OPTUM®

Examining and mitigating opioid-induced side effects

Opioid analgesics are commonly prescribed to treat the pain associated with workers' compensation and auto no-fault injuries. These medications have an important role in pain management treatment and therapy and may be effective for certain indications, including acute pain not relieved by non-opioid analgesics, pain associated with various types of fractures, and some post-surgical pain. Opioid analgesics may also be useful in treating chronic pain when there is evidence of improved pain control, improved level of function or an approved return to work. As with all medications, however, opioid analgesics carry risks, alongside their benefits, and their use may be associated with numerous and potentially serious side effects. Some of those more frequently occurring include sleep disturbance, hyperalgesia, constipation, nausea and vomiting or androgen deficiency.

Sleep disturbance

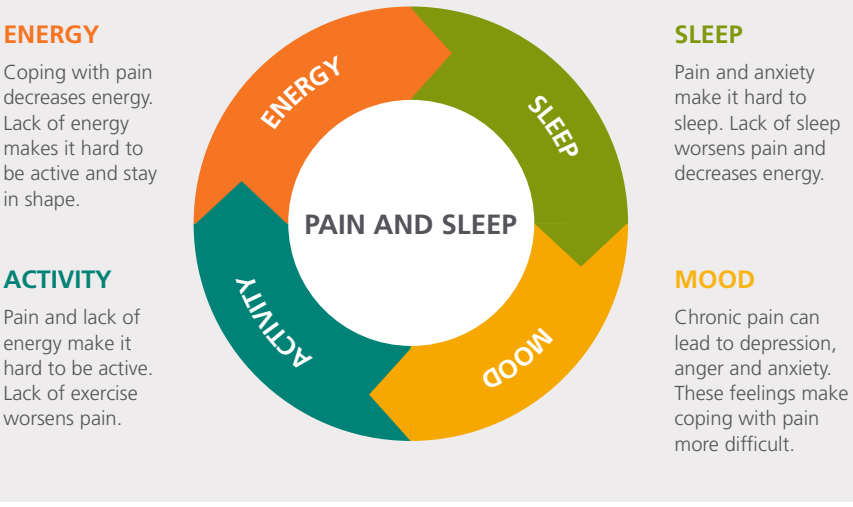
Most of us encounter periods of poor sleep from time to time. Social obligations, entertainment, household/job responsibilities and the many activities of daily living can impede one's ability to obtain the recommended seven to nine hours of nightly rest. The existence of aches and musculoskeletal pain are other factors that may make it difficult to fall or stay asleep throughout the night. As such, chronic pain resulting from a workplace or auto injury is often associated with sleep disturbances. These disturbances can lead to a total loss of sleep time or fractured sleep, preventing the body's completion of a sleep cycle, thus what little sleep is attained is not restorative. Although occasional bouts of insomnia can be frustrating and disruptive, they are relatively harmless to one's overall sense of well-being. Chronic sleep loss, however, is a more serious concern due to its influence on metabolism, mood and memory, as well as cardiovascular health and immune function. Chronic sleep loss impairs our ability to cope with pain and can lead to a state of lowered stamina, decreasing activity and exercise. These things all have the potential to exacerbate pain. The outcome is a vicious cycle in which a lack of sleep worsens pain, thereby making it more difficult to sleep.

When the use of opioid analgesics results in sleep disturbance, including insomnia and excessive daytime sleepiness (drowsiness), it may be related to dose. For some individuals, the higher the dose, the greater the sleep disturbance or drowsiness. When this is the case, decreasing the dose may be all that is needed to combat this troublesome side effect.

Sleep disturbance may also be a result of taking multiple medications at once, such as benzodiazepines, sedative-hypnotics and/or antidepressants. These medications depress the central nervous system (CNS). As with opioid analgesics, reducing the doses of these medications as part of a treatment regimen may reduce the sedative effects.

Another approach seen in workers' compensation and auto no-fault claims is the prescribing of CNS stimulants such as methylphenidate (Ritalin®), modafinil (Provigil®) and armodafinil (Nuvigil®) to counteract the sedation. The use of stimulant medications to combat this opioid analgesic side effect is not without concerns, however, as these medications may raise blood pressure and increase heart rate, both of which must be closely monitored for adverse events arising in claimants with comorbid cardiovascular conditions. Stimulants may cause sleep disturbances and further perpetuate the opioid-induced sleep-pain cycle, especially if the individual fluctuates between insomnia and daytime sleepiness.

