



UNIVERSITY OF UTAH  
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## **UTAH MEDICAID DUR REPORT JULY 2016**

### **SHORT-ACTING OPIOIDS FOR CHRONIC NON-CANCER PAIN**

#### **Opiate agonists**

Codeine

Hydrocodone

Hydromorphone

Levorphanol

Meperidine

Morphine

Oxycodone

Oxymorphone

Tapentadol

Tramadol

#### **Drug Regimen Review Center**

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## Introduction

The Centers for Disease Control and Prevention (CDC) describes prescription painkiller overdoses as a public health epidemic and states that the number of prescription painkiller overdose deaths is now greater than those of deaths from heroin and cocaine combined.<sup>1</sup> There has been an alarming increase in deaths in Utah related to misuse of prescription drugs. Prescription drug-related deaths now exceed deaths resulting from automobile crashes in the US and in our state, and it is now the number one cause of unintentional death.<sup>2</sup> According to the National Vital Statistics System Mortality File, opioid analgesics were involved in more than 40% of all drug poisoning deaths in 2008; nearly 15,000 deaths.<sup>1</sup> In Utah, drug overdose deaths began to increase substantially in 2001 and the increase has continued through 2007.<sup>3</sup> In 2005, Utah had the highest rates in the nation of reported nonmedical use of pain relievers and increase in prescription opioid-related deaths.<sup>4</sup> “In 2012, an average of 21 Utah residents each month died as a result of prescription painkiller overdoses, according to the Utah Department of Health.”<sup>5</sup> The CDC drug overdose state information include Utah as one of the states with the highest drug overdose death rates: 14.9-27.0 per 100,000 people (National Vital Statistics System, 2008).<sup>1</sup> According to the CDC, “states with higher sales per person and more nonmedical use of prescription painkillers tend to have more deaths from drug overdoses.”<sup>1</sup> The CDC stated in a recent report that unintentional drug overdose death rates in the United States have increased five-fold since 1990 and has been driven by increased use of opioid analgesics.<sup>4</sup> “The opioid epidemic that is afflicting our nation resulted in nearly 30,000 deaths last year.”<sup>6</sup>

The CDC report that a big part of the problem is nonmedical use of prescription painkillers. “In 2010, about 12 million Americans (age 12 or older) reported nonmedical use of prescription painkillers in the past year.”<sup>1</sup> Prescription opioid abuse and misuse is associated with many adverse sequela (i.e. overdose death and increasing transition to heroin use) and has significant associated societal costs and excess medical costs. The CDC report that Nonmedical use of prescription painkillers costs health insurers up to \$72.5 billion annually in direct health care costs. A recent systematic review found that “Mean costs to the payer for abusers were \$23,000-\$25,000 per year and excess costs approximately \$15,000 per patient.”<sup>7</sup>

Controlled prescription drug (CPD) diversion has an increasing financial impact on the Medicaid program and it is not just the cost of the prescription drugs, but also doctor’s visits, emergency department (ED) treatment, rehabilitation centers and other health care needs. According to the National Drug Threat Assessment report, National Survey of Drug Use and Health (NSDUH) data and the Drug Enforcement Agency (DEA), opioid pain relievers are the most commonly diverted CPDs. In 2008, opioid painkillers were associated with approximately 305,885 ED visits (Drug Abuse Warning Network; DAWN).<sup>8</sup> In 2009, misuse or abuse of prescription painkillers resulted in nearly half a million emergency department visits (CDC).<sup>1</sup>

Groups that are more likely to abuse or overdose on prescription painkillers include men, middle-aged adults, people in rural counties, and Whites (1 in 20) and American Indian or Alaska Natives (1 in 10).<sup>1</sup>

In Utah, opioid pain medications have been mostly responsible for the increase in deaths in prescription drugs. These include rapid-onset, medium and long-acting opioids, including methadone, morphine, oxycodone, hydrocodone and fentanyl.<sup>2,9</sup>

The purpose of this review is to ensure appropriate opioid use in chronic non-cancer pain. “Careful recordkeeping of prescribing information, including quantity, frequency, and renewal requests as required by state and federal law, is strongly advised. Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.”<sup>10</sup>

“There is currently no well-validated objective means of accurately identifying patients likely to experience good analgesia with low side effects and abuse risk prior to initiating opioid therapy” and “Currently available research is insufficient to inform development of quantitative analgesic-prescribing algorithms.”<sup>11</sup> Quantity limitations that allow sufficient quantities to ensure patients have access to appropriate pain medications whilst limiting access to excessive quantities that could lead to overdose or diversion would help. “Decreasing opioid misuse and abuse, while at the same time assuring that patients with chronic and acute pain have access to treatment to control their pain needs to be a major goal for all health professionals, government, pharmaceutical manufacturers and payers and will require a substantial effort from all parties.”<sup>7</sup>

This review will discuss the available evidence for dosages and quantity limitations. This report will focus on the short-acting opioids (opiate agonists), followed by a report on the long-acting opioids (opiate agonists). The partial agonists (such as buprenorphine) and mixed agonist-antagonists used in the management of pain will not be covered in this review. Opioid dependence treatment is outside the scope of this project. The rapid-onset opioids (fentanyl transmucosal) are indicated for the management of breakthrough pain (BTP) in patients with cancer and have been reviewed by the Utah DUR Board in April 2012. A motion was approved to require a cancer diagnosis for transmucosal fentanyl preparations.

## **Methodology**

The Agency for Healthcare Research and Quality (AHRQ; [www.guideline.gov](http://www.guideline.gov)), Cochrane Library, the FDA website (including product labeling information), PubMed, UpToDate, Micromedex, Lexicomp, the Institute for Clinical and Economic Review (ICER) website, the National Institute for Health and Clinical Excellence (NICE) website, and ClinicalKey were searched for systematic reviews, clinical trials, guidelines, other reports, reviews, efficacy and safety information. As per the hierarchy of evidence, high quality systematic reviews and evidence based guidelines were searched for first, followed by phase 3 randomized controlled trials, etc.

## **Opioid classes and mechanism of action**

Appendix 1 contains a drug summary table containing information on the short-acting opioids.

Opioids are classified as full agonists, partial agonists, or mixed agonist-antagonists. Full agonists’ effectiveness with increasing doses is not limited by a ceiling and they will not reverse or antagonize the effects of other full agonists given simultaneously. Morphine, hydromorphone, codeine, oxycodone, oxymorphone, hydrocodone, methadone, levorphanol, and fentanyl are classified as full agonists. Partial agonists (such as buprenorphine) are subject to a ceiling effect and are less effective analgesics than full agonists at opioid receptors. Mixed agonist-antagonists block or are neutral at one opioid receptor while activating a different opioid receptor and their analgesic effectiveness is also limited by a dose-related ceiling effect. Examples include pentazocine (Talwin), butorphanol tartrate (Stadol), dezocine (Dalgan), and nalbuphine hydrochloride (Nubain). They are contraindicated for use in patients receiving an opioid agonist because they may precipitate a withdrawal syndrome and increase pain.<sup>12</sup>

Opioids are also classified according to their duration of action and formulation which can be seen in the table below.

**Table 1. Opioid Classes**

| Long-Acting Opioids               | Short-Acting Opioids | Rapid-Onset Opioids                       |
|-----------------------------------|----------------------|---|
| Transdermal systems with fentanyl | Codeine              | Oral transmucosal fentanyl citrate (OTFC) |
| Buprenorphine patch               | Buprenorphine        | Fentanyl buccal tablet (FBT)              |
| Extended release morphine         | Morphine (MSIR)      | Fentanyl buccal soluble film (FBSF)       |
| Extended release oxycodone        | Oxycodone            | Sublingual fentanyl                       |
| Extended release oxycodone        | Oxycodone            | Intranasal fentanyl                       |
| Extended release tapentadol       | Tapentadol           |   |
| Extended release hydrocodone      | Hydrocodone          |   |
| Extended release hydromorphone    | Hydromorphone        |   |
| Extended release tramadol         | Tramadol             |   |
| Methadone                         |                      |   |

Table adapted from Pain World Congress Report<sup>13</sup> and product information.

Opioids act mostly on the mu-opioid receptors in the dorsal horn of the spine and in multiple regions in the brain. The activation is highly variable and the response seen between patients and the various opioids therefore vary. Factors such as renal and hepatic function, age and genetic factors also affect an individual’s response to opioids.<sup>14,15</sup> Tramadol has recently been made a controlled prescription in the state of Utah due to the risk of abuse/misuse/diversion associated with tramadol therapy. Similar to other opioid agents, tramadol therapy decreases GI motility and may result in constipation. Tramadol also interacts with other serotonergic medications and CNS depressants and may lower the seizure threshold.

**Definitions relating to opioid misuse and abuse**

“Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

Drug-seeking behavior is very common to persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other healthcare provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.”<sup>10</sup>

## Opioid therapy for chronic non-cancer pain (CNCP)

The source of chronic pain cannot always be identified; it can be neuropathic, nociceptive, or mixed nociceptive and neuropathic in nature.<sup>16</sup> The goal of chronic pain management is to control the pain sufficiently to allow the patient to function and improve his or her quality of life.<sup>16</sup> "Chronic pain is most successfully treated using a multidisciplinary, multimodal approach."<sup>16</sup>

Pharmacologic agents for pain management include nonopioid analgesic agents (eg acetaminophen, nonsteroidal anti-inflammatory drugs; NSAIDs), antidepressants, anticonvulsants, alpha<sub>2</sub>-adrenergic agonist, muscle relaxants, and topical analgesic agents.<sup>16,17</sup> "The initial choice of agent often depends upon the severity, pathophysiology, and etiology of the pain (nociceptive, neuropathic, psychogenic)."

### Neuropathic Pain

The International Association for the Study of Pain (IASP) defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory system".<sup>18,19</sup> Neuropathic pain is experienced as a result of central (e.g. post-stroke thalamic pain, spinal cord injury pain) and peripheral (e.g. diabetic neuropathy, postherpetic neuralgia caused by shingles) disorders, and it is usually chronic.<sup>19,20</sup> The prevalence of neuropathic pain ranges between 5-10% (vs. the prevalence of any chronic pain in one of these studies was 48%).<sup>19,21-23</sup> Torrance et al. found that respondents with chronic neuropathic pain (UK study) were significantly more likely to be female, slightly older, no longer married, living in council rented accommodation, unable to work, have no educational qualifications, and be smokers than all other respondents.<sup>22</sup> "Multiple logistic regression modeling found that pain of predominantly neuropathic origin was independently associated with older age, gender, employment (being unable to work), and lower educational attainment."<sup>22</sup> The authors also found that neuropathic pain respondents reported significantly greater pain intensity, higher scores on the NPS, higher levels of expressed need, and longer duration of pain.<sup>22</sup> Treatment options include antidepressants (e.g. duloxetine<sup>24</sup> or amitriptyline<sup>25</sup>) and anticonvulsants (e.g. gabapentin<sup>26</sup> or pregabalin<sup>26,27</sup>) whereas paracetamol or ibuprofen are used, but not usually effective in neuropathic pain.<sup>20,28,29</sup> "Neuropathic pain is very challenging to manage because of the heterogeneity of its aetiologies, symptoms and underlying mechanisms."<sup>30</sup>

### Nociceptive pain

Nociceptive pain is experienced when there is tissue damage or potentially tissue-damaging stimuli such as caused by an injury, pain after surgery, arthritis pain, and mechanical low back pain.<sup>31</sup> Nociceptive pain is primarily treated with nonnarcotic (NSAIDs or acetaminophen) and opioid analgesia.<sup>17</sup>

### Opioid use

"Opioids are used in the treatment of chronic pain when the pain is malignant or when other conservative or procedure-type approaches have failed and the pain is significantly affecting the patients' quality of life."<sup>16</sup> Table 2 contains examples of medications that could be considered (depending on the type of pain) prior to using opioids.

In the US, opioid use for acute pain, postsurgical pain, and palliative care is considered acceptable and efficacy has been demonstrated in short-term trials for CNCP, but evidence is lacking for longer term use in CNCP.<sup>32,33</sup> "Opioid therapy for chronic noncancer pain (CNCP) is controversial due to concerns regarding long-term effectiveness and safety, particularly the risk of tolerance, dependence, or abuse."<sup>32</sup> Chronic pain is defined as "pain which persists past the normal time of healing," which is considered to be three months or longer.<sup>32,34</sup> Chronic non-cancer pain include chronic headache, neck pain, fibromyalgia, rheumatoid arthritis, osteoarthritis, diabetic neuropathy, and postherpetic neuralgia.<sup>35</sup> Patients could also experience opioid-induced hyperalgesia with prolonged use (heightened pain sensitivity and pain syndromes that did not

previously exist) which is improved by decreasing the dose (vs tolerance where pain is improved by increasing the dose; pain is also in the original anatomic location).<sup>36-39</sup>

Commonly used short-acting agents include morphine, oxycodone, and hydromorphone. Table 4 (appendix 1) include these agents and various different formulations to provide options for patients who are unable to receive it via certain routes.<sup>16</sup>

## **Products not recommended**

### **Meperidine (Demerol; pethidine)**

The high doses needed to achieve an analgesic affect are often accompanied by nausea and sedation. It undergoes extensive first-pass metabolism and significant amounts of its renally-eliminated toxic metabolite (normeperidine) is formed.<sup>16</sup> This can build up in the central nervous system and cause anxiety, tremors, myoclonus, and seizures when the dose of meperidine is high and/or repeated doses are administered.<sup>16</sup> It also has serotonergic activity (serotonergic toxicity risk with other serotonergics).<sup>16</sup> It is therefore no longer considered a first-line pain medication and is not recommended for long-term use; it has no place in chronic pain management.<sup>16,40</sup>

The American Pain Society (2008) and ISMP (2007) do not recommend meperidine's use as an analgesic.<sup>41</sup> "If use in acute pain (in patients without renal or CNS disease) cannot be avoided, treatment should be limited to ≤48 hours and doses should not exceed 600 mg/24 hours."<sup>41</sup> The oral route is not recommended for treatment of acute or chronic pain and it is recommended to consider a reduced dose if the IV route is required.<sup>41</sup> Meperidine is also not recommended as a drug of first choice for the treatment of chronic pain in the elderly due to potential serious CNS side effects (eg, tremor, seizures).<sup>41</sup> The safety and effectiveness of meperidine has not been established in pediatric patients.<sup>42-44</sup>

Meperidine is mentioned in "*The acute treatment of migraine in adults: the American headache society evidence assessment of migraine pharmacotherapies*".<sup>45</sup> There is inadequate evidence for meperidine injections for this use.<sup>45</sup>

### **Propoxyphene (Darvocet)**

Propoxyphene is metabolized to norpropoxyphene, which has a long half-life (renally eliminated) and may accumulate with chronic use.<sup>16,40,42</sup> "On November 19, 2010, the US Food and Drug Administration requested that manufacturers voluntarily withdraw propoxyphene from the United States market due to new data from the multiple-ascending dose (MAD) study demonstrating serious cardiotoxicity (eg, significantly prolonged QT interval, prolonged PR interval, and widened QRS complex) in healthy adults who received recommended doses of propoxyphene."<sup>42</sup>

**Table 2. Agents preferable to opioids in chronic non-malignant pain (adapted from Chronic Pain Management, Lexi-Drugs<sup>16</sup> and Overview of the treatment of chronic pain, UpToDate<sup>17</sup>)**

|                            | <b>Acetaminophen</b>  | <b>NSAIDS</b>  | <b>Antidepressants</b>  | <b>Anticonvulsants</b>  | <b>Other agents</b>   |
|----------------------------|---|--|---|---|---|
| <b>Properties</b>          | Analgesic   | Anti-inflammatory, analgesic, and antipyretic  | Analgesic effect at lower doses (than antidepressant effect dose)   | Refer to mechanism of action  | Oral Muscle relaxants e.g. tizanidine (antinociceptive, anti-inflammatory, and alpha-2-agonist properties)<br><br>Topical agents e.g. capsaicin, lidocaine  |
| <b>Mechanism of action</b> | Analgesic mechanism is uncertain (not anti-inflammatory)  | Inhibiting cyclooxygenase activity (peripherally and centrally) to prevent the formation of prostaglandins | Theoretical: by altering a biochemical mechanism (through inhibition of norepinephrine and/or serotonin reuptake) that may be related to both depression and pain; may also enhance or modulate endogenous opioid analgesia | Analgesic effects by decreasing spontaneous sensory nerve firing after nerve injury   | Oral muscle relaxants (eg, cyclobenzaprine, carisoprodol, methocarbamol): depressing spinal polysynaptic pathways and producing sedation.   |
| <b>Place in therapy</b>    | Recommended for analgesia in multiple guidelines for the management of hip or knee osteoarthritis <sup>46-48</sup><br><br>Commonly combined with opioid medications to reduce the amount of opioid needed | Considered first-line agents for managing mild to moderate pain  | First- or second-line therapy for neuropathic pain  | Specifically for neuropathic pain and trigeminal neuralgia.<br>First- or second-line therapy for neuropathic pain; usually used when other treatments, such as antidepressants, are unsuccessful. Gabapentin or pregabalin, however, may be administered as first-line therapy. | Muscle relaxants: Most helpful in acute musculoskeletal conditions such as neck and back pain.<br>Topical agents: When the pain is localized and could be helpful in chronic conditions such as arthritic and neuropathic pain. |
| <b>Contraindications</b>   | Significant liver disease or heavy alcohol use should be considered a relative contraindication   | Patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or        | Refer to product labels   | Refer to product labels   | Refer to product labels   |

|  |  |  |  |  |  |
|--|--|--|--|--|--|
| <p><b>Patient screening</b></p> <p><b>Considerations</b></p> <p><b>Adverse effects</b></p> | <p>May cause hepatic damage in patients with underlying liver disease or at higher doses.</p> <p>“The safety of long-term use of acetaminophen at a dose of 4 g per day have been questioned.”<sup>17,49,50</sup></p> <p>FDA maximum dose: 4 g per day.</p> <p>“The FDA has conducted multiple advisory committee meetings to evaluate acetaminophen and its safety profile, and has suggested (but not mandated) a reduction in the maximum daily dosage from 3900-4000 mg to 3000-3250 mg.”<sup>51</sup></p> <p>Some manufacturers of over-the-counter acetaminophen: decreased the maximum daily dose to 3 to 3.25 g.</p> | <p>other NSAIDs</p> <p>Age, cardiovascular disease, renal dysfunction, gastritis, gastric ulcers, or bleeding disorders due to platelet dysfunction and use of the lowest effective dose for the least amount of time is important for minimizing the risk of serious cardiovascular events and/or gastrointestinal bleeding</p> | <p>Tricyclic antidepressants (TCAs) effective for neuropathic pain, but anticholinergic effects (dry mouth, constipation, blurred vision, sedation, dizziness, urinary retention) can occur, particularly with amitriptyline (tertiary amine). Nortriptyline and desipramine (secondary amines) cause less sedation and anticholinergic effects than amitriptyline, making them a better choice for older or debilitated patients.</p> <p>“Cardiovascular effects of TCAs (particularly amitriptyline) include orthostatic hypotension, conduction defects, and arrhythmias due to their quinidine-like effect.”</p> <p>“Selective serotonin reuptake inhibitors (SSRIs) are better tolerated than TCAs but have not been shown to be as effective as TCAs for managing neuropathic pain symptoms in nondepressed patients.”</p> <p>“Duloxetine, an antidepressant that acts by highly specific inhibition of serotonin and norepinephrine reuptake, has been shown to effectively manage painful diabetic neuropathy, fibromyalgia, and chronic musculoskeletal pain. Nausea, headache, and xerostomia are its most common adverse effects.”</p> <p>“Venlafaxine, a bicyclic antidepressant, inhibits the reuptake of serotonin at low doses and norepinephrine at moderate doses. Adverse effects are similar to that of SSRIs. Venlafaxine may be considered for neuropathic pain that does not respond to TCAs, duloxetine, or anticonvulsants.”</p> <p>“All of the antidepressants require anywhere from one (eg, duloxetine) to three weeks (eg, TCAs) for an adequate trial for managing neuropathic pain.”</p> | <p>“When using anticonvulsants as an analgesic, efficacy does not correlate with therapeutic serum concentrations. Newer agents (gabapentin, pregabalin) are less toxic than the older agents (carbamazepine, divalproex, phenytoin, and valproic acid) and are preferred. The adverse effects of gabapentin and pregabalin include sedation, dizziness, dry mouth, and peripheral edema.</p> <p>Carbamazepine can produce a rash, has a toxic epoxide metabolite (for which regular blood tests are warranted), has a negative effect on bone density, and has significant drug-drug interactions. It has also been associated with Stevens-Johnson syndrome and toxic epidermal necrosis. Topiramate, zonisamide, levetiracetam, and tiagabine may provide analgesia in patients unresponsive to more proven anticonvulsants. Lamotrigine, another second-line agent, also has antidepressant properties. Strict dose titration of lamotrigine is necessary to minimize the risk of serious adverse effects such as Stevens-Johnson Syndrome and toxic epidermal necrosis. Discontinue lamotrigine with the first sign of a rash. Clonazepam has been effectively used for trigeminal neuralgia, post-traumatic neuralgia, paroxysmal postlaminectomy pain, and lancinating phantom limb pain. Like other benzodiazepines, drowsiness is common and withdrawal symptoms may occur following abrupt discontinuation.”</p> | <p>Muscle relaxants:</p> <p>Efficacy from long-term administration has not been demonstrated and abrupt discontinuation following prolonged administration can cause withdrawal symptoms.</p> <p>Tizanidine requires gradual dose titration over 2 to 4 weeks.</p> |
|--|--|--|--|--|--|

## Opioid prescribing and use of short-acting opioids

Opioid medication prescribing and use is a complex issue and people have different views on guidelines and rules where some believe these are too lax and others believe they impose barriers to access of much needed narcotic medications for control of pain.<sup>2</sup>

The CDC report that prescribing rates for opioids vary widely across different states.

