

Long-Acting Opioids Clinical Pearls for the Washington Rx Preferred Drug List

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Background

In 2003, the Washington State Pharmacy and Therapeutics Committee (P&T), the agency directors of the Department of Social and Health Services-Medical Assistance Administration (DSHS-MAA), Labor and Industries (L&I), and the Health Care Authority-Uniform Medical Plan (UMP) declared generic extended-release morphine sulfate and methadone to be the “preferred” long-acting opioids for patients covered by their prescription insurance. This policy will go into effect on May 1st, 2004. Patients currently using “non-preferred” agents should be evaluated for conversion to preferred agents.

Purpose

The purpose of this document is to inform pharmacists of the clinical efficacy, safety and cost rationale for these policy changes, and to optimize their ability to assure safe and effective conversion of patients to the appropriate agent.

Washington State Evidence Based Preferred Drug List Long-Acting (LA) Opioids

- **Generic, long-acting morphine**
- **Methadone**

For patients with cancer-related pain these additional opioids are allowed via expedited prior authorization (EPA):

- OxyContin[®] (oxycodone sustained-release)
- Duragesic[®] (fentanyl transdermal)
- Levorphanol
- Avinza[®] & Kadian[®] (branded long-acting morphine)

Clinical Efficacy

- At equianalgesic doses, all opioids are equally effective. In general, to achieve adequate analgesia with a particular opioid the dose should be increased unless adverse effects occur.
- Head-to-head trials have not found significant differences in efficacy with any of the opioids.
- Equipotency is complicated by differences in opioid receptor binding affinity, pharmacokinetics, and side effect profiles of the individual agents.
- It is difficult to predict responses to opioids due to significant inpatient variability. What works for one patient may not work for another.
- Reports of lack of effect should be evaluated for appropriateness of dosing regimen and adherence, and are not necessarily therapeutic failures.
- Methadone’s chemical structure differs from other opioids and incomplete cross-tolerance may occur when converting to other agents. When high doses of other opioids cannot control pain, a trial of methadone may be beneficial, as the patient may achieve effective analgesia with relatively lower doses of methadone.

Safety

MORPHINE

- Structurally related to codeine, therefore allergic cross-reactivity is more likely than with methadone.
- Associated with non-allergic, dose-related histamine release that may precipitate itching and related symptoms. These symptoms can often be controlled with antihistamine therapy.
- Few potential pharmacokinetic drug interactions
- Dosage reductions recommended in patients with renal and liver failure. (See Dosing section)

METHADONE

- Accumulation of drug ($t_{1/2}$ 15-30 hours) in tissue can lead to increased adverse effects, necessitating a slow titration phase (5-10 days for steady-state). This may delay the onset of effective analgesia.
- Elimination half-life does not correspond with duration of analgesia, which is 6-8 hours.
- Multiple factors cause variable patient responses to methadone and make conversion from other opioids more difficult. Generally, it is easier to start methadone as initial opioid therapy and titrate as needed.

- Potential drug interactions: inhibitors or inducers of CYP 3A4, 2D6, 1A2 can increase or decrease methadone levels respectively. (See appendix I) Methadone is a CYP 2D6 enzyme inhibitor.
- Decreased incidence of constipation compared with oxycodone and morphine.
- Methadone is associated with a negative social stigma that may dissuade some patients from using the agent. Pharmacists should acknowledge patient ambiguity, educate on the beneficial analgesic effects of methadone, and relate that many patients that are not “addicts” use methadone for pain control.

