

Treatment of Opioid-induced Constipation: A Therapeutic Update

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Abstract

Opioids remain the most effective therapeutic agents for the management of moderate to severe pain. A significant number of patients receive long-term opioid therapy for chronic pain. While a number of opioid side effects such as sedation, nausea and vomiting, and respiratory depression diminish over time due to the development of tolerance, the constipating effects of opioid persist throughout the course of therapy. Opioid-induced constipation (OIC) is associated with marked bowel dysfunction that can significantly impact a patient's quality of life and affect their drug adherence. A step-wise approach to treating OIC should be considered which includes life style modifications, administration of laxatives and stool-softeners, and if necessary, pharmacologic agents to enhance bowel motility and antagonize peripheral μ -opioid receptors. Although OIC is a significant adverse effect associated with opioid use, clinical studies have shown that a number of effective treatment strategies are available for both preventing OIC or reducing its severity.

Keywords: Opioids; Opioid-induced constipation; μ -opioid receptors; Laxatives

Introduction

In 2013, an estimated 207 million opioid prescriptions were dispensed by retail pharmacies in the U.S. (<https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse>). While opioids are highly efficacious for the treatment of acute and chronic pain, they may cause a number of significant side effects. One of the most commonly reported side effects of opioid use is opioid-induced constipation (OIC). According to recent studies, 41-47% of patients using opioids for chronic pain experience significant OIC [1,2]. In patients on chronic opioid therapy, the degree of OIC can be quite severe and even debilitating [3]. A number of therapeutic interventions are currently available to treat OIC with varying degrees of efficacy. Treatment for OIC may include over-the-counter (OTC) options such as stimulant laxatives, stool softeners and osmotic laxatives, as well as prescription drugs that antagonize peripheral μ -opioid receptors, and directly stimulate intestinal secretions and motility. The various treatment options will be discussed below with emphasis on their mechanism of action, efficacy, and potential side-effects.

Opioids and OIC

The human opioid system is highly complex and includes three main endogenous opioid receptors (μ , κ and δ receptors), as well as a number of endogenous opioid peptides such as endorphins, enkephalins, and dynorphins which activate these receptors. Opioid receptors are widely distributed in the brain and spinal cord, as well as in a variety of peripheral tissues such as the gut, airways, blood vessels, and heart. When activated, the opioid receptors located in the brain and spinal cord mediate the analgesic effects of the opioids. Unfortunately, activation of opioid receptors in the gut can significantly impair intestinal activity and lead to OIC.

Mu-opioid receptors, and to a lesser extent κ -opioid receptors, are expressed extensively throughout the gastrointestinal tract and enteric nervous system. Activation of these opioid receptors decreases peristalsis, inhibits intestinal transit, increases intestinal fluid absorption and decreases intestinal secretions. All of these effects combine to cause significant constipation [4]. A clinical syndrome of opioid-induced bowel dysfunction may occur with chronic opioid use

that is characterized by abdominal pain, hard stools, fecal impaction, anorexia, nausea and vomiting [5].

The presence of OIC can significantly impact a patient's quality of life and can lead to dose reduction or even cessation of opioid pain therapy. A 2009 study by Bell et al. [6], examined the prevalence, severity and impact of OIC in 322 patients taking daily opioids. The investigators found that 81% of the patients in their study reported OIC and that the majority of patients with OIC reported at least a moderate negative impact on quality of life and activities of daily living. One third of patients with OIC missed doses, decreased dosage or stopped using opioids completely in order to improve their bowel function. A second study by Bell [7] found that patients with OIC were more likely to take time off from work and were less productive in both their work and home environments.

A 2010 study by Hjalte, et al. [8], examined the direct and indirect costs of OIC in a population (n=331) of patients treated with opioids for six months. The investigators reported that the total cost per patient per month was significantly higher in those patients who experienced significant OIC when compared to those who had mild, moderate or no symptoms of OIC. The costs examined included the direct cost of in-patient needs, out-patient visits, supplemental drug costs and indirect costs related to sick leave and lost productivity at the workplace. Patients in this study with more severe OIC also reported significantly lower quality life scores than those with mild or no symptoms. Data also suggests that health care providers may not always be aware of the fact that patients are experiencing significant OIC. In a recent study with 489 patients receiving opioid therapy, 94% of patients reported suffering from constipation; however, only 61% of their healthcare providers knew that a patient in their care was suffering from significant constipation [9].