“Factors may influence prescribing rates include:

- Health care providers in different parts of the country don't agree on when to prescribe opioid painkillers and how much to prescribe.
- Some of the increased demand for prescription opioids is from people who use them nonmedically (using drugs without a prescription or just for the high they cause), who sell them, or who obtain them from multiple prescribers.
- Many states report problems with for-profit, high-volume pain clinics (so-called "pill mills") that prescribe large quantities of painkillers to people who don't need them medically.”<sup>1</sup>

## Factors to consider regarding appropriate short-acting opioid use

### Opioid tolerance

Summary table 4 in Appendix 1 contains information regarding opioids and opioid-naïve patients. Respiratory depression occurs rarely in patients receiving opioids regularly as tolerance to the respiratory depressant effects develop rapidly, but there is an increased risk of respiratory depression when it is used in opioid-naïve patients with respiratory impairment (pneumonia, those with CO<sub>2</sub> retention or chronic obstructive pulmonary disease) or if the opioids are titrated too rapidly.<sup>13,52,53</sup>

Identification of opioid-tolerant patients is complicated by interindividual variability in opioid responsiveness. It is recommended that patients be monitored during initial dosing and titration with rapid-onset opioids. Threshold levels were established to ensure patients are opioid-tolerant before rapid-onset opioids are taken.<sup>13</sup> Patients considered opioid tolerant are those who are taking around-the-clock medicine, for one week or longer<sup>54</sup>:

- 60 mg/d oral morphine
- at least 25 mcg/hr of transdermal fentanyl
- at least 30 mg of oral oxycodone daily
- at least 8 mg of oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- an equianalgesic dose of another opioid

### Opioid sharing, storage and disposing opioid medications

Authors of a recent survey found that about 20% of respondents (1,032 adult Americans with recent opioid prescriptions) admitted to sharing their medications with other people and the main reason provided was to help the other person to manage pain.<sup>55</sup> Also, more than half of participants that were taking opioids had or expected to have excess medication, and 61% of those with excess medication intended to keep it for future

use.<sup>55</sup> “Nearly half of the adults with recent opioid medication use did not recall receiving information on safe storage (48.7%) or proper disposal (45.3%).”<sup>55</sup> Strategies to limit the opportunities for nonmedical use of drugs need to be considered. The authors suggest “reducing the prescribing of large quantities of opioid medications and disseminating clear recommendations on safe storage and disposal of opioid medications widely to the public and prescribers may reduce risks.”<sup>55</sup>

In Utah, an excessive amount of opioids prescribed is also a problem. The Utah Department of Health state's Behavioral Risk Factor Surveillance System (BRFSS) survey indicated that one in five Utah adults had been prescribed an opioid pain medication during the preceding 12 months.<sup>56,57</sup> “Of those prescribed an opioid pain medication, 3.2% reported using their medication more frequently or in higher doses than had been directed by their doctor; 72.0% reported having leftover medication, and 71.0% of those with leftover medication reported that they had kept the medication.”<sup>57</sup> Bateman and Choudhry state that this is approximately 10% of the adult population of Utah who held on to leftover opioids over just a 1-year period.<sup>56</sup>

Renthal report that “among diverted opioid prescriptions, more than 50% are obtained freely from a family member or friend with a valid prescription” and it is therefore not just the patient’s risk for overdose that needs to be considered, but also the risk of opioids being diverted and the risk of harming others.<sup>58</sup>

## Repeated dose escalations

Repeated dose escalations can be a sign of substance abuse or diversion and it is therefore important to evaluate the reason for the need of higher doses for pain control and to manage it appropriately which could include rotating or switching opioids, or, weaning or discontinuing opioid therapy.<sup>59</sup> Intensive monitoring in these patients is necessary.<sup>59</sup>

## Clinical Guidelines and related evidence

Please note that this is a brief summary of some of the information in these guidelines. Please refer to the guidelines for complete information.

**Table 3. Guidelines**

**CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016.**<sup>60,61</sup>

“OBJECTIVE: To provide recommendations about opioid prescribing for primary care clinicians treating adult patients with chronic pain outside of active cancer treatment, palliative care, and end-of-life care.”

1) when to initiate or continue opioids for chronic pain; 2) opioid selection, dosage, duration, follow-up, and discontinuation; and 3) assessing risk and addressing harms of opioid use.

This is just a summary of some of the recommendations. Please refer to guidelines for all 12 recommendations.

- Treatment of chronic pain: non-opioid therapy is preferred
- “Opioids should be used only when benefits for pain and function are expected to outweigh risks.”
- Immediate-release opioids should be prescribed instead of LA/ER opioids when starting opioid therapy for pain.
- “When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to 50 morphine milligram equivalents (MME) or more per day, and should avoid increasing dosage to 90 MME or more per day or carefully justify a decision to titrate dosage to 90 MME or more per day.”<sup>61</sup>
- The lowest effective dose of IR opioids should be prescribed.
- Only the quantity needed for the expected duration of pain severe enough to require opioids should be prescribed. “Three days or less will often be sufficient; more than 7 days will rarely be needed.”
- “Clinicians should evaluate benefits and harms with patient within 1 to 4 weeks starting opioid therapy for chronic pain

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or dose escalation.”

- “Clinicians should evaluate benefits and harms of continued opioid therapy with patients every 3 months or more frequently and review prescription drug monitoring program data, when available, for high-risk combinations or dosages.”
- Higher opioid dosages (≥50 MME/d) is one of the risk factors that clinicians need to evaluate for opioid-related harm/overdose (also, history of overdose or substance use disorder) and for which strategies to mitigate risk into the management plan needs to be incorporated.
- State prescription drug monitoring data should be reviewed by clinicians
- Avoid concurrent opioids and benzodiazepines whenever possible.
- Treatment should be offered to patients with opioid use disorder.

## 2012 American College of Emergency Physicians

### Clinical policy: critical issues in the prescribing of opioids for adult patients in the emergency department.

#### “Major Recommendations

1. In the adult Emergency Department (ED) patient with noncancer pain for whom opioid prescriptions are considered, what is the utility of state prescription drug monitoring programs in identifying patients who are at high risk for opioid abuse?

*Level A recommendations.* None specified.

*Level B recommendations.* None specified.

*Level C recommendations.* The use of a state prescription monitoring program may help identify patients who are at high risk for prescription opioid diversion or doctor shopping.

2. In the adult ED patient with acute low back pain, are prescriptions for opioids more effective during the acute phase than other medications?

*Level A recommendations.* None specified.

*Level B recommendations.* None specified.

*Level C recommendations.*

1. For the patient being discharged from the ED with acute low back pain, the emergency physician should ascertain whether nonopioid analgesics and nonpharmacologic therapies will be adequate for initial pain management.
  2. Given a lack of demonstrated evidence of superior efficacy of either opioid or nonopioid analgesics and the individual and community risks associated with opioid use, misuse, and abuse, opioids should be reserved for more severe pain or pain refractory to other analgesics rather than routinely prescribed.
  3. If opioids are indicated, the prescription should be for the lowest practical dose for a limited duration (e.g., <1 week), and the prescriber should consider the patient’s risk for opioid misuse, abuse, or diversion.
3. In the adult ED patient for whom opioid prescription is considered appropriate for treatment of new-onset acute pain, are short-acting schedule II opioids more effective than short-acting schedule III opioids?

*Level A recommendations.* None specified.

*Level B recommendations.* For the short-term relief of acute musculoskeletal pain, emergency physicians may prescribe short-acting opioids such as oxycodone or hydrocodone products while considering the benefits and risks for the individual patient.

*Level C recommendations.* Research evidence to support superior pain relief for short-acting schedule II over schedule III opioids is inadequate.

4. In the adult ED patient with an acute exacerbation of noncancer chronic pain, do the benefits of prescribing opioids on discharge from the ED outweigh the potential harms?

*Level A recommendations.* None specified.

*Level B recommendations.* None specified.

*Level C recommendations.*

1. Physicians should avoid the routine prescribing of outpatient opioids for a patient with an acute exacerbation of chronic noncancer pain seen in the ED.
2. If opioids are prescribed on discharge, the prescription should be for the lowest practical dose for a limited duration (e.g., <1 week), and the prescriber should consider the patient’s risk for opioid misuse, abuse, or diversion.

The clinician should, if practicable, honor existing patient-physician pain contracts/treatment agreements and consider past prescription patterns from information sources such as prescription drug monitoring programs.”

**2012 American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part I—evidence assessment.**<sup>62</sup>

- 1) *There is good evidence that non-medical use of opioids is extensive; one-third of chronic pain patients may not use prescribed opioids as prescribed or may abuse them, and illicit drug use is significantly higher in these patients.*
- 2) *There is good evidence that opioid prescriptions are increasing rapidly, as the majority of prescriptions are from non-pain physicians, many patients are on long-acting opioids, and many patients are provided with combinations of long-acting and short-acting opioids.*
- 3) *There is good evidence that the increased supply of opioids, use of high dose opioids, doctor shoppers, and patients with multiple comorbid factors contribute to the majority of the fatalities.*
- 4) *There is fair evidence that long-acting opioids and a combination of long-acting and short-acting opioids contribute to increasing fatalities and that even low-doses of 40 mg or 50 mg of daily morphine equivalent doses may be responsible for emergency room admissions with overdoses and deaths.*
- 5) *There is good evidence that approximately 60% of fatalities originate from opioids prescribed within the guidelines, with approximately 40% of fatalities occurring in 10% of drug abusers.*
- 6) *The short-term effectiveness of opioids is fair, whereas the long-term effectiveness of opioids is limited due to a lack of long-term (> 3 months) high quality studies, with fair evidence with no significant difference between long-acting and short-acting opioids.*
- 7) *Among the individual drugs, most opioids have fair evidence for short-term and limited evidence for long-term due to a lack of quality studies.*
- 8) *The evidence for the effectiveness and safety of chronic opioid therapy in the elderly for chronic non-cancer pain is fair for short-term and limited for long-term due to lack of high quality studies; limited in children and adolescents and patients with comorbid psychological disorders due to lack of quality studies; and the evidence is poor in pregnant women.*
- 9) *There is limited evidence for reliability and accuracy of screening tests for opioid abuse due to lack of high quality studies.*
- 10) *There is fair evidence to support the identification of patients who are non-compliant or abusing prescription drugs or illicit drugs through urine drug testing and prescription drug monitoring programs, both of which can reduce prescription drug abuse or doctor shopping.”*

**2012 American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible prescribing in chronic non-cancer pain: part 2 – guidance**<sup>63</sup>

“Part 2 of the guidelines on responsible opioid prescribing provides the following recommendations for initiating and maintaining chronic opioid therapy of 90 days or longer.”<sup>63</sup>

- “The long-acting opioids in high doses are recommended only in specific circumstances with severe intractable pain that is not amenable to short-acting or moderate doses of long-acting opioids, as there is no significant difference between long-acting and short-acting opioids for their effectiveness or adverse effects. (Evidence: fair)”
- “A trial of opioid rotation may be considered for patients requiring escalating doses. (Evidence: limited)”
- “Once medical necessity is established, opioid therapy may be initiated with low doses and short-acting drugs with appropriate monitoring to provide effective relief and avoid side effects. (Evidence: fair for short-term effectiveness, limited for long-term effectiveness)”
- “Up to 40 mg of morphine equivalent doses are being recommended as low dose, 41 to 90 mg of morphine equivalent dose as a moderate dose, and greater than 91 mg of morphine equivalence as high doses. (Evidence: fair)”
- “In reference to long-acting opioids, titration must be carried out with caution and overdose and misuse must be avoided. (Evidence: good)”
- “Methadone is recommended for use in late stages after failure of other opioid therapy and only by clinicians with specific training in the risks and uses. (Evidence: limited)”

**Adherence Monitoring**

1. “Monitoring recommendation for methadone prescription is that an electrocardiogram should be obtained prior to initiation, at 30 days and yearly thereafter. (Evidence: fair)”
2. In order to reduce prescription drug abuse and doctor shopping, adherence monitoring by urine drug testing and PMDPs provide evidence that is essential to the identification of those patients who are non-compliant or abusing prescription drugs or illicit drugs. (Evidence: fair)”

**2009 Clinical Guidelines from the American Pain Society and the American Academy of Pain Medicine on the use of chronic opioid therapy in chronic noncancer pain**<sup>64</sup>

Please refer to the guideline for all recommendations. This is just the section regarding dosage.

**Dose escalations and high dose opioids**

“Theoretically, opioids have no maximum or ceiling dose. In practice, progressively higher opioid doses may improve symptom control in some patients, but can also result in additional adverse effects with little incremental benefit, or be a marker for substance abuse or diversion. The guideline defines high dose opioid therapy as >200 mg daily of oral morphine (or equivalent).”<sup>65</sup>

These doses are outside the ranges evaluated in randomized trials and prescribed in only a small minority of patients in observational studies.<sup>33,66,67</sup> When opioid doses reach this threshold, more frequent and intense monitoring is recommended.

Clinicians should consider weaning or discontinuation of chronic opioid therapy if assessments indicate reduced analgesia, function, or quality of life; aberrant drug-related behaviors; or the presence of intolerable adverse effects.”<sup>64</sup>

## 2010 Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain<sup>68</sup>

≥200 mg/day MED is considered a “watchful dose”

“Chronic non-cancer pain can be managed effectively in most patients with dosages at or below 200 mg/day of morphine or equivalent (Grade A). Consideration of a higher dosage requires careful reassessment of the pain and of risk for misuse, and frequent monitoring with evidence of improved patient outcomes (Grade C).”<sup>68</sup>

## NICE guidelines [CG173] Neuropathic pain in adults: pharmacological management in non-specialist settings<sup>69</sup>

Published date: November 2013 Last updated: December 2014

### Treatment

- For **all neuropathic pain (except trigeminal neuralgia)** offering a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatments suggested (If the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated).
- “Consider tramadol only if acute rescue therapy is needed (see recommendation below about long-term use).”
- “Consider capsaicin cream for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.”

### Treatments that should not be used

“Do not start the following to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so:

- cannabis sativa extract
- capsaicin patch
- lacosamide
- lamotrigine
- levetiracetam
- morphine
- oxcarbazepine
- topiramate
- tramadol (this is referring to long-term use; see recommendation above for short-term use)
- venlafaxine.”

### Trigeminal neuralgia

- “Offer carbamazepine as initial treatment for trigeminal neuralgia.
- If initial treatment with carbamazepine is not effective, is not tolerated or is contraindicated, consider seeking expert advice from a specialist and consider early referral to a specialist pain service or a condition-specific service.”

## Systematic Reviews

### Dosage or titration

#### ❖ Cochrane Library

No Cochrane reviews or other reviews meeting the criteria for the Database of Abstracts of Reviews of Effects (DARE) were identified regarding dosage/quantity limitations (maximum daily dosage) or the association of prescribed opioid dosages and optimal treatment or adverse outcomes in chronic non-cancer pain. One review and a protocol were identified in postoperative pain and use in labor.

Erskine et al. (2015) report that administering the appropriate analgesia to children is a complex process and they assessed the efficacy of “as required” versus “fixed schedule analgesic administration” for the management of postoperative pain in children under the age of 16 years.<sup>70</sup> Three RCTs (four reports) of 246 children aged under 16 years undergoing tonsillectomy were included in this review in which children were given weight-appropriate doses of the study medication orally or rectally (all studies paracetamol, and opioid added to paracetamol in 2 studies), either PRN or ATC, by a parent or carer at home for up to four days

following surgery.<sup>70</sup> Reporting quality was poor and a meta-analysis was not possible (three small studies).<sup>70</sup> The authors therefore concluded that “There was limited evidence available to draw any conclusions about the efficacy of PRN versus ATC analgesic administration for the management of postoperative pain in children.”<sup>70</sup>

Jordan et al. (Editorial Group: Cochrane Pregnancy and Childbirth Group) published a protocol (2016) to evaluate high dose versus low dose opioid epidural regimens for pain relief in labor:

1. *“To compare the effects (see outcomes below) of different total\* doses (in terms of boluses, concentration, volume and timeframe) of opioid epidural (excluding combined-spinal epidural and intrathecal) analgesia administered (alone or as adjunctive) during labour on the woman and the infant.*
2. *To compare the safety (see outcomes below) of different total\* doses (as above) of opioid epidural analgesia administered during labour for the woman and the infant.”*<sup>71</sup>

## Opioid Uses

Cochrane Systematic reviews identified regarding opioid use in chronic non-cancer pain include chronic low back pain, neuropathic pain, phantom limb pain, rheumatoid and osteoarthritis pain.