Figure 1. The sleep-pain cycle



Opioid-induced hyperalgesia

Opioid-induced hyperalgesia (OIH) is excessive pain sensitization caused by exposure to opioid analgesics. Claimants with OIH have a heightened sensitivity to pain that may even increase despite escalating dosage of opioid analgesics. This phenomenon, while not well understood, is thought to be due to changes in the peripheral and central nervous systems, leading to sensitization of pain-generating nerve pathways, which may partially explain the loss of opioid analgesic efficacy in treating pain.

Pain associated with OIH is typically described as diffuse (extending to other areas of the body), and can mimic opioid analgesic withdrawal in claimants. OIH may be difficult to differentiate from tolerance; however, the key variance lies in the claimant's response to an increase in opioid analgesic dose. Initial stabilization of pain symptoms with an increased opioid analgesic dose, followed by escalation of pain generally indicates tolerance. Alternatively, a short period of pain relief at the site of injury followed by a diffuse spreading of pain to other areas after an increased opioid analgesic dose should alert the prescriber to possible OIH.

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In cases of suspected OIH, the prescriber may consider opioid analgesic rotation, where the claimant is switched to a different opioid analgesic medication. Weaning the claimant off opioid analgesics or implementing a drug holiday to determine the root cause of the increased pain level are also options.

Opioid-induced constipation

Opioid-induced constipation (OIC), also known as opioid-induced bowel dysfunction, is a change in bowel habits, including reduced frequency in bowel movements (less than three bowel movements per week), straining to pass stool, a sense of incomplete evacuation and/or harder stool. Left untreated, OIC may lead to pain, bloating, nausea, vomiting, fecal impaction, bowel obstruction or bowel perforation. As a result, this side effect is considered one of the more common and troublesome. And unfortunately, while tolerance to other side effects such as nausea, vomiting and sleep disturbances may occur, tolerance to constipation typically does not.

OIC can be managed, if not alleviated, through the use of non-pharmacologic and pharmacologic therapies. Non-pharmacologic therapies for OIC include eating a diet rich in fiber-containing foods, maintaining hydration and continuing physical activity, as appropriate for the injury (under the guidance of the provider). Pharmacologic therapies may include those listed below. Additionally, both over-the-counter and prescription medication may help.

- **Bowel stimulants (bisacodyl)** are recognized as a first-line therapy because of their ability to increase gastrointestinal (GI) motility and are typically prescribed at the onset of planned, long-term opioid analgesic use. Stimulant laxatives typically have an onset of six to twelve hours, and should be taken on a schedule prior to commencing opioid analgesic therapy, not on an as needed basis. It is not uncommon for the treatment of OIC to require larger laxative doses; however, because stimulant laxatives cause intestinal contractions, side effects may include abdominal cramps and pain. These can typically be improved with divided dosing.
- **Osmotic laxatives (lactulose, sorbitol and polyethylene glycol (PEG))** have limited intestinal absorption and work by increasing fluid in the colon, causing distention and leading to wave-like contractions that cause an increase in movement through the GI tract. The increase in fluid in the colon produces softer stool and leads to easier bowel movements.

  The onset of action is variable, ranging from 12 to 48 hours. Side effects include abdominal cramping, pain and flatulence, with lactulose and sorbitol being greater offenders than PEG. Other osmotic laxatives include milk of magnesium and magnesium citrate.
- **Stool softeners (docusate)** are often used in combination with a stimulant laxative, such as Senna, as first-line prevention of OIC.
- **Rectally administered laxatives** work by causing distention of the intestines, leading to a reflex movement of the intestines and include stimulant laxatives (bisacodyl) and rectal vault lubricants (glycerin). A lack of research supporting rectal-based laxatives limits their use, reserving their use for cases where other treatments have failed.

- **Chloride channel activator,** (Amitiza® (lubiprostone)), is a gastrointestinal medication approved by the Food and Drug Administration (FDA) in April 2013 for the treatment of OIC, although it was initially approved in 2006 for chronic idiopathic constipation. The medication works by activating certain channels in the intestinal tract, which increases intestinal fluid secretion and ultimately promotes bowel movements without decreasing claimant electrolyte levels, which is often a problem encountered with the use of laxatives.