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Received May 06, 2016; **Accepted** June 07, 2016; **Published** June 14, 2016

Citation: Zdanowicz MM (2016) Treatment of Opioid-induced Constipation: A Therapeutic Update. Adv Practice Nurs 2:118. doi:10.4172/2573-0347.1000118

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Opioid Tolerance and OIC

With continued opioid use, patients often exhibit tolerance to the analgesic effects of the opioids. The mechanism of opioid tolerance is likely related to down-regulation (decreased numbers) or desensitization of μ -opioid receptors in the CNS. Binding of opioids to the μ receptor activates numerous downstream intracellular pathways. Activated G-protein-dependent signaling pathways appear involved in receptor desensitization while G-protein-independent signaling pathways appear to facilitate μ receptor endocytosis and subsequent downregulation of receptors [10]. Fortunately, tolerance to the respiratory depressant effects of the opioids also develops in parallel to the tolerance seen with the analgesic effects. Interestingly however, tolerance does not occur to the constipating effect of the opioids. A recent comprehensive review by Akbarali [11] reported that tolerance to the inhibitory effects of opioids does appear to occur in the upper GI tract, but tolerance does not develop in the colon and rectum. This regional difference in the development of GI tolerance appears to be related to differences in signaling and regulation of opioid receptors in the two anatomical regions. Specifically, the activity of the regulatory protein β -arrestin2 may differ between the small and large intestines. In animal studies, chronic administration of morphine to the ileum resulted in down-regulation of β -arrestin2 and the development of tolerance while chronic administration of morphine in colon does not affect β -arrestin2 levels and as a result tolerance does not occur [11]. An understanding of the regional differences in μ -opioid receptor regulation is important because it not only enhances our overall understanding of the molecular basis for opioid tolerance but may also lead to the identification of possible future therapeutic targets for the treatment of OIC.

Diagnosis of OIC

Opioid-induced constipation and opioid bowel dysfunction presents with a myriad of symptoms. The Rome III criterion for functional gastrointestinal disorders presents detailed diagnostic criteria for constipation. Diagnosis of OIC should begin with a detailed patient history that includes frequency of bowel movements, the consistency of stool, and the presence of straining, pain, nausea and vomiting. A physical examination should also be conducted that includes bowel sounds, and abdominal palpation for firmness, distention and the presence of pain. The possibility of fecal impaction should also be assessed in patients with persistent and severe constipation. Health care providers should also be aware of the possibility that the constipation observed in their patients might be related to an ongoing disease processes. In cancer patients for example, tumors in the intestine or abdomen may cause bowel obstruction. Likewise, tumors developing in or around the spine may compress nerves that innervate the gastrointestinal tract and thus impair gastric motility and function. A number of other drugs that a patient might be taking such as anticholinergics, tricyclic antidepressants, antihistamines, calcium or iron supplements and aluminum-containing antacids might also be contributing to their constipation.

The symptoms of opioid-induced constipation and bowel dysfunction:

- Constipation – 3 or fewer bowel movements per week
- Abdominal cramping, bloating and distention
- Dry, hard stools
- Pain, straining

- Incomplete evacuation
- Delayed digestions
- Nausea, vomiting

Rome III functional constipation diagnostic criteria*

- Must include two or more of the following:
- Straining during at least 25% of defecations
- Lumpy or hard stools in at least 25% of defecations
- Sensation of incomplete evacuation for at least 25% of defecations
- Sensation of anorectal obstruction/blockage for at least 25% of defecations
- Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
- Fewer than three defecations per week
- Loose stools are rarely present without the use of laxatives
- Insufficient criteria for irritable bowel syndrome

Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Treatment strategies for OIC

A number of non-pharmacologic and pharmacologic options are available for the treatment and prevention of OIC. Although current treatment recommendations support the prophylactic use of various bowel regimens in patients receiving opioid therapy, definitive studies showing the superiority of one treatment regimen over another are currently lacking.

Non-pharmacologic management of OIC: Non-pharmacologic treatment options for the prevention and treatment of OIC should be a component of the overall strategy to prevent OIC and should start with the onset of opioid therapy. Non-pharmacologic interventions include adequate fluid and fiber intake, and increased physical activity. A study by Dukas, showed that physical activity two to six times per week was associated with a 35 percent lower risk of constipation in older women [12]. Abdominal massage has also been shown to help relieve constipation and improve patient quality of life without side effects. A recent study by Turan & Asti, showed that patients with post-operative constipation who received bowel massage by nurses had reduced symptoms of constipation, increased stool output and improved quality of life with no significant adverse side effects [13]. However, a 2009 study by Lamas, et al. showed that while abdominal massage was useful for decreasing the severity of constipation symptoms, it did not lead to a decreased use of laxative. This finding suggests that abdominal massage may be used to complement the actions of laxatives but may not fully replace them [14]. Bowel “diaries” which track the frequency of bowel movements might also be helpful for determining the severity of the OIC that is occurring. While helpful, non-pharmacologic interventions are seldom successful alone for the management of OIC [4,15].