### Chronic non-cancer pain (CNCP)

Noble et al. (2010 Cochrane review), assessed the safety, efficacy, and effectiveness of opioids taken long-term for CNCP.<sup>32</sup> Most participants had back pain (often following failed back surgery), osteoarthritis, or neuropathic pain.<sup>32</sup> The authors found limited evidence in terms of quantity and quality. They concluded that *“many patients discontinue long-term opioid therapy (especially oral opioids) due to adverse events or insufficient pain relief; however, weak evidence suggests that patients who are able to continue opioids long-term experience clinically significant pain relief. Whether quality of life or functioning improves is inconclusive. Many minor adverse events (like nausea and headache) occurred, but serious adverse events, including iatrogenic opioid addiction, were rare.”*<sup>32</sup>

Kalso et al. (2004 Other review in Cochrane Library) assessed the efficacy and safety of opioids in patients with chronic non-cancer pain.<sup>66</sup> The authors concluded that *“Opioids were effective for neuropathic and musculoskeletal pain in the short term in selected patients, but few patients continued with them in the longer term. There was insufficient information to draw conclusions about tolerance and addiction.”*<sup>72</sup> According to the Centre for Reviews and Dissemination (CRD) summary, *“Although only high-quality randomised controlled trials were included, the review methods were not described in full and this weakens the strength of the evidence.”*<sup>72</sup> They also state that because of some limitations, the conclusions of the review should be interpreted cautiously.<sup>72</sup>

### Neuropathic pain

McNicol et al. (2013 updated Cochrane review) assessed the efficacy and safety of opioid agonists for the treatment of neuropathic pain.<sup>73</sup> The authors concluded that *“Short-term studies provide only equivocal evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain. Intermediate-term studies demonstrated significant efficacy of opioids over placebo, but these results are likely to be subject to significant bias because of small size, short duration, and potentially inadequate handling of dropouts. Analgesic efficacy of opioids in chronic neuropathic pain is subject to considerable uncertainty. Reported adverse events of opioids were common but not life-threatening. Further randomized controlled trials are needed to establish unbiased estimates of long-term efficacy, safety (including addiction potential), and effects on quality of life.”*

Stannard et al. (2016 Cochrane review) assessed the analgesic efficacy of hydromorphone for chronic neuropathic pain in adults, and the adverse events associated with its use, but found insufficient evidence to support or refute this use.<sup>74</sup>

Wiffen et al. (2015 Cochrane review) assessed the efficacy and safety of buprenorphine for chronic neuropathic pain in adults, but found insufficient evidence to support or refute this use.<sup>75</sup>

Gaskell et al. (2014 Cochrane review) assessed the analgesic efficacy and adverse events of oxycodone for chronic neuropathic pain and fibromyalgia.<sup>76</sup> The authors concluded that *“No convincing, unbiased evidence suggests that oxycodone (as oxycodone CR) is of value in treating people with painful diabetic neuropathy or postherpetic neuralgia. There is no evidence at all for other neuropathic pain conditions, or for fibromyalgia. Adverse events typical of opioids appear to be common.”*<sup>76</sup>

Drug combinations are commonly used in individuals suffering from neuropathic pain.<sup>19</sup> Chaparro et al. (2012 Cochrane review) evaluated the efficacy, tolerability and safety of various drug combinations for the treatment of neuropathic pain because evidence suggests substantial mechanistic diversity among patients experiencing neuropathic pain, and to reduce potential dose-related side-effects by combining drugs with different mechanisms.<sup>19</sup> This review included 21 eligible studies of which eight involved opioids; four (578 participants) evaluated the combination of an opioid with gabapentin or pregabalin; two (77 participants) evaluated an opioid with a tricyclic antidepressant; one (313 participants) of tramadol with acetaminophen; and another one (44 participants) of a cholecystokinin blocker (L-365,260) with morphine.<sup>19</sup> Limitations reported include the number of available studies for any one specific combination, as well as other study factors such as limited trial size and duration.<sup>19</sup> *“Meta-analysis was possible for only one comparison of only one combination, i.e. gabapentin + opioid versus gabapentin alone. This meta-analysis involving 386 participants from two studies demonstrated modest, yet statistically significant, superiority of a gabapentin + opioid combination over gabapentin alone. However, this combination also produced significantly more frequent side effect-related trial dropouts compared to gabapentin alone.”* The authors concluded that it was not possible to make any one specific drug combination recommendation for neuropathic pain and that further studies would be useful.

### **Phantom limb pain (PLP)**

PLP is pain in a missing limb after amputation that is experienced by about 80% of patients.<sup>77</sup> Its mechanism is not well understood, but peripheral and central mechanisms are involved and it is therefore often considered neuropathic pain.<sup>77</sup> PLP has been described as severe, intractable and disabling.<sup>77</sup> Alviar et al. (2011 Cochrane review) assessed the effectiveness of pharmacologic interventions in treating PLP.<sup>77</sup> The authors concluded that *“The short- and long-term effectiveness of opioids, NMDA receptor antagonists, anticonvulsants, antidepressants, calcitonins, and anaesthetics for clinically relevant outcomes that include pain, function, mood, sleep, quality of life, satisfaction and adverse effects remains unclear. Morphine, gabapentin and ketamine demonstrate trends towards short-term analgesic efficacy. Memantine and amitriptyline were ineffective for PLP. Results, however, are to be interpreted with caution as these were based mostly on a small number of studies with limited sample sizes that varied considerably and also lacked long-term efficacy and safety outcomes. The direction of efficacy of calcitonin, anaesthetics and dextromethorphan need further clarification. Larger and more rigorous randomised controlled trials are needed to make stronger recommendations about which medications would be useful for clinical practice.”*<sup>77</sup>

### **Rheumatoid arthritis pain**

Whittle et al. (2011 Cochrane review) assessed the efficacy and safety of opioid analgesics for treating pain in patients with RA.<sup>78</sup> The authors concluded that *“There is limited evidence that weak oral opioids may be effective analgesics for some patients with RA, but adverse effects are common and may offset the benefits of*

*this class of medications. There is insufficient evidence to draw conclusions regarding the use of weak opioids for longer than six weeks, or the role of strong opioids.*<sup>778</sup>

### **Osteoarthritis**

Da Costa, et al. (2014 updated Cochrane review) assessed the effects of oral or transdermal opioids on pain, function, safety, and addiction in people with knee or hip osteoarthritis (compared with placebo or no intervention).<sup>79</sup> The authors concluded that *“The small mean benefit of non-tramadol opioids are contrasted by significant increases in the risk of adverse events. For the pain outcome in particular, observed effects were of questionable clinical relevance since the 95% CI did not include the minimal clinically important difference of 0.37 SMDs, which corresponds to 0.9 cm on a 10-cm VAS.”*<sup>79</sup>

Cepeda et al. (2006 Cochrane review) assessed the analgesic effectiveness, the effect on physical function, the duration of benefit and the safety of oral tramadol in people with osteoarthritis.<sup>80</sup> The authors reported that they could not evaluate how tramadol or tramadol/paracetamol compared with available pharmacological treatments because of the limited number of studies that evaluated such therapies.<sup>80</sup> The authors concluded that *“Tramadol or tramadol/paracetamol decreases pain intensity, produces symptom relief and improves function, but these benefits are small. Adverse events, although reversible and not life threatening, often cause participants to stop taking the medication and could limit tramadol or tramadol plus paracetamol usefulness.”*

### **Chronic low back pain**

Chaparro et al. (2013 Cochrane review) report that chronic opioid use in the long-term management of chronic low-back pain (CLBP) has increased dramatically.<sup>81</sup> The quality of evidence in this review ranged between "very low" and "moderate" and high quality randomized trials are needed.<sup>81</sup> The authors concluded that *“There is some evidence (very low to moderate quality) for short-term efficacy (for both pain and function) of opioids to treat CLBP compared to placebo. The very few trials that compared opioids to non-steroidal anti-inflammatory drugs (NSAIDs) or antidepressants did not show any differences regarding pain and function. The initiation of a trial of opioids for long-term management should be done with extreme caution, especially after a comprehensive assessment of potential risks. There are no placebo-RCTs supporting the effectiveness and safety of long-term opioid therapy for treatment of CLBP.”*<sup>81</sup>

## **Acute uses**

This review focuses on chronic pain and the information below is only included to be aware of some potential uses when reviewing data.

### **Epidural analgesia during labor**

Usually the injection of both a local anaesthetic (bupivacaine; levobupivacaine, ropivacaine, or lidocaine/lignocaine) and an opioid (fentanyl; morphine, diamorphine, or sufentanil) into the epidural space.<sup>71</sup>

### **Acute postoperative pain**<sup>82-85</sup>

### **Acute pancreatitis**<sup>86</sup>

### **Acute renal colic**<sup>87</sup>

### **Meperidine use in pediatric patients requiring extensive dentist treatment**

## **Non-opioid therapy for pain**

Cochrane reviews include an earlier review that included all antidepressants for neuropathic pain and newer reviews of individual drugs examining individual neuropathic pain conditions e.g.

Derry et al.<sup>20</sup> Nortriptyline for neuropathic pain in adults

Lunn et al.<sup>24</sup> Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia

Moore et al.<sup>25</sup> Amitriptyline for neuropathic pain and fibromyalgia in adults

Moore et al.<sup>27</sup> Pregabalin for acute and chronic pain in adults

This is beyond the scope of this review and will not be included.

## Other evidence - opioid maximum daily dosage/quantity limitations

### ❖ PubMed

Only one PubMed search result was identified regarding opioid maximum daily dosage/quantity limitations. This was a letter published in the letters column of the American Journal of Health Systems Pharmacists by Nerenberg and Fudin regarding the maximum daily dose of hydrocodone.<sup>88</sup> The authors state that opioids have no well-defined maximum dosage to achieve appropriate therapeutic benefit.<sup>88</sup> They list reasons why exact opioid dosing and accurate equivalency tables are lacking as inpatient variability in physical dependence, opioid tolerance, subjectivity of pain and biophysical influences.<sup>88</sup> The differences between sources with regards to the maximum dose of hydrocodone are discussed. Some sources state that 60 mg is the maximum daily dosage whereas the 2009 Clinical Guidelines from the American Pain Society and the American Academy of Pain Medicine on the use of chronic opioid therapy in chronic noncancer pain state that a “reasonable definition for high dose opioid therapy is >200 mg daily of oral morphine [sulfate] (or equivalent), based on maximum opioid doses studied in randomized trials.”<sup>64,88</sup> Due to similarities in pharmacokinetic profiles (shares dehydroxylated phenanthrene ring) and a similar adverse effect profile, oxycodone is suggested as a good comparison for hydrocodone and because the extended-release oxycodone is available as 80-mg tablets, the authors feel that the maximum limit suggested for hydrocodone is not reasonable.<sup>88</sup> Note that hydrocodone is now also available in extended-release formulations Hysingla ER (available as 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, and 120 mg dosed once daily) and Zohydro ER (available as 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg dosed every 12 hours) with specific recommendations with regards to opioid-naïve patients.<sup>41</sup> Daily dosage limits were not listed for other opioids and the authors communicated with the Clinical Pharmacology databases which resulted in the removal of the 60 mg maximum daily dose of hydrocodone bitartrate.<sup>88</sup> The authors conclude that “There is no reason to suspect that the maximum daily dose of hydrocodone should be limited any differently than other similar phenanthrene opioids, with the proviso that the products are dosed to effect, patients are monitored for adverse effects, and the dosage does not exceed dosing limitations of the secondary agent, which most often is acetaminophen.”<sup>88</sup>

### ❖ ClinicalKey

A nested case-control study was identified through ClinicalKey that was conducted to explore the association of prescribed opioid dosage and overdose deaths among patients with chronic pain.<sup>30,89</sup> The authors state that “high opioid dosage has been associated with overdose, and clinical guidelines have cautioned against escalating dosages above 100 morphine-equivalent mg (MEM) based on the potential harm and the absence of evidence of benefit from high dosages. However, this 100 MEM threshold was chosen somewhat arbitrarily.”<sup>30,89</sup>

In this study of patients of the Veterans Health Administration, opioid overdose cases and controls were identified who were prescribed opioids and who have a chronic pain diagnosis.<sup>89</sup> The National Death Index records was used to identify unintentional fatal opioid analgesic overdose and pharmacy records for prescribed opioid dosage.<sup>89</sup> “The average prescribed opioid dosage was higher ( $P<0.001$ ) for cases (mean=98.1 MEM, SD=112.7; median=60, interquartile range, 30-120), than controls (mean=47.7 MEM, SD=65.2; median=25, interquartile range, 15-45). In a ROC analysis, dosage was a moderately good

*"predictor" of opioid overdose death, indicating that, on average, overdose cases had a prescribed opioid dosage higher than 71% of controls." Bohnert et al. conclude that "A clear cut-point in opioid dosage to distinguish between overdose cases and controls was not found. However, lowering the recommended dosage threshold below the 100 MEM used in many recent guidelines would affect proportionately few patients not at risk for overdose while potentially benefitting many of those at risk for overdose."*

## Dosage limitations

It should be recognized that opioid overdoses are associated with higher opioid doses (increases with increasing doses), higher prescription painkiller sales per person, multiple prescribers, and more nonmedical use of prescription painkillers.<sup>1,17,90,91</sup>

In 2012, the CDC reported on the risk groups among patients who are prescribed opioids in the US in terms of estimated percentage of patients and drug overdoses<sup>91</sup>:

| Percentage of patients & single or multiple prescribers                              | Account for what % of prescription drug overdosed |
|--|---|
| 80% are prescribed low doses (<100 mg MED/day) by a single practitioner              | 20%   |
| 10% of patients are prescribed high doses (≥100 mg MED/day) by a single practitioner | 40%   |
| 10% of patients seek care from multiple doctors, are prescribed high daily doses*    | 40%   |

\* This group is also likely to divert or provide drugs to others

*"These data suggest that prevention of opioid overdose deaths should focus on strategies that target 1) high-dosage medical users and 2) persons who seek care from multiple doctors, receive high doses, and likely are involved in drug diversion."*<sup>91</sup>

The CDC guidelines advise caution when increasing dosage to ≥50 MME, and recommend to avoid dosages ≥ 90 MME.<sup>61</sup> The risk of overdose is at least double at dosages of ≥50 MME compared to <20 MME/day and higher doses have not shown to reduce pain over the long term.<sup>92</sup> "One randomized trial found no difference in pain or function between a more liberal opioid dose escalation strategy (with average final dosage of 52 MME) and maintenance of current dosage (average final dosage 40 MME)."<sup>92</sup> "In a national sample of Veterans Health Administration (VHA) patients with chronic pain receiving opioids from 2004-2009, patients who died of opioid overdose were prescribed an average of 98 MME/day, while other patients were prescribed an average of 48 MME/day."<sup>92</sup> The CDC prescribing guideline document (available at: [http://www.cdc.gov/drugoverdose/pdf/calculating\\_total\\_daily\\_dose-a.pdf](http://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf)) explains how total daily dose of opioids should be calculated with the conversion factor. However, it states that the conversions are estimated and cannot account for all individual differences in genetics and pharmacokinetics. It also includes a caution that the calculated dose in MMEs should not be used to determine dosage for converting one opioid to another. *"The new opioid should be lower to avoid unintentional overdose caused by incomplete cross-tolerance and individual differences in opioid pharmacokinetics. Consult the medication label."*<sup>92</sup>

According to the CDC guidance it is important to calculate the total daily dose of opioids as this will help to identify patients who may benefit from:

- closer monitoring
- reduction or tapering of opioids
- prescribing of naloxone
- or other measures to reduce risk of overdose.<sup>92</sup>

Some guidelines like the American Pain Society/American Academy of Pain Medicine and the Canadian guidelines consider higher doses (200 mg/day MME) a “high” dose or a “watchful” dose.<sup>64,68</sup>

Jackman and Purvis reiterate that, “in theory, opioids have no maximum ceiling dose and that there are no studies dictating what is a maximum “safe” and “standard” dose.”<sup>59</sup> “The determined maximum dose of morphine was by consensus statement based on maximum opioid doses used in some randomized trials and the average doses used in some observational studies.”<sup>33,59,64,66,67</sup> Combination products containing acetaminophen, aspirin, or ibuprofen have maximum dosages because of the additional component limit and are therefore not ideal and not recommended to be used for severe pain.<sup>16</sup>

Fudin reports that treatment of chronic noncancer pain (CNCP) with long-term opioid use is a challenging task for all health care providers, and opioid rotation (change in opioid drug or route of administration) is often necessary because of inadequate response to a particular opioid, or when side effects limit further dose escalation, and/or other risks (e.g. QT prolongation with methadone).<sup>93,94</sup>

Appropriate dosages are determined by considering the patient’s opioid history, physical tolerance and other individual patient characteristics (e.g. pharmacogenetics, drug-drug interactions, disease states, physical attributes, allergies, etc.), the presence of acetaminophen (maximum 4 g/day), ibuprofen, or aspirin, and conversion guidance which are aimed to assist prescribers, but substantial variability exist and there is a lack of validated data to support these conversion strategies.<sup>93,95,96</sup> “Concerns identified with conversion estimates include overestimating ‘equianalgesic’ doses and failure to consider incomplete cross-tolerance, the likely pain trajectory, comorbidities, concomitant medicine, and inter-patient variability.”<sup>95</sup> Incomplete cross-tolerance means that a patient’s tolerance to one agent may be very different from another agent even though equianalgesic doses are used. Dose reductions between 15-50% are recommended (variability between resources) when switching to another opioid.<sup>96</sup>

Erensen et al. conducted a review of guidelines issued by North American professional societies or federal and State government entities, and the source data cited by the guidelines and reported that variability exists in the recommendations for conversion ratios, incomplete cross-tolerance, and supplemental analgesia.<sup>97</sup> The authors also report that the sources for the opioid conversion ratios in most guidelines are not well-controlled, multiple-dose trials in chronic pain patients.<sup>97</sup>

Dr Fudin (his professional website, [www.paindr.com](http://www.paindr.com)) state that therapeutic conversion of opioids requires prescribers and pharmacists to pay careful attention and use good clinical therapeutic judgment and common sense.<sup>93</sup> “It is the classic case of where science, mathematics, and experience intersect.”<sup>93</sup>

Opioid conversion is not as straightforward as many may have thought. Variation exist in both the resources used and calculation of morphine equivalent doses.<sup>93,94,98</sup> Fudin reports on two studies that show the significant variability when using different online opioid calculators.<sup>93,94</sup> In the first study various opioids were converted to their morphine-equivalent daily dose (MEDD) while comparing different online opioid conversion calculators with manual calculations (7 different calculators).<sup>93,94</sup> This resulted in a variation range of -55% to +242%.<sup>93,94</sup> Variation was the greatest for fentanyl (100%) and for methadone (242%).<sup>93,94</sup> In the second study (2015 survey), physicians, pharmacists, and nurse practitioners (NPs); many with specialty training in pain and/or palliative care; had to convert hydrocodone 80 mg, fentanyl transdermal patches 1800 mcg (75 mcg/hr), methadone 40 mg, oxycodone 120 mg, and hydromorphone 48 mg to their oral MEDD using any resource.<sup>93,98</sup> “The results showed that the overall mean morphine equivalent doses ( $\pm$  standard deviation) were 183 ( $\pm$  136) mg for fentanyl, 88 ( $\pm$  42) mg for hydrocodone, 192 ( $\pm$  55) mg for hydromorphone, 188 ( $\pm$  122) mg for methadone, and 176 ( $\pm$  38) mg for oxycodone. Participants identified using personal knowledge (46%), an online calculator (31%), textbook table (17%), and conversion table from

a journal (6%) to properly calculate the conversions.<sup>93,98</sup> It is important to consider the implications of the variance: it could result in inadequate pain relief if the dosage is too low or overdose if it is too high.<sup>93</sup>

MEDD calculations currently do not appear to be the best way for determining quantity limitation because of all the limitations discussed, but it could help to identify patients at risk as discussed earlier. Another approach for opioid rotation has been suggested that involves three easy-to-remember steps in opioid rotation without using a conversion table.<sup>93,99</sup> This may be a much safer process.<sup>99</sup> The new paradigm involves a 3-4 week conversion by slow downward titration of the original opioid while introducing the new opioid using an opioid-naïve starting dose.<sup>93,99</sup> An immediate-release opioid should be provided during the conversion to prevent withdrawal and/or for insufficient pain control.<sup>93</sup>

Passik in response to this paradigm (which he describes as a distinctly useful clinical approach) testified highly on the role that Drs. Webster and Fine have played in safer pain management to reduce deaths through many strategies (including work with the Utah Department of Health).<sup>100</sup>

A sensible approach for preventing inappropriate use and adverse outcomes appear to be:

- Using FDA-approved dosage recommendations and limits, whilst considering
- Individual patient factors/characteristics
- the CDC recommendations with regards to total daily dosage ( $\geq 50$  MME/d) and opioid recommendation for acute pain (only the quantity needed for the expected duration of pain severe enough to require opioids should be prescribed. “Three days or less will often be sufficient; more than 7 days will rarely be needed.”),
- the above-mentioned new Webster & Fine paradigm<sup>99</sup> (when opioid rotation is needed),
- and common sense and experience.

