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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.

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**

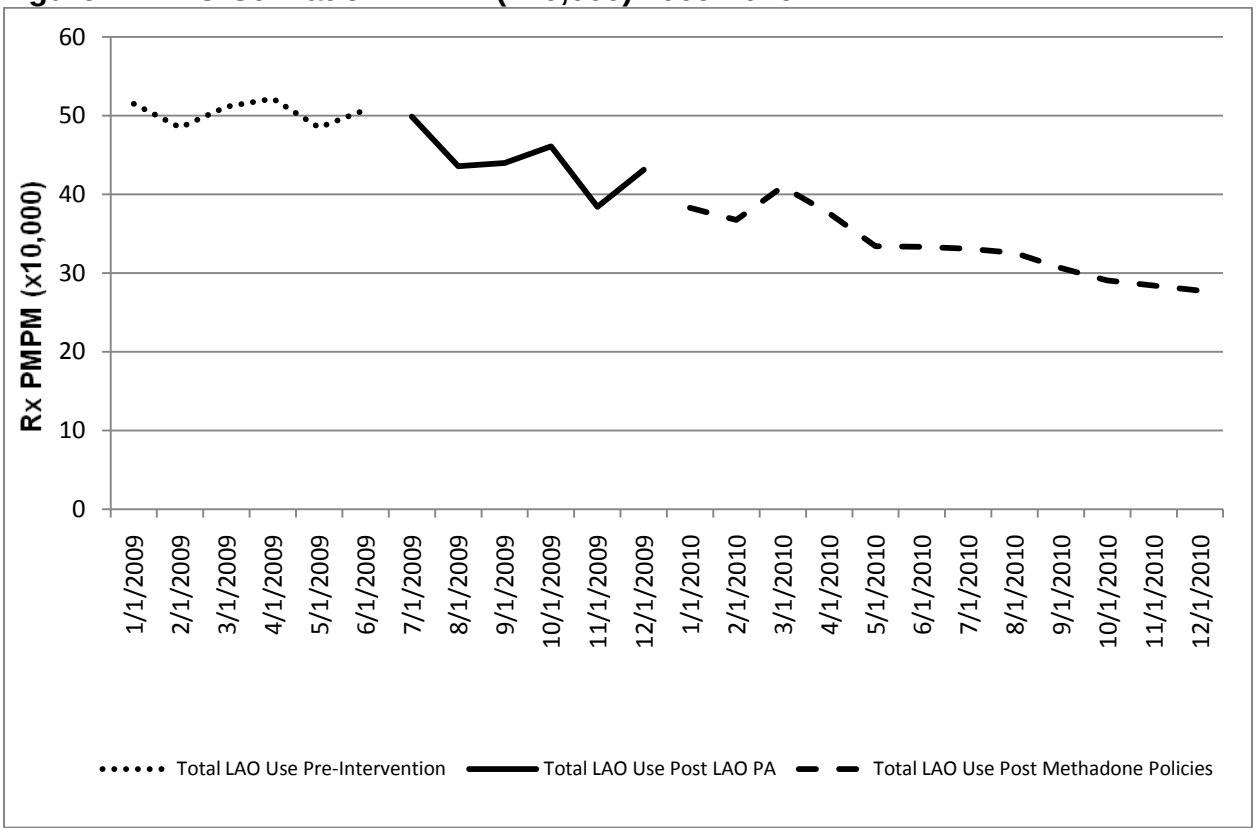
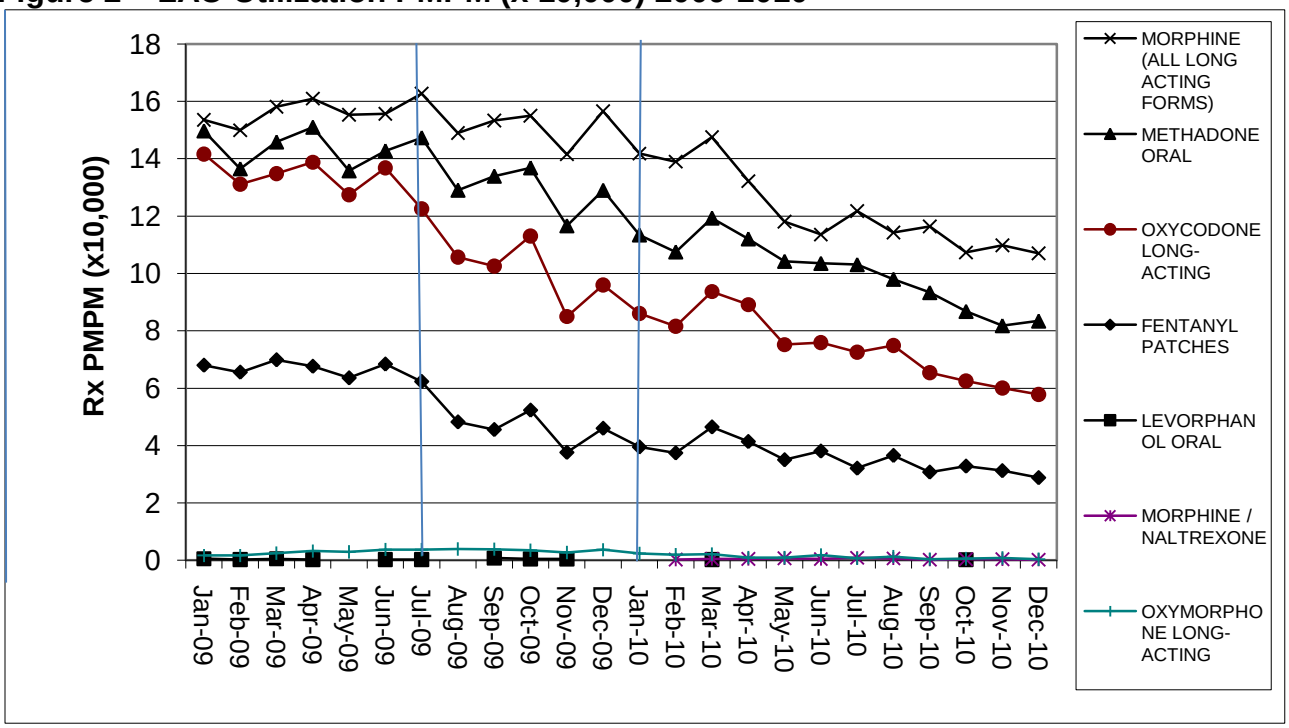


