Oregon State University College of Pharmacy

Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Health Authority

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, January 26, 2012 1:00-4:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070
Meeting Agenda

I. CALL TO ORDER 1:00 pm – 1:05 pm
- a. Roll Call & Introductions — B. Origer (Chair)
- b. Conflict of Interest Declaration — R. Citron (OSU)
- c. Approval of Agenda and Minutes — B. Origer (Chair)

II. PROCESS 1:05 pm – 1:15 pm
- a. Review Procedure Document — M. Herink (OSU)
- b. EBM Review — D. Haxby (OSU)
- c. Approval

III. OLD BUSINESS 1:15 pm – 1:30 pm
- a. Methadone / LAO Drug Use Evaluation — K.Ketchum (OSU)
  1. Proposed PA Criteria
  2. Public comment
  3. Discussion of clinical recommendations to OHA

IV. NEW BUSINESS 1:30 pm – 2:00 pm
- a. Dose Consolidation concept — R. Citron (OSU)
- b. Approval Pathway for New Drugs not in PDL classes* — R. Magrish (DMAP)
  1. Proposed policy
  2. Public Comment
  3. Discussion of Clinical recommendations to OHA

BREAK 2:00 pm – 2:10 pm

IV. NEW BUSINESS (continued) 2:10 pm – 3:30 pm
- c. Oral Anticoagulants Abbreviated Class Review* — K. Sentena (OSU)
  1. Pradaxa (dabigatran)
  2. Xarelto (rivaroxaban)
  3. Public comment
  4. Discussion of clinical recommendations to OHA
- d. Hepatitis C New Drug Reviews* — S. Willard (OSU)
  1. Incivek (telaprevir)
  2. Victrelis (boceprevir)
  3. Public comment
  4. Discussion of clinical recommendations to OHA
- e. ACE-Is/ARBs/DRIs Class Update* — M. Herink (OSU)
  1. Edarbi (azilsartan)
  2. Public comment
  3. Discussion of clinical recommendations to OHA

Agenda items with an asterisk will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)

f. Drug Class Scans* M. Herink (OSU)
   1. HSV Antivirals
   2. Influenza Antivirals
   3. Beta Blockers
   4. Calcium Channel Blockers
   5. Public Comment

V. EXECUTIVE SESSION 3:30 PM

VI. RECONVENE for PUBLIC RECOMMENDATIONS*

VII. FUTURE BUSINESS
Tentative Review Schedule and Prioritization

VIII. ADJOURN

Agenda items with an asterisk will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)

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OREGON PHARMACY & THERAPEUTICS COMMITTEE MEMBERSHIP REPORT

First Name	LastName	Title	Position	Date Began	Term Ends	DUR Office	Specialty/Practice Setting	Geography
Andris	Antoniskis	MD	Physician	Nov-11	Dec-12		Internal Medicine	Portland
Joshua	Bishop	PharmD	Pharmacist	Nov-11	Dec-14		Pharmacy Director	Bend
Zahia	Esber	MD	Physician	Nov-11	Dec-13		Internal Medicine	Eugene
Tracy	Klein	PhD, FNP	Public	Nov-11	Dec-14	Vice Chair	Nurse Practitioner	Portland
Phillip	Levine	PhD	Public	Nov-11	Dec-12		Retired	Lake Oswego
Meena	Mital	MD	Physician	Nov-11	Dec-14		Deputy Medical Director	Portland
William	Origer	MD	Physician	Nov-11	Dec-14	Chair	Medical Director	Corvallis
David	Pass	MD	Physician	Nov-11	Dec-13		Medical Director	West Linn
Stacy	Ramirez	PharmD	Pharmacist	Nov-11	Dec-13		Ambulatory Care/Community Pharmacist	Albany
James	Slater	PharmD	Pharmacist	Nov-11	Dec-14		Associate Pharmacy Director	Beaverton
Cathy	Zehrung	RPh	Pharmacist	Nov-11	Dec-12		Pharmacy Manager	Silverton

Created on 1/24/2012 11:54:00 AM
Modified on 1/25/2012

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Oregon Pharmacy & Therapeutics Committee
Thursday, November 17, 2011 2:00-5:00 PM
Barbara Roberts Human Resources Building Rm#137
500 Summer Street NE, Salem, OR
DRAFT Meeting Minutes

Members Present: Andris Antoniskis, MD; Joshua Bishop, PharmD; Zahia Esber, MD; Tracy Klein, PhD, FNP; Phillip Levine, PhD; Meena Mital, MD; William Origer, MD; David Pass, MD; Stacy Ramirez, PharmD; James Slater, PharmD; Cathy Zehrung, RPh
Staff Present: Dean Haxby, PharmD; Roger Citron, RPh; Megan Herink, PharmD, BCPS; Ann Hamer, PharmD, BCPP; Kathy Sentena, PharmD; Ted Williams, PharmD, BCPS; Valerie Smith; Trevor Douglass, DC, MPH; Richard Holsapple, RPh; Ralph Magrish, MPA
Audience Present: Shannon Beatty (Med Immune); Linda Krueger (Eli Lilly); Venus Holder (Eli Lilly); Deron Grothe (Teva); Jim Graves (BMS); Bob Viadorx (BMS); John Stockton (Astellas); Amy Burus (OSU/OHSU Cop); David Barba (Forest); Barry Benson (Merck); Anne Marie Licos (Med Immune); Jeana Colabianchi (Sunovion); Lori Howarth (Bayer); Kate Ryan (Astra Zeneca); Dave Barrows (Merck); Tom Barrows (Merck); Cheryl Fletcher (Abbott); Bruce Smith (GSK); Jim Hoover (Bayer); Kathy Kirk (OPMC); Kathy Hahn (OPMC); Don Stoches (Novartis); Trish McDaid-O'Neill (Astra Zeneca); Darlene Halverson (Astra Zeneca); James Mattencci (MSD); Paul Nielsen (Med Immune); Shane Hall (Purdue); Mike Willett (Pfizer)

I. CALL TO ORDER
- a. The meeting was called to order at 2:10 pm and introductions were made
- b. Presentation by Dr. Bruce Goldberg, Director OHA
- c. Presentation by Linda Grimms, Legal Counsel to OHA
- d. Conflict of interest declaration; no new conflicts were disclosed

II. ELECTION of CHAIR and VICE CHAIR
- a. Dr. William Origer was nominated to chair the committee

ACTION: Committee voted unanimously to appoint Dr. Origer as chair
- b. Dr. Tracy Klein was nominated as vice-chair of the committee

ACTION: Committee voted unanimously to appoint Dr. Klein as vice-chair

SUSPEND P&T MEETING

III. RULES ADVISORY COMMITTEE for TEMP RULES
- a. Minutes from this meeting were recorded separately

CONTINUE P&T MEETING

IV. PROCESS
- a. Members were asked to review a draft document and provide feedback at the next meeting

ACTION: No action at this time

V. PLANNING

b. Future meeting dates, times and locations were discussed

ACTION: Future meetings will be held on the last Thursday of each month beginning in January 2012 from approximately 1-4 pm in the SW Portland Metro area

VI. NEW BUSINESS

a. Dr. Sentena presented a new drug evaluation on Prasugrel. Public comment was offered by Linda Krueger from Eli Lilly.
b. Dr. Sentena presented new drug evaluation on Ticagrelor. Public comment was offered by Kate Ryan from Astra Zeneca.

ACTION: Committee approved prior authorization criteria after adding the following:

- Diagnosis codes for the approved drug indications
- Length of treatment allowed for up to 12 months
- Allow for continuation of therapy for 30 days after hospitalization
- Grandfather patients currently taking medications for 12 months
- Make Prasugrel 2nd line and Prasugrel 3rd line therapy

VII. REPORTS/ DUR ACTIVITIES

a. The committee did not review the Methadone / LAO Drug Use Evaluation (DUE); however public comment was offered by Kathy Kirk and Kathy Hahn from Oregon Pain Management Commission

The meeting adjourned at approximately 5:25 pm

Methadone – New starts @ doses >20 mg

Goals:

- Promote safe use of methadone upon initiation

Prescribing Recommendations

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

See Oregon DUR Board newsletter at:
http://pharmacy.oregonstate.edu/drug_policy/pages/dur_board/newsletter/articles/volume11/DURV11I2.pdf
http://pharmacy.oregonstate.edu/drug_policy/pages/dur_board/newsletter/articles/volume5/5_5.html

Length of Authorization: Up to 1 year

Requires PA: Patients initiated on methadone (i.e. no previous claim within 90 days) on a daily dose of ≥ 20mg

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD9 code.	
2. Has patient been continuously on opioids other than codeine over the past 90 days?	**Yes: Go to #3**	**No: Pass to RPH; Deny** (Medical Appropriateness) Opioid naïve or patients receiving codeine preparations should start methadone @ 2.5 mg BID-TID; upward titration by 2.5 mg q8h no sooner than weekly
3. Is the total Morphine Equivalent Dose per Day < 200mg? Dose Calculator at: http://pharmacy.oregonstate.edu/drug_policy/prescriber_tools/Opioid_Conversion_Suggestions.pdf	**Yes: Pass to RPH; Deny** (Medical Appropriateness) Recomment initiat methadone @ 2.5mg - 5 mg q8h; upward titration by 2.5 mg q8h no sooner than weekly and use short-acting opioids for break-through pain	**No: Go to #4**
4. Is this patient terminal (< 6 months) or admitted to hospice?	**Yes: Approve for up to 6 months.**	**No**: Go to #5.
5. Is patient being treated for oncology pain?	**Yes: Approve for up to 6 months.**	**No: Pass to RPH; Deny** (Medical Appropriateness)

DUR Board Action: *11/17/11 (KK), 5/19/11KK), 3/17/11(KK)*
Revision(s)
Initiated: *1/1/12*

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Drug Use Evaluation: Long-Acting Opioids (LAO)

Summary

- The LAO prior authorization policy was successful in lowering both utilization and cost of LAOs
- The LAO prior authorization policy reduced LAO excessive dose and duplication rates
- The methadone dose limit reduced the number of patients on more than 100mg per day
- Approximately 50% of patients on any LAO exceed 120mg morphine equivalent dose per day.
- About 30% of patients on any LAO concurrently take a benzodiazepine
- 5% of all methadone patients are started without any previous LAO therapy.
- 46% of patients newly started on methadone, without previous LAO therapy, exceed 120mg morphine equivalents per day.

Drug Use Evaluation: Long-Acting Opioids (LAO)

The use of long-acting opioids (LAO) has been steadily increasing despite concerns over efficacy and safety. Medicaid prescriptions for opioids doubled between 1998 and 2003, accounting for approximately 4% of all Medicaid prescriptions by 2003.[1] With increasing use of LAO there has been a corresponding increase in morbidity, as illustrated by an increasing amount of emergency department (ED) visits. The Drug Abuse Warning Network (DAWN) studied ED visits from 2004-2008 and saw a 111% increase in visits related to nonmedical use of opioid analgesics. Methadone, oxycodone and hydrocodone use were associated with the highest number of visits. The non-medical use of benzodiazepines accounted for an 89% increase in ED visits for the same study period.[2]

The consequences of escalating opioid use was reflected in a report from the 2010 Oregon Prescription Opioid Poisoning Workgroup. In 2007 opioid related poisonings accounted for 22.3% of all medication and drug-related hospitalizations in Oregon. Deaths due to prescription opioids in 2008 represented 53% of all deaths due to poisonings by medications and drugs. Methadone poisonings increased 70-fold since 1997 and deaths due to methadone accounted for 33% of the deaths due to poisonings in Oregon in 2008. In 75% of the deaths due to methadone, patients had a history of substance abuse listed in their charts.[3] Other studies have demonstrated that 18-41% of patients using opioids for chronic pain, showed drug abuse behavior.[4]

Deaths associated with LAO have also been increasing. Some states have reported proportional increases in deaths with the number of opioids prescribed, however, this phenomenon is not consistent in other states with rising mortality rates. It is unknown if increasing LAO deaths are due to an increased distribution of opioids, higher doses, specific LAO or other factors.[5]

Adverse Effects and Safety Issues

The most common adverse effects with LAO treatment are gastrointestinal, headache, fatigue and urinary complications. More severe, but less common, consequences of LAO therapy include sedation, hypoventilation, hallucinations, and abdominal pain. Methadone has been associated with additional serious warnings, outlined in the methadone section. Chronic opioid use has also been shown to effect hormone levels, cause abuse and addiction, tolerance and hyperalgesia.[6]

LAO products include black box warnings for respiratory depression, inappropriate use and drug/alcohol interactions. Methadone prescribing information specifically warns against rapid-titration of methadone with consequential drug accumulation leading to respiratory and cardiac effects. Additionally, warnings of QTc prolongation and arrhythmias in patients on high doses of methadone, and less commonly on maintenance doses, are described.[7] Fentanyl prescribing also contains additional warnings of life-threatening hypoventilation, even in opioid-tolerant patients, due to peak fentanyl concentrations occurring between 20-72 hours of treatment and because of its high potency.[8]

Although rare, serious consequences of LAO therapy include death due to drug abuse and misuse issues. Opioid treatment guidelines identify personal or family history of alcohol or drug abuse as one of the strongest predictors of aberrant drug use.[6] Additionally, patients with comorbid psychiatric conditions and younger age have also been shown to be at increased risk of opioid abuse in some studies.[9]

Drug Interactions

Many LAO are prone to drug interactions due to metabolism via CYP enzyme metabolic pathways. Commonly LAO are used in combination with benzodiazepines, which also utilize the CYP3A4 enzyme system. Studies have shown that patients on LAO therapy, taking benzodiazepines, routinely show more harms than non-benzodiazepine users. Newly published guidelines from the Canadian Guideline for the Safe and Effective Use of Opioids recommend that patients on benzodiazepines, starting opioid therapy, undergo a tapering trial or proceed with opioids with a slow titration and at lower doses if the combination is necessary.[10] A pharmacodynamic study of a single dose of diazepam in patients taking methadone resulted in greater subjective effects, or drug "high", but no acute physiological effects were seen.[11] Other studies have noted increased sedation and deterioration of reaction time when methadone and diazepam were given together. A study using "abuse" conditions – 0 and 40 mg diazepam in addition to 100% and 150% normal opioid-assisted therapy doses in four methadone and seven buprenorphine patients, demonstrated evidence of respiratory depression in some patients. Patients on LAO therapy requesting benzodiazepines should be assessed for appropriate use, other substance abuse, and source of benzodiazepines and likelihood of high-risk behaviors. LAO prescribing information warns against combining benzodiazepines, and other sedatives, and that these combinations may result in respiratory depression, profound sedation, hypotension and coma. Alcohol has been shown to further decrease respiration resulting in fatal overdoses in patients taking LAO, benzodiazepines and alcohol together.[11]

Methadone

As outline above, specific attention has been focused on the adverse effect profile of methadone, with an increased number of poisonings and death in Oregon and nation-wide. A 2004 Substance Abuse and Mental Health Services Administration (SAMHSA) report concluded that methadone related deaths were often a result of combining the drug with other central nervous system depressants, such as benzodiazepines, alcohol and other opioids.[12] Methadone is known to cause QTc prolongation and cardiac arrhythmias at higher doses or when give with interacting drugs. A small case series found episodes of torsades de pointes in high dose methadone uses (>400mg/day). Another case series in patients taking lower doses of methadone (median 110 mg/day) found that 32% had QTc prolongation but no incidences of torsades de pointes.[13] A recent study of QTc effects in advanced cancer patients taking methadone, found clinically significant increases in the QTc interval in only 1.6% of patients at week 2 and no changes at weeks 4 or 8.[14] However, there has been criticism of how this study

measured the QTc changes in addition to other design flaws. [15] To minimize this risk methadone should not be given to patients at increased risk of cardiac disease, arrhythmias or presentation of a prolonged QT interval prior to starting methadone therapy.[13]

Methadone pharmacokinetics and pharmacodynamics further complicate its use, as it has an unpredictable half-life, ranging from 15-60 hours and up to 120 hours in some patients.[6] Additionally, it is generally accepted that the analgesic efficacy wanes before its corresponding half-life, lending itself to be re-dosed leading to drug accumulation.[16] Guidelines recommend starting opioid naïve patients on 2.5mg every 8 hours, titrating the dose no more than weekly. It is also recommended that when switching patients to methadone from other LAO, doses above 40mg not be used even in patients taking high doses of LAO. Patients taking other LAO may be incompletely tolerant to the effects of methadone and deaths have resulted when converting patients from other chronic, high-dose opioid treatment regimens.[7]

Drug use criteria for appropriate methadone use has been suggested in the literature.[17] Recommendations include:

- Naïve patients should be initiated at a low dose and increased slowly.
- Patients converting from other opioids should be initiated on no more than 40mg/day and titrated no sooner than weekly.
- Patients should be assessed for QTc risk especially at high methadone doses. Doses of 60-150mg/day are recommended thresholds.