Cost Comparisons

Methadone (generic)	\$0.26
Morphine extended release (generic)	\$2.36
Kadian (Morphine 12 - 24 hr)	\$3.56
Levorphanol (generic)	\$3.68
Avinza (Morphine 24 hr)	\$4.09
Duragesic (Fentanyl patch)	\$4.34
OxyContin	\$4.73

*Based on equivalent doses to morphine 60mg/day and DSHS reimbursement costs

Steps to Converting Patients to Preferred Long-acting Opioids

#1. Patient assessment and preferred agent selection

To make a reasonable recommendation when converting long-acting opioid therapy, you will want to know:

- ***Is this opioid therapy new or continuing?*** If new, methadone might be a reasonable consideration if your patient is agreeable to some dosage adjustments during the titration phase. This might be best attempted when the pain is not severe or acute, and, the use of breakthrough pain medications may be helpful.
- ***What is the indication for the opioid therapy?*** The preferred agents are the most cost-effective and should be considered first-line therapy for all indications. However, there are secondary LA opioids available utilizing the cancer-related EPA code.
- ***Does the patient have any opioid allergies?*** If allergic to codeine and/or morphine, methadone would be the recommended option. However, confirm that the reaction was a true allergy and not intolerance.
- ***Which opioids has this patient tried?*** Rationale for the use of non-preferred agents includes therapeutic failure (effective analgesia not obtained despite appropriate dose escalation) and intolerance (the occurrence of adverse effects that are not responsive to dosage adjustments or are not reasonable to treat with adjunctive therapies). The patient should be converted to the preferred agents unless this is legitimate medical rationale for using non-preferred options.
- ***What other medications is the patient taking?*** Review concurrent medications for drugs that may interact with methadone (see appendix I). Morphine may be the preferred agent in the presence of clinically significant interactions with methadone.
- ***Do they have active renal disease?*** If so, decrease initial doses of morphine accordingly. If CrCl is 10-50mL/minute, decrease dose by 25%. If CrCl is <10mL/minute, decrease dose by 50%.
- ***Is this patient adherent?*** If there is a concern for the patient exceeding the prescribed dose, caution them on the dangers of long-acting opioid overdose. Also, use methadone very cautiously in these patients, and counsel on the potential delay in onset of analgesic effect.

#2. Determining the most appropriate conversion dose

General Dosing Information

- Consideration should always be given to monitoring the patient for:
 - Adequate analgesia and use of “rescue” medications
 - Adverse effects (nausea, constipation, oversedation, itching, etc.)
- When converting to a new opioid, if pain is not adequately controlled, consider a higher conversion dose.

MORPHINE

- Long-acting morphine is usually dosed every 8-12 hours routinely. It is not recommended for PRN use.

- When initiating long-acting morphine, the recommended starting dose is 15mg BID. Allow at least 3 days between dose adjustments, and increase total daily doses by 15-30mg as necessary to establish effective analgesia. Initial dosing and dose increases should include consideration for concurrent utilization of short-acting opioids.
- Morphine exhibits linear kinetics, which simplifies dosing and conversion from other opioids.
- Dosage reductions are recommended in patients with renal and liver failure. If CrCl is 10-50mL/minute, decrease dose by 25%. If CrCl is <10mL/minute, decrease dose by 50%.

METHADONE

- Methadone is dosed 2-4 times a day when used for pain management.
- When starting new pain management therapy with methadone the recommended starting dose is 2.5-5mg BID-TID.
- When converting a patient to methadone the total daily dose of methadone should be divided TID-QID initially however, the frequency can be adjusted to BID-TID when a stable dose is reached.
- Allow at least 1 week between dose adjustments, and increase total daily doses by 2.5-5mg as necessary to establish effective analgesia.
- All dosing should include consideration for concurrent utilization of short-acting opioids.
- Methadone has unique pharmacokinetic qualities that make dose conversions more difficult. Disproportionately smaller doses of methadone are required when converting from larger doses of opioids. There are many formulas to assist with these dosage conversions, however, results may vary with each. While methadone can be used safely and effectively for pain management, it typically requires some experience with the agent to gain skill and confidence in optimizing dosing.
- When converting to methadone from doses greater than 480mg of morphine or 320mg of oxycodone, consult with a pain specialist or someone with expertise in methadone use.
- It is crucial to educate patients regarding the appropriate use of methadone and to caution about the potential risks of exceeding the prescribed dosage. (See patient assessment and counseling section).