## Safety

Doses above 180-200 mg of morphine equivalent per day has been reported to be associated with several risks.<sup>59,101</sup> It changes pain perception (e.g. hyperalgesia and allodynia), induce numerous hormonal changes (increased prolactin, decreasing luteinizing hormone, decreased cortisol, decreased follicle-stimulating hormone, decreased testosterone, and decreased estrogen levels), and are possibly immunosuppressive (e.g. in patients with human immunodeficiency virus).<sup>66,67,101</sup>

Dr Katz in a recent article in JAMA Internal Medicine entitled “Opioid Prescribing for Chronic Pain Not for the Faint of Heart”, said that when he prescribes opioids for chronic pain, he tries to keep the doses safe.<sup>102</sup>  
*“When I prescribe opioids for chronic pain, I try to keep the doses safe. I only prescribe immediate-release opioids. I do not use extended-release or long-acting agents (recommendation 4). I do not prescribe methadone or fentanyl, and I do not prescribe in excess of 50 morphine milligram equivalents (MME)/d (recommendation 5). A typical pain prescription from me is 5 mg of hydrocodone with 325 mg of acetaminophen, 4 times a day as needed (50 mg of morphine = 50 mg of hydrocodone = 33 mg of oxycodone). I never prescribe more than a month of medication and never authorize refills. I think visits at least monthly are an important part of the assessment and treatment of chronic pain.”<sup>102</sup>*

“All opioids are metabolized by the liver (several to an active metabolite) and excreted in the urine.”<sup>16</sup>

In March 2016 the FDA issued an Opioid Pain Medicine Safety Alert regarding risks (including class-wide safety labeling changes regarding these) including:

- potentially harmful interactions with numerous other medications, leading to serotonin syndrome => if suspected health care providers should discontinue opioid treatment and/or use of other contributing medications;

- problems in which the adrenal glands do not produce adequate amounts of cortisol => if suspected, health care providers should perform diagnostic testing and initiate treatment with corticosteroids and wean the patient off of the opioid, if appropriate; if the opioid can be discontinued, follow-up assessment of adrenal function should be performed to determine if treatment with corticosteroids can be discontinued;
- and decreased sex hormone levels, possibly leading to reduced interest in sex, impotence, or infertility => if signs or symptoms of decreased sex hormone levels, health care providers should conduct a laboratory evaluation.<sup>41,103</sup>

Also, “the FDA is requiring a new boxed warning in the labeling of immediate-release opioids about the serious risks of misuse, abuse, addiction, overdose, and death, as well an updated indication clarifying that, because of these risks, immediate-release opioids should be reserved for pain severe enough to require opioid treatment and for which alternative treatment options are inadequate or not tolerated.”<sup>41,103</sup>

Moore et al. (Other review in Cochrane Library) found that when comparing oral opioid with placebo, “The rate of adverse events varied widely among the trials, particularly between the small trials.”<sup>104,105</sup> “The rates for each type of adverse event were as follows: dry mouth, 25% for intervention group versus 3.2% for placebo group; nausea, 21% versus 5.6%; constipation, 15% versus 5%; dizziness, 14% versus 4.5%; drowsiness or somnolence, 14% versus 4%; pruritus, 13% versus 2.1%; and vomiting, 10% versus 2.4%. Withdrawal due to adverse events was 22% in the intervention group (95% CI: 21, 23) and 7.1% in the placebo group (95% CI: 5.2, 8.9). Withdrawal due to lack of efficacy was 6.5% in the intervention group (95% CI: 5.6, 7.4) and 20% in the placebo group (95% CI: 17, 23).”<sup>105</sup> The authors state that “there was no obvious relationship between the opioid type, dose or dosing regimen and the rate of adverse events”, and that “different painful conditions produced similar patterns of results.”<sup>105</sup>

The CRD summary states that “The review concluded that the majority of patients using opioids for chronic non-malignant pain experience at least one adverse event, and that a significant proportion stop using them because of an adverse event. The conclusion appears to follow from the evidence presented, although lack of detail about the methods and the short duration of the trials make it difficult to verify the findings.”<sup>105</sup>

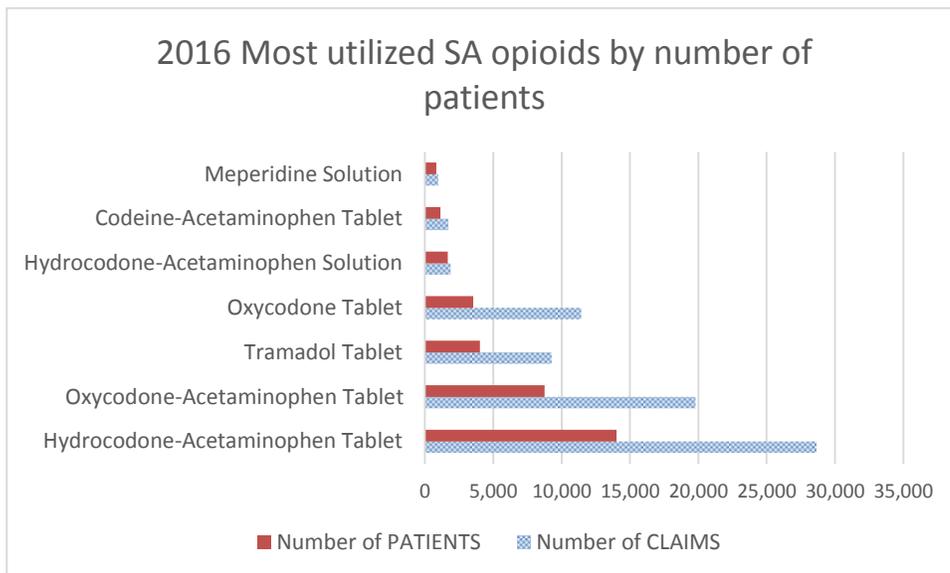
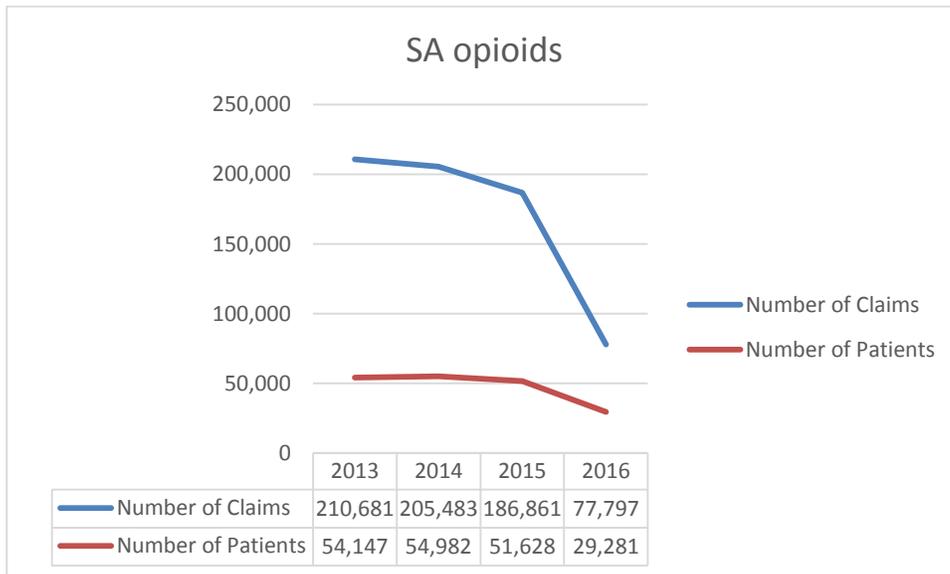
## Short-acting opioids’ place in therapy and factors to consider

- **Chronic non-cancer pain:** Nonopioid therapy and nonpharmacologic therapy are preferred to opioids because of the dangerous adverse effect profile of opioids.<sup>58,60</sup>
  - **Neuropathic pain:** Nonopioid therapies (e.g. antidepressants or anticonvulsants; table 2) that have been proven to be effective in neuropathic pain should be considered and “The use of such medications can be explained to patients as being specifically designed to treat the pain they have, which is nerve related.”<sup>106</sup>
  - **Analgesics** (e.g. APAP, NSAIDs, topical such as diclofenac gel or capsaicin patches) should be considered instead of opioids or may allow opioid dose reduction.<sup>106</sup>
- **Dose escalations:** “Repeated dose escalations can be a sign of substance abuse or diversion.”
- **Place in therapy:** IR opioids should be used when opioid therapy is initiated.<sup>60</sup>
- **Dosage:** The lowest effective dose should be used. CDC guidelines: <50 MME/day<sup>60</sup>, but several limitations (refer to tablet limitation section). Risk of overdose increases with increasing doses.
- **Duration of use/quantity:** Only the quantity that is needed for the expected duration of use. “Three days or less will often be sufficient; more than 7 days will rarely be needed.”<sup>60</sup> Excessive quantities increase the risk for overdose and the risk of opioids being diverted and the risk of harming others. There is insufficient evidence for long-term use.

- **Challenges:**
  - Patients already receiving high-dose opioids. Responsibility of physicians to communicate risks to patient and work with patient to lower dose to a safer level over time.<sup>102</sup>
  - Patients already receiving both benzodiazepines and opioids (should be avoided; CDC recommendations). Responsibility of physicians to communicate risks of overdose with patient and to discuss with other physician to determine whether both medications are really needed.<sup>102</sup>
  - Misuse/abuse/Potential diversion/selling medication or using other drugs (e.g. amphetamine, barbiturates, or cocaine) or multiple prescribers: Urine testing (CDC recommendation) may be useful in some patients if these are potential concerns.<sup>102</sup> Also, the Utah Controlled Substance Database can provide useful information (CDC recommendation regarding state's PMP). Wright et al. reported on a case where a patient with a history of alcohol and cocaine use disorders, and depression presented to the emergency department with suicidal ideation.<sup>106</sup> The state's prescription monitoring program revealed that the patient had received a 90- to 120-day supply of oxycodone and clonazepam every month for the last 7 months all from the same primary care physician and the prescriptions were found to be legitimate in the electronic health record (not photocopied prescriptions).<sup>106</sup> It was discovered that the patient would request a postdated prescription for the next month in addition to his prescription for that month every time when he visited the clinic to avoid difficulties of returning for a monthly visit.<sup>106</sup> "The physician added clear instructions for the pharmacist not to fill the second prescription until an exact date 30 days after the first prescription", but the postdated prescriptions were difficult to track and the patient visited the clinic weeks earlier and asked for 2 prescriptions every time.<sup>106</sup> "Although the physician assumed that the pharmacy and insurer would prevent any early refills, the patient creatively used a number of small local pharmacies and paid out of pocket to avoid the restrictions imposed by his insurance plan. Because his primary care physician wrote all the prescriptions, the alerts for "doctor shoppers" in the state's monitoring program were not triggered."<sup>106</sup> Ensuring that the electronic health records is programmed to display the amount of medication prescribed during the last 30 days and alerts for early refills (at the time of prescribing) would help prescribers with this problem.<sup>106</sup> Monitoring the Controlled Substance Database would also prevent this from happening (especially when other prescribers are involved). However, medications obtained from someone else or street drugs would not be recorded in the controlled substance database.<sup>102</sup>
  - Excessive prescribing leading to leftover medications which is an important source of opioids that are misused or diverted.<sup>56,107</sup>
- **Special Populations:** e.g. meperidine in the elderly and pediatric patients
- **Age and gender:** Witkin et al. evaluated the influence of age and gender on opioid dosage in chronic noncancer pain clinic patients and found that males and patients aged 45-64 receive higher opioid doses than females and patients aged >=65.<sup>108</sup>
- **Adverse effects/Safety:** Refer to safety section and appendix 1.

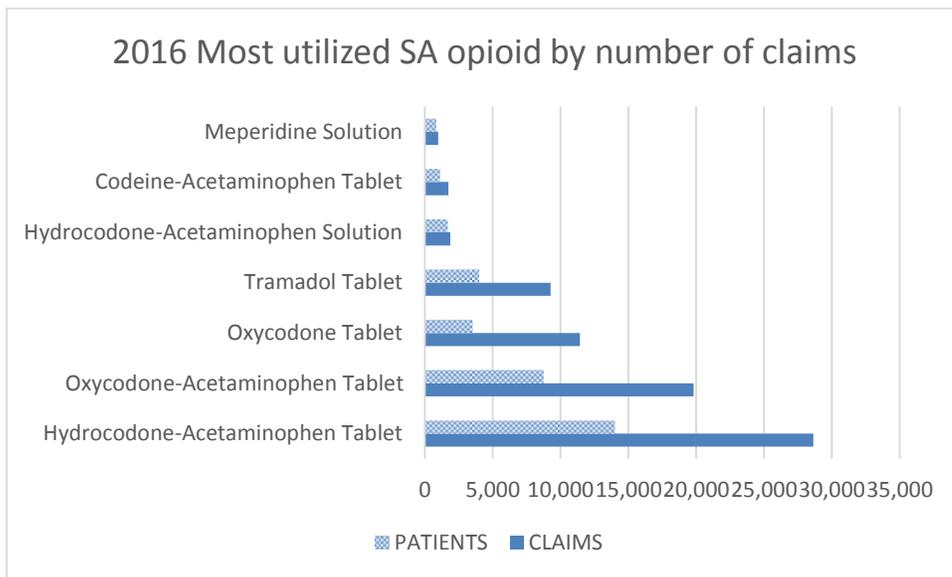
## Utah Medicaid Utilization Data

Please refer to appendix 2 for additional information. The chart below shows the utilization trend over the last few years. Please note that the data for 2016 is not for an entire year. Also, this includes all claims for opioids which would include cancer patients and acute use. There appears to be a slight decrease in utilization from 2013-2015. However, utilization remains high.

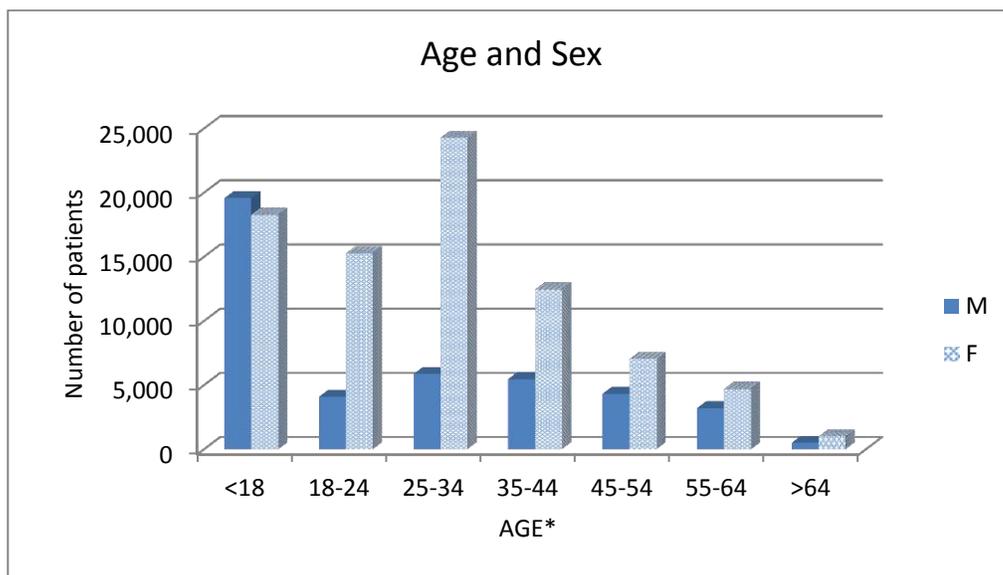


| DESCRIPTION                        | Number of CLAIMS | Number of PATIENTS |
|------------------------------------|------------------|--------------------|
| Hydrocodone-Acetaminophen Tablet   | 28,647           | 14,011             |
| Oxycodone-Acetaminophen Tablet     | 19,799           | 8,757              |
| Tramadol Tablet                    | 9,256            | 4,008              |
| Oxycodone Tablet                   | 11,420           | 3,521              |
| Hydrocodone-Acetaminophen Solution | 1,869            | 1,677              |
| Codeine-Acetaminophen Tablet       | 1,722            | 1,121              |
| Meperidine Solution                | 966              | 825                |
| Oxycodone Solution                 | 636              | 575                |

When reviewing the most utilized SA opioid by number of claims, the order remains the same apart from tramadol and oxycodone tablets that switched places.