Guideline Recommendations

Using LAO for cancer or end of life pain is widely accepted but treating chronic noncancer pain with opioid therapy is more controversial. Many pain guidelines advocate the use of LAO for chronic noncancer pain despite limitations in evidence, escalating use, abuse and potential for life-threatening adverse effects.[6,18] The Veterans Affairs/Department of Defense Guidelines state that there is good evidence that LAO are effective for continuous pain.[19] The Cochrane report concluded that there is data to support that there is clinically important long-term pain relief for patients taking opioids for more than 6 months.[20]

Guidelines and systematic reviews on using LAO for non-cancer pain cite that there is no clear evidence that a specific opioid has demonstrated superior efficacy or safety over another.[6,10,21] There is limited evidence on the safest and most effective way to initiate, titrate, transition and select LAO therapy. Guidelines recommend initiating opioids at a low dose and titrating the drug slowly, taking into account the specific pharmacokinetics of the drugs, in order to minimize adverse effects. No LAO has specifically been shown to be safer of more effective as initial therapy.[6] Although opioids are viewed as having no maximum dose, guidelines recommend not exceeding

200mg/day of oral morphine, or equivalent, in patients with chronic noncancer pain (table 1).[6,10]

Table 1. Morphine Equivalents

Morphine 120mg	Fentanyl 50mcg/day	Morphine 200mg	Fentanyl 83mcg/day
	Hydromorphone 30mg/day		Hydromorphone 50mg/day
	Oxycodone 80mg/day		Oxycodone 133mg/day
	Oxymorphone 40mg/day		Oxymorphone 67mg/day
	Methadone 40mg/day		Methadone 67mg/day

Literature Review

A recent retrospective claim analysis of chronic opioid therapy in patients with non-cancer pain in commercial insured and Arkansas Medicaid populations was preformed. Regression analysis was used to determine risk factors for emergency department visits (EDV) and alcohol- or drug-related encounters (ADEs). ED visits were more commonly associated with younger age, females, more medical comorbidities, presence of headaches and greater number of nontracer pain conditions (less common pain conditions not specifically tracked). Opioid doses >120mg/day ME was associated with more ADEs but only statistically significant in the commercial insured population. In the Medicaid population the use of Schedule II long-acting drugs, alone or with non-Schedule II drugs, was significantly associated with more ADEs. Statistically significant RR increases in ADEs were seen with alcohol and/or nonopioid drug abuse or dependence in the Medicaid population. Combining sedative and/or hypnotic drugs with prescription opioids were also associated with ADEs and ED visits.[22]

In an additional analysis of the same populations, risk of possible and probable opioid misuse was performed. Twenty percent of the Medicaid population using chronic opioids were estimated to be misusing the drugs and 3% were probably misusing. The most common factors associated with misuse was younger age, back pain, multiple pain complaints, and substance abuse disorders. High dose opioids (>120 mg MED) and short-acting Schedule II opioids were also associated with misuse. There were also correlations between misuse and increasing numbers of prescribers and pharmacies.[9]

Additional studies of health plans have showed increased utilization of LAO for chronic noncancer pain. A study by Boudreau et al found that along with increased utilization there were also 28.6%-30.2% of plan members also using sedative hypnotics concomitantly with opioids.[22] Another study looking at opioid prescribing from 1991 to 2007 found an 850% increase in the number of oxycodone prescriptions, in which 28% were for long-acting oxycodone. There was a 5-fold increase in the number of oxycodone related deaths over the same period.[23]

Drug Use Evaluations

In response to LAO safety concerns, Oregon FFS Medicaid LAO drug use was evaluated from January 2000 through December 2004. A retrospective observational study of 5684 patients with prescriptions for at least 28 days were analyzed. First reported adverse outcome among patients with new prescriptions for methadone, extended-release (ER) oxycodone, morphine ER, or transdermal fentanyl were documented. Patients in the oxycodone ER cohort were 35% less likely to have an event compared to the morphine ER cohort. Patients taking fentanyl for non-cancer pain had a higher risk of emergency department (ED) encounters compared to morphine ER. Patients with non-cancer pain taking methadone had a 57% increased risk of having symptoms of overdose compared to the morphine ER cohort. However, subjects taking methadone were less likely to be hospitalized than those taking morphine ER.[24]

More recently, methadone use in the Oregon FFS Medicaid population was analyzed. Drug claims from December 2007 through November 2008 in 1,045 patients showed 10% of the population taking methadone doses associated with QTc prolongation. Doses >120/day are known to cause QTc changes, putting patients at increased risk of sudden death. In 39% of new methadone users there was no record of prior claims for opioid medications and average daily doses were 47mg, exceeding recommendations for new starts and conversion from other opioid therapies. [17]

New policies were adopted to address these concerns regarding the safety risks associated with methadone and LAO use:

1. A prior authorization for Methadone doses > 100mg/day was implemented 1/1/10.
2. RetroDUR letters were sent to prescribers of methadone > 40mg/day, starting early 2010.
3. A prior authorization for non-preferred LAO was initiated, focusing on dose and duplication issues, for patients with OHP coverage on 7/1/2009.

The effectiveness of these policies were evaluated.

Methods

Trend analysis

A LAO was defined as an opioid drug that can be dosed one or two times daily. LAOs include fentanyl patches, levorphanol and methadone as well as long acting formulations of morphine, oxycodone, oxymorphone and morphine combined with naltrexone. See Appendix A for complete list of Generic Sequence Numbers used to identify these drugs.

Paid, clean, fee-for-service pharmacy claims from January 1, 2009 thru December 31, 2010 were queried for trends in LAO costs and utilization and quantified as a monthly per member per month (PMPM) value. Costs were defined as ingredient cost (paid

amount + copay amount + other insurance paid – dispensing fee) and utilization was defined as the claim count. Rebates were not included in the reported costs. Total eligibility figures for BMH (OHP Plus) and KIT (OHP standard) benefit packages were used for the denominator. Finally, total and average costs for 30 days were quantified during the pre-intervention period (1/1/09 - 6/30/09) and post intervention period (7/1/10-12/31/10).

LAO User Analysis
For pre-intervention period (1/1/09 – 6/30/2010) and the post-intervention period (7/1/10-12/31/10), LAO users were identified if a single claim was paid for a LAO. Each LAO user with at least 90 continuous days of therapy was included in the chronic use cohort. Continuous therapy is defined as sequential claims where the beginning of the next claim is no greater than 14 days after the end of the previous claim. The "end" of a claim is defined as claim date + day supply. Demographic information such as age, sex, and race were quantified in all LAO users as well as the chronic use cohort.

The prevalence of patients on more than one LAO was characterized pre- and post-intervention. The average dose and number of subjects exceeding 120mg of morphine equivalent per day (MED) was also described pre- and post intervention. Finally the number of patients exceeding 100mg per day of methadone was quantified pre- and post interventions. Dose calculations are included in Appendix A.

Duplicate LAO use was defined claims for two unique LAO with a continuous overlap of at least 60 days. This analysis was done in chronic users pre- and post- intervention. Additionally, those chronic LAO users on 60 days concurrently with drugs of concern (benzodiazepine, skeletal muscle relaxants and drugs affecting the QTc interval) were quantified. The complete lists of drugs of concern is in Appendix B.

The number of opioid naïve patients initiating methadone was quantified in the post period. This included any patient starting on methadone with no LAO in the previous 90-days. Patients in this analysis were restricted to those with >75% eligibility for the period.

Among the chronic users the prevalence of diagnoses thought to be common for LAO users was characterized. Specifically, ICD9CM codes from paid, clean, FFS or FCHP medical claims within 6 months prior of an index LAO claim were used to quantify the number of patients with conditions known to be treated with LAOs. A patient may have more than one condition of interest.

Results

Trend Analyses
From January 1, 2009 to December 31, 2010 utilization of LAO trended steadily downward (Figure 1). When the trend is examined for the three independent segments of pre-intervention, post LAO prior authorization (PA) and post methadone dose limit there is a discernable reduction in use temporal to the policies. The LAO PA affected all LAOs except generic long-acting morphine, methadone and levophanol and was

started July 1, 2009. It requires a covered OHP diagnosis and limits duplication and excessive dose. The LAO PA reduced use by 32% annually. Methadone doses exceeding 100mg required PA starting January 1, 2010. A RetroDUR intervention targeted doses greater than 40mg for education began in Q1-2010. There does not appear to be an additional reduction in response to the methadone policies. The trend is downward in all drugs with no apparent increases from drugs requiring PA to those that do not. One confounding factor is the increase in denominator overall during the same time period due to increasing enrollment which may account for the general downward trend in use PMPM.