OTC management of OIC: Pharmacologic interventions for OIC include both OTC agents as well as prescription drugs. Common OTC agents used to treat OIC include Stool softeners, bowel stimulants and osmotic laxatives. Stool softeners such as docusate sodium are essentially surfactants that facilitate the mixing of fats and water in the stool and are most useful in patients with hard, dry feces. Stool softeners alone have been shown to be of little benefit in patients with significant

constipation [16] and are thus often combined with a stimulant laxatives for increased effectiveness. Stimulant laxatives such as senna and cascara directly stimulate the myenteric plexus in the gut which in turn enhances intestinal secretions and peristalsis. Although effective in OIC, there is evidence that certain patients may become tolerant to the therapeutic actions of stimulant laxatives over time [17]. Osmotic laxatives (polyethylene glycol (PEG), lactulose, magnesium hydroxide) may also be of value in treating OIC since they act by drawing water into the intestinal lumen which in turn increases intraluminal pressure and stimulates peristalsis. Magnesium-containing osmotic laxatives should be avoided in patients with renal insufficiency since they may result in hypermagnesemia. A comprehensive review of the literature by Ramkumar and Rao [18] found that while PEG and lactulose were both effective in treating chronic constipation, PEG was somewhat more effective than lactulose and had fewer overall side effects.

Patients with OIC should be counseled to avoid bulk laxatives that contain psyllium. Bulk laxatives are designed to draw fluid into the intestinal lumen where the indigestible fibers swell to form a bulky mass that stimulates peristalsis. However, given the fact that opioids impair peristalsis, the increased bulk is now more likely to become an immobile mass that can lead to bowel distention, pain and obstruction.

Although laxatives are generally well-tolerated, they can cause significant side effects such as diarrhea, abdominal pain, distention, nausea and vomiting. Likewise, laxatives do not directly affect or alter the mechanism by which opioids cause constipation. Despite their widespread use in OIC, Pappagallo [19] reported that only 46% of patients receiving laxative therapy for OIC achieved the desired symptomatic relief at least 50% of the time.

Prescription drugs for treating OIC: Lubiprostone (Amitiza) is an orally active prostone that selectively activates chloride channels in the intestine to increase both fluid secretion and intestinal motility. It is currently approved by the Food and Drug Administration (FDA) for the treatment of idiopathic chronic constipation, irritable bowel syndrome in women, and in adults with OIC being treated for chronic non-cancer pain. A recent study by Jamal, et al. [20], examined the therapeutic effects of lubiprostone administration (24 µg twice daily) in 431 adults with OIC who were being treated for chronic non-cancer pain. Administration of lubiprostone significantly improved spontaneous bowel movements, reduced straining and improved the consistency of stools. The percentage of patients who required “rescue” medications to treat their OIC was also significantly lower in the lubiprostone-treated group than the placebo-treated group. Lubiprostone appeared to be well-tolerated by patients with the most common side effects being diarrhea, nausea, vomiting and abdominal pain. No serious adverse effects were seen in the lubiprostone-treated group. An earlier multi-center study by Cryer et al., also demonstrated that lubiprostone (24 µg twice daily) significantly relieved symptoms of OIC for an 11 week period. The drug was well-tolerated and overall side effects were minimal [21].

Peripheral opioid receptor antagonists are agents that are designed to antagonize the effects of opioid at their receptors in the gut and periphery but not in the CNS. Using this strategy, peripheral opioid receptor antagonists counter the constipating effects of opioids that are mediated via peripheral opioid receptors but do not antagonize the analgesic effect of opioids that is mediated via central opioid receptors. Oral naloxone was tested initially for the treatment of OIC since it has a very limited systemic absorption when administered orally [22]. However, a lack of consistent therapeutic effects, difficulty with appropriate dosing and potential for antagonism of CNS opioid receptors significantly limits the use of naloxone in the treatment of

OIC. Later agents such as methylnaltrexone (Reistor), are quarternary N-methyl derivatives of naloxone that are designed to have very low systemic bioavailability and very low CNS penetration, even if administered parenterally. Methylnaltrexone significantly improved symptoms of OIC without inducing opioid withdrawal or impairing analgesia [23,24]. The most common adverse effects associated with the use of methylnaltrexone were abdominal pain, flatulence and nausea. Serious adverse effects were not observed. Reistor was approved by the FDA in 2014 for the treatment of OIC. The normal dose of Reistor is 12 mg/0.6 ml s.c. once every other day but not more than once in a 24 hour period. Methylnaltrexone is contraindicated in patients with known or suspected bowel obstruction.