**Figure 2 – LAO Utilization PMPM (x 10,000) 2009-2010**




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**

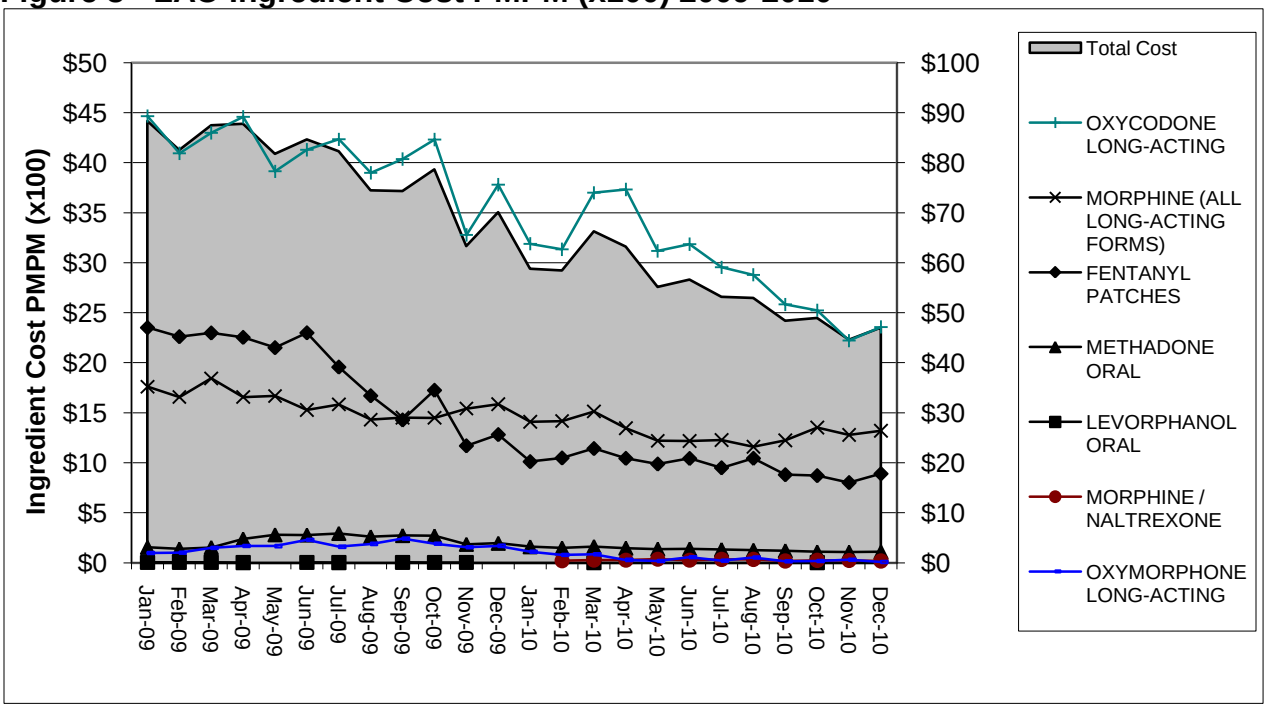


**Table 1: Oregon FFS LAO Cost Summary**

| | % 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.

**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.

**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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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 |