Figure 1 - LAO Utilization PMPM (x10,000) 2009-2010

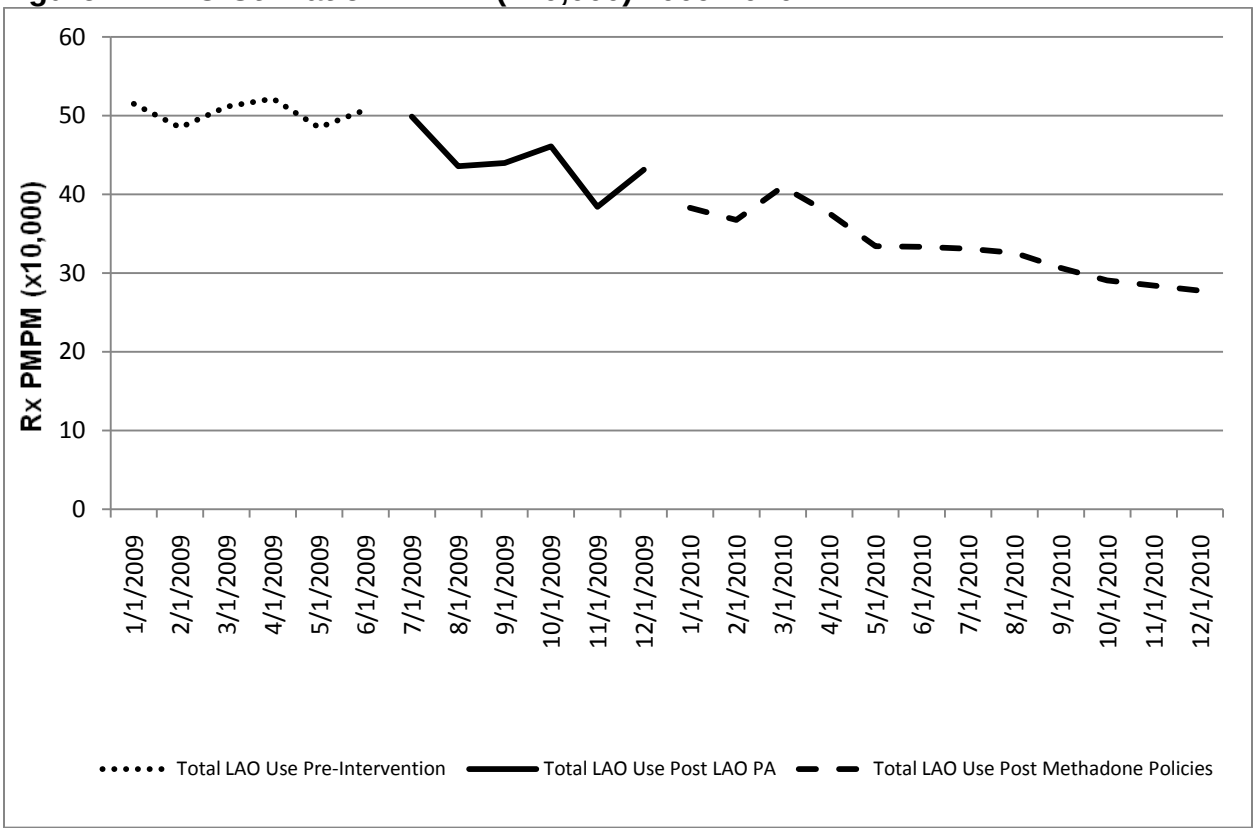
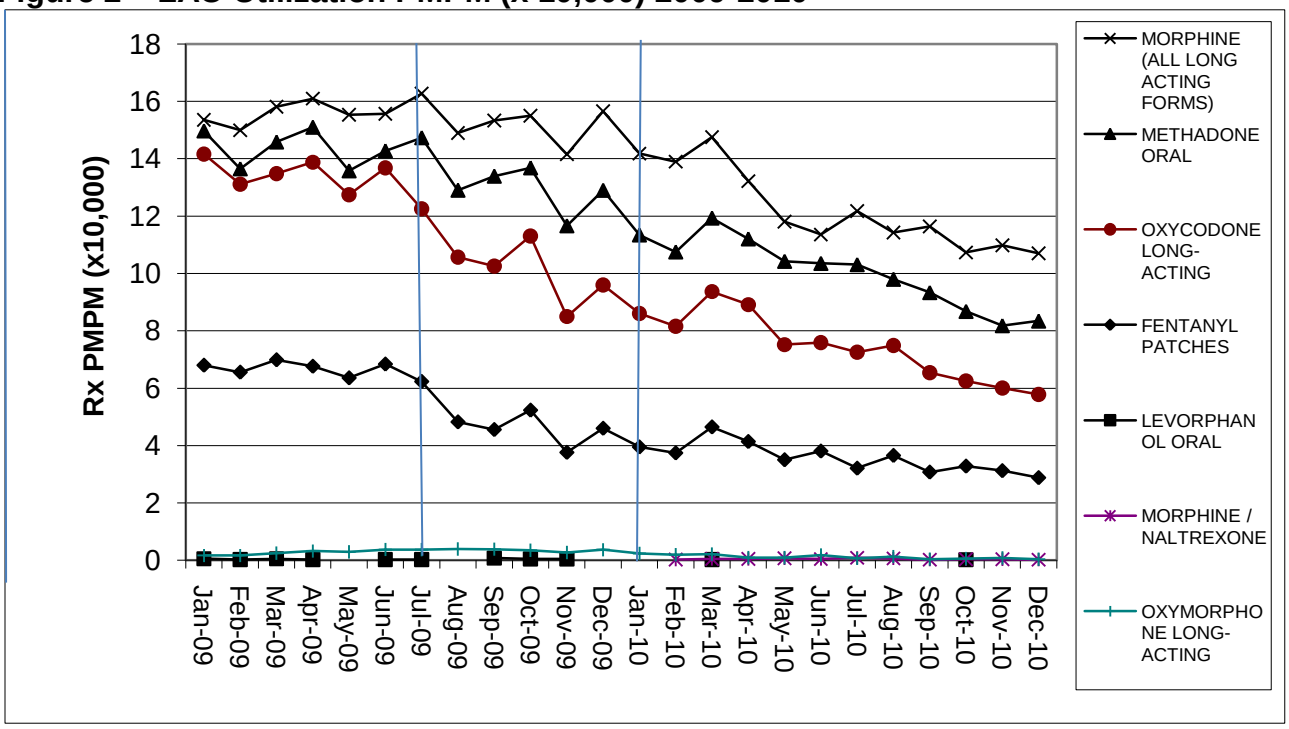
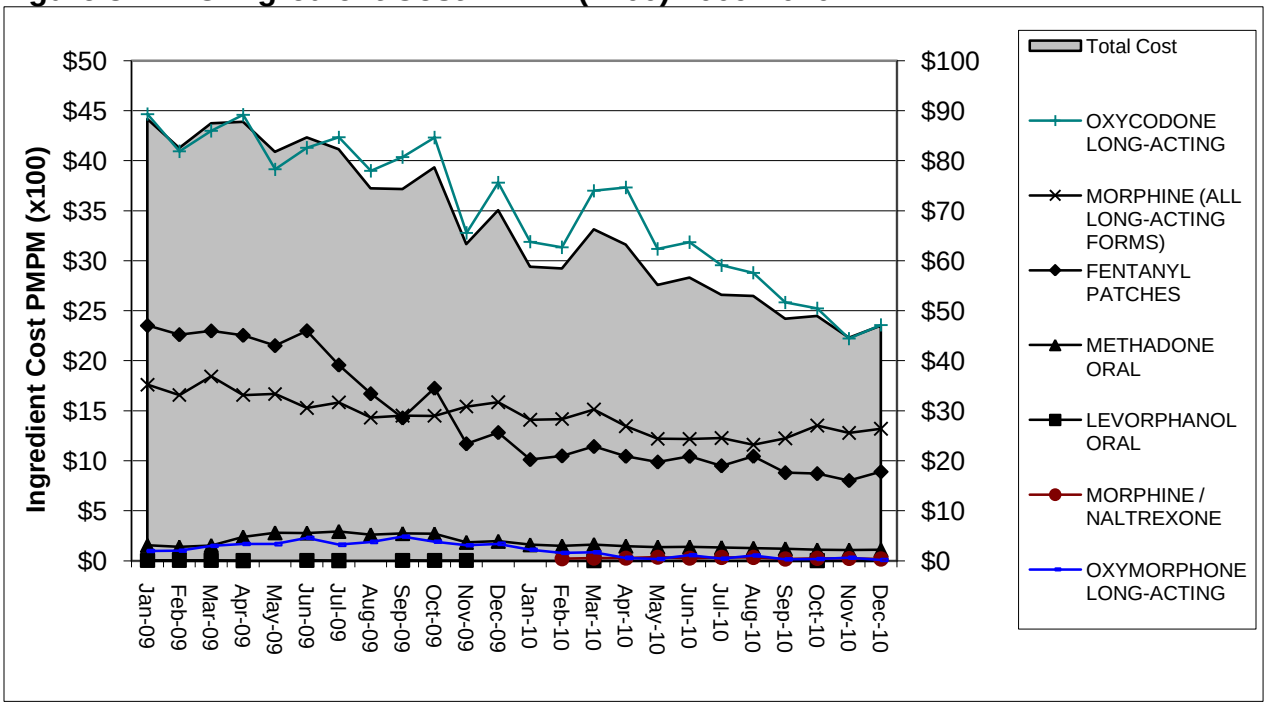


Figure 2 – LAO Utilization PMPM (x 10,000) 2009-2010



There is a similar downward trend in LAO PMPM costs with the total cost curve primarily following the oxycodone long-acting curve (Figure 3). Table 1 confirms that long-acting oxycodone is the primary cost driver. It captures 52.5% of the total gross drug costs while ranked 3rd by utilization (Figure 2).

Figure 3 - LAO Ingredient Cost PMPM (x100) 2009-2010



Drug Use Evaluation: Long-Acting Opioids (LAO)

Table 1: Oregon FFS LAO Cost Summary

	% Change Pre-period to Post-Period		Post Period Costs		
	PMPM Utilization (x10,000)	PMPM Cost (x100)	Total Cost	(%) Total LAO Costs	Avg Cost / 30 Days
FENTANYL PATCHES	-52.4%	-60.1%	$255,723	18.4%	$325
LEVORPHANOL ORAL	-88.9%	-95.1%	$46	0.0%	$195
METHADONE ORAL	-36.7%	-43.7%	$33,138	2.4%	$16
MORPHINE (ALL LONG-ACTING FORMS)	-27.7%	-25.1%	$356,573	25.7%	$122
MORPHINE / NALTREXONE			$7,084	0.5%	$646
OXYCODONE LONG-ACTING	-51.6%	-39.0%	$727,972	52.5%	$473
OXYMORPHONE LONG-ACTING	-73.2%	-84.3%	$6,772	0.5%	$339
			$1,387,308		**$189**

LAO User Analysis

A total of 2273 unique patients had at least one claim for an LAO in the pre-intervention period of which 1437 (63%) were considered a chronic user of an LAO. During the post intervention period there were 1690 unique LAO patients identified and 941 (56%) were considered a chronic user. The demographics, shown in table 2, suggest that chronic users were similar to all users in terms of measurable patient characteristics. The mean age was ~48 years, however the range was from the very young (<1) to the very old (91). Most LAO users are in the 19-65 age group. There is perhaps a more prevalent LAO use among American Indians than the overall OHP population which is reported at just 1.8%.

Table 2: Demographics of all LAO users and chronic users

	Pre - Period				Post - Period			
	All Users		Chronic Users		All Users		Chronic Users	
Total	2,273	(%)	1,437	(%)	1,690	(%)	941	(%)
Mean Age	47		48		48		49	
Range	1-91		4-91		0-77		12-67	
<6	5	0.2%	1	0.1%	4	0.2%		0.0%
6-12	4	0.2%	1	0.1%	1	0.1%	1	0.1%
13-18	9	0.4%	5	0.3%	7	0.4%	3	0.3%
19-65	2,244	98.7%	1,424	99.1%	1,672	98.9%	933	99.1%
>65	11	0.5%	6	0.4%	6	0.4%	4	0.4%
Female	1,421	62.5%	904	62.9%	1,045	61.8%	591	62.8%
Race								
White	1,943	85.5%	1,227	85.4%	1,414	83.7%	805	85.5%
Am.Indian	153	6.7%	117	8.1%	157	9.3%	85	9.0%
Black	45	2.0%	20	1.4%	27	1.6%	13	1.4%
Asian	5	0.2%	3	0.2%	6	0.4%	3	0.3%
Other	127	5.6%	70	4.9%	86	5.1%	35	3.7%

Most chronic LAO users were taking long-acting forms of morphine followed by methadone. A market share shifted from both oxycodone long-acting and fentanyl patches toward morphine can be detected in this table. There was a 1% increase in the number of patients on methadone. Table 3 summarizes the distribution of specific LAO use.

Table 3: Distribution of LAO users pre- and post- interventions

Drug	Pre-Period% All Users	Post-Period % All Users
MORPHINE (ALL LONG-ACTING FORMS)	33%	41%
METHADONE ORAL	34%	35%
OXYCODONE LONG-ACTING	28%	19%
FENTANYL PATCHES	14%	10%
OXYMORPHONE LONG-ACTING	1%	0%
MORPHINE / NALTREXONE	0%	0%
LEVORPHANOL ORAL	0%	0%
Total	100%	100%

Table 4 depicts the average dose per day for each drug. With the exception of oxycodone and the naltrexone combination product the average dose declined or remained constant in the post-intervention period. The table also identifies the number of patients exceeding 120 mg MED before and after the interventions. The absolute numbers declined across the entire class but percentages remain concerning with 50% or more of patients on LAO exceeding the 120mg MED per day. Finally, the number of patients exceeding 100mg per day of methadone declined both in absolute numbers and percentage of patients on methadone.

Drug Use Evaluation: Long-Acting Opioids (LAO)

Table 4: Dose Analysis of Chronic LAO users

	Pre - Period					Post - Period				
Drug	Avg Daily Dose (mg)	Patients >120mg ME/ day	(%) of patients on drug	Patients >100mg / day	(%) of patients on drug	Avg Daily Dose (mg)	Patients >120mg ME/day	(%) of patients on drug	Patients >100mg / day	(%) of patients on drug
FENTANYL PATCH TD72	2	37	16%			2	15	15%		
LEVORPHANOL TABLET	9					-				
METHADONE ORAL CONC	73	3	75%	1	25%	10				
METHADONE SOLUTION	58	1	50%	1	50%	30				
METHADONE TABLET	62	309	60%	110	21%	56	184	57%	29	9%
MORPHINE CAP ER PEL	139	14	50%			142	8	53%		
MORPHINE CPMP 24HR	134	5	33%			120	1	50%		
MORPHINE TABLET ER	142	212	42%			140	134	38%		
MORPHINE / NALTREXONE CAP ER PEL	40					120	1	50%		
OXYCODONE TAB ER 12H	90	202	47%			101	107	50%		
OXYMORPHONE TAB ER 12H	62	14	88%			37	2	67%		

Tables 5a and 5b compare 60 day duplication of LAO therapy pre- and post intervention. Prior to the intervention 6.7% of fentanyl patch users also used methadone concurrently, 5.1% used long-acting oxycodone concurrently and 2.8% used long-acting morphine concurrently. No other combinations exceeded 2%. Fentanyl patch users remain the only group that duplicated LAO by more than 2% in the post period but rates reduced to 3.3% with methadone, 2.2% with long-acting oxycodone and 3.3% with long-acting morphine. Absolute numbers were <3 for each combination in the post period.

Drug Use Evaluation: Long-Acting Opioids (LAO)

Table 5a: Prevalence of concurrent LAO drugs among chronic users in the PRE period (n=1437)

	FENTANYL PATCHES (%)	LEVORPHANOL ORAL (%)	METHADONE ORAL (%)	MORPHINE (ALL LONG-ACTING FORMS) (%)	MORPHINE / NALTREXONE (%)	OXYCODONE LONG-ACTING (%)	OXYMORPHONE LONG-ACTING (%)
n	**178**	**1**	**446**	**416**	**0**	**372**	**10**
FENTANYL PATCHES		0 0.0%	12 2.7%	5 1.2%		9 2.4%	0 0.0%
LEVORPHANOL	0 0.0%		0 0.0%	0 0.0%		0 0.0%	0 0.0%
METHADONE	12 6.7%	0 0.0%		7 1.7%		5 1.3%	0 0.0%
MORPHINE (ALL LONG-ACTING FORMS)	5 2.8%	0 0.0%	7 1.6%			2 0.5%	0 0.0%
MORPHINE / NALTREXONE	0 0.0%	0 0.0%	0 0.0%	0 0.0%		0 0.0%	0 0.0%
OXYCODONE LONG-ACTING	9 5.1%	0 0.0%	5 1.1%	2 0.5%			0 0.0%
OXYMORPHONE LONG-ACTING	0 0.0%	0 0.0%	0 0.0%	0 0.0%		0 0.0%	

Table 5b: Prevalence of concurrent LAO drugs among chronic users in the POST period (n=941)

	FENTANYL PATCHES (%)	LEVORPHANOL ORAL (%)	METHADONE ORAL (%)	MORPHINE (ALL LONG-ACTING FORMS) (%)	MORPHINE / NALTREXONE (%)	OXYCODONE LONG-ACTING (%)	OXYMORPHONE LONG-ACTING (%)
n	**92**	**0**	**312**	**340**	**2**	**204**	**3**
FENTANYL PATCHES			3 1.0%	3 0.9%	0 0.0%	2 1.0%	0 0.0%
LEVORPHANOL	0 0.0%		0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%
METHADONE	3 3.3%			2 0.6%	0 0.0%	2 1.0%	0 0.0%
MORPHINE (ALL LONG-ACTING FORMS)	3 3.3%		2 0.6%		0 0.0%	0 0.0%	0 0.0%
MORPHINE / NALTREXONE	0 0.0%		0 0.0%	0 0.0%		0 0.0%	0 0.0%
OXYCODONE LONG-ACTING	2 2.2%		2 0.6%	0 0.0%	0 0.0%		0 0.0%
OXYMORPHONE LONG-ACTING	0 0.0%		0 0.0%	0 0.0%	0 0.0%	0 0.0%	

Table 6 indicates that there is a 29-34% incidence of 60-day concurrent use of LAOs with benzodiazepines, a 16-24% incidence of 60-day concurrent use of LAOs with skeletal muscle relaxants and 11-21% incidence of 60-day concurrent use of LAOs with drugs affecting the QTc interval.

Table 6: Chronic users with concurrent medications of concern in Post period

		Concurrent with:					
	Chronic Users	Benzodiazepine		Skeletal Muscle Relaxant		QTc Interval Drug	
Drug	n= 941	n=	(%)	n=	(%)	n=	(%)
FENTANYL PATCHES	102	32	31%	24	24%	20	20%
METHADONE ORAL	324	109	34%	64	20%	67	21%
MORPHINE (ALL LONG-ACTING FORMS)	371	107	29%	61	16%	67	18%
OXYCODONE LONG-ACTING	214	68	32%	40	19%	24	11%
OXYMORPHONE LONG-ACTING	3			1	33%		0%

Table 7 quantifies the number patients initiated on methadone with no prior LAO claim in the previous 90 days. There were 26 new patients that were LAO naïve. This represented 5% of all methadone users in the post-period. Of these, the average dose was 44mg per day. Sixteen patients exceeded 120mg MED and 1 exceed 100mg of methadone per day.