Long-acting Opioid Dosing Conversion Table

Note: This conversion table is a tool to assist in approximating an equivalent morphine or methadone dose when converting from stable doses of OxyContin[®]. Clinical judgment must be exercised in utilizing the conversion table and in making adjustments to the suggested conversion dose. There are numerous conversion tools available, one of which is Global RPh's narcotic dosing converter found at <http://www.globalrph.com/narcoticonv.htm>.

OxyContin [®] dose (mg/day)	Long-acting morphine dose* (mg/day)	Methadone dose (mg/day)
20mg	30mg	10mg
40mg	60mg	20mg
80mg	120mg	20 - 25mg
120mg	180mg	25 - 30mg
160mg	240mg	30 - 35mg
200mg	300mg	30 - 35mg
240mg	360mg	35mg
280mg	420mg	40mg
320mg	480mg	45mg
<ul style="list-style-type: none"> • The total daily dose of long-acting morphine should be divided BID, doses (>240mg/day) may require TID dosing. • The total daily dose of methadone should be divided TID-QID initially, however, the frequency can be adjusted to BID-TID when a stable dose is reached. 		

*Renal adjustments for morphine: CrCl =10-50mL/minute → decrease dose by 25%. CrCl <10mL/minute → decrease dose by 50%.

#3. Patient Education and Consultation

For your patients who are affected by a switch to a preferred agent, educate them on the following points:

- Inform patients that all long-acting opioids are equally effective at equianalgesic doses. Therefore, the agents that are generically available are preferred by the state in order to reduce drug expenditures.
- The patient's physician and pharmacist will work with them to find the best drug and dose to control their pain and prevent adverse effects. Reassure them that the dose will be titrated to achieve adequate analgesia.

- Remind patients taking methadone that achieving the full analgesic effects may take up to one week following dose adjustments. Pain relief during the last few days of that week may be greater than during the first few days of that week.
- Educate patients to look for these signs and symptoms that indicate the dose may not be adequate for analgesia:
 - Pain is more severe
 - Increased use of breakthrough pain medications
- Educate patients to look for these signs and symptoms that indicate the opioid dose may be too high (leading to adverse effects):
 - Increased sedation
 - Dizziness, drowsiness
 - Itching
 - Constipation or urinary retention
 - Nausea, vomiting
 - Euphoria
 - Miosis or visual disturbances
 - Shortness of breath
 - Bradycardia or tachycardia
 - Hypotension
 - Syncope
- Advise patients to avoid abrupt discontinuation of their opioid medication without consulting their physician. Educate patients about withdrawal symptoms, which include flu-like symptoms, malaise, irritability, abdominal pains, runny-nose, and diarrhea.
- For their safety, advise patients to take their medication only as prescribed. The patient should be specifically instructed to stop the previous long-acting opioid agent and begin taking the new agent with emphasis on the risk of using both medications.
- If patients have questions or concerns, or are experiencing adverse effects or changes in pain control, they should contact their physician or pharmacist.

References and Resources

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Appendix I: Methadone drug-drug interactions

Methadone is metabolized primarily by CYP 3A4, but also by CYP 1A2 and 2D6.

Note: This table lists some commonly reported cytochrome P450 enzyme inhibitors and inducers, but may not be all inclusive.