  The estimated clinical response of Amitiza is typically within one week, while bowel movements may be noted within 24 hours. Typically, the use of Amitiza should be reserved for cases where other more traditional treatments have failed. Additionally, while studies have found Amitiza is effective with opioid analgesics such as morphine, oxycodone and fentanyl, it may not be as effective with other opioid analgesics, such as methadone.

- **Peripherally Acting Mu Opioid Receptor Antagonists (PAMORAs)**, naloxegol and methylnaltrexone, are a class of medications used for the treatment of OIC in adult claimants with chronic, non-cancer pain. These medications work by blocking mu opioid analgesic receptors located throughout the body, particularly in the GI tract. These medications do not block receptors in the brain and spinal cord thus, preserving pain control.

  - **Relistor®** (methylnaltrexone) is available as an oral and injectable medication and is the first product in this class that was approved. Studies indicate an increase in quality of life with Relistor; however, there is no concurrent decrease in the use of laxatives. The most commonly reported side effect is mild to moderate abdominal pain.
  - **Movantik™** (naloxegol) is available as an oral medication and was approved in September 2014 specifically for treatment of OIC. Side effects include abdominal pain, diarrhea, nausea, flatulence, vomiting, headache and hyperhydrosis (excessive sweating).

  These medications are generally not recommended for use until other, more traditional first-line therapies are tried and failed.

The goal of pharmacologic treatment should be an unforced bowel movement every 48 hours. If no bowel movement has been achieved after 48 hours, an increase in dosing or the addition of another medication may be necessary. Use of laxatives at regularly scheduled intervals instead of on an as-needed basis in order to prevent constipation. Regularly scheduled use also decreases the probability of constipation.

The Official Disability Guidelines (ODG) recommend use of a prophylactic stimulant laxative with a stool softener, such as docusate/senna (Peri-Colace), for claimants receiving opioid analgesics long-term. If symptoms persist, a second-line therapy may be needed.

Opioid-induced nausea and vomiting

The ability of an opioid analgesic to induce nausea and vomiting (OINV) is dependent on the opioid analgesic's attachment to a variety of receptors. Sometimes, inaccurately described as an allergy, OINV occurs in response to the normal functioning of the vomiting center in the brain when it receives signals to vomit.

Non-pharmacological therapies for OINV include using distraction and relaxation techniques, breathing fresh air and avoiding certain foods, including those that are salty, sweet, fatty or spicy.

Pharmacological therapy is typically dependent on the severity of symptoms and includes many options effecting different areas in the body, for example:

- **Chemoreceptor trigger zone (CTZ):** Dopamine receptor antagonists like Compazine® (prochlorperazine) to block receptors in the CTZ.
- **Serotonin (5-HT3) antagonists:** Medications such as ondansetron may be used to help target receptors that control nausea and vomiting.
- **Inner ear:** The use of promethazine, diphenhydramine and meclizine are typically intended to decrease opioid-induced vestibular sensitivity. Claimants who experience OINV with movement may benefit from these medications; however, because they are antihistamines and anticholinergic medications, their use is not without the potential for side effects. These side effects include dry mouth, constipation, blurred vision, sedation or confusion.

The relationship between opioid analgesic use and the incidence of OINV is quite variable. In addition, within three to seven days, tolerance to OINV may occur, in which case pharmacologic treatment is generally unnecessary. If pharmacologic therapy is needed, it is important to note medications used to treat OINV typically cause central nervous system depression which is additive to opioid analgesic therapy and may be a dangerous combination. The risks versus benefits of pharmacologic therapy for OINV should be carefully considered.

Within three to seven days, tolerance to OINV may occur, in which case pharmacologic treatment is generally unnecessary. Similarly, OPIAD typically resolves within days when the opioid analgesic is stopped.

Opioid-induced androgen deficiency

Opioid-induced androgen deficiency (OPIAD) can result in response to prolonged opioid analgesic therapy during which the medication inhibits secretion of hormones in the body that control the production and release of the many sex hormones in the body. This is most recognized in the inhibition of testicular testosterone synthesis and hypogonadism. Symptoms of low sex hormone include decreased libido, erectile dysfunction, fatigue, irregular menstrual cycles, weight gain, depression, osteoporosis, hot flashes, decreased facial and body hair, reduced muscle mass, increased body fat and small or shrinking testes.

Although there is no direct evidence that OPIAD improves or resolves with opioid analgesic rotation or dose reduction, OPIAD typically resolves within days when the opioid analgesic is stopped. If hormone replacement therapy (HRT) is initiated, such as the administration of testosterone, it is important to monitor the treatment's efficacy to determine the level of success. Due to the risks associated with HRT, careful evaluation and medical monitoring should be maintained through therapy.

