

## ***Chronic Non-Cancer Pain: Opioid-Induced Constipation Module***

### **Key Message 4:**

- **Opioid-induced constipation (OIC) is the most common adverse event associated with use of opioids and should be treated prophylactically with a bowel regimen**
- **Per treatment guidelines and expert opinion, prophylaxis of OIC should consist of non-pharmacologic measures (increased fiber/fluid intake), stool softeners, and laxatives (Table 2)**
  - **Lubiprostone (Amitiza®), methylnaltrexone (Relistor®), and naloxegol (Movantik™) are not recommended as first-line treatment (Tables 3a and 3b)**
- **Although evidence is lacking, rectal-based laxatives and enemas may be used to treat refractory OIC. Manual evacuation such as digital stimulation and manual disimpaction are only used as a last resort**

### **Background: OIC**

- Constipation is one of the most common adverse events associated with opioid use and is characterized by hard, dry stools, incomplete evacuation, straining, bloating, abdominal distention, and increased gastric reflux<sup>1-6</sup>
- OIC is caused by the effects of opioids on the mu ( $\mu$ ) receptors in the gastrointestinal tract leading to decreased motility and secretion
- Risk factors for OIC include advanced age, certain medications and disease states, and long-term use of opioids
- OIC may decrease quality of life and may cause patients to decrease or discontinue opioid treatment leading to suboptimal pain management
- OIC that is not effectively treated may cause fecal impaction, pain, and bowel rupture
- Diagnosis of OIC varies across discipline and includes objective and subjective measures.<sup>5</sup> A recent working group of experts defined OIC as a change from baseline bowel habits after starting opioid treatment over a period of  $\geq 7$  days. These included reduced bowel movement frequency, development or worsening of straining, a sense of incomplete evacuation, and harder stool consistency
- Treatment with a bowel regimen consisting of increased fiber/fluid intake, stool softeners, and laxatives (stimulant and/or osmotic) should be maintained throughout the entire duration of opioid treatment for patients with chronic pain

**Table 1: Guideline/expert recommended prophylactic treatment options.**

Guideline/consensus statement	Recommended first-line prophylactic treatment of OIC
Expert consensus statement on OIC (2014)* <sup>5</sup>	<ul style="list-style-type: none"> <li>-Prophylaxis of OIC when initiating an opioid may be appropriate</li> <li>-Traditional agents for OIC (osmotic and/or stimulant laxatives), in combination with a stool softener as first-line</li> <li>-Traditional agents may be considered first-line based on their safety and cost</li> <li>-Cautions that opioid antagonists may block the analgesic effects of opioids (notes this effect may be less likely with peripherally-acting opioid antagonists)</li> </ul>
AGA technical review and medical position statement on constipation (2013) <sup>3,4</sup>	<ul style="list-style-type: none"> <li>-Traditional osmotic and/or stimulant laxatives plus fiber supplementation prior to use of newer agents for constipation (lubiprostone, methylnaltrexone, and naloxegol; note: does not specifically address OIC)</li> <li>-Traditional agents are considered to be effective, safe, and usually inexpensive</li> </ul>
ASIPP guidelines for opioid use in CNCP (2012)** <sup>1</sup>	<ul style="list-style-type: none"> <li>-Prophylactic treatment of OIC with a bowel regimen (increased fluid/fiber intake, stool softeners, laxatives; notes evidence is anecdotal)</li> </ul>
VA/DoD guidelines for chronic pain (2010)** <sup>2</sup>	<ul style="list-style-type: none"> <li>-Prophylactic treatment of OIC with a bowel regimen (increased fluid/fiber intake, stool softeners, laxatives; notes most evidence is anecdotal)</li> <li>-Bulk-forming laxatives should be used with caution (may worsen constipation, cause fecal impaction or intestinal obstruction)</li> </ul>
APS/AAPM guidelines for chronic opioid use in CNCP (2009)** <sup>7</sup>	<ul style="list-style-type: none"> <li>-Prophylactic treatment of OIC with a bowel regimen (increased fluid/fiber intake, stool softeners, laxatives; notes evidence is anecdotal)</li> </ul>
<p><b>SUMMARY</b></p> <p><b>-Based on the available evidence, guidelines/expert consensus recommend that all patients receiving opioids for CNCP should be receiving a prophylactic bowel regimen consisting of increased fiber/fluid intake, stool softeners, and laxatives (stimulant and osmotic are preferred)</b></p> <p><b>-Lubiprostone, methylnaltrexone, and naloxegol are considered second-line; traditional agents (stool softeners, laxatives) are considered first-line based on their cost and safety</b></p>	

