (ACP) in 2017.[16] Recommendations were made based on a systematic review of RCTs evaluating reduction or elimination of low back pain, improvement in back specific and overall function, improvement in health-related quality of life, reduction in work disability and return to work, global improvement, number of back pain episodes or time between episodes, patient satisfaction, and adverse effects. The guidelines recommend tramadol or duloxetine as second-line pharmacological therapy after NSAIDs and nonpharmacological treatment. Tramadol is recommended before opioids are considered due to the known risks and realistic benefits of opioids (weak recommendation; moderate-quality evidence). The guidelines specify that the risk of abuse with tramadol is similar to other opioids. However, moderate-quality evidence demonstrated tramadol had a moderate effect on pain and a small effect on function in the short term, while opioids were shown to have a small effect on both.[16]

The VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain found insufficient evidence to recommend for or against any specific opioid or opioid formulation, specifically for tramadol and other dual-mechanism opioids.[17] The guidelines recommend non-opioid therapy over opioid therapy and against long-term opioid therapy for pain in patients with untreated substance use disorder. Although the guidelines recommend against opioid doses over 90 mg morphine equivalent daily for treating chronic pain, they do not make any specific recommendations for or against tramadol therapy in relation to other long-acting

opioids. All recommendations for safety measures and risk mitigation strategies applied to tramadol as well, and authors found no evidence on the safety of tramadol that met inclusion criteria.

Dependence/Abuse Potential:
The literature describing tramadol dependence is mostly limited to case reports and case series. Data demonstrates that tramadol dependence may occur when used daily for more than a few weeks, but there is limited data comparing the abuse potential between tramadol and other opioids. Those who are ultra-rapid CYP2D6 metabolizers appear to be more susceptible to opioid effects from tramadol, including dependency and sedation.[6,18]

A CADTH health technology assessment evaluated the evidence for addition potential with tramadol compared to other opioids for the treatment of pain. The 2010 report identified 2 RCTs in which the addiction potential of tramadol was compared to buprenorphine patches and hydrocodone. The RCT comparing buprenorphine patches to tramadol for the treatment of osteoarthritis pain found no indication of abuse or diversion in either treatment group. Conclusions were not able to be made regarding the abuse potential of either therapy. The second 12-month trial compared the prevalence of tramadol abuse with nonsteroidal anti-inflammatory drugs (NSAIDs) and hydrocodone-containing analgesics in chronic noncancer pain. Individuals with current substance abuse problems were excluded. Abuse was assessed with the Abuse Index questionnaire which was not validated. After 12 months, 2.7% of tramadol users and 4.9% of hydrocodone users ($p<0.01$) were identified as abusing the drug, suggesting that tramadol had significantly lower rates of abuse and dependence compared to hydrocodone. However, there were many limitations to this study including unclear randomization and a lack of intention-to-treat analysis. Furthermore, those subjects at highest risk of abuse were not included in the trials. CADTH reported insufficient evidence to evaluate whether tramadol has a lower addiction risk than other opioid analgesics.

A post-marketing surveillance program reported that withdrawal symptoms were common following abrupt discontinuation of tramadol. Both typical signs and symptoms seen from withdrawal of other opioids (nausea, sweating, restlessness, anxiety, or insomnia) as well as atypical symptoms (confusion, paranoia, severe panic attacks, hallucinations, or numbness) were reported.[19] From 1995 through 2000, 422 cases of opiate withdrawal were observed for tramadol. There were 644 cases of positive, possible, or alleged abuse.

A retrospective analysis included data from the National Poison Data System for both tramadol and tapentadol exposures from June 2009 through December 2011.[20] A total of 8566 tramadol cases were reviewed. The most common reason for exposure to tapentadol was suspected suicide (43.4%) followed by intentional misuse (16.4%). The majority of patients experienced a mild outcome, and there were a total of 10 deaths following exposure to tramadol (0.1%). Compared to tapentadol, there was a significant increase in the risk of seizures (14% vs. 1.8%; RR 7.94; 95% CI 2.99 to 10.91) and vomiting (RR 1.96; 95% CI 1.07 to 3.60). For patients on tramadol, the rates of seizures were 14.6%, vomiting 9.0%, coma 1.2%, and respiratory depression was 1.6%.[20]

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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.

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); 05/16*
Implementation: *TBD*

Appendix 2: Search Strategy

# ▲	Searches	Results
2	opioid.mp. or Analgesics, Opioid/	59257
3	Chronic Pain/ or noncancer pain.mp.	7714
4	1 and 2 and 3	60
5	limit 4 to (english language and humans and yr="2007 -Current" and (clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews))	9

☐	1	tramadol.mp. or Tramadol/	3328
☐	2	abuse potential.mp.	960
☐	3	addiction.mp.	23524
☐	4	dependence.mp. or Morphine Dependence/	105589
☐	5	Drug Overdose/ or overdose.mp.	11256
☐	6	withdrawal.mp.	50933
☐	7	2 or 3 or 4 or 5 or 6	179414
☐	8	1 and 7	343
☐	9	limit 8 to (english language and humans and yr="2005 -Current" and (controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews))	30