### Age and Sex of patients that received SA opioids

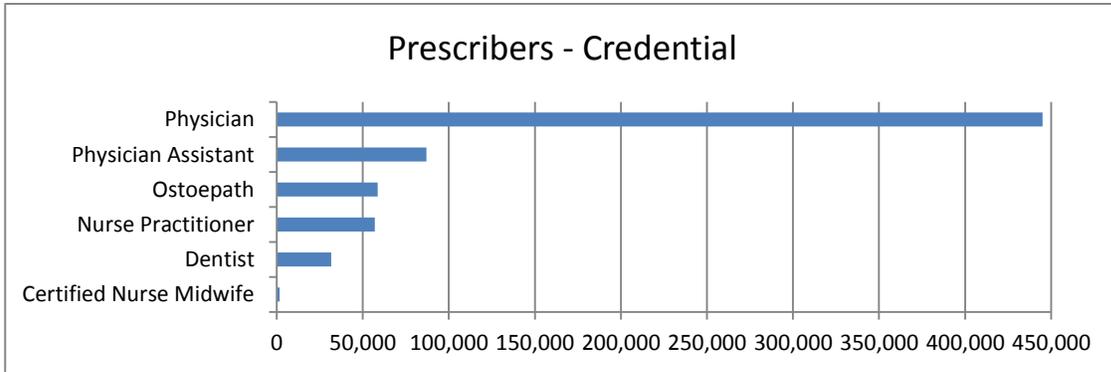


#### TOTAL PATIENTS 2013-2016

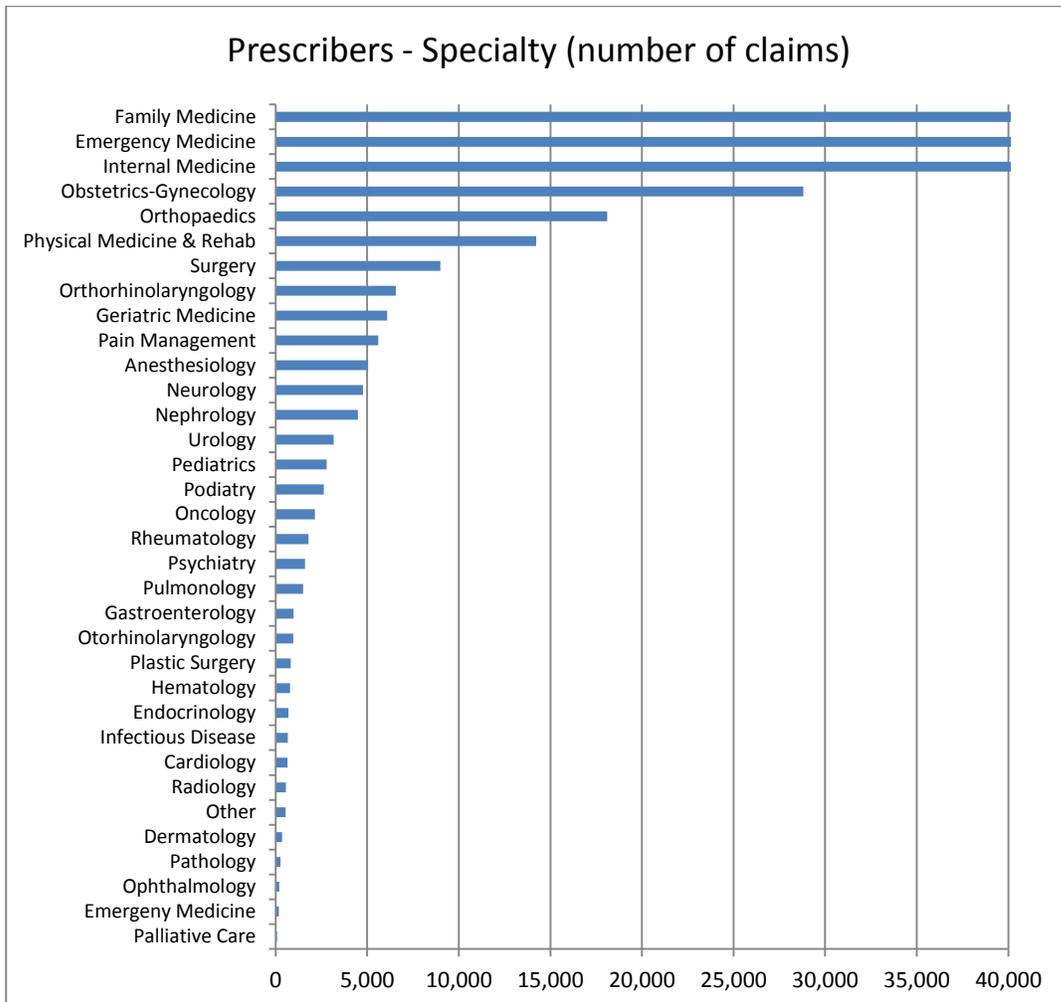
| AGE*         | M             | F             | Total  |
|--------------|---------------|---------------|--------|
| <18          | 19,563        | 18,279        | 37,842 |
| 18-24        | 4,090         | 15,275        | 19,365 |
| 25-34        | 5,856         | 24,281        | 30,137 |
| 35-44        | 5,455         | 12,457        | 17,912 |
| 45-54        | 4,323         | 7,045         | 11,368 |
| 55-64        | 3,206         | 4,705         | 7,911  |
| >64          | 499           | 1,007         | 1,506  |
| <b>TOTAL</b> | <b>42,992</b> | <b>83,049</b> |        |

\* Age at first claim.

**Prescribers of SA opioids**



| PRESCRIBER TYPE         | TOTAL CLAIMS<br>2013-16 |        |
|-------------------------|-------------------------|--------|
| Certified Nurse Midwife | 1,626                   | 0.24%  |
| Dentist                 | 31,628                  | 4.65%  |
| Nurse Practitioner      | 56,999                  | 8.37%  |
| Osteopath               | 58,635                  | 8.61%  |
| Physician Assistant     | 86,916                  | 12.77% |
| Physician               | 445,018                 | 65.36% |
| <b>TOTAL CLAIMS</b>     | <b>680,822</b>          |        |



“The involvement of the anesthesiologist, as a pain specialist, in the management of chronic pain is becoming increasingly evident.”<sup>16</sup> Prescribers with a specialty in anesthesiology accounted for 5,041 claims in the Utah Medicaid population over this time period (0.74% of SA opioid claims).

### Injectables

There was some utilization for fentanyl injections and no claims for the other SA opioid injectables.

| Product                      | 2013   |          | 2014   |          | 2015   |          | 2016*  |          | ALL    |          |
|------------------------------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|
|                              | CLAIMS | PATIENTS |
| Fentanyl Injectable Solution | 1      | 1        | 5      | 2        | 2      | 2        | 1      | 1        | 9      | 5        |

### Mepiridine utilization

In 2016, 825 patients have received meperidine solution to date. Overall, during the time period reviewed, 5427 patients received meperidine (7100 claims) which appears high especially considering that it is not recommended for use in pain management. Meperidine is also indicated in preoperative sedation and obstetrical analgesia.

| DESCRIPTION                    | 2013         |              | 2014         |              | 2015         |              | 2016*        |            | ALL          |              |
|--------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|------------|--------------|--------------|
|                                | CLAIMS       | PATIENTS     | CLAIMS       | PATIENTS     | CLAIMS       | PATIENTS     | CLAIMS       | PATIENTS   | CLAIMS       | PATIENTS     |
| Meperidine Injectable Solution | 0            | 0            | 1            | 1            | 0            | 0            | 2            | 1          | 3            | 2            |
| Meperidine Solution            | 1,543        | 1,200        | 1,775        | 1,357        | 2,298        | 1,768        | 966          | 825        | 6,582        | 4,308        |
| Meperidine Tablet              | 159          | 86           | 148          | 75           | 141          | 76           | 67           | 38         | 515          | 239          |
| <b>TOTAL</b>                   | <b>1,702</b> | <b>1,286</b> | <b>1,924</b> | <b>1,433</b> | <b>2,439</b> | <b>1,844</b> | <b>1,035</b> | <b>864</b> | <b>7,100</b> | <b>4549*</b> |

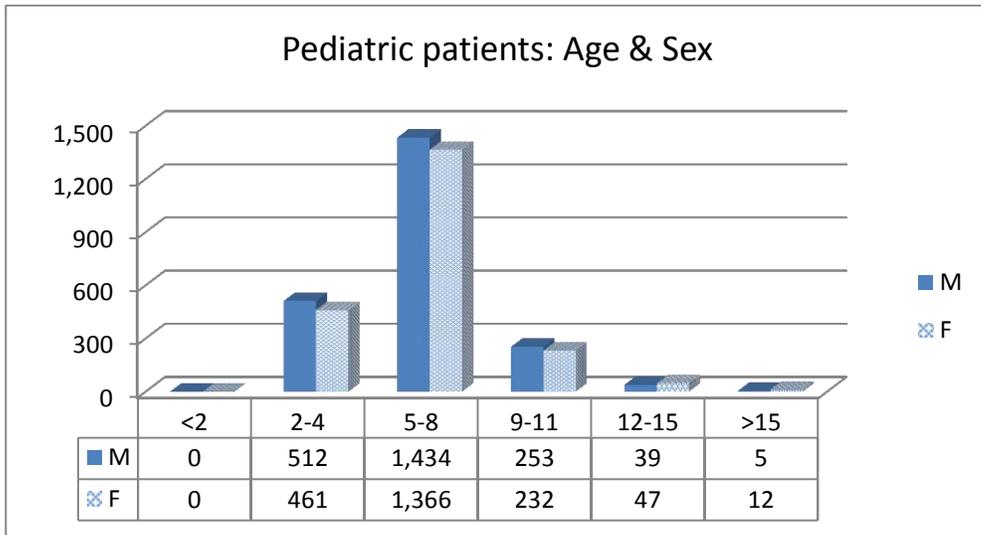
\*Six patients received two different formulations, so the unique patient count for all 3 formulations is 4543

### Elderly

Meperidine is not recommended as a drug of first choice for the treatment of chronic pain in the elderly due to potential serious CNS side effects (eg, tremor, seizures).<sup>41</sup>

- ONE patient >65 years-of-age received meperidine.

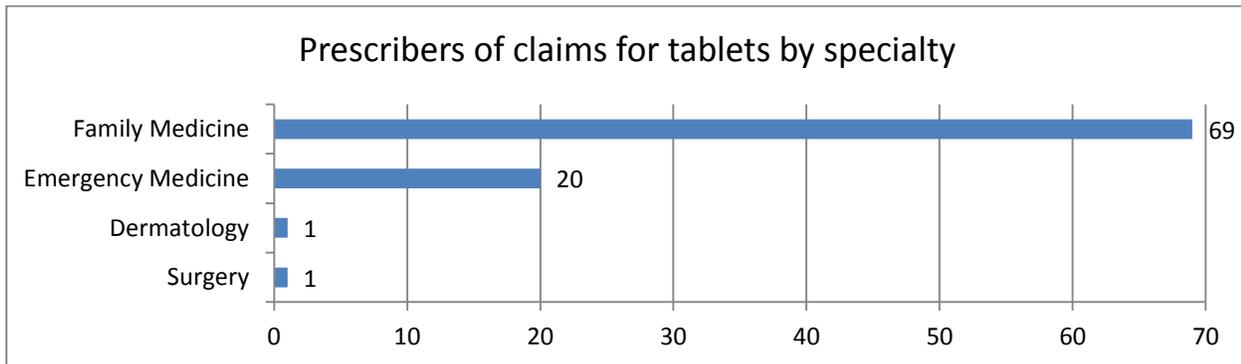
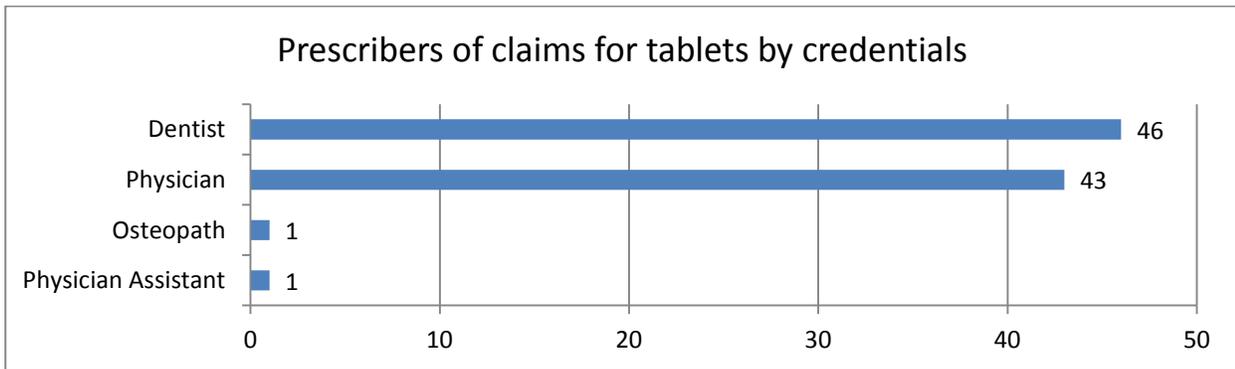
Pediatric patients

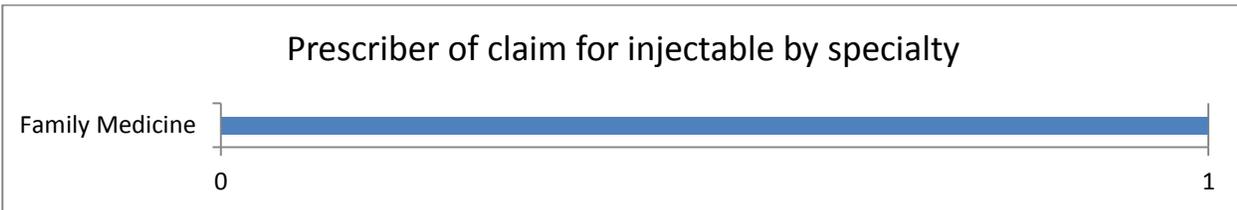
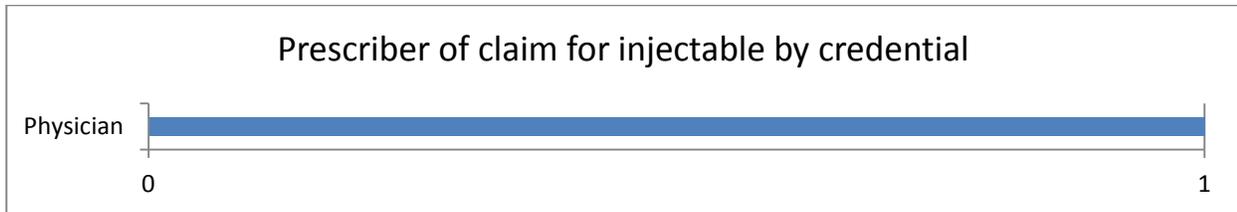
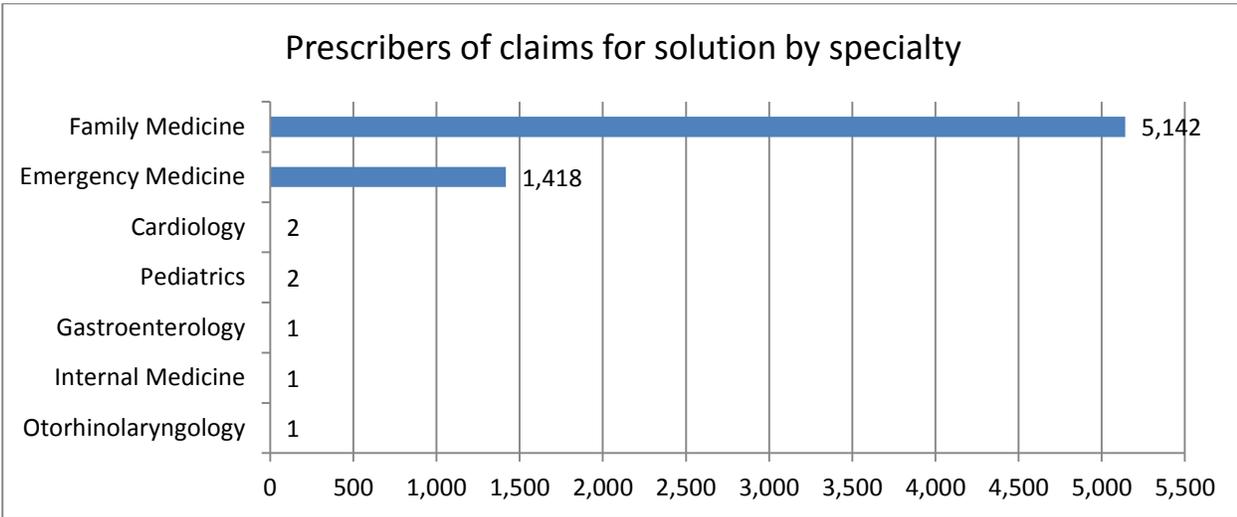
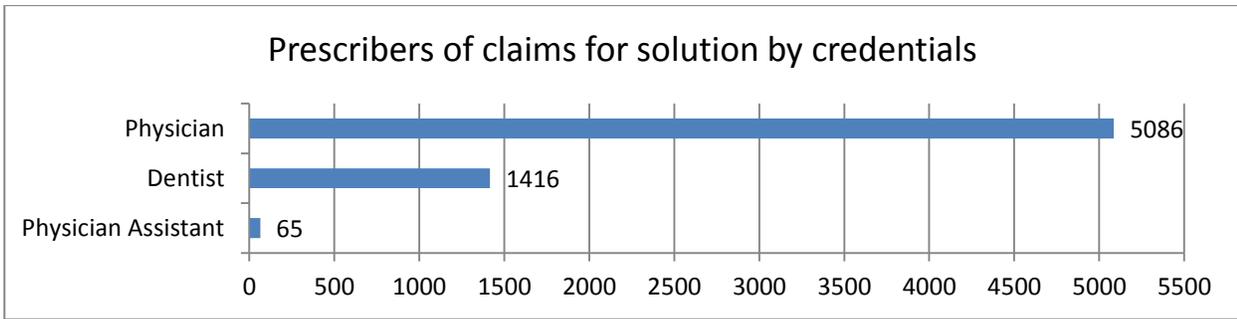


- Almost all of the meperidine pediatric use was for kids 2-11 years old, most specifically ages 5-8, and just for a day or less.

As mentioned earlier, the safety and effectiveness of meperidine has not been established in pediatric patients.<sup>42-44</sup>

**Prescribers of meperidine in pediatrics**





Dentists prescribed a large percentage of pediatric meperidine claims. This review focuses on chronic non-cancer pain, but it is important to consider whether the use of meperidine is appropriate especially in pediatrics and an additional search was therefore conducted.

When young children require extensive dental treatment, conscious sedation or general anesthesia is used because fear of treatment may cause uncooperative and problematic behavior that could become challenging for the dentist.<sup>109,110</sup> According to a 2013 report in Pediatric Anesthesia, sedation “is increasingly popular and viewed lower-risk in community settings”.<sup>111</sup> Meperidine has been used to premedicate/sedate pediatric patients that require extensive dental work.<sup>110</sup> Some dentists for example use triple sedation with

chloral hydrate, hydroxyzine and meperidine.<sup>112</sup> However, Hasty et al. reported in 1991 that the use of narcotics during conscious sedation of pediatric patients has been controversial for years.<sup>110</sup>

“Following oral administration, the analgesic effects are detectable within about 15 minutes, reach a peak in about 2 hours, and subside gradually over several hours.”<sup>110</sup>

Concerns with the use of meperidine in pediatric patients include aspiration of vomitus (N&V is a side-effect of meperidine) and respiratory depression.<sup>110</sup> It is therefore important to weigh the risks and benefits involved, to ensure NPO if meperidine is administered, and to ensure sufficient safety measures are in place e.g. sufficiently trained dentist and personnel with the necessary oxygen supplementation, and antidote (Narcan) available.<sup>110</sup>

The efficacy and relative efficacy of conscious sedation agents and dosages for behavior management in pediatric dentistry was evaluated in a recently published Cochrane review (2012).<sup>109</sup> This review included 36 studies of 2810 participants including 28 different sedatives with or without nitrous oxide (NO), but the authors report that 30 trials (83%) were at high risk of bias, six (17%) were at unclear risk of bias, and dosages, mode of administration and time of administration varied widely.<sup>109</sup> *“Meta-analysis of the available data was possible for studies investigating oral midazolam vs placebo only. There is weak evidence from five small clinically heterogeneous trials at high risk of bias, that the use of oral midazolam in doses between 0.25 mg/kg to 0.75 mg/kg is associated with more co-operative behaviour compared to placebo; standardised mean difference (SMD) favoured midazolam (SMD 2.98, 95% confidence interval (CI) 1.58 to 4.37, P < 0.001, I<sup>2</sup> = 91%), which translates to an increase of approximately 1.8 points on the six-point Houpt behaviour scale. There is very weak evidence from two trials which could not be pooled that inhalational nitrous oxide is more effective than placebo.”*<sup>109</sup> The authors conclude that *“there is some weak evidence that oral midazolam is an effective sedative agent for children undergoing dental treatment. There is very weak evidence that nitrous oxide inhalation may also be effective. There is a need for further well designed and well reported clinical trials to evaluate other potential sedation agents.”*<sup>109</sup> Evidence regarding the use of meperidine is therefore lacking.