Mitigating opioid-induced side effects improves outcomes

To decrease the incidence of adverse events associated with the use of opioid analgesics, one of the primary goals of therapy should be to manage pain using the lowest effective dose for the shortest duration of time as possible. Another goal should also be to look at non-pharmacologic treatments.

If opioid analgesic therapy is determined the most appropriate treatment choice for the claimant, careful management of opioid-induced side effects is essential. Two aspects of that management to consider are medication therapy modifications and side effect control.

To decrease the incidence of adverse events associated with the use of opioid analgesics, one of the primary goals of therapy should be to manage pain using the lowest effective dose for the shortest duration of time as possible.

- **Medication therapy modifications** are often required to mitigate opioid-induced side effects and typically involve modifying the claimant's medication therapy depending on the type of side effect the claimant is experiencing. Some of the more common therapy modifications are detailed below.
  - **Modifying the dosage** involves either reducing the opioid analgesic dose. For example, decreasing the dose of oxycodone from 30mg per day to 15mg per day may be effective in alleviating opioid-induced sleep disturbances.
  - **Altering the route of administration** is accomplished by changing from one dosage form to another. An example is moving from an oral product (tablet or capsule) to a transdermal (patch) one. This approach is also helpful if a claimant is unable to swallow tablets or capsules, therefore, switching to a transdermal (patch) product may be more effective.
  - **Changing the dosing interval**, for example moving from taking a medication every eight hours to every twelve, is yet another option than may be useful in alleviating opioid-induced side effects.
  - **Rotating opioid analgesic medications** may be considered when there is a need to help improve pain control or reduce unwanted side effects. This may be accomplished through a trial use of an alternate product. For example, switching from oxycodone to morphine. This approach might be recommended when a prescriber is trying to manage OIH or when trying to distinguish the presence of OIH versus medication tolerance.
  - **Taking an opioid holiday** is accomplished through weaning the claimant off of the opioid analgesic for a period to alleviate their side effects and help determine if OIH is present, or if non-pharmacological treatment will relieve the claimant's pain.
  - **Removing opioid analgesics** from the therapy plan altogether following a claimant-specific weaning plan is also an option. Instead of opioid analgesics, adjuvant medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) as well as certain anticonvulsants and antidepressants may be prescribed to more adequately treat certain types of chronic pain.
- **Side effect controls** may be useful in minimizing side effects in the event that discontinuing opioid analgesics is not feasible. These strategies exist to help address and mitigate the impact of medication on the body without altering the opioid analgesic therapy.
  - **Adding pharmacologic therapies** that are managed appropriately can be safe and effective. However, there are additional risks that must be considered alongside those benefits. Adding a laxative medication to the claimant's opioid regimen may be beneficial in managing opioid-induced constipation, a very common side effect, but also needs to be monitored for adherence.
  - **Incorporating non-pharmacologic treatments into the therapy regimen** vary depending on the opioid-induced side effect; however, proper diet, exercise and good sleep hygiene are commonly recommended. Keeping a pain journal to document the claimant's response to the therapy is also useful, not only for tracking success but facilitating discussions with the prescriber.

Achieving better outcomes

Regardless of the route pursued, when taking steps to mitigate opioid-induced side effects, it is always important to consider the claimant as a whole. This includes the presence of comorbid conditions, whether associated and compensable under the claim or not. Similarly, ruling out other causes that may be contributing to the claimant's symptoms is another important consideration. This is often accomplished by ensuring there is a comprehensive review of medications being prescribed, as well as by using resources such as medication reviews and other clinical tools available from your pharmacy benefit manager to better understand, and holistically manage, the claim.

Key terms

A **divided dose** is a fraction of a full dose, given repeatedly at short intervals so that the full dose is taken within a specified period, usually one day.

Hypogonadism occurs when the male testes or female ovaries produce little or no hormones.

Tolerance is a person's diminished response to a medication, which occurs when the medication is used repeatedly and the body adapts to the continued presence of the medication.

Vestibular apparatus is a sensory system found in the ear, which contributes to an individual's sense of balance and spatial orientation.

Weaning is a very claimant-centric process and care must be given when decreasing opioid analgestic doses so as to avoid precipitating withdrawal.

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