\*International working group of experts in pain management and gastroenterology; \*\*guidelines were published prior to FDA-approval of lubiprostone, methylnaltrexone, and naloxegol for OIC; AGA=American Gastroenterological Association; APS/AAPM=American Pain Society/American Academy of Pain Medicine; ASIPP=American Society of Interventional Pain Physicians; CNCP=chronic non-cancer pain; FDA=Food & Drug Administration; OIC=opioid-induced constipation; VA/DoD=Department of Veterans Affairs/Department of Defense

**Table 2: First-line agents for OIC (fiber products, stool softeners, and laxatives).<sup>3,8</sup>**

<b>Medication(s)</b>	<b>Mechanism of action</b>	<b>Side effects and precautions</b>	<b>Available products</b>
<b>Fiber supplements/bulk-producing agents:</b> <ul style="list-style-type: none"> <li>• Methylcellulose</li> <li>• Calcium polycarbophil</li> <li>• Psyllium</li> <li>• Wheat dextrin</li> </ul>	Holds water in stool and increases bulk; increases colonic distension/motility	-Abdominal pain, bloating, flatulence, nausea, vomiting *Use bulk agents with caution as they may worsen constipation and cause fecal impaction. <sup>2</sup> Avoid in patients who have difficulty swallowing, are immobile, or on fluid restriction	Citrucel®, FiberCon®, Metamucil®, Benefiber® and various generic products
<b>Stool softener:</b> <ul style="list-style-type: none"> <li>• Docusate</li> </ul>	Increases water into the stool, softening the stool and increasing bowel movements	Bloating, flatulence, diarrhea, cramping	Colace® and various generic products
<b>Emollient/lubricant:</b> <ul style="list-style-type: none"> <li>• Mineral oil</li> </ul>	Softens and lubricates hard stools, easing their passage without irritating the mucosa	-Incontinence, aspiration, lipid pneumonitis -Mineral oil: contraindicated in children < 6 years, pregnancy, bedridden patients, elderly, patients who have difficulty swallowing	Various generic products
<b>Irritant/stimulant laxatives:</b> <ul style="list-style-type: none"> <li>• Senna</li> <li>• Bisacodyl</li> <li>• Castor oil</li> </ul>	Stimulates sensory nerve endings in the large intestine to produce parasympathetic reflexes which results in peristalsis and increased motility and colonic secretions	-Cramping, nausea, vomiting, urine discoloration -Senna may cause urine discoloration and chronic use may result in melanosis coli	Senokot®, Ex-Lax®, Dulcolax®, Carters Little Pills® and various generic products
<b>Saline laxatives:</b> <ul style="list-style-type: none"> <li>• Magnesium citrate</li> <li>• Magnesium hydroxide</li> </ul>	Often used for bowel preparation procedures; draws water into the bowel from surrounding body tissues; softens stool and increases bowel action	-Diarrhea, hypermagnesemia, cramping, dizziness -Avoid in elderly, renal failure, heart failure, patients on diuretics	Various generic products
<b>Osmotic laxatives:</b> <ul style="list-style-type: none"> <li>• Lactulose</li> <li>• Polyethylene glycol 3350</li> <li>• Sorbitol 70%</li> </ul>	Causes retention of water resulting in softer stool and more frequent bowel movements	Diarrhea, flatulence, cramping, swollen abdomen	GlycoLax®, Miralax®, and various generic products