Lenahan et al. reported on a retrospective study that evaluated the overall safety and effectiveness of meperidine/hydroxyzine drug combination for pre-cooperative and anxious pediatric patients for dental treatment.<sup>113</sup> This involved 248 pediatric cases from electronic health records in a university setting that were evaluated and rated, and various factors were analyzed e.g. age at time of treatment, gender, ASA status, Frankl score at various points during treatment, sextant of treatment, operator experience, dosage, use of nitrous oxide, and any complications encountered during treatment, both major and minor.<sup>113</sup> *“Over 81% of sedations were considered effective or very effective. Statistically significant findings included age of patient, pre-sedation behavior, and willingness to take the medication. Less than 5% of sedations were aborted due to behavior. Only one major complication was found, which was not related to the sedation.”*<sup>113</sup> The authors concluded that *“Meperidine combined with hydroxyzine is a safe and effective sedation regimen for uncooperative or pre-cooperative children during dental treatment.”*<sup>113</sup>

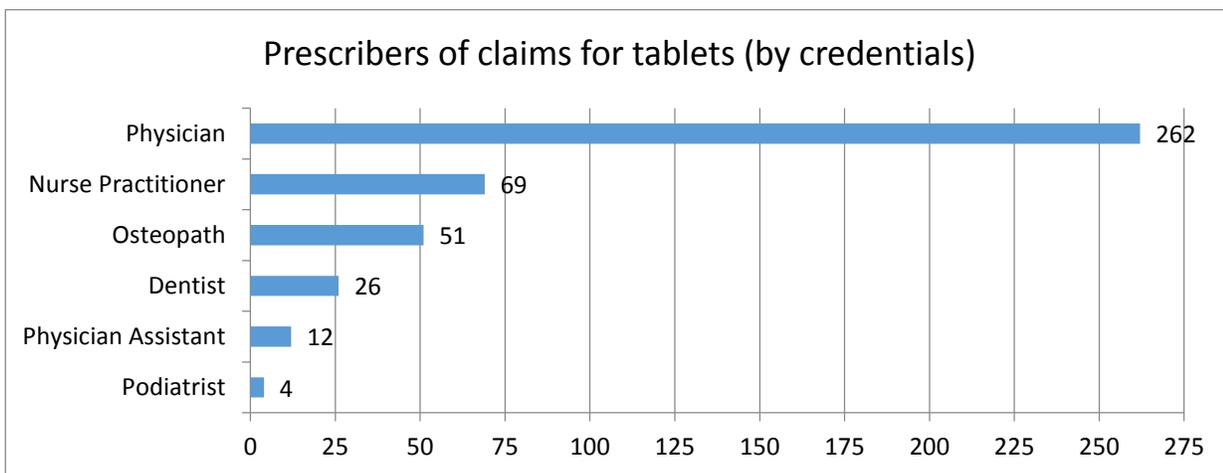
Huang and Tanbonliong in a prospective study investigated patient discharge parameters and postdischarge adverse events after discharge among 51 children who received oral conscious sedation for dental treatment *["one of various regimens involving combinations of a narcotic (ie, morphine or meperidine), a sedative-hypnotic (ie, chloral hydrate), a benzodiazepine (ie, midazolam or diazepam), and/or an antihistamine (ie, hydroxyzine HCl). Nitrous oxide and local anesthesia were used in conjunction with all regimens"]*<sup>114</sup>. Following the dental appointment, guardians were contacted by phone to collect specific adverse event information.<sup>114</sup> *“Postdischarge excessive somnolence, nausea, and emesis were frequent complications. The time to normality ranged until the following morning demonstrating the importance of careful postdischarge adult supervision.”*<sup>114</sup>

Dosani et al. also investigated postdischarge events occurring in 50 children during the 24 hours following sedation with combinations of midazolam, hydroxyzine, and meperidine for dentistry.<sup>115</sup> Standardized information was recorded by parents using a timesheet provided and families were contacted via telephone after 24 hours to collect the information.<sup>115</sup> The authors concluded that *“Postdischarge sleepiness, drug-specific motor imbalance, sleep during transit, and recovery times greater than four hours were common and warrant vigilant adult supervision.”*<sup>115</sup>

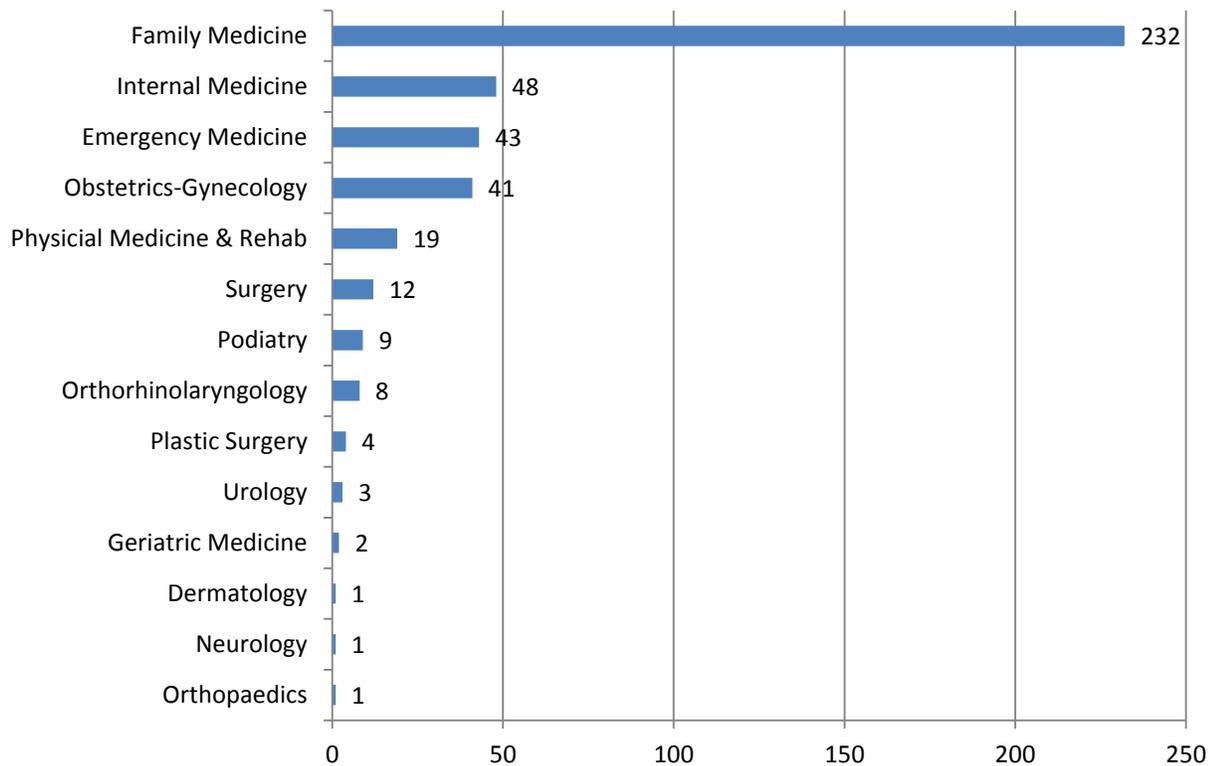
McCormack et al. reported on the different sedation-related events for two multiagent oral sedation regimens; chloral hydrate, meperidine, and hydroxyzine with nitrous oxide (CH/M/H/N<sub>2</sub>O; N=19) or a regimen of midazolam, meperidine, and hydroxyzine with nitrous oxide (MZ/M/H/N<sub>2</sub>O; N=21); in pediatric dental patients.<sup>116</sup> The first was associated with a significant increase in hyperactivity during dental treatment, slurring/difficulty speaking, and difficulty walking postoperatively within eight hours after discharge and the latter with a significant increase in frequency of sleeping, talking less than normal after arriving home, and an increased need for postoperative pain medication.<sup>116</sup> The authors state that *“The provider of pediatric oral sedation should select a sedative regimen with an adverse sedation-related profile that he/she believes is optimal for the patient being treated. Parents should be counseled as to possible postsedation effects anticipated based on the sedative regimen administered.”*<sup>116</sup>

Ultimately the question whether sedation is really required is an important question that every parent and healthcare professional should consider. The use of meperidine in pediatric patients seems risky and should be discouraged in community settings. There have been reports of children dying while receiving dental treatment and because sedation in pediatric patients for dental procedures is becoming increasingly popular, and taking into consideration that providers have variable training and may not have sufficient support, it is important to consider the appropriateness of this use. Parents should be made aware of the risks involved and that this is a controversial use accepted by many, but sometimes maybe prescribed/used when dental work could be performed without sedation, or in an environment where sufficient support is available.

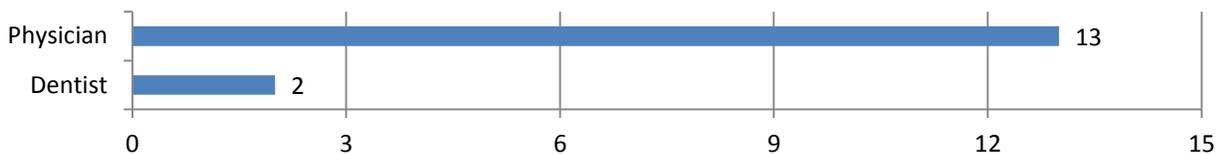
**Prescribers of meperidine in adults**



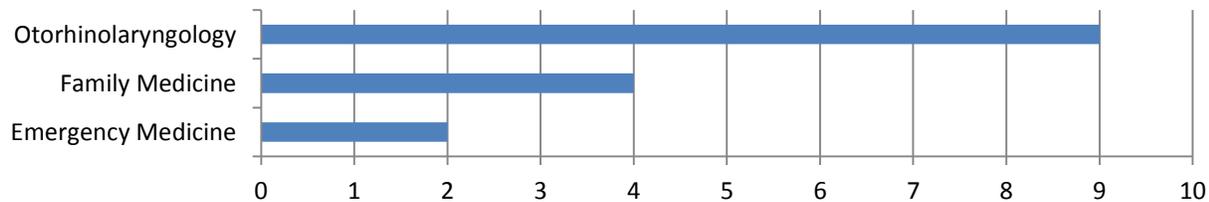
Prescribers of claims for tablets (by specialty)



Prescribers of claims of solution by credentials

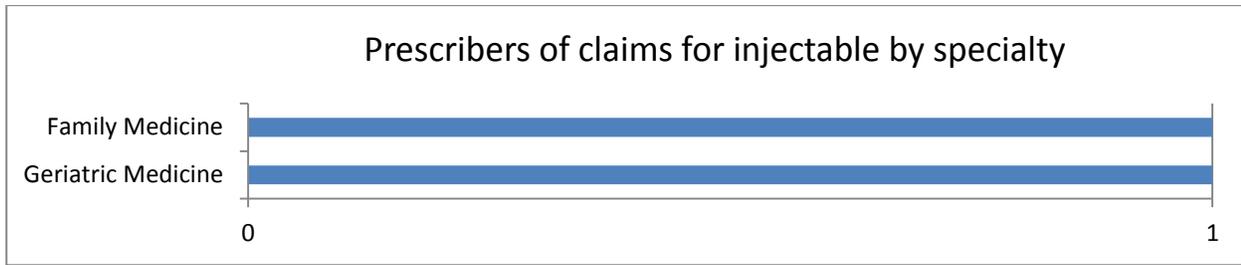


Prescribers of claims for solution by specialty



Prescribers of claims for injectable by credentials

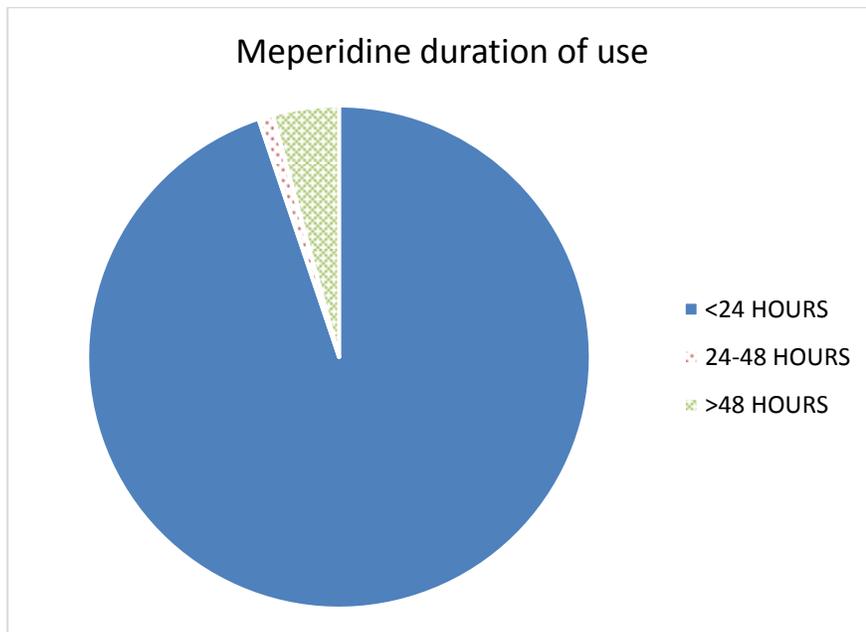




Utilization (especially family medicine) appears high given that meperidine is no longer considered a first-line pain medication (reasons mentioned earlier in report) and it is not recommended for long-term use; it has no place in chronic pain management.<sup>16,40</sup> The American Pain Society (2008) and ISMP (2007) do not recommend meperidine’s use as an analgesic.<sup>41</sup> The oral route is not recommended for treatment of acute or chronic pain and it is recommended to consider a reduced dose if the IV route is required.<sup>41</sup>

Meperidine is also used for preoperative sedation, and obstetrical analgesia. Meperidine may be used for some procedures e.g. “Sedative and analgesic medications have been used routinely for decades to provide patient comfort, reduce procedure time, and improve examination quality during colonoscopy.”<sup>117</sup> Childers et al. evaluate trends of sedation during colonoscopy in the United States (main outcome was the dose of midazolam, diazepam, fentanyl, meperidine, diphenhydramine, promethazine, and propofol) and found that midazolam, fentanyl, and propofol have become the most commonly used sedatives for colonoscopy.<sup>117</sup>

#### Meperidine duration of use



| DURATION OF USE*             | PTS          |        |
|------------------------------|--------------|--------|
| <24 HOURS                    | 4,348        | 95.71% |
| 24-48 HOURS                  | 43           | 0.95%  |
| >48 HOURS                    | 195          | 4.29%  |
| <b>TOTAL unique patients</b> | <b>4543*</b> |        |

\*Note that the 3 categories do not add up because some patients took a course of meperidine more than once during the study period for different durations.

“If use in acute pain (in patients without renal or CNS disease) cannot be avoided, treatment should be limited to  $\leq 48$  hours and doses should not exceed 600 mg/24 hours.”<sup>41</sup>

- 195 Patients have been receiving meperidine for more than 48 hours

## Conclusions

Well-controlled clinical studies on opioid-prescribing methods for chronic pain are lacking, and evidence of long-term efficacy of opioids for chronic non-cancer pain is limited.<sup>61,62</sup> However, the CDC guidelines which have been endorsed by the FDA re-iterate “well-accepted medical principles of drug prescribing: to use the lowest effective dose for the shortest possible duration.”<sup>58</sup> Opioid use is associated with serious risks (including misuse, abuse and overdose), and excessive prescriptions and fills lead to leftover medications which is an important source of opioids that are misused or diverted.<sup>56,107</sup> Meperidine’s use should be discouraged.

“Decreasing opioid misuse and abuse, while at the same time assuring that patients with chronic and acute pain have access to treatment to control their pain, needs to be a major goal for all health professionals, government, pharmaceutical manufacturers, and payers and will require a substantial effort from all parties.”<sup>7</sup>

## Appendix 1 – Drug information

**Table 4. Short-acting opioid products (opiate agonists) & opioid-naïve patients warnings – Adapted from Micromedex, Lexicomp, product labels and Narcotic summary table<sup>118</sup>**

| Dosage form              | Brand name                               | Indication  | Opioid-naïve patients & dosage   | Notes  |
|--------------------------|--|---|--|--|
| <i>Immediate-release</i> |  | <i>Start low in opiate-naïve patients</i>   |  |  |
| <b>Hydromorphone</b>     |  |   |  |  |
| Injection                | Hydromorphone<br>Dilaudid<br>Dilaudid-HP | Dilaudid-HP(R) is a highly concentrated solution of hydromorphone intended <b>for use in opioid-tolerant patients</b> . Do not confuse Dilaudid-HP(R) with standard parenteral formulations of hydromorphone or other opioids as overdose and death could result. | Should <b>not be used</b> for in patients who are opioid-non-tolerant. Use in non-opioid-tolerant patients may lead to fatal respiratory depression<br><br><i>IV</i> : Initial: Opioid naive: 0.2 to 1 mg every 2 to 3 hours as needed; patients with prior opioid exposure may require higher initial doses. <b>Dilaudid HP should NOT be used in opioid-naïve patients.</b><br><br>Continuous infusion: Usual dosage range: 0.5 to 3 mg/hour (Barr 2013)<br><br><i>IM, SubQ</i> : <b>Note</b> : Equianalgesic doses: Morphine 10 mg IM = hydromorphone 1.5 mg IM.<br><i>US labeling</i> : Initial: 1 to 2 mg every 2 to 3 hours as needed; lower initial doses may be used in opioid-naïve patients. Patients with prior opioid exposure may require higher initial doses. | Sometimes effective when analgesia from other narcotics has waned. Acceptable with renal disease. High equianalgesic potency.<br><br>IM use may result in variable absorption and lag time to peak effect; <b>IM route not recommended for use</b> (American Pain Society 2008). |
| Oral liquid and tablets  | Dilaudid<br>Generic                      | Management of pain in patients where an opioid analgesic is appropriate.  | In non-opioid-tolerant patients, therapy with hydromorphone is <b>typically initiated at an oral dose of 2-4 mg every 4-6 hours as needed (tablets) or 2.5 mg to 10 mg every 3 to 6 hours as needed (liquid)</b> ;<br><ul style="list-style-type: none"> <li>• elderly/debilitated patients may require lower doses</li> <li>• patients with prior opioid exposure may require higher initial doses.</li> </ul>  | Note: In adults with severe pain, the American Pain Society recommends an initial dose of 4 to 8 mg.   |
| Rectal Suppository       | Generic                                  |   | Rectal: 3 mg (1 suppository) every 6 to 8 hours as needed  |  |