Table 7: New Methadone Starts in Post Period with no history of other LAOs in prior 90 Days

Total	**N=26**	**5% (all methadone users)**
Age		
Mean	45	
Range	19-62	
<6		
6-12		
13-18		
19-65	26	100%
>65		
Female	21	81%
Race		
White	21	81%
American Indian	4	15%
Black		
Asian		
Other	1	4%
Average Daily Methadone Dose	44mg	
Patients exceeding 120mg MED	12	46%
Patients exceeding 100mg methadone / day	1	4%

Diagnoses within the previous 6 months of an index claim for an LAO among chronic users in the post period are represented in Table 8. The most prevalent diagnosis present was dorsopathies.

Table 8: Presence of Pain Diagnosis in Prior 6 months, Chronic Users in Post Period only

		Chronic Users Post Period		
Pain Diagnoses	**ICD9**	n=	941	(%)
Cancer:	140x-239x		115	12.2%
Dorsopathy:	720x-724x		221	23.5%
Fibromyalgia:	7291		71	7.5%
Neuropathy:	350x-359x		66	7.0%
Osteoarthritis:	715x		96	10.2%

Discussion:

There has been a significant decrease in both the utilization and cost of LAOs since a prior authorization policy for the class was initiated on July 1, 2009 and a methadone dose limit and educational intervention was initiated on January 1, 2010. While the trend line is temporal to the PA policy, it is confounded by significant increases in OHP enrollment overall during the time period. However, absolute numbers have decreased in addition to PMPM trends and thus the policy likely had a significant effect on both use and cost.

Long-acting oxycodone remains the drug associated with the most cost despite losing 8% of patients between the pre- and post- intervention periods. Fentanyl patches also lost 4% market share by patient. Long-acting morphine gained 8% market share by patient and methadone gained 1%. This likely reflects the PA policy that exempted both long-acting morphine and methadone.

Several utilization markers of concern improved in the post- intervention period. Excessive doses remain with over 50% of users of most LAOs exceeding 120mg MED. However, absolute numbers have diminished. Methadone doses exceeding 100mg per day has declined from 110 patients (21%) to just 29 patients (9%).

There was also a reduction the concurrent use of LAOs. Patients on fentanyl patches remain the only patients that require duplicate LAO used in excess of 2% but absolute numbers are very low (<3). Finally, there appears to be a significant concurrent use (10-30%) of LAOs with drugs of concern for interaction. Benzodiazepines are the most prevalent.

Twenty-six patients (5%) were LAO naïve when initiated on methadone and the average dose exceeded 40mg per day. These clients are at the most risk for adverse outcome from methadone use.

Conclusions:

The LAO PA policy was successful in lowering both utilization and cost of LAOs. It has also improved LAO dosing and duplication. The methadone dose limit has improved methadone dosing. However, approximately 50% of patients on any LAO exceed 120mg MED. And, there is a significant incidence of concurrent use with drugs of concern, particularly benzodiazepines. Finally, over half of new methadone patients were started on doses exceeding 120 MED.

Recommendation:

- Consider adding LAO patients with concurrent use criteria for benzodiazepines or skeletal muscle relaxants to Pharmacy Lock-in Program (add current Lock-in Program screening criteria).
- Consider adding any patient the methadone dose limit *to* >40mg to Pharmacy Lock-in Program (add to current Lock-in Program screening criteria)
- Consider requiring a prior authorization for new methadone starts with no prior LAO use in last 90 days.

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Drug Use Evaluation: Long-Acting Opioids (LAO)

Appendix A

GSN	Generic Name	Strength	120mg Morphine Equivalent (ME)	Approx 120mg ME Disp Quantity / Day =	Max Dose / Day	Max Quantity / Day
15883	FENTANYL	100 mcg/ho	50 mcg / hr	0		
59102	FENTANYL	12 mcg/hou	50 mcg / hr	1.33333333		
15880	FENTANYL	25 mcg/hou	50 mcg / hr	0.66666666		
15881	FENTANYL	50 mcg/hou	50 mcg / hr	0.33333333		
15882	FENTANYL	75 mcg/hou	50 mcg / hr	0		
4228	LEVORPHANOL TARTRATE	2 mg	24 mg / day	12		
4240	METHADONE HCL	10 mg	40mg / day	4	100mg	10
4237	METHADONE HCL	10 mg/5 mL	40mg / day	20	100mg	50
4239	METHADONE HCL	10 mg/mL	40mg / day	4	100mg	10
23767	METHADONE HCL	40 mg	40mg / day	1	100mg	2.5
4242	METHADONE HCL	5 mg	40mg / day	8	100mg	20
4238	METHADONE HCL	5 mg/5 mL	40mg / day	40	100mg	100
60355	MORPHINE SULFATE	10 mg	120mg / day	12		
11886	MORPHINE SULFATE	100 mg	120mg / day	1		
60358	MORPHINE SULFATE	100 mg	120mg / day	1		
50219	MORPHINE SULFATE	120 mg	120mg / day	1		
11887	MORPHINE SULFATE	15 mg	120mg / day	8		
60356	MORPHINE SULFATE	20 mg	120mg / day	6		
16522	MORPHINE SULFATE	200 mg	120mg / day	0		
62358	MORPHINE SULFATE	200 mg	120mg / day	0		
4096	MORPHINE SULFATE	30 mg	120mg / day	4		
50222	MORPHINE SULFATE	30 mg	120mg / day	4		
61748	MORPHINE SULFATE	30 mg	120mg / day	4		
64739	MORPHINE SULFATE	45 mg	120mg / day	2.5		
60357	MORPHINE SULFATE	50 mg	120mg / day	2.5		
4097	MORPHINE SULFATE	60 mg	120mg / day	2		
50221	MORPHINE SULFATE	60 mg	120mg / day	2		
61749	MORPHINE SULFATE	60 mg	120mg / day	2		
64740	MORPHINE SULFATE	75 mg	120mg / day	1.5		
61722	MORPHINE SULFATE	80 mg	120mg / day	1.5		
50220	MORPHINE SULFATE	90 mg	120mg / day	1		
65549	MORPHINE SULFATE/NALTREXONE	100 mg-4 m	120mg / day	1		
65544	MORPHINE SULFATE/NALTREXONE	20 mg-0.8	120mg / day	6		
65545	MORPHINE SULFATE/NALTREXONE	30 mg-1.2	120mg / day	4		
65546	MORPHINE SULFATE/NALTREXONE	50 mg-2 mg	120mg / day	2.5		

65547	MORPHINE SULFATE/NALTREXONE	60 mg-2.4	120mg / day	2		
65548	MORPHINE SULFATE/NALTREXONE	80 mg-3.2	120mg / day	1.5		
24504	OXYCODONE HCL	10 mg	70mg / day	7		
63515	OXYCODONE HCL	15 mg	70mg / day	6		
24505	OXYCODONE HCL	20 mg	70mg / day	6		
63516	OXYCODONE HCL	30 mg	70mg / day	2		
24506	OXYCODONE HCL	40 mg	70mg / day	2		
63517	OXYCODONE HCL	60 mg	70mg / day	1		
25702	OXYCODONE HCL	80 mg	70mg / day	1		
61092	OXYMORPHONE HCL	10 mg	35mg / day	3.5		
63783	OXYMORPHONE HCL	15 mg	35mg / day	2		
61093	OXYMORPHONE HCL	20 mg	35mg / day	1.5		
63784	OXYMORPHONE HCL	30 mg	35mg / day	1		
61094	OXYMORPHONE HCL	40 mg	35mg / day	1		
61091	OXYMORPHONE HCL	5 mg	35mg / day	7		
63782	OXYMORPHONE HCL	7.5 mg	35mg / day	5		

Appendix B

Benzodiazepine List

GenName	HSN	RtCode
ESTAZOLAM	6036	PO
FLURAZEPAM HCL	1593	PO
MIDAZOLAM HCL	1619	PO
QUAZEPAM	1595	PO
TEMAZEPAM	1592	PO
TRIAZOLAM	1594	PO
ALPRAZOLAM	1617	PO
CLORAZEPATE DIPOTASSIUM	1612	PO
DIAZEPAM	1615	PO
LORAZEPAM	4846	PO
OXAZEPAM	1616	PO
CLONAZEPAM	1894	PO
TEMAZEPAM/DIET8	33614	PO
ALPRAZOLAM/DIETARY SUPPL NO.17	34747	PO

Skelatal Muscle Relaxants; any drug in STC = 08

Qtc Intx Drugs

GenName	HSN	RtCode
CLARITHROMYCIN	6228	PO

ERYTHROMYCIN BASE	4022	PO
ERYTHROMYCIN ESTOLATE	4017	PO
ERYTHROMYCIN ETHYLSUCCINATE	4018	PO
ERYTHROMYCIN STEARATE	4021	PO
TELITHROMYCIN	23095	PO
ITRACONAZOLE	6503	PO
KETOCONAZOLE	4132	PO
POSACONAZOLE	33461	PO
VORICONAZOLE	23720	PO
AMIODARONE HCL	83	PO
QUINIDINE GLUCONATE	73	PO
QUINIDINE SULFATE	75	PO
ISONIAZID	4080	PO
ATAZANAVIR SULFATE	25390	PO
FOSAMPRENAVIR CALCIUM	25662	PO
INDINAVIR SULFATE	10683	PO
NELFINAVIR MESYLATE	10858	PO
RITONAVIR	10412	PO
SAQUINAVIR MESYLATE	10232	PO
ABACAVIR SULFATE/LAMIVUDINE	26524	PO
ABACAVIR/LAMIVUDINE/ZIDOVUDINE	21800	PO
DELAVIRDINE MESYLATE	12954	PO
EFAVIRENZ	18748	PO
ETRAVIRINE	35342	PO
LAMIVUDINE/ZIDOVUDINE	14014	PO
NEVIRAPINE	11592	PO
GATIFLOXACIN	20788	PO
LEVOFLOXACIN	12384	PO
MOXIFLOXACIN HCL	20690	PO
NORFLOXACIN	4123	PO
OFLOXACIN	6035	PO
CLOZAPINE	4834	PO
ILOPERIDONE	36778	PO
OLANZAPINE	11814	PO
PALIPERIDONE	34343	PO
QUETIAPINE FUMARATE	14015	PO
RISPERIDONE	8721	PO
ZIPRASIDONE HCL	21974	PO
ARIPIPRAZOLE	24551	PO
CHLORPROMAZINE HCL	1621	PO
FLUPHENAZINE HCL	1626	PO
PERPHENAZINE	1627	PO
THIORIDAZINE HCL	1631	PO

TRIFLUOPERAZINE HCL	1630	PO
DRONEDARONE HYDROCHLORIDE	36444	PO
PROCHLORPERAZINE EDISYLATE	1628	PO
PROCHLORPERAZINE MALEATE	1629	PO
PROMETHAZINE HCL	12014	PO
CIPROFLOXACIN	13446	PO
CIPROFLOXACIN HCL	4124	PO
CIPROFLOXACIN/CIPROFLOXA HCL	32882	PO
AMITRIPTYLINE HCL	1643	PO
AMOXAPINE	1648	PO
CLOMIPRAMINE HCL	4744	PO
DESIPRAMINE HCL	1645	PO
DOXEPIN HCL	1650	PO
IMIPRAMINE HCL	1641	PO
IMIPRAMINE PAMOATE	1642	PO
MAPROTILINE HCL	1651	PO
NORTRIPTYLINE HCL	1644	PO
PROTRIPTYLINE HCL	1646	PO
TRIMIPRAMINE MALEATE	1649	PO

Opioids, Long-Acting – High Dose Limit

Goal(s):

- *Ensure safe use of long-acting opiods.*
  - *Opioids have been associated with an increasing proportion of deaths in Oregon and the US.*
  - *Opioid deaths in Oregon are often associated with concurrent use of other drugs (e.g. other opioids, benzodiazepines, skeletal muscle relaxants)*
  - *Opioid deaths in Oregon are often associated with patients with a history of drug abuse.*
- *Buprenorphine, Fentanyl and Methadone carry FDA Black Box Warnings and have been associated with adverse cardiac effects associated with QTc prolongation and/or life-threatening hypoventalation.*
  - *This risk is increased with concurrent use of other drugs prolonging the QTc interval or other drugs affecting metablolism of methadone or fentanyl.*

See Oregon DUR Board newsletter at:
http://pharmacy.oregonstate.edu/drug_policy/pages/dur_board/newsletter/articles/volume11/DURV11I2.pdf
http://pharmacy.oregonstate.edu/drug_policy/pages/dur_board/newsletter/articles/volume5/5_5.html

Initiative: Long-Acting Opioid High Dose Limit - Prior authorization is required for daily doses above the Dose Threshold in the table below. Patients with metastatic neoplasms (ICD9 = 190xx – 199xx) are exempt for the PA requirement.
Length of Authorization: up to 6 months

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

Opioid	Dose threshold	Recommended starting dose for opioid-naïve patients	Considerations
Buprenorphine Transdermal	20mcg/hour (q 7 days)	5mcg/hr patch q 7 days	May increase dose q72 hours patients up to a max of 20mcg/hr q 7 days. Doses >20mcg/hr q7days increase risk of QTc prolongation.
Fentanyl Transdermal	50mcg/hour (q 72 hr)	Use only in opioid-tolerantpatients who have been taking ≥ 60mg MED daily for a week or longer	
Hydromorphone	30mg per 24 hours	2mg q 4–6 hours	
Methadone	80mg per 24 hours	2.5-5mg BID – TID	Methadone is difficult to titrate due to its half-life variability. It may take a long time to reach a stable level in the body. Methadone dose should not be increased more frequently than every 7 days. Do not use as PRN or combine with other long-acting (LA) opioids.
Morphine	120mg per 24 hours	Immediate-release: 10mg q 4 hours Sustained-release: 15mg q 12 hours	Adjust dose for renal impairment.
Oxycodone	80mg per 24 hours	Immediate-release: 5mg q 4–6 hours Sustained Release: 10mg q 12 hours	See individual product labeling for maximum dosing of combination products. Avoid concurrent use of any OTC products containing acetaminophen (maximum dose = 4000mg/day x <10day or 2500mg/day for 10 days or more)
Oxymorphone	40mg per 24 hours	Immediate-release: 5–10mg q 4–6 hours Sustained Release: 10mg q 12 hours	**Use with extreme caution due to potential fatal interaction with alcohol or medications containing alcohol**.

Approval Criteria		
1. What is the patient's diagnosis?		
2. Is this patient terminal (< 6 months) or admitted to hospice?	**Yes: Approve for up to 6 months**.	**No**: Go to #3
3. Is patient being treated for oncology pain?	**Yes: Approve for up to 6 months.**	**No:** Go to #4

Comment [KLK1]: DUR Board recommended that any patient with claim with a "metastatic CA" diagnosis be excluded from PA altogether.