Effect	Mechanism	Drugs involved
Increased methadone levels	CYP1A2 inhibition	ciprofloxacin, cimetidine, fluvoxamine, enoxacin, ethinyl estradiol, isoniazid, mexilitine, norfloxacin, tacrine, zileuton
	CYP2D6 inhibition	Amiodarone, bupropion, chloroquine, cimetidine, diphenhydramine, fluoxetine, haloperidol, paroxetine, perphenazine, propafenone, propoxyphene, quinacrine, quinidine, quinine, risperidone, ritonavir, sertraline, terbinafine, thioridazine, chronic alcohol ingestion
	CYP3A4 inhibition	Amprenavir, clarithromycin, cyclosporine, danazol, delavirdine, diltiazem, erythromycin, ethinyl estradiol, fluconazole, fluoxetine, fluvoxamine, gemfibrozil, grapefruit juice, indinavir, isoniazid, itraconazole, ketoconazole, miconazole, nefazodone, nelfinavir, nicardipine, quinupristin/dalfopristin, ritonavir, saquinavir, troleandomycin, verapamil, zafirlukast
Decreased methadone levels	CYP1A2 induction	barbiturates, carbamazepine, rifampin, nicotine
	CYP2D6 induction	Chronic alcohol ingestion
	CYP3A4 induction	Aminoglutethimide, barbiturates, carbamazepine, efavirenz, griseofulvin, nafcillin, nevirapine, oxcarbazine, phenytoin, primidone, rifabutin, rifampin, St. John's Wort
Increased methadone toxicity	Adverse effects of methadone potentiated	CNS depressants, MAO inhibitors, phenothiazines, tricyclic antidepressants
Increased concomitant drug levels	CYP2D6 inhibition by methadone	Alprenolol, amitriptyline, carvedilol, cevimeline, chlorpromazine, citalopram, clomipramine, codeine, debrisoquin, desipramine, dextromethorphan, efavirenz, encainide, flecainide, fluoxetine, fluvoxamine, haloperidol, hydrocodone, imipramine, loratadine, maprotiline, methamphetamine, metoprolol, mexiletine, mianserin, nortriptyline ondansetron, oxycodone, paroxetine, perphenazine, promethazine, propafenone, propoxyphene, propranolol, risperidone, sertraline, tamoxifen, thioridazine, timolol, tolterodine, tramadol, trazodone, venlafazine, zidovudine

Adapted from: Hansten PD, Horn JR. *The top 100 drug interactions: A guide to patient management*. 2001.



Your OxyContin Prescription is Changing!

Patients currently taking long-acting oxycodone - OxyContin[®] - for pain will now be prescribed a different long-acting pain medication, either morphine extended-release or methadone.

WHAT are morphine extended-release and methadone?

Morphine extended-release and methadone are long-acting medications for pain similar to long-acting oxycodone (OxyContin[®]). Morphine and methadone have been used for many years to treat pain. Results from scientific studies have shown that the long-acting pain medications, including, oxycodone, morphine and methadone, have similar actions and work equally well. Because each person is different, the key is finding the right dose that will provide pain relief for each patient. In addition, no pain medication has been shown to be better than the others when it comes to side effects.

WHY are we making this change?

The Washington State Preferred Drug List for patients of MAA/DSHS, Uniform Health Plan and Labor and Industries (L&I), no longer considers OxyContin[®] a “preferred” drug. Morphine extended-release and methadone are now the preferred medications for your insurers. If you have been paying cash for your OxyContin[®] prescription, you will see a reduction in price when you switch to morphine extended-release or methadone. While one of the factors involved in this decision was cost, the alternatives to OxyContin[®] are equally safe and effective for patients.

HOW are morphine extended-release and methadone taken?

You, your physician and your pharmacist will decide which new medication you will take and how it should be used. Your healthcare provider will help determine the dose that works the best for you. Please note that once you start your new pain medication, you should stop taking OxyContin[®].

WHO can I talk to if I have questions or concerns about this change?

We encourage you to work with the healthcare provider and/or pharmacist with whom you usually discuss your pain therapy. Your physician or pharmacist may want to speak with or see you soon after you have started the new pain medication. You may directly contact MAA/DSHS, Uniform Medical Plan or L&I with any questions. To contact other insurers check the customer service information on your insurance card.

The main goal is to assure that the new medicine is working well for you.