In 2014, the FDA also approved the drug naloxegol (Movantik) which is a pegylated (with added polyethylene glycol) form of naloxone. Naloxegol is the first orally administered, once a day, peripheral-acting mu opioid receptor antagonist (PAMORA) approved for treating OIC. A comprehensive review of studies related to the therapeutic efficacy of naloxegol was performed by Leonard & Baker [25]. Their findings showed that naloxegol was effective for the long-term (9-12 weeks) of OIC. Significant improvements in spontaneous bowel movements were reported in several moderate to large scale clinical trials with patients experiencing OIC. The long-term (52 week) safety of naloxegol was also demonstrated. The most common side effects observed in patients receiving naloxegol were abdominal pain, nausea, diarrhea, and flatulence. Naloxegol is available in 12 or 25 mg tablets for once a day dosing. A new high affinity, high potency PAMORA, Axelopran is also currently under development by Theravance Biopharma.

While opioid analgesics all exert their constipating effects through activation of opioid receptors, not all opioids agonists appear to be equally constipating. Thus an “opioid rotation” might be considered in selected patients to reduce the severity of constipation. A number of studies have reported that transdermal fentanyl was not only effective for the treatment of chronic cancer and non-cancer pain, but was also significantly better than oral morphine at preserving normal bowel function [26-28]. Despite these findings, a systematic review conducted by Dale [29] concluded that there was only a low level of evidence that opioid rotation significantly reduced the adverse effects of opioids.

Tapentadol (Nucynta), a dual-acting µ-opioid receptor agonist and norepinephrine reuptake inhibitor, is another agent that might be considered for use in patients with chronic pain in place of a traditional opioid. Given that tapentadol has only moderate affinity for µ-opioid receptors, one would anticipate significantly less opioid-related adverse effects. In 2013 study by Kwong, et al. [30], patients with lower back pain or osteoarthritis who were treated with tapentadol had significantly better bowel function and less constipation than similar patients treated with oxycodone. Tramadol (Ultram) is a second dual action opioid analgesic that might be considered for use in selected patients. The affinity of tramadol for µ-opioid receptors is less than that of tapentadol so it is less likely to cause significant OIC when compared to a traditional opioid or tapentadol [31].

Role of the advanced practice nurse in OIC: Advance practice nurses can play an important role in identifying and treating OIC since they are in regular contact with patients. They are also ideally situated with regards to identifying patients at high risk for OIC and ruling out other causes of chronic constipation. A detailed patient history should be obtained that includes diet, physical activity, and a review of all medications the patient is currently taking. A thorough patient examination should be conducted and accompanying signs and symptoms such as nausea, vomiting or abdominal pain/distention should

be noted. Nurses should monitor patient bowel habits as well as the quantity and quality of stools.

Advance practice nurses can also take a lead role in patient education to ensure that lifestyle changes such as increased fluid intake and physical activity are implemented. Nurses can also make certain that laxatives are prescribed prophylactically in patients they identify as high risk for OIC. Nurses can also play an important role in ensuring patient compliance with treatments designed to alleviate OIC as well as monitoring the effectiveness of such therapies once they are instituted.

Discussion

Despite the significance and prevalence of OIC, there are no clear consensus guidelines for its treatment. One reason for this lack of consensus may be the wide variety of instruments currently available to characterize chronic constipation and the varying array of symptoms that may present in different patients with OIC. Poulsen (2015) makes the point that 'a substantial drawback to using a patients bowel habits for the assessment of OIC is that many patients may have been treated with opioids for a long period of time and in fact may not recall what their normal bowel habits were' [32].

The current consensus for the management of OIC involves a comprehensive step-wise approach. Step one begins with measures designed to prevent the occurrence of OIC and include prophylactic laxatives (stimulant +stool softener and/or an osmotic laxative). Preventative measures should also include lifestyle modifications such as maintaining adequate fluid and fiber intake along with regular exercise. Should OIC still occur in a patient despite the above prophylactic interventions, one should first rule out bowel obstruction and other potential causes of constipation, then titrate doses of laxative/softener to enhance bowel activity and consider opioid rotation or a dual-action opioid (i.e. tapentadol, tramadol). If constipation persists despite these measures, the provider should then consider prokinetic agents or peripherally-restricted μ -receptor antagonists. Finally, in more extreme cases, one might consider spinal or epidural analgesics or neuroablation to reduce the amount of opioid that is needed.

A potential disconnect may also exist between the OIC that patients are experiencing and their providers awareness of the issue in the patients they are caring for. It is imperative that all health care providers keep an ongoing dialog with their patients so they can be aware of the impact that OIC may be having on their patient's therapeutic compliance, well-being an overall quality of life.

Conclusion

While opioid analgesics remain the most effective class of agents for the treatment of moderate to severe pain, chronic opioid use is associated with a number of significant adverse effects including constipation. Fortunately, a number of effective therapeutic regimens are available for both treating and preventing opioid-induced constipation. Ongoing research and clinical trials will likely yield additional treatments in the near future to better prevent OIC or provide potent analgesia without significant effects on bowel function.

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