4. Is the diagnosis chronic back pain? (ICD-9 = 721.0, 721.2-721.3, 721.7-721.8, 721.90, 722.0 -722.6, 722.8-722.9, 723.1, 723.5-723.9, 724.1 -724.2, 724.5-724.9, 739, 839.2, or 847)	**Yes: Pass to RPh,** Go to #5.	**No:** Go to #6
5. Is there neurologic impairment defined as objective evidence of at least 1 of the following: a. Reflex loss b. Dermatomal muscle weakness c. Dermatomal sensory loss d. EMG or NCV evidence of nerve root impingement e. Cauda equina syndrome f. Neurogenic bowel or bladder	**Yes:** Document objective evidence with chart notes; Go to #8	**No: Deny.** (Not Covered by the OHP)
6. Is the diagnosis fibromyalgia (ICD-9 = 729.0 -729.2, 729.31-729.39,729.4-729.9 or V53.02)?	**Yes: Pass to RPh, Deny** (Not Covered by the OHP)	No: Go to #7
7. Is the diagnosis covered by the OHP?	**Yes:** Go to #8	**No: Pass to RPh, Deny** (Not Covered by the OHP)
8. Is this new therapy (i.e. no previous prescription for the same dose last month)?	**Yes: Pass to RPH; Deny** (Medical Appropriateness) In general, the total daily dose of opioid should not exceed 120 mg oral MED. Risks substantially increase at doses at or above 100mg.[1] Alternatives: Preferred NSAIDs or LAOs @ doses < 120mg MED.	**No**: Go to #9
9. Is the patient seeing a single prescribing practice & pharmacy for pain treatment?	**Yes: Pass to RPh,** Go to #10	**No: Pass to RPh, Approve 30-90 days to allow for case review.** Refer to Rx Lock-In program for evaluation, monitoring & potential taper. Further approvals pending RetroDUR/Medical Director review of case.
10. Can the prescriber provide documentation of sustained improvement in both function and pain AND is prescriber is aware of additional risk factors (e.g. concurrent benzodiazepines, skeletal muscle relaxants, other LAOs or history of drug abuse)?	**Yes: Approve up to 6 months.** **Quantity Limits Apply:** Avinza: 1 dose / day Butrans: 1 patch / week Embeda: 2 doses / day Exalgo: 1 dose / day Fentanyl: 1 patch / 72 hours Kadian: 2 doses / day Opana XR: 2 doses / day Oxycodone ER: 2 doses / day	**No: Pass to RPh, Approve 30-90 days to allow for potential tapering of dose.** Refer to Rx Lock-In program for evaluation, monitoring & potential taper. Further approvals pending RetroDUR/Medical Director review of case.

Comment [KLK2]: DUR Board recommended that upon implementation all current patients be "grandfathered". This criteria will only apply to new patients to the OHP or new therapy.

[1] Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, Weisner CM, Silverberg MJ, Campbell CI, Psaty BM, Von Korff M. Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med 2010;152(2):85-92

P&T or DUR Board Action: *11/17/11(KK), 3/17/11(KK), 5/19/11KK), 9/24/09(DO/KK), 5//21/09(KK)*
Revision(s) *1/1/12*
Initiated: *1/1/10 (Methadone only)*

Opioids - Long-Acting

Initiative: Long Acting Opioids for PDL

Length of Authorization: Up to 1 year

Approve use of non-preferred long-acting opioids only for covered diagnosis.

OHP does not cover:				
Disorders of soft tissue	*Includes ICD9:* *729.0-729.2, 729.31-729.39, 729.4-729.9, V53.02*	**OR**	**Acute and chronic disorders of spine without neurologic impairment**	*Includes ICD9:* *721.0 721.2-721.3 721.7-721.8 721.90 722.0-722.6 722.8-722.9 723.1 723.5-723.9 724.1-724.2 724.5-724.9 739 839.2 847*

Preferred Alternatives at doses below 120 Morphine Equivalent per day: Listed at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Non-Preferred LAOs require PA at any dose.

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD9 code.	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA at doses below 120mg Morphine Equivalent per days.	**Yes:** Inform provider of covered alternatives in class. http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/main.html	**No:** Go to #3.
3. Is patient being treated for oncology pain?	**Yes: Approve for up to 6 months**	**No:** Go to #4
4. Is this patient terminal (< 6 months) or admitted to hospice?	**Yes: Approve for up to 6 months.**	**No**: Go to #5.

5. Is the diagnosis chronic back pain ***721.0*** ***721.2-721.3*** ***721.7-721.8*** ***721.90*** ***722.0-722.6*** ***722.8-722.9*** ***723.1*** ***723.5-723.9*** ***724.1-724.2*** ***724.5-724.9*** ***739*** ***839.2*** ***847***	**Yes:** Pass to RPH, Go to #5.	**No:** Go to #**7.**
6. Is there neurologic impairment defined as objective evidence of at least 1 of the following: **a. Reflex loss** **b. Dermatomal muscle weakness** **c. Dermatomal sensory loss** **d. EMG or NCV evidence of nerve root impingement** **e. Cauda equina syndrome** **f. Neurogenic bowel or bladder**	**Yes:** Document objective evidence with chart notes; Go to #8.	**No: Deny** **(Not Covered by the OHP)**
7. Is the diagnosis fibromyalgia (ICD-9 = 729.0 -729.2, 729.31-729.39,729.4-729.9 or V53.02)?	**Yes: Pass to RPh, Deny** **(Not Covered by the OHP)**	No: Go to #8
8. Is the diagnosis covered by the OHP?	**Yes:** Go to #9	**No: Pass to RPh, Deny** (Not Covered by the OHP)
9. Is this new therapy (i.e. no previous prescription for the same drug last month)?	**Yes:** Go to #9	**No:** Go to #10**.**
9. Does dose exceed 120mg Morphine Equivalents per day? **a. Fentanyl 50mcg/day** **b. Hydromorphone 30mg/day** **c. Oxycodone 80mg/day** **d. Oxymorphone 40mg/day** **e. Methadone 40mg/day**	**Yes: Pass to RPh, Deny** (Medical Appropriateness) In general, the total daily dose of opioid should not exceed 120 mg oral MED. Risks substantially increase at doses at or above 100mg.[i] Alternatives: Preferred NSAIDs or LAOs @ doses < 120mg MED.	**No:** Go to #10.
10. Is the patient seeing a single prescribing practice & pharmacy for pain treatment?	**Yes:** Go to #11	**No:** <u>Approve 30-90 days;</u> Refer to Rx Lock-In program for evaluation, monitoring & potential taper. Further approvals pending RetroDUR/Medical Director review of case.

11. Is the patient concurrently on other long-acting opioids (e.g. fentanyl patches, methadone, or long-acting morphine, long-acting oxycodone, long-acting oxymorphone)?	**Yes:** Pass to RPH. Go to #12.	**No: Approve up to 6 months.** **Quantity Limits Apply:** Avinza: 1 dose / day Butrans: 1 patch / week Embeda: 2 doses / day Exalgo: 1 dose / day Fentanyl: 1 patch / 72 hours Kadian: 2 doses / day Opana XR: 2 doses / day Oxycodone ER: 2 doses / day
12. Is the duplication due to tapering or switching products? The concurrent use of multiple long-acting narcotics is not recommended unless tapering and switching products. Consider a higher daily dose of a single long-acting opioid combined with an immediate release product for breakthrough pain. http://www.ohsu.edu/ahec/pain/home.html	**Yes**: Approve for 30-90 days at which time duplication LAO therapy will no longer be approved.	**No: Deny, Appropriateness.** **May approve for taper only.** If necessary, inform prescriber of provider reconsideration process and refer to RetroDUR for review.

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

Prescription Opioid Overdose Prevention Workgroup (POP)
Interim Report
May 3, 2011

Executive Summary

OHA staff formed the POP in 2010 to determine how to reduce prescription opioid analgesic overdose deaths in Oregon. This report is an interim summary of information and recommendations from the Prescription Opioid Overdose Prevention Workgroup (POP). The POP formed four subcommittees to focus on data, education, policy, and clinical practice. The subcommittees considered three questions:

1. **What is the current state of knowledge for each specific POP areas of focus: data, policy, education, and clinical practice?**
   What is known about the frequency and risk factors for opioid overdose (data group)?
   What policies might contribute to the current state of affairs (policy group)?
   What education strategies have been employed (education group)?
   What do we know about the pharmacology of methadone and pain management practices (clinical practice group)?

2. **What questions do we still have unanswered?**
   What patient factors are likely to contribute to fatal overdose?
   To what extent have insurance reimbursement policies contributed to this problem?

3. **What are the next steps for each specific subject area (data, education, policy, and clinical practice)?**

Summary of Next Step Findings

- Need to reduce methadone overdose deaths - the cause of the majority of overdose mortalities occurring among Oregonians aged 25-54.
- Conduct a study to identify risk factors and circumstances among decedents.
- Identify healthcare provider education needs.
- Increase healthcare provider awareness of the efficacy of pharmacological and non-pharmacological pain treatment to relieve acute and chronic pain.

- Promote and disseminate standards for the use of opioids to relieve acute and chronic pain
- Encourage healthcare providers to use the Prescription Drug Monitoring Program beginning in September 2011.
- Assure that providers:
    - understand the side effects and risks of opioid use,
    - are knowledgeable about the use of medications used to treat opioid dependence,
    - Are able to recognize and screen for behaviors indicating potential substance abuse, and make appropriate referrals to addiction treatment providers.
- Develop and implement statewide public education and awareness focused on methadone misuse and overdose.
- Determine what best practice prescription opioid policies are needed to provide adequate patient management when using opioids to treat acute and chronic pain.
- Develop a policy recommendation that removes barriers and increases the availability and payment of Buprenorphine to treat chronic pain, opioid dependence and addiction.
- Develop a pilot project and test the usefulness of notifying primary care providers when a patients is referred to addiction treatment
- Develop a pilot project and test the usefulness of notifying the primary care provider when a patient dies of drug overdose.
- Develop a pilot project and test the usefulness of hospitals notifying the primary care provider when a patient is hospitalized for overdose.
- Develop a pilot project and test the usefulness of police notifying the primary care provider when a patient is cited or arrested on a drug charge.
- Develop survey questions for the Behavioral Risk Factor Surveillance Survey to determine what factors influence drug sharing and what factors might decrease this practice among Oregonians.

The POP will continue to meet monthly to coordinate OHA efforts.

Introduction

The Oregon Health Authority's (OHA) Addictions and Mental Health Division (AMH) and Public Health Division (PHD) formed the POP in 2010 to address prescription opioid analgesic overdose deaths in Oregon. A sharp increase in deaths related to opioid medications began in the late 1990's and continues to rise.

The POPP has two co-chairs, one from AMH, and one from PHD. The group consists of members from the OHA Division of Medical Assistance Programs (DMAP), OHA Addictions and Mental Health Division (AMH), Criminal Justice Commission (CJC), OHA Public Health Division (PHD), local health department representatives, Oregon Board of Pharmacy (OBP), Oregon Pain Commission (OPC), Advisory Commission for the Oregon Prescription Drug Monitoring Program, Kaiser Permanente, and the OHA Directors Office.

Methods

The POPP meets monthly to define and understand the scope of the problem (i.e. what is the magnitude and trend in overdose deaths, and what factors are associated with the increase in prescription opioid deaths). The POPP chartered four subcommittees to define the problem, explore current resources and practice, and examine evidence to formulate recommendations for the state. The subcommittee subject areas include: 1) data analysis, 2) clinical practice, 3) education; and 4) policy

Subcommittee Findings

I. Data

1. Deaths due to opioid analgesics have increased in Oregon.
   - Since 1999, prescription opioid overdose/poisoning deaths increased over 900%.
   - Between 1999 and 2009, there were over 1,250 prescription opioid; unintentional overdose/poisoning deaths in the state. Overall, this was a rate of 4.8 deaths per 100,000 persons in 2009.
   - Increases in hospitalizations also occurred. In 1997, opioid-related overdose/poisonings represented 5.6% of all medication and drug-related overdose/poisoning hospitalizations. In 2007, opioid-related

overdose/poisonings represented 22.3% of all medication and drug-related hospitalizations in Oregon.
- In 1999, prescription opioids represented 11% of all deaths due to overdose/poisoning by medications and drugs; in 2008, prescription opioids represented 53% of all deaths due to overdose/ poisoning by medications and drugs in Oregon.

2. The increase in opioid overdose deaths is primarily driven by methadone.
   - Methadone is commonly used to treat chronic pain, which accounts for much of its current use.
   - Methadone is more frequently mentioned on overdose death certificates than any other licit or illicit drug including heroin.
   - In 1999, methadone represented 3% of all deaths due to overdose/poisoning by medications and drugs; in 2008, methadone represented 33% of all deaths due to overdose/ poisoning by medications and drugs (both licit and illicit) in Oregon.
   - Methadone has unique pharmacological properties that increase the risk of adverse outcomes compared to other drugs used to treat chronic pain such as Percocet, OxyContin, Oxycodone, Hydromorphone and others. Methadone has a longer “half life” meaning that it takes longer for the medication to be eliminated from the bloodstream.
   - Individuals may accidentally or intentionally take more than the prescribed dose of methadone or take the medication more often than prescribed for a variety of reasons including confusion, forgetting the time of the last dose, inability to experience pain relief, or seeking a euphoric high from medications known to produce these effects.
   - Methadone is inexpensive compared to other opioid pain treatment options (an approximate 30 day cost of $8.10 compared to $360 for equianalgesic equivalent treatment with OxyContin).
   - Most deaths occur among Oregonians aged 35-54 age group.
   - Medical examiner records indicate that about 75% of methadone overdose decedents have a history of substance use disorder; about 50% had a history of mental illness.
   - Many deaths are occurring among persons prescribed methadone for pain treatment. Preliminary analysis of medical examiner data shows that about 40% of methadone overdose/poisoning decedents had evidence of being prescribed methadone. About an equal number had no evidence for a methadone prescription or authorized treatment.

3. Use of prescription opioid analgesics has increased in Oregon.
   - In 2007 Oregon was the 3rd largest per capita consumer of retail methadone (distributed from pharmacies) in the US (*US DOJ, Automation of Reports& Consolidated Orders System (ARCOS), 2007*).
   - Distribution of methadone (per capita) in Oregon increased over 2,000% between 1997 and 2006.
   - The increase in methadone distribution for retail (i.e. pharmacies) closely parallels the death rate associated with methadone overdose.
   - Oregon is among the states with the highest proportion of prescription painkiller misuse (National Survey on Drug Use and Health).

Unanswered questions:

1. What proportion of opioid deaths in Oregon is among Medicaid enrollees?

   Washington State found that 45% of opioid poisoning decedents were Medicaid enrollees, and that Medicaid enrollees were about six times more likely to die of opioid overdose compared to the non-Medicaid population. Research in Oregon should focus on determining whether a similar level of risk is present among the Medicaid population here.

2. Are Medicaid enrollees in Oregon disproportionately prescribed methadone?

   Methadone is inexpensive when compared to other prescription opioids. The low cost of methadone may increase incentives to prescribe the drug, possibly putting vulnerable populations at increased risk for opioid overdose/poisoning.

3. What proportion of deaths occurs among persons prescribed methadone (versus those using methadone, who don't have a prescription, i.e. diverted)?

   About 40% of methadone poisoning decedents were prescribed methadone, but do not know about decedents poisoned by other drugs.

4. What factors are associated with mortality among those under medical care for pain treatment (through pain specialty clinics, general practice, or other)?