| Dosage form  | Brand name  | Indication   | Opioid-naïve patients & dosage   | Notes  |  |
|--|---|--|--|--|--|
| <b>Morphine</b>  |   |  |  |  |  |
| Immediate release oral solution & tablets<br>Injection<br>Rectal suppository | MSIR  | Relief of moderate to severe acute and chronic pain for which use of an opioid analgesic is appropriate. | <p>Opioid naïve: Initial: <b>Note:</b> Usual dosage range: 10 to 30 mg every 4 hours as needed. Patients with prior opioid exposure may require higher initial doses.<br/>Solution: 10 to 20 mg every 4 hours as needed<br/>Tablet: 15 to 30 mg every 4 hours as needed</p> <p>Morphine oral solution is available in 10 mg/5 mL, 20 mg/5 mL and 100 mg/5 mL (20 mg/mL) concentrations. The <b>100 mg/5 mL (20 mg/mL) concentration is indicated for use in opioid-tolerant patients only.</b> Take care to avoid dosing errors due to confusion between different concentrations and between mg and mL, which could result in accidental overdose and death. Keep morphine oral solution out of the reach of children</p> <p>IM, SubQ: Initial: Opioid naïve: 5 to 10 mg every 4 hours as needed; usual dosage range: 5 to 15 mg every 4 hours as needed.<br/>IV: Initial: Opioid naïve: 2.5 to 5 mg every 3 to 4 hours;</p> <p><i>Rectal:</i> 10 to 20 mg every 3 to 4 hours</p> | <p>Be careful not to confuse with the extended-release formulation when prescribing.<br/>Caution in severe renal failure; accumulation of metabolites can cause agitation, delirium.<br/>Medication errors: Serious adverse events and deaths resulting from accidental overdose of high concentration morphine sulfate oral solutions. Morphine oral solutions ordered in <i>milligrams (mg)</i> were mistakenly interchanged for <i>milliliters (mL)</i> of the product, resulting in 20-fold overdoses.</p> <p>Repeated SubQ administration causes local tissue irritation, pain, and induration. The use of IM injections is no longer recommended especially for repeated administration due to painful administration, variable absorption and lag time to peak effect; other routes are more reliable and less painful (APS, 2008).</p> |  |
| <b>Oxycodone</b>   |   |  |  |  |  |
| Capsules, tablets, oral concentrate (20 mg/mL), oral solution (5 mg/5 mL)    | Roxicodone<br>Oxaydo (abuse deterrent)<br>Oxecta (discontinued) | Management of moderate-to-severe pain, normally used in combination with nonopioid analgesics            | Initial: 5 to 15 mg every 4 to 6 hours as needed; dosing range: 5 to 20 mg per dose (APS 6th edition). For severe chronic pain, administer on a regularly scheduled basis, every 4 to 6 hours, at the lowest dose that will achieve adequate analgesia.  | A good choice for breakthrough pain, particularly when there is a need to avoid acetaminophen. Be careful not to confuse with the extended-release formulation when prescribing.   |  |
| Oxycodone/APAP oral solution, tablets  | Endocet; Percocet;<br>Primlev; Roxicet                          |  | Highly-concentrated oral solutions: [U.S. Boxed Warning]: <b>Concentrated oral solutions (20 mg/mL) should only be used in opioid tolerant patients</b> (taking $\geq 30$ mg/day of oxycodone or equivalent for $\geq 1$ week); orders should be clearly written to include the intended dose (in mg vs mL) and the intended product concentration to be dispensed.  |  | Acetaminophen/NSAID often becomes the dose-limiting factor. Be careful not to confuse with extended-release formulations when prescribing. |
| Oxycodone/Aspirin oral tablets   | Percodan<br>Endodan (discontinued)                              |  |  |  |  |

| Dosage form  | Brand name  | Indication  | Opioid-naïve patients & dosage  | Notes  |
|--|---|---|---|--|
|  |   |   | <p>Warning regarding oral solution to avoid dosing errors due to confusion between milligram and milliliter, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death.</p> <p><u>Acetaminophen-containing: Manufacturer's labeling:</u> Moderate to moderately severe pain: Initial dose, <b>based on oxycodone content:</b> 2.5-10 mg every 6 hours as needed. Titrate according to pain severity and individual response. <u>Do not exceed acetaminophen 4 g daily.</u></p> <p><u>Aspirin-containing:</u> One tablet every 6 hours as needed for pain; <u>maximum aspirin dose should not exceed 4 g/day.</u></p> |  |
| <b>Codeine</b>   |   |   |   |  |
| Codeine oral tablets, solution<br>Codeine and APAP             | Generic<br>Tylenol® with Codeine No. 3: APAP 300 mg and codeine phosphate 30 mg<br>Tylenol® with Codeine No. 4: APAP 300 mg and codeine phosphate 60 mg | Management of mild-to-moderately-severe pain                        | <p>Initial: 15 to 60 mg <u>every 4 hours as needed</u>; <u>maximum total daily dose: 360 mg/day</u>; patients with prior opioid exposure may require higher initial doses. <b>Note:</b> The American Pain Society recommends an initial dose of 30 to 60 mg for adults with moderate pain (American Pain Society 2008).</p> <p>Codeine+APAP: Solution or suspension: Acetaminophen 120 mg and codeine 12 mg per 5 mL: 15 mL <u>every 4 hours</u> as needed. Tablets: Acetaminophen (300 to 1,000 mg/dose) and codeine (15 to 60 mg/dose) <u>every 4 hours as needed (maximum: Acetaminophen 4,000 mg and codeine 360 mg per 24 hours)</u></p>                               | <p>Acetaminophen is often the limiting dosing factor. Low potency. Relatively high incidence of itching and nausea. Up to 10% of Caucasians lack the enzyme to activate.</p> <p>Codeine 30 mg per 5 mL oral solution has been discontinued in the US for more than 1 year.</p>   |
| Butalbital, Acetaminophen, Caffeine, and Codeine Oral Capsules | Fioricet with Codeine<br>Generic  | Relief of symptoms of complex tension (muscle contraction) headache | Oral: Adults: 1-2 capsules <u>every 4 hours</u> . Total daily dosage should not exceed 6 capsules.  | Butalbital is identified in the Beers Criteria as a potentially inappropriate medication to be avoided in patients 65 years and older (independent of diagnosis or condition) due to its high rate of physical dependence, tolerance to sleep benefits, and increased risk of overdose at low dosages (Beers Criteria [AGS 2015]). |
| Butalbital, Aspirin, Caffeine, and Codeine                     | Ascomp® with Codeine<br>Fiorinal® with Codeine  | Relief of symptoms of complex tension (muscle contraction)          | 1-2 capsules <u>every 4 hours</u> as needed ( <u>maximum: 6 capsules per day</u> )  |  |

| Dosage form   | Brand name  | Indication   | Opioid-naïve patients & dosage   | Notes  |
|---|---|--|--|--|
| Capsules  | Generic   | headache   |  |  |
| <b>Dihydrocodeine</b>                                     |   |  |  |  |
| Acetaminophen, Caffeine, and Dihydrocodeine Oral Capsules | Trelix<br>Generic   | For the relief of moderate to moderately severe pain   | <u>Two capsules every 4 hours</u> as needed; adjust dose based on severity of pain ( <u>maximum dose: 10 capsules/24 hours</u> )   |  |
| Dihydrocodeine, Aspirin, and Caffeine Oral Capsules       | Synalgos®-DC<br>Generic   | Management of moderate to moderately severe pain   | <u>Two capsules</u> (aspirin 712.8 mg/caffeine 60 mg/dihydrocodeine 32 mg) <u>every 4 hours</u> as needed for pain   |  |
| <b>Hydrocodone</b>  |   |  |  |  |
| Hydrocodone/APAP elixir, solution, tablets                | Lortab<br>Lorcet<br>Norco<br>Xodol<br>Verdrocet<br>Vicodin<br>Hycet<br>Zamicet<br><br>Co-gesic (LI)<br>International brand name for Hydrocodone and Acetaminophen | Relief of moderate-to-severe pain  | Average starting dose in opioid naive patients: Hydrocodone <b>5-10 mg 4 times/day</b> ; the dosage of <u>acetaminophen should be limited to &lt;4 g/day (and possibly less in patients with hepatic impairment or ethanol use)</u> . The usual precautions for opioids should be observed and the possibility of respiratory depression should be kept in mind. | A good first choice for breakthrough pain, if the acetaminophen or ibuprofen components are not limiting.<br><br><b>Note:</b> Single oral doses >40 mg, a total daily dose ≥80 mg, the 50 mg extended-release capsules (Zohydro ER), and Hysingla(TM) ER total daily doses of 80 mg/day or higher are only for patients who are opioid tolerant. |
| Hydrocodone and Ibuprofen Oral tablets                    | Ibudone<br>Reprexain<br>Vicoprofen<br>Xylon<br>Generic  | Short-term (generally less than 10 days) management of acute pain (not indicated for treatment of chronic conditions [eg, osteoarthritis or rheumatoid arthritis]).  | One tablet (hydrocodone 2.5 mg to 10 mg/ibuprofen 200 mg) <u>every 4 to 6 hours as needed; (maximum: 5 tablets/24 hours)</u> .<br><b>Note: Short-term use is recommended (&lt;10 days total therapy).</b>  |  |
| <b>Oxymorphone</b>  |   |  |  |  |
| Oxymorphone IR injection, oral tablets                    | Opana, Generic  | <u>Parenteral:</u> Management of moderate-to-severe acute pain; analgesia during labor; preoperative medication; anesthesia support; relief of anxiety in patients with dyspnea associated with pulmonary edema secondary to acute left ventricular failure<br><u>Oral, regular release:</u> Management of moderate-to-severe acute pain | Immediate release: Acute pain:<br>Opioid-naïve: Initial: 5 to 10 mg every 4 to 6 hours as needed (American Pain Society [Miaskowski, 2008]). Dosage adjustment should be based on level of analgesia, side effects, pain intensity, and patient comorbidities.   | Expensive, even as generic. Give PO doses 1 hr before or 2 hours after meals. High equianalgesic potency.  |
| <b>Levorphanol</b>  |   |  |  |  |
| Levorphanol oral tablets                                  | (Levodromoran, Generic)   | Management of moderate to severe pain where an opioid analgesic is appropriate   | Acute pain (moderate-to-severe): Initial:<br>Opioid-naïve: 2 mg every 6 to 8 hours as needed; may increase to 3 mg every 6 to 8  | Very long half-life of 16-18 hrs, despite the need for dosing Q 6-8 hrs. Risk of accumulation; wait 72 hrs between dosage  |

| Dosage form   | Brand name                               | Indication   | Opioid-naïve patients & dosage  | Notes  |
|---|--|--|---|--|
|   |  | Premedication for anesthetic procedure - Surgical procedure  | hours if needed (maximum: 12 mg per 24 hours initially); higher doses may be appropriate in opioid tolerant patients. Reduce initial dose by $\geq 50\%$ in patients with conditions affecting respiratory reserve or with coadministration with other drugs affecting the respiratory center.<br><br><b>Note:</b> The American Pain Society recommends an initial dose of 2 to 4 mg for severe pain in adults (APS 2008) | increases. Q 6-8 hr dosing makes it most commonly used as a breakthrough med, though may be useful as maintenance drug in some patients.<br><br><u>Chronic pain:</u> Patients taking opioids chronically may become tolerant and require doses higher than the usual dosage range to maintain the desired effect. Tolerance can be managed by appropriate dose titration. <u>There is no optimal or maximal dose for levorphanol in chronic pain.</u> The appropriate dose is one that relieves pain throughout its dosing interval without causing unmanageable side effects. |
| <b>Tapentadol</b>   |  |  |   |  |
| Tapentadol oral tablets                                   | Nucynta                                  | Management of moderate-to-severe acute pain in adults  | Day 1: 50 to 100 mg (2.5 to 5 mL) every 4 to 6 hours as needed; may administer a second dose $\geq 1$ hour after the initial dose (maximum dose on first day: 700 mg daily); Day 2 and subsequent dosing: 50 to 100 mg (2.5 to 5 mL) every 4 to 6 hours as needed (maximum: <u>600 mg daily</u> )   | Weak mu agonist/norepinephrine reuptake inhibitor. Weaker than morphine, perhaps fewer GI effects, same CNS effects. Expensive.  |
| <b>Tramadol</b>   |  |  |   |  |
| Tramadol oral tablets                                     | Ultram<br>Generic<br>Rybix ODT (discont) | Relief of moderate to moderately-severe pain   | 50-100 mg every 4-6 hours (not to exceed <u>400 mg/day</u> ).<br><br>Respiratory disease: Patients with respiratory disorders (eg, significant chronic obstructive pulmonary disease (COPD), cor pulmonale, hypoxia, hypercapnia) may be at greater risk of respiratory depression.   | Central opioid agonist/SNRI. Lowers seizure threshold.   |
| Compounding kit for the preparation of an oral suspension | Synapryn FusePaq                         |  |   |  |
| Tramadol and APAP Oral tablets                            | Ultracet<br>Generic                      | Short-term ( $\leq 5$ days) management of acute pain   | <u>Two tablets every 4 to 6 hours</u> as needed for pain relief (maximum: 8 tablets daily); treatment should not exceed 5 days  |  |
| <b>Meperidine</b>   |  |  |   |  |
| Meperidine Injection<br>Oral solution<br>Oral tablet      | Demerol<br>Generic                       | Management of moderate to severe pain; preoperative sedation, and obstetrical analgesia<br><br>Dental Use: Adjunct in preoperative intravenous conscious sedation in patients undergoing dental surgery; alternate oral opioid in patients | Pain, moderate to severe (analgesic): Oral, IM, SubQ: 50 to 150 mg every 3 to 4 hours as needed<br><br>Preoperatively: IM, SubQ: 50 to 100 mg given 30 to 90 minutes before the beginning   | The American Pain Society (2008) and ISMP (2007) <u>do not recommend meperidine's use as an analgesic.</u> If use in acute pain (in patients without renal or CNS disease) cannot be avoided, <u>treatment should be limited to <math>&lt;48</math> hours and doses should not exceed 600 mg/24 hours.</u> Oral route is not recommended for   |

| Dosage form                               | Brand name | Indication  | Opioid-naïve patients & dosage   | Notes  |
|---|------------|---|--|--|
|   |            | allergic to codeine to treat moderate to moderate-severe pain           | of anesthesia<br><br>Obstetrical analgesia: IM, SubQ: 50 to 100 mg when pain becomes regular; may repeat at every 1- to 3-hour intervals | treatment of acute or chronic pain. If IV route is required, consider a reduced dose. Patients with prior opioid exposure may require higher initial doses.<br><br><u>Elderly:</u> Meperidine is not recommended as a drug of first choice for the treatment of chronic pain in the elderly due to the accumulation of its metabolite, normeperidine, which leads to serious CNS side effects (eg, tremor, seizures). If used for acute pain, its use should be limited to 1 to 2 doses.<br><br><u>Pediatric:</u> Safety and effectiveness of oral meperidine in pediatric patients have not been established. |
| Meperidine and Promethazine Oral Capsules | Generic    | Possibly effective as analgesia for moderate to moderately severe pain. | <u>One</u> meperidine 50 mg/promethazine 25 mg capsule <u>every 4 to 6 hours as needed.</u>  |  |

### Opioid products indicated only in cancer pain

| Dosage form                                  | Brand name | Indication   | Opioid-naïve patients & dosage  | Notes   |
|--|------------|--|---|---|
| <b>Fentanyl</b>                              |            |  |   |   |
| Buccal tablets (fentanyl citrate)            | Fentora    | Should only be used in the management of breakthrough pain in adult <b>patients with cancer</b> who are already receiving and who are <b>tolerant to around-the-clock opioid therapy</b> consisting of daily doses of at least morphine 60 mg orally or daily use of an equianalgesic dose of another opioid for a week or longer.<br><br>Oral transmucosal: Start with lowest dose, allowing to dissolve over 30 minutes, titrating up as needed. | <b>Contraindicated</b> in opioid non-tolerant patients.<br>Refer to product labels. | Oral transmucosal forms expensive; different products not directly interchangeable. Do not cut/chew/crush/swallow. High equianalgesic potency.<br><br>Contraindicated in the management of acute or postoperative pain, including headache/migraines. |
| Oral transmucosal lozenge (fentanyl citrate) | Actiq      |  |   |   |
| Buccal film                                  | Onsolis    |  |   |   |
| Sublingual tablets                           | Abstral    |  |   |   |
| Intranasal spray                             | Lazanda    |  |   |   |
| Sublingual spray                             | Subsys     |  |   |   |

## Opioid products not usually used as outpatient drugs

| Dosage form          | Brand name           | Indication  | Dosing   | Notes  |
|----------------------|----------------------|---|--|--|
| <b>Remifentanil</b>  |                      |   |  |  |
| Intravenous solution | Ultiva               | <p>Analgesic for use during the induction and maintenance of general anesthesia; for continued analgesia into the immediate postoperative period; analgesic component of monitored anesthesia</p> <p><u>Off-label use:</u> Based on the American College of Critical Care Medicine (ACCM) Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit<sup>119</sup>, remifentanil is an effective and recommended agent for management of pain in critically ill patients.</p>  | Refer to product label   | Remifentanil is a highly potent opioid with a rapid onset and short duration of action (due to its rapid hydrolysis by esterases), and recovery from the effects of remifentanil occurs rapidly (within 5 to 10 minutes). <sup>120</sup> |
| <b>Fentanyl</b>      |                      |   |  |  |
| Injection            | Generic<br>Sublimaze | <p><b>Pain management:</b> Relief of pain, preoperative medication.</p> <p><b>Surgery:</b> Adjunct to general or regional anesthesia.</p>   | Refer to product label.<br>General: Dosage should be individualized.   |  |
| Transdermal device   | Ionsys               | <p><b>Postoperative pain, acute:</b> Short-term management of acute postoperative pain in adult patients requiring opioid analgesia in the hospital.</p> <p>Limitations of use: Only for use in patients who are alert enough and have adequate cognitive ability to understand the directions for use. <u>Not for home use.</u> Transdermal device is for use only in patients in the hospital. Discontinue treatment with the device before patients leave the hospital. The device is for use after patients have been titrated to an acceptable level of analgesia using alternate opioid analgesics.</p> | Apply one device to chest or upper outer arm only. Only the patient may activate the device (40 mcg dose of fentanyl per activation; maximum 6 doses per hour). Only one device may be applied at a time for up to 24 hours or 80 doses, whichever comes first. <u>May be used for a maximum of 72 hours (Treatment is limited to a maximum of 3 days)</u> , with each subsequent device applied to a different skin site. If inadequate analgesia is achieved with one device, either provide additional supplemental analgesic medication or replace with an alternate analgesic medication. Refer to manufacturer's labeling for activation instructions. | <b>Note:</b> For hospital use only by patients under medical supervision and direction and only after patients have been titrated to an acceptable level of analgesia using another opioid analgesic.                                    |
| <b>Sufentanil</b>    |                      |   |  |  |
| Intravenous solution | Sufenta              | <b>Epidural analgesia:</b> For epidural   | <b>Analgesia for labor and delivery:</b> Epidural:   |  |

| Dosage form   | Brand name  | Indication  | Dosing   | Notes   |
|---|---|---|--|---|
|   | Generic<br><br>Sufenta: 50 mcg/mL (1 mL); 100 mcg/2 mL (2 mL); 250 mcg/5 mL (5 mL)<br>Generic: 50 mcg/mL (1 mL); 100 mcg/2 mL (2 mL); 250 mcg/5 mL (5 mL) | administration as an analgesic combined with low-dose bupivacaine during labor and vaginal delivery.<br><br><b>Surgical analgesia</b>   | <b>10 to 15 mcg</b> with bupivacaine 0.125% with/without epinephrine. Dose can be repeated twice (for a total of 3 doses) at not less than 1-hour intervals until delivery. Refer to product label for surgical analgesia.   |   |
| <b>Alfentanil</b>   |   |   |  |   |
| Injection   | Alfenta<br>Generic  | <b>Analgesia:</b> Analgesic adjunct for the maintenance of anesthesia with barbiturate/nitrous oxide/oxygen; analgesic with nitrous oxide/oxygen in the maintenance of general anesthesia; analgesic component for monitored anesthesia care<br><b>Anesthetic:</b> Primary anesthetic for induction of anesthesia in general surgery when endotracheal intubation and mechanical ventilation are required | Refer to product label   |   |
| <b>Morphine</b>   |   |   |  |   |
| Preservative-free injectable solution                     | Infumorph<br>Duramorph  | Infumorph: Used in continuous microinfusion devices for intrathecal or epidural administration in treatment of intractable chronic pain<br>Duramorph: For intravenous, epidural, or intrathecal administration in the management of pain for extended periods without attendant loss of motor, sensory, or sympathetic function. <b>Note:Not</b> for use in continuous microinfusion devices.             | Refer to product label   |   |
| Extended-release liposome injection (epidural suspension) | Depodur   | <b>Surgical anesthesia:</b> Epidural (lumbar) single-dose management of pain following major surgery  | Cesarean section: 10 mg single dose (after clamping umbilical cord)<br>Lower abdominal/pelvic surgery: 10 to 15 mg single dose; <b>Note:</b> Some patients may benefit from a 20 mg dose; however, the incidence of adverse effects may be increased.<br>Major orthopedic surgery of lower extremity: 15 mg single dose; <b>Note:</b> Some patients may benefit from a 20 mg dose; however, the incidence of adverse effects may be increased. | Epidural: For lumbar administration only; not for IV, IM, or intrathecal administration. Thoracic administration is not recommended (has not been studied). |

## Appendix 2 – Utah Medicaid Utilization Data

Remifentanil IV solution (Ultiva), fentanyl injection, Ionsys (transdermal device), Sufentanil IV solution (Sufenta), Alfentanil injection (Alfenta), Infumorph, Duramorph, and Depodur are not usually used as outpatient drugs. There are no outpatient utilization data claims for any of these products apart from fentanyl citrate injectable solution.