History of substance use disorders among methadone poisoning decedents is high (among those prescribed methadone). Standard screening practices might reduce risk of death among those being treated for pain with prescription opioids.

5. What factors contribute to diversion of prescription painkillers?

   Data show that 60% of those who report misuse or nonmedical use of prescription pain relievers got those medicines from friends or family.

Next steps

Collect data on decedent risk factors by carrying out a study of opioid overdose decedents through the OHA Public Health Division.

Develop survey questions for the Behavioral Risk Factor Surveillance Survey to determine what factors influence drug sharing and what factors might decrease this practice among Oregonians.

II. Policy

Current state of knowledge:

- Policies might contribute to overdoses.
- Prescription benefit limits on chronic pain treatment may limit medications available (promotes use of methadone), may limit non-pharmacological options.
- Lack of adequate addiction and mental health treatment.

1. Policies already in place may help improve the situation.
   - Prescription Monitoring Program slated to start September 1, 2011 will provide prescribers access to information about patient drug use.
   - All prescribers of opiates are required to take continuing education in pain management (OR).
   - Federal Drug Administration (FDA) Risk Evaluation and Mitigation Strategies (REM) program will provide education and training to ensure

physicians prescribe opioids appropriately, and counsel their patients on safe use and disposal.

Unanswered questions:

1. How do policies affect:
   - Prescribing opioids for pain relief?
   - Counseling and monitoring?
   - Patients' misuse or abuse of drugs?
   - Sharing of pain pills with relatives or friends?
   - Doctor shopping to obtain multiple prescriptions?
   - Diversion of opioids leading to illicit sales, abuse and unintended deaths?
2. What are effective policies in place in other states?

Next steps:

1. Look at the policies created in Washington and Utah (and elsewhere).
2. Determine what balanced policy in Oregon would look like; consider what is already in place and what is in development.

III. Clinical Practice

Current knowledge:

1. What might contribute to opiate overdose?
   - Standardized prescribing guidelines for chronic pain are not widely adopted by prescribers.
   - Patients using opioids to manage chronic pain are not consistently screened for risk factors associated with substance use disorders using standardized risk assessment tools. Policy directives governing practice in this regard are generally applied at the individual clinic or provider network level, not a statewide policy level.
   - Healthcare providers lack understanding of addiction and therefore overlook signs of addiction.
   - When substance use disorders are recognized by healthcare providers or even patients, appropriate treatment for opioid addiction is hindered by

the stigma associated with using medication assisted treatments (methadone, Buprenorphine, Naltrexone) and the general lack of understanding of the benefits associated with medication assisted treatment. Medications other than methadone are fairly new and not widely understood by the medical community or even the addiction treatment community. However, there is a growing body of research about the substantial benefits related to using medications to treat addictions, particularly as related to opioid addiction.

- Clinicians are not informed when their patients enroll in a chemical dependency treatment programs.
- Clinicians are not informed when their patient overdoses.
- Cost limits treatment options for chronic pain patients.
  - Reliance upon methadone because it's inexpensive and preferred on drug formularies; and
  - Inability to provide Complementary Alternative Medicine (CAM) because it's not a covered benefit or due to cost if uninsured.
- Clinicians are not allowed to prescribe Buprenorphine without prior authorization.
- While many clinicians will treat their existing patients using Buprenorphine, they are reluctant to accept new patients with serious addiction histories.
- Patients expect and demand clinicians to prescribe opioids even if an opioid is not indicated.
- Patients and the public do not understand the risk of opioid misuse.
- Drug interactions increase risk of overdose and death. At highest risk are those prescribed methadone due to the cardiac and respiratory depression that occurs with methadone and the long half life of methadone.

2. What policies already in place may help improve the situation?
   - The Oregon Prescription Drug Monitoring Program.
   - Professional Board statements and recommendations.
   - Oregon Pain Commission policies.
   - Professional guidelines.

3. What questions do we still have unanswered?
   - What evidence is there for multidisciplinary treatments for chronic pain?
   - What populations are at risk for dying from opioids?

- What can prescribers do to reduce the risk of overdose and death?

4. What are our next steps?
   Prescriber education:
   - Improve prescriber continuing education about the use of opioids to treat acute pain, chronic pain, and addiction in every clinical discipline;
   - Improve professional addiction and pain treatment education;
   - Expand the capacity for physicians to receive continuing medical education hours related to this topic;
   - Include a minimum number of questions on certification examinations that relate to the topic of chronic pain management:
     - Include a minimum number of questions on certification examinations on addressing substance use disorders and use of medication assisted treatments particularly where opioids are concerned; and
     - Require specific information on prescription of methadone and patient medication management of methadone.
   - Disseminate standards of care for managing chronic pain;
   - Create and disseminate standards for prescribing opioids safely and effectively;
   - Standardize evaluation of safety and effectiveness of opioid therapy:
     - Track and document functional improvement and pain relief; and
     - Consider specialty consultation if there is evidence of adverse effects or lack of response.
   - When prescribing opioid therapy:
     - Assess patient to determine current or past alcohol or other substance abuse, including nicotine (Opioid Risk Tool, AUDIT, DAST, CAGE-AID);
     - Augment pharmacological care with behavioral therapies;
     - Assess depression severity and treat;
     - Document a baseline urine drug test with each patient;
     - Document a baseline assessment of function and pain;
     - Conduct a risk/benefit discussion with each patient;
     - Provide mandatory patient education that teaches self-management of chronic pain when initiating chronic opioid therapy; and
     - Document treatment goals that include improvements in function and pain and track and document patient progress or lack thereof.
   - After prescribing:

  - Routinely monitor patients for adverse effects and document treatment strategies and patient progress or lack thereof using standard measurements;
  - Routinely administer and document patient urine testing;
  - Conduct and document pill counts; and
  - Patient follow-up in treatment plan should include specify time intervals to monitor treatment.
- Safety:
  - Each patient should use a single prescriber or clinical practice;
  - Each patient should use a single pharmacy;
  - Prescribers should use the lowest effective dose;
  - Prescribers and patients should continuously assess for conditions that can potentiate opioid adverse effects, document those conditions and follow up on those conditions on a routine basis;
  - Prescribers should avoid prescribing opiates at the same time a patient is taking sedative-hypnotics, benzodiazepines, or barbiturates; and
  - Prescribers must monitor for medication misuse.
- Barriers:
  - There are a limited number of pain specialists and addictions medicine specialists;
  - Limited access to addiction treatment, behavioral therapy and mental health treatment. Roughly 25-40% of those individuals in need of these services access services annually according to estimates from national survey data and treatment episode data; and
  - Improve communication about opiate use and misuse between all care providers including primary care, emergency departments, alcohol and drug treatment providers, case workers, emergency medical services (EMS).
- Advocate for the increased availability of Buprenorphine:
  - Incentivize physicians to become Buprenorphine prescribers.
  - Encourage managed care companies to pay for Buprenorphine treatment.
  - Encourage managed care companies to remove prior authorizations requirements for Buprenorphine and other medications that demonstrate efficacy in treating opioid addiction.
- Create a feedback loop for prescribers so they can learn about their patients who experience negative consequences related to prescription drug misuse (legal issues, use of crisis or other emergency services);

- The medical examiner should notify the primary care provider of deceased when the death is caused by drug overdose;
- Chemical dependency treatment programs should notify patient primary care providers of their patient's entry into treatment for chemical dependency;
- Create patient education materials/website;
- Promote clinician use of the prescription drug monitoring program beginning in September 2011;
- Increase healthcare provider awareness of the efficacy of non-pharmacological treatments for pain;
- Educate the public about safe use and storage of opioids.

IV. Education

Current knowledge:

1. There are gaps in clinical education among prescribers:
   - Insufficient addiction and pain management education for health care payers, prescribers and medical students, patients, pharmacists, law makers, policy developers, and the general public.
   - Education for clinicians on the use of prescription methadone is not standardized nor is it evaluated.

2. Education policies already in place:
   - Mandatory continuing education in pain management (OR).
   - Screening, Brief Intervention and Referral to Treatment (SBIRT) for alcohol misuse and addition is incorporated into physician residency program at Oregon Health and Science University.

3. There is low public awareness of the dangers of opioid misuse and overdose.

Unanswered questions:

1. How do current clinical education policies and practices effect:
   - Clinician prescribing by specialty;
   - Counseling and monitoring patients using prescribed methadone for pain;
   - Patients' misuse or abuse of prescribed methadone for pain;

- Sharing of methadone with relatives or friends;
- Doctor shopping to obtain multiple prescriptions; and
- Diversion of opioids leading to illicit sales, abuse and unintended deaths.

Next steps for education:

1. Review the curriculum content, requirements, policies, and outcomes of clinical education in Washington and Utah (and elsewhere).

2. Assess the gaps in clinical education and determine appropriate standards and requirements needed to establish improved clinical education in Oregon for prescribers in each discipline that prescribe opiates for the relief of acute pain, the relief of chronic pain, and addiction.

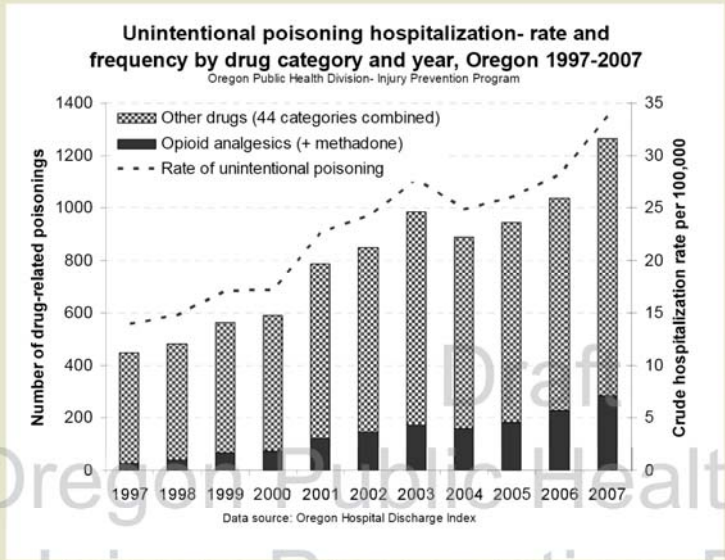
3. Study the needs and messaging content that would contribute to increased awareness and behavior change among Oregonians.

Methadone Poisoning in Oregon

Data produced for the Oregon Prescription Opioid Poisoning Workgroup
October 6, 2010

Data: Oregon Public Health Division
Injury Prevention & Epidemiology Program
Contact: matthew.laidler@state.or.us

Hospitalizations for unintentional poisoning

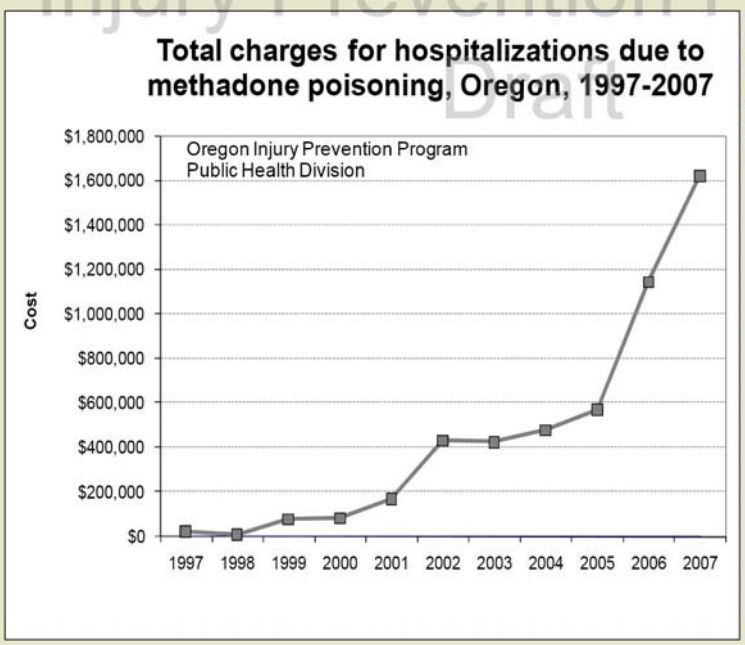


In 1997, opioid-related poisonings represented 5.6% of all medication and drug-related poisoning hospitalizations. In 2007, opioid-related poisonings represented 22.3% of all medication and drug-related hospitalizations in Oregon.

In 1997, methadone-related poisonings represented 0.7% of all medication and drug-related hospitalizations. In 2007, methadone-related poisonings represented 7.3% of all medication and drug-related hospitalizations in Oregon.

Hospitalization charges associated with methadone poisoning have increased 70-fold since 1997.

In 2007 Oregon was the 3rd largest per capita consumer of retail methadone (distributed from pharmacies) in the US. (*US Dept. of Justice, Automation of Reports and Consolidated Orders System (ARCOS), 2006*).



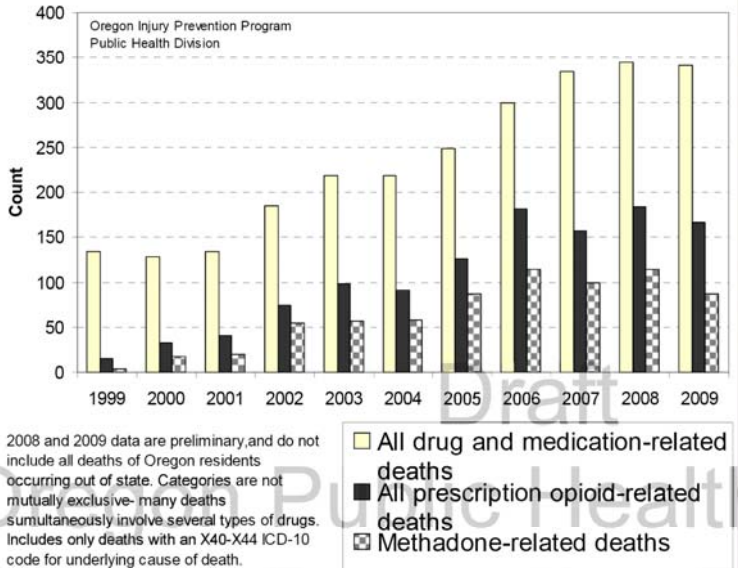
1

Methadone Poisoning in Oregon

Data produced for the Oregon Prescription Opioid Poisoning Workgroup
October 6, 2010

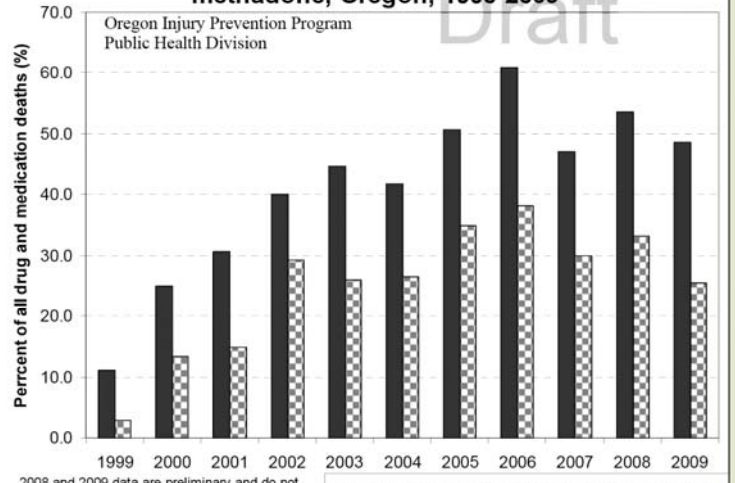
Data: Oregon Public Health Division
Injury Prevention & Epidemiology Program
Contact: matthew.laidler@state.or.us

Number of deaths due to medications and illicit drugs, Oregon, 1999-2009



2008 and 2009 data are preliminary,and do not include all deaths of Oregon residents occurring out of state. Categories are not mutually exclusive- many deaths sumultaneously involve several types of drugs. Includes only deaths with an X40-X44 ICD-10 code for underlying cause of death.

Percent of medication and illicit drug-related deaths that involve prescription opioids and methadone, Oregon, 1999-2009



2008 and 2009 data are preliminary,and do not include all deaths of Oregon residents occurring out of state. Categories are not mutually exclusive- many deaths sumultaneously involve several types of drugs. Includes only deaths with an X40-X44 ICD-10 code for underlying cause of death.

Deaths-unintentional poisoning

In 1999, methadone represented 3% of all deaths due to poisoning by medications and drugs; in 2008, methadone represented 33% of all deaths due to poisoning by medications and drugs in Oregon.

In 1999, prescription opioids represented 11% of all deaths due to poisoning by medications and drugs; in 2008, prescription opioids represented 53% of all deaths due to poisoning by medications and drugs in Oregon.

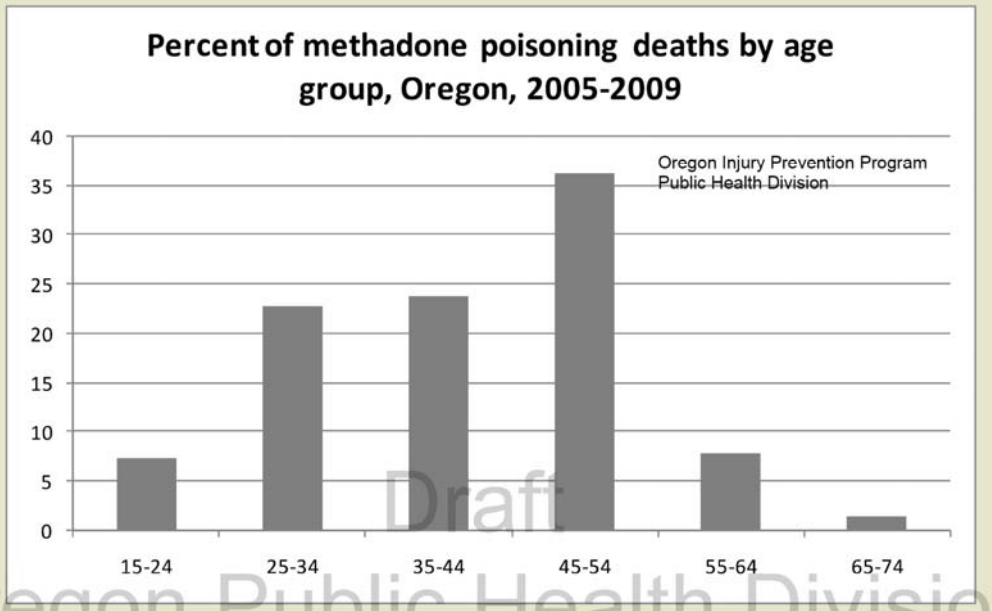
**2008-2009 mortality data are preliminary

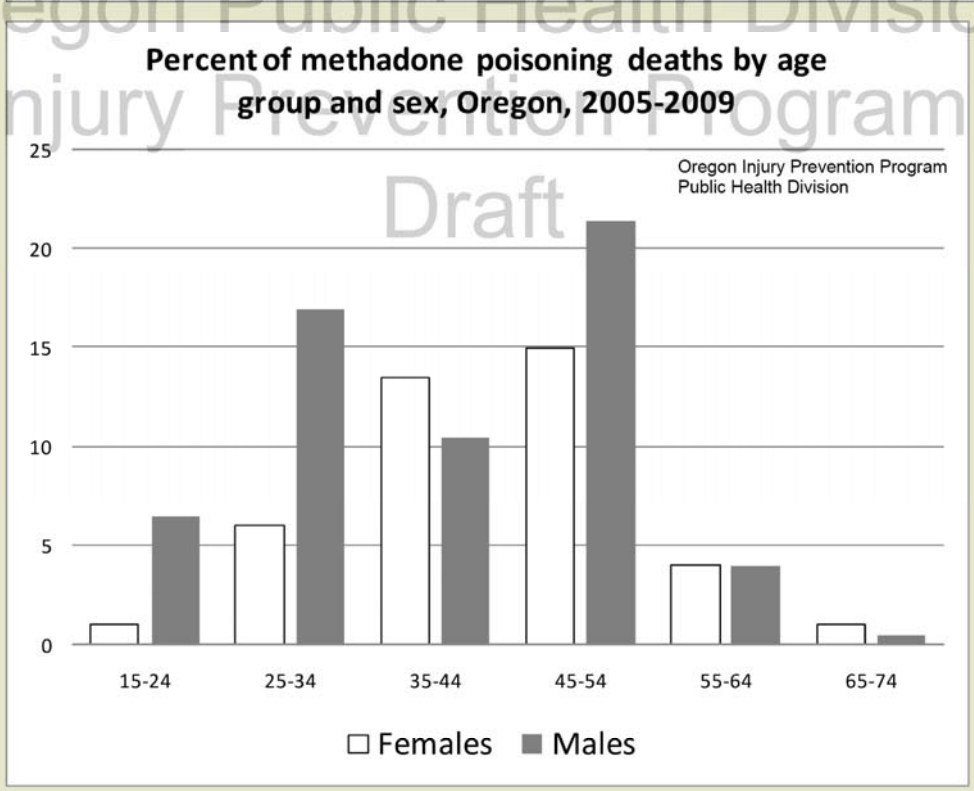
Methadone Poisoning in Oregon

Data produced for the Oregon Prescription Opioid Poisoning Workgroup

Data: Oregon Public Health Division
Injury Prevention & Epidemiology Program
Contact: matthew.laidler@state.or.us

Deaths-unintentional poisoning





3

Methadone Poisoning in Oregon

Data produced for the Oregon Prescription Opioid Poisoning Workgroup
October 6, 2010

Data: Oregon Public Health Division
Injury Prevention & Epidemiology Program
Contact: matthew.laidler@state.or.us

Deaths– medical examiner data

SAMPLE: 56 Decedents identified from ME records where methadone was listed as a cause of death and manner of death was not listed as intentional.

PRESCRIBED:
- 41% (23) had been prescribed methadone
- 30% (17) were not prescribed methadone
- For 29% (16), it was unknown whether methadone was prescribed or not

For those prescribed methadone (41%):
- 43% (10) had been prescribed the drug for pain treatment
- 26% (6) were prescribed for NTP/Methadone maintenance
- For 30% (7), it was unknown why they were prescribed methadone

OTHER DRUGS:
- 21% (12) had been prescribed other drugs (opioid or otherwise) in addition to methadone

ABUSE:
- For 77% (43) of decedents, abuse/misuse of methadone likely contributed to death (informants disclosed abuse, investigator stated abuse, patient was using more than prescribed dose, patient obtained same drug from multiple doctors, patient obtained drug from illicit source, multiple doses missing).
- For those prescribed methadone for pain, abuse likely contributed to death for 60% (6) of cases.

HISTORY OF ABUSE:
- For 75% (42) of decedents, there was a history of substance abuse mentioned in the report
- Among those prescribed methadone for pain, 60% (6) had a history of substance abuse

HISTORY OF TREATMENT
- 21% (12) of decedents had a history of addiction/substance abuse treatment
- 16% (9) had a history of methadone maintenance/NTP (including the 6 NTP/MM decedents)

MENTAL ILLNESS
- 52% (29) had mention of mental illness in the ME report

CHRONIC ILLNESS
- 25% (14) had mention of chronic illness in the ME report

HEROIN
- 25% (14) had a history of heroin use

POLYPHARMACY
- 29% (16) deaths involved polypharmacy with other Rx drugs; 18% (10) involved polypharmacy with illicit drugs; in total 46% (26) involved polypharmacy

EMPLOYMENT
- 39% (22) were unemployed
- 39% (22) were employed
- 11% (6) were students (college or HS)
- 11% (6) had unknown current employment status (missing data)

4

410-121-0040 Prior Authorization Required for Drugs and Products

(1) Prescribing practitioners are responsible for obtaining prior authorization (PA) for the drugs and categories of drugs requiring PA in this rule, using the procedures required in OAR 410-121-0060.

(2) All drugs and categories of drugs, including but not limited to those drugs and categories of drugs that require PA as described in this rule, are subject to the following requirements for coverage:

(a) Each drug must be prescribed for conditions funded by Oregon Health Plan (OHP) in a manner consistent with the Oregon Health Services Commission's Prioritized List of Health Services (OAR 410-141-0480 through 410-141-0520). If the medication is for a non-covered diagnosis, the medication shall not be covered unless there is a co-morbid condition for which coverage would be extended. The use of the medication must meet corresponding treatment guidelines, be included within the client's benefit package of covered services, and not otherwise excluded or limited;

(b) Each drug must also meet other criteria applicable to the drug or category of drug in these pharmacy provider rules, including PA requirements imposed in this rule.

(3) The Oregon Health Authority (Authority) may require PA for individual drugs and categories of drugs to ensure that the drugs prescribed are indicated for conditions funded by OHP and consistent with the Prioritized List of Health Services and its corresponding treatment guidelines (*see* OAR 410-141-0480). The drugs and categories of drugs that the Authority requires PA for this purpose are found in the OHP Fee-For-Service Pharmacy PA Criteria Guide (PA Criteria Guide) dated Jan. 1, 2011, incorporated in rule by reference and found on our Web page at:
http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html

(4) The Authority may require PA for individual drugs and categories of drugs to ensure medically appropriate use or to address potential client safety risk associated with the particular drug or category of drug, as recommended by the Pharmacy & Therapeutics Committee

(P&T) and adopted by the Authority in this rule (*see* OAR 410-121-0100 for a description of the DUR program). The drugs and categories of drugs for which the Authority requires PA for this purpose are found in the Pharmacy PA Criteria Guide.

(5) PA is required for all new drugs added to the National Drug Data File (NDDF):

(a) The new drug will be prioritized to be presented to the P & T Committee after the drug's NDDF add date. The P & T Committee will make additional drug specific recommendations to the Authority regarding PA criteria, if any, that should be adopted for the new drug:

(i) If the new drug is in a class where current PA criteria apply, all PA criteria associated with that class shall be required at the time the new drug is added to the NDDF;

(ii) If the new drug is indicated for a condition below the funding line on the Prioritized List of Health Services, PA shall be required to ensure that the drug is prescribed for a condition funded by OHP;

(b) PA for the new drug under section (5) of this rule remains in effect until such time as the Authority makes a determination regarding the applicability of PA criteria for the new drug or six months elapse from the drug's NDDF add date without a decision regarding PA criteria for that drug, whichever occurs first;

(c) Oral oncology medications, anti-retrovirals, and family planning drugs are excluded from the PA requirements in section (5) of this rule.

(6) PA is required for brand name drugs that have two or more generically equivalent products available and that are NOT determined Narrow Therapeutic Index drugs by the Oregon P&T Committee:

(a) Immunosuppressant drugs used in connection with an organ transplant must be evaluated for narrow therapeutic index within 180 days after United States patent expiration;

(b) Manufacturers of immunosuppressant drugs used in connection with an organ transplant must notify the department of patent expiration within 30 days of patent expiration for (5)(a) to apply;

(c) Criteria for approval are:

(A) If criteria established in subsection (3) or (4) of this rule applies, follow that criteria;

(B) If (6)(A) does not apply, the prescribing practitioner must document that the use of the generically equivalent drug is medically contraindicated, and provide evidence that either the drug has been used and has failed or that its use is contraindicated based on evidence-based peer reviewed literature that is appropriate to the client's medical condition.

(7) PA is required for non-preferred Preferred Drug List (PDL) products in a class evaluated for the PDL except in the following cases:

(a) The drug is a mental health drug as defined in OAR 410-121-0000;

(b) The original prescription is written prior to 1/1/10;

(c) The prescription is a refill for the treatment of seizures, cancer, HIV or AIDS; or

(d) The prescription is a refill of an immunosuppressant.

(8) PA may not be required:

(a) When the prescription ingredient cost plus the dispensing fee is less than the PA processing fees as determined by the Authority;

(b) For over-the-counter (OTC) covered drugs when prescribed for conditions covered under OHP or;

(c) If a drug is in a class not evaluated from the Practitioner-Managed Prescription Drug Plan under ORS 414.334.

Stat. Auth.: ORS Chap. 409.110, 413.042, 414.065, and 414.334

Stats. Implemented: 414.065

1-1-12

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Oral Anticoagulants Class Review – Addition of Warfarin

Month/Year of Review: January 2012
PDL Class: No current PDL class
Suggested Revision: Add warfarin to PDL
Current Status of Anticoagulants:
No PDL-status/no restrictions: warfarin
Non-preferred Oral Anticoagulants: rivaroxaban (pending) and dabigatran (pending)

FDA Approved Indications: Warfarin is approved for prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism; prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement; and reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction.[1]

Summary:
The vitamin K antagonist (VKA), warfarin, has served as the gold standard for oral anticoagulation and is a covered therapy for Oregon Health Plan (OHP) patients. Approximately 350 patients utilized long term anticoagulation (>45 days), representing over 2,000 prescription claims within the last six months within the OHP population.

A meta-analysis for stroke prevention in patients with non-valvular AF found warfarin therapy to reduce stroke by 60%, which was 40% more efficacious than anti-platelet therapy.[2] The Cochrane Database for Systematic Reviews estimates that approximately 25 strokes and 12 disabling or fatal strokes would be prevented per year, for every 1000 primary prevention patients with AF treated with warfarin.[3]

Acute DVT treatment is an additional indication for anticoagulation. DVT is a serious medical condition that affects 1 in 1000 people and can lead to PE and related risk of morbidity and mortality.[4] CHEST guidelines recommend initial treatment with LMWH, unfractionated heparin (UFH) or fondaparinux for at least 5 days and initiation of warfarin on the first treatment day.[5] Discontinuation of heparin preparations should occur when the INR reaches 2.0 or more for at least 24 hours. For patients with DVT or PE secondary to a reversible risk factor, the guidelines recommend treatment with warfarin for 3 months. Treatment recommendations for patients with unprovoked DVT or PE include warfarin for at least 3 months and up to a year or longer based on clinical judgment.