### OPIOIDS listed above

| GENERIC          | DESCRIPTION                  | 2013   |          | 2014   |          | 2015   |          | 2016*  |          | ALL    |          |
|------------------|------------------------------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|
|                  |                              | CLAIMS | PATIENTS |
| Fentanyl Citrate | Fentanyl Injectable Solution | 1      | 1        | 5      | 2        | 2      | 2        | 1      | 1        | 9      | 5        |

### SHORT ACTING OPIOIDS – Adult and Pediatric

| GENERIC                                   | DESCRIPTION                                       | 2013   |          | 2014   |          | 2015   |          | 2016*  |          | ALL     |          |
|---|---|--------|----------|--------|----------|--------|----------|--------|----------|---------|----------|
|   |   | CLAIMS | PATIENTS | CLAIMS | PATIENTS | CLAIMS | PATIENTS | CLAIMS | PATIENTS | CLAIMS  | PATIENTS |
| Codeine Sulfate                           | Codeine Sulfate Tablet                            | 26     | 7        | 37     | 12       | 59     | 13       | 29     | 16       | 151     | 37       |
| Codeine-Acetaminophen                     | Codeine-Acetaminophen Solution                    | 2,107  | 1,930    | 1,740  | 1,573    | 1,448  | 1,345    | 516    | 496      | 5,811   | 5,095    |
| Codeine-Acetaminophen                     | Codeine-Acetaminophen Tablet                      | 3,996  | 2,203    | 3,752  | 2,129    | 3,895  | 2,248    | 1,722  | 1,121    | 13,365  | 6,734    |
| Codeine-Butalbital-Acetaminophen-Caffeine | Codeine-Butalbital-Acetaminophen-Caffeine Capsule | 152    | 62       | 212    | 75       | 352    | 92       | 101    | 45       | 817     | 219      |
| Codeine-Butalbital-Aspirin-Caffeine       | Codeine-Butalbital-Aspirin-Caffeine Capsule       | 77     | 26       | 101    | 29       | 77     | 20       | 31     | 11       | 286     | 69       |
| Dihydrocodone-Acetaminophen               | Dihydrocodone-Acetaminophen Tablet                | 15     | 2        | 0      | 0        | 0      | 0        | 0      | 0        | 15      | 2        |
| Hydrocodone-Acetaminophen                 | Hydrocodone-Acetaminophen Solution                | 5,815  | 4,556    | 4,639  | 3,868    | 4,626  | 4,051    | 1,869  | 1,677    | 16,949  | 13,391   |
| Hydrocodone-Acetaminophen                 | Hydrocodone-Acetaminophen Tablet                  | 94,326 | 30,457   | 88,144 | 30,652   | 71,895 | 26,933   | 28,647 | 14,011   | 283,012 | 71,288   |
| Hydrocodone-Acetaminophen                 | Lortab Elixir                                     | 0      | 0        | 1      | 1        | 9      | 6        | 6      | 3        | 16      | 9        |
| Hydrocodone-Acetaminophen                 | Lortab Tablet                                     | 2      | 2        | 0      | 0        | 0      | 0        | 0      | 0        | 2       | 2        |
| Hydrocodone-Acetaminophen                 | Norco Tablet                                      | 0      | 0        | 13     | 1        | 13     | 1        | 5      | 1        | 31      | 1        |
| Hydrocodone-Acetaminophen                 | Vicodin Tablet                                    | 37     | 24       | 74     | 51       | 35     | 32       | 7      | 6        | 153     | 108      |

**SHORT ACTING OPIOIDS – Adult and Pediatric**

| GENERIC                 | DESCRIPTION                          | 2013   |          | 2014   |          | 2015   |          | 2016*  |          | ALL     |          |
|-------------------------|--------------------------------------|--------|----------|--------|----------|--------|----------|--------|----------|---------|----------|
|                         |                                      | CLAIMS | PATIENTS | CLAIMS | PATIENTS | CLAIMS | PATIENTS | CLAIMS | PATIENTS | CLAIMS  | PATIENTS |
| Hydrocodone-Ibuprofen   | Hydrocodone-Ibuprofen Tablet         | 622    | 290      | 525    | 297      | 281    | 164      | 127    | 72       | 1,555   | 742      |
| Hydromorphone HCl       | Dilaudid Liquid                      | 29     | 1        | 0      | 0        | 0      | 0        | 0      | 0        | 29      | 1        |
| Hydromorphone HCl       | Hydromorphone Injectable Solution    | 23     | 12       | 42     | 12       | 28     | 14       | 8      | 7        | 101     | 41       |
| Hydromorphone HCl       | Hydromorphone Liquid                 | 37     | 8        | 33     | 5        | 12     | 8        | 1      | 1        | 83      | 21       |
| Hydromorphone HCl       | Hydromorphone Suppository            | 25     | 2        | 0      | 0        | 0      | 0        | 0      | 0        | 25      | 2        |
| Hydromorphone HCl       | Hydromorphone Tablet                 | 1,598  | 563      | 1,977  | 660      | 1,965  | 691      | 872    | 354      | 6,412   | 1,840    |
| Levorphanol Tartrate    | Levorphanol Tablet                   | 0      | 0        | 0      | 0        | 0      | 0        | 1      | 1        | 1       | 1        |
| Meperidine HCl          | Meperidine Injectable Solution       | 0      | 0        | 1      | 1        | 0      | 0        | 2      | 1        | 3       | 2        |
| Meperidine HCl          | Meperidine Solution                  | 1,543  | 1,200    | 1,775  | 1,357    | 2,298  | 1,768    | 966    | 825      | 6,582   | 4,308    |
| Meperidine HCl          | Meperidine Tablet                    | 159    | 86       | 148    | 75       | 141    | 76       | 67     | 38       | 515     | 239      |
| Morphine Sulfate        | Morphine Sulfate Injectable Solution | 192    | 33       | 132    | 35       | 84     | 22       | 34     | 10       | 442     | 95       |
| Morphine Sulfate        | Morphine Sulfate Solution            | 166    | 66       | 90     | 46       | 98     | 55       | 59     | 32       | 413     | 184      |
| Morphine Sulfate        | Morphine Sulfate Tablet              | 852    | 235      | 968    | 266      | 1,060  | 267      | 563    | 182      | 3,443   | 695      |
| Oxycodone HCl           | Oxycodone Capsule                    | 38     | 29       | 40     | 36       | 32     | 24       | 12     | 7        | 122     | 92       |
| Oxycodone HCl           | Oxycodone Solution                   | 801    | 532      | 1,115  | 887      | 1,108  | 939      | 636    | 575      | 3,660   | 2,740    |
| Oxycodone HCl           | Oxycodone Tablet                     | 21,625 | 4,296    | 24,976 | 5,005    | 24,485 | 4,855    | 11,420 | 3,521    | 82,506  | 11,212   |
| Oxycodone-Acetaminophen | Endocet Tablet                       | 2,898  | 1,405    | 3,313  | 1,358    | 2,154  | 914      | 867    | 470      | 9,232   | 3,411    |
| Oxycodone-Acetaminophen | Oxycodone-Acetaminophen Capsule      | 50     | 43       | 5      | 5        | 0      | 0        | 0      | 0        | 55      | 48       |
| Oxycodone-Acetaminophen | Oxycodone-Acetaminophen Tablet       | 44,715 | 16,964   | 46,585 | 17,596   | 47,994 | 17,088   | 19,799 | 8,757    | 159,093 | 44,510   |
| Oxycodone-Acetaminophen | Roxicet Solution                     | 20     | 15       | 20     | 17       | 1      | 1        | 0      | 0        | 41      | 33       |
| Oxycodone-Acetaminophen | Roxicet Tablet                       | 977    | 747      | 130    | 114      | 0      | 0        | 0      | 0        | 1,107   | 838      |

**SHORT ACTING OPIOIDS – Adult and Pediatric**

| GENERIC                | DESCRIPTION                   | 2013           |               | 2014           |               | 2015           |               | 2016*         |               | ALL            |                |
|------------------------|-------------------------------|----------------|---------------|----------------|---------------|----------------|---------------|---------------|---------------|----------------|----------------|
|                        |                               | CLAIMS         | PATIENTS      | CLAIMS         | PATIENTS      | CLAIMS         | PATIENTS      | CLAIMS        | PATIENTS      | CLAIMS         | PATIENTS       |
| Oxycodone-Aspirin      | Oxycodone-Aspirin Tablet      | 22             | 6             | 35             | 9             | 41             | 10            | 15            | 2             | 113            | 20             |
| Oxycodone-Ibuprofen    | Oxycodone-Ibuprofen Tablet    | 2              | 2             | 0              | 0             | 0              | 0             | 0             | 0             | 2              | 2              |
| Oxymorphone HCl        | Opana Tablet                  | 0              | 0             | 0              | 0             | 34             | 9             | 23            | 6             | 57             | 13             |
| Oxymorphone HCl        | Oxymorphone Tablet            | 122            | 27            | 194            | 33            | 160            | 40            | 52            | 16            | 528            | 85             |
| Tapentadol HCl         | Nucynta Tablet                | 69             | 24            | 49             | 21            | 53             | 18            | 37            | 15            | 208            | 69             |
| Tramadol HCl           | Tramadol Tablet               | 27,317         | 8,076         | 24,457         | 7,814         | 22,288         | 6,974         | 9,256         | 4,008         | 83,318         | 18,878         |
| Tramadol-Acetaminophen | Tramadol-Acetaminophen Tablet | 226            | 123           | 160            | 103           | 135            | 91            | 47            | 34            | 568            | 324            |
| <b>TOTALS</b>          |                               | <b>210,681</b> | <b>54,147</b> | <b>205,483</b> | <b>54,982</b> | <b>186,861</b> | <b>51,628</b> | <b>77,797</b> | <b>29,281</b> | <b>680,822</b> | <b>126,041</b> |

**SHORT ACTING OPIOIDS - PEDIATRIC CLAIMS**

| GENERIC                                   | DESCRIPTION                                       | 2013   |          | 2014   |          | 2015   |          | 2016*  |          | ALL    |          |
|---|---|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|
|   |   | CLAIMS | PATIENTS |
| Codeine Sulfate                           | Codeine Sulfate Tablet                            | 0      | 0        | 0      | 0        | 1      | 1        | 1      | 1        | 2      | 2        |
| Codeine-Acetaminophen                     | Codeine-Acetaminophen Solution                    | 2,035  | 1,878    | 1,665  | 1,521    | 1,392  | 1,304    | 497    | 481      | 5,589  | 4,949    |
| Codeine-Acetaminophen                     | Codeine-Acetaminophen Tablet                      | 718    | 604      | 647    | 554      | 713    | 574      | 275    | 248      | 2,353  | 1,868    |
| Codeine-Butalbital-Acetaminophen-Caffeine | Codeine-Butalbital-Acetaminophen-Caffeine Capsule | 2      | 1        | 0      | 0        | 11     | 10       | 5      | 4        | 18     | 15       |
| Codeine-Butalbital-Aspirin-Caffeine       | Codeine-Butalbital-Aspirin-Caffeine Capsule       | 0      | 0        | 3      | 3        | 0      | 0        | 0      | 0        | 3      | 3        |
| Dihydrocodone-Acetaminophen               | Dihydrocodone-Acetaminophen Tablet                | 0      | 0        | 0      | 0        | 0      | 0        | 0      | 0        | 0      | 0        |
| Hydrocodone-Acetaminophen                 | Hydrocodone-Acetaminophen Solution                | 4,890  | 4,058    | 4,111  | 3,526    | 4,071  | 3,656    | 1,621  | 1,495    | 14,693 | 12,067   |
| Hydrocodone-Acetaminophen                 | Hydrocodone-Acetaminophen Tablet                  | 5,105  | 3,616    | 5,550  | 4,155    | 5,018  | 4,002    | 1,875  | 1,597    | 17,548 | 11,934   |
| Hydrocodone-Acetaminophen                 | Lortab Elixir                                     | 0      | 0        | 1      | 1        | 5      | 5        | 2      | 2        | 8      | 8        |

**SHORT ACTING OPIOIDS - PEDIATRIC CLAIMS**

| GENERIC                   | DESCRIPTION                          | 2013   |          | 2014   |          | 2015   |          | 2016*  |          | ALL    |          |
|---------------------------|--------------------------------------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|
|                           |                                      | CLAIMS | PATIENTS |
| Hydrocodone-Acetaminophen | Lortab Tablet                        | 0      | 0        | 0      | 0        | 0      | 0        | 0      | 0        | 0      | 0        |
| Hydrocodone-Acetaminophen | Norco Tablet                         | 0      | 0        | 0      | 0        | 0      | 0        | 0      | 0        | 0      | 0        |
| Hydrocodone-Acetaminophen | Vicodin Tablet                       | 2      | 2        | 3      | 3        | 5      | 5        | 1      | 1        | 11     | 11       |
| Hydrocodone-Ibuprofen     | Hydrocodone-Ibuprofen Tablet         | 65     | 42       | 68     | 48       | 42     | 35       | 4      | 4        | 179    | 123      |
| Hydromorphone HCl         | Dilaudid Liquid                      | 0      | 0        | 0      | 0        | 0      | 0        | 0      | 0        | 0      | 0        |
| Hydromorphone HCl         | Hydromorphone Injectable Solution    | 0      | 0        | 0      | 0        | 0      | 0        | 0      | 0        | 0      | 0        |
| Hydromorphone HCl         | Hydromorphone Liquid                 | 4      | 1        | 0      | 0        | 4      | 2        | 1      | 1        | 9      | 4        |
| Hydromorphone HCl         | Hydromorphone Suppository            | 0      | 0        | 0      | 0        | 0      | 0        | 0      | 0        | 0      | 0        |
| Hydromorphone HCl         | Hydromorphone Tablet                 | 11     | 6        | 8      | 7        | 10     | 7        | 6      | 2        | 35     | 22       |
| Levorphanol Tartrate      | Levorphanol Tablet                   | 0      | 0        | 0      | 0        | 0      | 0        | 0      | 0        | 0      | 0        |
| Meperidine HCl            | Meperidine Injectable Solution       | 0      | 0        | 1      | 1        | 0      | 0        | 0      | 0        | 1      | 1        |
| Meperidine HCl            | Meperidine Solution                  | 1,539  | 1,196    | 1,771  | 1,354    | 2,292  | 1,762    | 965    | 824      | 6,567  | 4,296    |
| Meperidine HCl            | Meperidine Tablet                    | 30     | 26       | 22     | 20       | 24     | 19       | 15     | 10       | 91     | 70       |
| Morphine Sulfate          | Morphine Sulfate Injectable Solution | 1      | 1        | 0      | 0        | 0      | 0        | 1      | 1        | 2      | 2        |
| Morphine Sulfate          | Morphine Sulfate Solution            | 14     | 8        | 11     | 6        | 19     | 10       | 19     | 13       | 63     | 36       |
| Morphine Sulfate          | Morphine Sulfate Tablet              | 15     | 3        | 7      | 5        | 10     | 3        | 0      | 0        | 32     | 9        |
| Oxycodone HCl             | Oxycodone Capsule                    | 2      | 2        | 0      | 0        | 3      | 3        | 0      | 0        | 5      | 5        |
| Oxycodone HCl             | Oxycodone Solution                   | 600    | 465      | 934    | 803      | 941    | 840      | 554    | 521      | 3,029  | 2,458    |
| Oxycodone HCl             | Oxycodone Tablet                     | 245    | 174      | 351    | 258      | 343    | 242      | 158    | 132      | 1,097  | 737      |
| Oxycodone-Acetaminophen   | Endocet Tablet                       | 58     | 51       | 55     | 43       | 50     | 46       | 21     | 20       | 184    | 159      |
| Oxycodone-Acetaminophen   | Oxycodone-Acetaminophen Capsule      | 6      | 6        | 0      | 0        | 0      | 0        | 0      | 0        | 6      | 6        |

**SHORT ACTING OPIOIDS - PEDIATRIC CLAIMS**

| GENERIC                 | DESCRIPTION                    | 2013          |               | 2014          |               | 2015          |               | 2016*        |              | ALL           |               |
|-------------------------|--------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|--------------|--------------|---------------|---------------|
|                         |                                | CLAIMS        | PATIENTS      | CLAIMS        | PATIENTS      | CLAIMS        | PATIENTS      | CLAIMS       | PATIENTS     | CLAIMS        | PATIENTS      |
| Oxycodone-Acetaminophen | Oxycodone-Acetaminophen Tablet | 1,142         | 910           | 1,440         | 1,187         | 1,561         | 1,246         | 540          | 468          | 4,683         | 3,617         |
| Oxycodone-Acetaminophen | Roxicet Solution               | 12            | 7             | 10            | 9             | 1             | 1             | 0            | 0            | 23            | 17            |
| Oxycodone-Acetaminophen | Roxicet Tablet                 | 59            | 58            | 6             | 6             | 0             | 0             | 0            | 0            | 65            | 64            |
| Oxycodone-Aspirin       | Oxycodone-Aspirin Tablet       | 0             | 0             | 0             | 0             | 0             | 0             | 0            | 0            | 0             | 0             |
| Oxycodone-Ibuprofen     | Oxycodone-Ibuprofen Tablet     | 0             | 0             | 0             | 0             | 0             | 0             | 0            | 0            | 0             | 0             |
| Oxymorphone HCl         | Opana Tablet                   | 0             | 0             | 0             | 0             | 0             | 0             | 0            | 0            | 0             | 0             |
| Oxymorphone HCl         | Oxymorphone Tablet             | 0             | 0             | 0             | 0             | 0             | 0             | 0            | 0            | 0             | 0             |
| Tapentadol HCl          | Nucynta Tablet                 | 0             | 0             | 0             | 0             | 0             | 0             | 0            | 0            | 0             | 0             |
| Tramadol HCl            | Tramadol Tablet                | 625           | 340           | 491           | 334           | 480           | 332           | 181          | 151          | 1,777         | 1,047         |
| Tramadol-Acetaminophen  | Tramadol-Acetaminophen Tablet  | 8             | 7             | 7             | 7             | 10            | 9             | 2            | 2            | 27            | 24            |
| <b>TOTALS</b>           |                                | <b>17,188</b> | <b>12,242</b> | <b>17,162</b> | <b>12,712</b> | <b>17,006</b> | <b>13,030</b> | <b>6,744</b> | <b>5,659</b> | <b>58,100</b> | <b>37,842</b> |

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