For patients undergoing THR or TKR prophylactic anticoagulants are considered standard practice. A recent guideline by the American Academy of Orthopaedic Surgeons gives a moderate recommendation for the use of prophylactic pharmacological agents for VTE prevention in those patients that are not at elevated risk. Due to insufficient evidence they are unable to recommend any particular preventative strategy or treatment duration.[6] The American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines (CHEST) on antithrombotic and thrombolytic therapy recommends treatment with warfarin, LMWH, or fondaparinux for 7 to 10 days for TKR and 10 to 35 days for THR.[7] Oregon Health Plan (OHP) fee-for-service FFS currently lists LMWHs, enoxaparin and dalteparin, as preferred, and fondaparinux (Arixtra®) and tinzaparin (Innohep®) as not preferred. Desirudin (Iprivask®) is not managed via PDL and currently has no utilization restrictions. In the previous six months approximately 200 patients received short term anticoagulation (<45 days) accounting for almost 200 prescription claims.

PDL Placement Recommendation:

Recommend maintaining warfarin as a preferred and first-line agent in the oral anticoagulant class for prophylaxis and treatment of thromboembolic disorders.

References:

1. Coumadin® Prescribing Information. Bristol-Myers Squibb, Inc. Princeton, NJ. January 2010.
2. Hart R, Pearce L, Aguilar M. Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation. Ann Intern Med. 2007;146:857-867.
3. Aguilar, M, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. The Cochrane Database of Syst Rev. 2009 (1): CD001927.
4. American Academy of Orthopaedic Surgeons. Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty Evidence-Based Guideline and Evidence Report, 2011. (Accessed October 27, 2011, at http://www.aaos.org/research/guidelines/VTE/VTE_full_guideline.pdf.)
5. Hirsh J, Guyatt G, Albers G, et al. Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133;71S-109S.
6. American Academy of Orthopaedic Surgeons. Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty Evidence-Based Guideline and Evidence Report, 2011. (Accessed October 27, 2011, at http://www.aaos.org/research/guidelines/VTE/VTE_full_guideline.pdf.)
7. Hirsh J, Guyatt G, Albers G, et al. Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133;71S-109S.

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Month/Year of Review: January 2011
Generic Name: Dabigatran

End date of literature search: December 2011
Brand Name (Manufacturer): Pradaxa (Boehringer Ingelheim)
Dossier received: Yes
Comparator Therapies: Enoxaparin and warfarin

PDL Class: No current PDL class
Preferred Anticoagulants: enoxaparin and dalteparin
Non-preferred Anticoagulants: fondiparinux, tinzaparin, rivaroxaban (pending) and dabigatran (pending)
No PDL-status/no restrictions: warfarin

FDA Approved Indications: To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF).

Summary:

- Dabigatran is a direct thrombin inhibitor used for oral stroke prophylaxis in patients with AF, as an alternative to vitamin K antagonists (VKA) such as warfarin. Dabigatran has few drug/food interactions and is not a substrate, inhibitor or inducer of CYP450 enzymes.[1]
- The recommended dabigatran dose is 150mg twice daily for AF. Dose adjustment to 75mg twice daily if CrCl 15-30 mL/min. No adjustments required with moderate hepatic dysfunction.

Efficacy and Safety Summary for FDA Approved Indications

Atrial Fibrillation

- Dabigatran approval was based on a large, prospective, non-blinded, randomized trial, the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY).[2] RE-LY was a multi-center, multi-national, parallel group, non-inferiority trial comparing two blinded doses of dabigatran (110mg twice daily or 150 mg twice daily) with open-label warfarin with a target international normalized ratio (INR) range of 2-3. Mean time in therapeutic range (TTR) was 64%.[2]
- A high degree of bias is associated with an open-label study design. The FDA cited this concern in their review but felt that because there were significant differences shown in the double-blind comparison between the dabigatran doses, this helped to substantiate the results.[3] The rates of intracranial bleeds was the primary factor contributing to the composite outcomes.
- Two doses were studied in RE-LY, a 110 mg dose and a 150 mg dose. The 110mg dose was not approved and did not demonstrate superiority over warfarin. There was moderate-strength of evidence that dabigatran 150mg was superior to warfarin for the primary composite endpoint of stroke or systemic embolism (RR 0.65; 95% CI, 0.52 to 0.81; p<0.001, NNT 167). There was low-strength of evidence

that dabigatran 150mg had similar rates of all-cause mortality compared to warfarin. FDA analysis of RE-LY states that in patients whom INRs are well controlled, warfarin and dabigatran 150 mg twice daily carry the same risk of stroke or fatal events.[3]

- There was low-strength of evidence of similar rates of major bleeding with dabigatran 150mg, compared to warfarin, which was influenced by the TTR. There were significantly more gastrointestinal bleeds in the dabigatran 150mg group compared to warfarin. Dabigatran was associated with less intracranial bleeding, which was statistically significant and independent of TTR.[4]

Other Considerations:

- Dabigatran is associated with dyspepsia, which is the most commonly cited reason for drug discontinuation. In the dabigatran 150mg group annual discontinuation rates were 2% compared to 0.6% of warfarin patients.[2]
- An increased rate of myocardial infarctions (MI) were seen with both doses of dabigatran but neither were statistically significant after newly identified events were included in the revised data.[5]
- There is no antidote to reverse bleeding in a bleeding emergency. Unlike warfarin, vitamin K administration will not reduce the anticoagulant effects of dabigatran in the event of a major bleed.[1]
- The FDA has recently announced that they will be conducting a safety review of post-marketing reports of serious bleeding associated with dabigatran. At this time the FDA believes the benefits of dabigatran still exceed the risk.

Efficacy and Safety Summary on off-label Uses

Surgery Prophylaxis

- Three studies evaluated the use of dabigatran for prevention of VTE after TKR and THR. In TKR, the evidence found that dabigatran was noninferior to enoxaparin (European dosing regimen of 40mg daily was used compared to North American regimen of 30 mg twice daily) however, it was deemed inferior to enoxaparin when the North American dosing regimen was used. One fair quality study in THR showed dabigatran to be non-inferior to enoxaparin. All surgery prophylaxis studies included asymptomatic and symptomatic DVTs, in which the clinical utility of asymptomatic DVTs is unknown. Overall, the use of dabigatran for prophylaxis of DVT in patients undergoing THR and TKR has low level evidence to support its use.

Acute DVT Treatment

- There is one fair quality study of dabigatran use in the acute treatment of VTE (RECOVER), which demonstrated that dabigatran was noninferior to warfarin with similar rates of bleeding.

Cost Considerations:

Costs will be discussed in the executive session.

PDL Placement Recommendation:
There is low-moderate level of evidence to support the use of dabigatran in AF. The relative efficacy of dabiagatran compared to warfarin is still uncertain due to potential bias toward dabigatran as a result of an open-label study design. Sub-optimal INR control in the warfarin group in RE-LY suggests patients with well controlled INRs may not benefit from dabigatran treatment. It is recommended dabigatran be added to the PDL as a second line agent requiring prior authorization.

Data on using dabigatran for acute VTE is limited, however, due to limited oral anticoagulant options, dabigatran should be added to the PDL with a PA restriction for this indication as a second line option.

BACKGROUND/CURRENT LANDSCAPE
The vitamin K antagonist (VKA), warfarin, has served as the gold standard for oral anticoagulation and is a covered therapy for Oregon Health Plan (OHP) patients. Approximately 350 patients utilized long term anticoagulation (>45 days), representing over 2,000 prescription claims within the last six months within the OHP population. A meta-analysis for stroke prevention in patients with non-valvular AF found warfarin therapy to reduce stroke by 60%, which was 40% more efficacious than anti-platelet therapy.[12] The Cochrane Database for Systematic Reviews estimates that approximately 25 strokes and 12 disabling or fatal strokes would be prevented per year, for every 1000 primary prevention patients with AF treated with warfarin.[13] However, there is a significant clinical need for an alternative to warfarin for treatment and prophylaxis of numerous conditions that require anticoagulation. Warfarin has a narrow therapeutic index, drug and dietary interactions, variable pharmacokinetics, and unpredictable pharmacodynamic responses, resulting in reduced protection against thromboembolic events and potentially causing serious bleeds.[14] Consequently, warfarin is often underutilized, with only 64% of eligible patients taking warfarin therapy.[15] Even with optimal management, some patients do not achieve adequate INR control.

Patients with AF are at a four to five-fold increased risk of stroke and systemic embolism compared to those without AF. Annual rates of stroke in patients with AF are estimated to be between 3-8%, depending on additional risk factors.[16] Anticoagulants are a key component to managing patients with AF that are at an increased risk of stroke from cardioembolic events. Stroke risk in AF patients is most commonly estimated using the $CHADS_2$ risk stratification scheme. This scheme estimates stroke risk based on: presence of heart failure, presence of hypertension, age ≥75 years, presence of diabetes mellitus, and a history of previous stroke or transient ischemic attack (Table 1).[17] The greater the number of risk factors present, the greater the risk of stroke. Current CHEST guidelines recommend anticoagulation for patients with AF and suggest aspirin therapy for patients with up to one risk factor and treatment with a VKA for patients with one or more risk factors or in secondary prevention patients.[18] The guidelines also recommend VKA therapy for patients with a $CHADS_2$ score of ≥2.

Table 1. $CHADS_2$ Classification Scheme for Stroke Risk[17]

	Risk Factor	Points
C	Congestive Heart Failure	1
H	Hypertension	1
A	Age ≥75 years	1
D	Diabetes	1
S_2	History of stroke or TIA	2

Observed rates of venous thromboembolism(VTE) after total hip and knee replacement surgery occurs in approximately 5% of patients without recommended prophylactic anticoagulation. A recent guideline by the American Academy of Orthopaedic Surgeons gives a moderate recommendation for the use of prophylactic pharmacological agents for VTE prevention in those patients that are not at elevated risk. Due to insufficient evidence they are unable to recommend any particular preventative strategy or treatment duration.[19] The CHEST guidelines recommend at least 10 days of therapy and up to 35 days with either warfarin, low molecular weight heparin (LMWH), or fondaparinux for knee and hip replacement.[18] OHP covers all LMWH products, fondaparinux (Arixtra®) and desirudin (Iprivask®). In the previous six months approximately 200 patients received short term anticoagulation (<45 days) accounting for almost 200 prescription claims.

VTE is a serious medical condition that can lead to pulmonary embolism and related risk of morbidity and mortality.[20] CHEST guidelines recommend initial treatment with LMWH, unfractionated heparin (UFH) or fondaparinux for at least 5 days and initiation of warfarin on the first treatment day.[18] Discontinuation of heparin preparations should occur when the INR reaches 2.0 or more for at least 24 hours. For patients with DVT or PE secondary to a reversible risk factor, the guidelines recommend treatment with warfarin for 3 months. Treatment recommendations for patients with unprovoked DVT or PE include warfarin for at least 3 months and up to a year or longer based on clinical judgment.

CLINICAL PHARMACOLOGY

Dabigatran is a competitive, direct thrombin inhibitor with active metabolites (acyl glucuronides). Dabigatran inhibits free and clot-bound thrombin, as well as thrombin-induced platelet aggregation. During the common pathway of the coagulation cascade, thrombin is required for the conversion of fibrinogen to fibrin which is then cross-linked to form a thrombus. Inhibition of this transformation prevents the development of thrombi.[1]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints

All Studies:	All-cause Mortality
	Major bleeding
DVT:	Symptomatic DVT
DVT Prophylaxis:	PE
	Symptomatic DVT
AF:	Stroke

Study Endpoints:

RE-LY: Stroke or Systemic Embolism

RECOVER: VTE and Related death

REMOBILIZE, REMODEL, RENOVATE: Total VTE and All-cause mortality

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR/ NNH[3]	Quality Rating[4]; Comments
RE-LY[2,5]									
Connolly SJ, et al Phase III, RCT, PG	1. Dabigatran 110mg bid 2. Dabigatran 150mg bid 3. Warfarin adjusted to INR of 2-3	Age: 71 yrs Male: 64% Prior stroke/TIA: 20% $CHADS_2$: 2 Avg. TTR (warfarin): 64%	1. 6015 2. 6076 3. 6022	Median F/U 24 months	<u>Stroke or Systemic Embolism:</u> D 110mg: 182 (1.54%) W: 199 (1.71%) RR 0.90 95% CI 0.74 to 1.10, p<0.001 for noninferiority P= 0.30 for superiority D 150mg: 134 (1.11%) W: 199 (1.71%) RR 0.65 95% CI 0.52-0.81, p<0.001 for superiority <u>Stroke:</u> D 110mg: 171 (1.44%) W: 185 (1.57%) RR .92 95% CI 0.74 to 1.13 P=0.41 D 150mg: 122 (1.01%)	NS ARR 0.60% NNT 167 NS ARR 0.56%	<u>Major Bleeds:</u> D 110mg: 2.87% RR 0.80 95% CI 0.70 to 0.93 p=0.003 D 150mg: 3.32% RR 0.93 95% CI 0.81 to 1.07 p=0.32 W: 3.57%	ARR 0.7% NNH 142 NS	• Fair • Open-label design may bias results in favor of dabigatran • TTR for warfarin patients wa 64% suggesting suboptimal warfarin use. • Major bleeds were less in dabigatran groups only in centers where TTRs were worse than median. • INR testing protocol was not clearly outlined. TTR has a direct effect on safety and efficacy. • Use in a broader patient population is needed to define MI risk, GI bleeding and effect of no antidote.

					W: 185 (1.57%) RR 0.64 95% CI 0.51 to 0.81 P<0.001 <u>All Cause Mortality:</u> D 110mg: 446 (3.75%) W: 487 (4.13%) RR 0.91 95% CI 0.80 to 1.03 P=0.13 D 150mg: 438 (3.64%) W: 487 (4.13%) RR 0.88 95% CI 0.77 to 1.00 P=0.051	NNT 179 NS NS			
RE-COVER[11]									
Schulman S, et al Phase III, RCT, DB, PG	1. Dabigatran 150mg bid 2. Warfarin adjusted to INR of 2-3 .	Age: 54 yrs Male: 58% Avg. TTR (warfarin): 60% <u>Inclusion:</u> Patients 18 or older with acute, symptomatic, objectively verifie proximal DVT of the legs or pulmonary embolism whom 6 mo. of anti-coagulation was deemed appropriate. <u>Exclusion:</u> Symptoms >14 days, PE with	1. 1273 2. 1266	Median F/U 5.5 months tx with 1 month F/U	<u>VTE or Related death:</u> D 150mg: 30 (2.4%) W: 27 (2.1%) HR 1.10 95% CI -0.65 to 1.84 p<0.001 <u>Symptomatic DVT:</u> D 150mg: 16 (1.3%) W: 18 (1.4%) HR 0.87 95% CI 0.44 to 1.71 <u>All Cause Mortality:</u> D 150mg: 21 (1.6%) W: 21 (1.7%) HR 0.98 95% CI 0.53 to 1.79	ARR 0.4% NNT 250	<u>Major Bleeding:</u> D 150mg: 20 (1.6%) W: 24 (1.9%) HR 0.82 95% CI 0.45 to 1.48 p=0.38	NS	• Fair • No protocol was given for INR testing. TTR for warfarin patients could influence efficacy and safety results • TTR for warfarin patients wa 60%.