**Table 3a: Second-line agents for OIC.**

<b>Agent (FDA-approval date)</b>	<b>FDA-approved indication(s)</b>	<b>Mechanism of action</b>	<b>Usual dosage</b>	<b>Special populations</b>
Lubiprostone (Amitiza®)  (April 2013 for OIC)	-OIC in adults (≥ 18y) with CNCP -CIC in adults (≥ 18y) -Constipation-predominant IBS in adult women (≥ 18y)	Locally-acting chloride channel activator; enhances fluid secretion, facilitating passage of stool	24 mcg PO BID with food and water	-Moderate hepatic impairment (Child-Pugh Class B): 16 mcg PO BID -Severe hepatic impairment (Child-Pugh Class C): 8 mcg PO BID
Methylnaltrexone (Relistor®)  (April 2008 for OIC in advanced illness; September 2014 for OIC in CNCP)	-OIC in adults (≥ 18y) with advanced illness receiving palliative care (when response to laxatives is insufficient) -OIC in adults (≥ 18y) with CNCP	Peripherally-acting mu-opioid receptor antagonist in the GI tract; decreases constipating effects of opioids	12 mg SC once daily (for OIC in advanced illness--dosed every other day as needed by weight)	-Severe hepatic impairment: avoid use -Severe renal impairment (CrCl <30 mL/min): reduce to half the recommended dose
Naloxegol (Movantik™)  (September 2014)	OIC in adults (≥ 18y) with CNCP	Peripherally-acting mu-opioid receptor antagonist in the GI tract; decreases constipating effects of opioids	25 mg PO once daily in morning. May decrease to 12.5 mg once daily if not tolerated	-Severe hepatic impairment: avoid use -Moderate/severe renal impairment (CrCl <60 mL/min): 12.5 mg PO daily

BID=twice daily; CIC=chronic idiopathic constipation; CNCP=chronic non-cancer pain; CrCl=creatinine clearance; FDA=Food & Drug Administration; GI=gastrointestinal; IBS=irritable bowel syndrome; OIC=opioid-induced constipation; PO=oral; SC=subcutaneous; y=years

**Table 3b: Safety of second-line agents for OIC.<sup>9-11</sup>**

<b>Agent</b>	<b>Contraindications</b>	<b>Warnings</b>	<b>Common adverse reactions</b>
Lubiprostone (Amitiza®)	Known or suspected mechanical GI obstruction	-May experience nausea (administer with food) -Avoid in patients with severe diarrhea -May experience dyspnea within an hour of 1 <sup>st</sup> dose (usually resolves in 3h & may recur with subsequent doses) -Assess for symptoms indicative of mechanical GI obstruction before initiation	Patients with OIC (>4%): nausea, diarrhea
Methylnaltrexone (Relistor®)	Known or suspected mechanical GI obstruction or at increased risk of recurrent obstruction	-Evaluate risk/benefit in patients with known or suspected lesions in GI tract & monitor for abdominal pain -Discontinue if severe/persistent diarrhea occurs	-Patients with non-cancer pain (≥1%): abdominal pain, nausea, diarrhea, hyperhidrosis, hot flushes, tremors, chills -Patients with advanced illness (≥5%): abdominal pain, flatulence, nausea, dizziness, diarrhea
Naloxegol (Movantik™)	-Known or suspected mechanical GI obstruction -Concomitant use with strong CYP3A4 inhibitors	-Evaluate risk/benefit in patients with known or suspected lesions in GI tract & monitor for abdominal pain -Evaluate risk/benefit in patients with BBB disruptions (may cause opioid withdrawal)	≥3%: abdominal pain, diarrhea, nausea, flatulence, vomiting, headache

BBB=blood-brain-barrier; CYP=cytochrome P450; GI=gastrointestinal; h=hours; OIC=opioid-induced constipation

### Refractory constipation:

- There is little evidence to support use of rectal-based laxatives and enemas for treatment of refractory constipation<sup>3,5,12</sup> (most guidelines do not address refractory constipation). Patients often resort to rectal-based laxatives, enemas, and manual evacuation procedures when traditional laxative agents are ineffective.<sup>5,12</sup>
  - Common stimulant agents used include bisacodyl and glycerin suppositories
  - Common enema agents used include phosphate, saline, tap water, or molasses enemas
    - Phosphate and saline enemas should be used with caution in patients with renal insufficiency due to the risk for electrolyte disturbances
  - Manual evacuation: includes digital stimulation and manual disimpaction and may be considered if fecal impaction is suspected
  - Use of rectal-based laxatives and enemas in addition to manual disimpaction may cause rectal bleeding, bowel perforation, and infections

### References:

1. Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2--guidance. *Pain physician*. 2012;15(3 Suppl):S67-116.
2. VA/DoD clinical practice guideline for management of opioid therapy for chronic pain. 2010; [http://www.va.gov/painmanagement/docs/cpg\\_opioidtherapy\\_fulltext.pdf](http://www.va.gov/painmanagement/docs/cpg_opioidtherapy_fulltext.pdf). Accessed January 19, 2016.
3. American Gastroenterological Association technical review on constipation. *Gastroenterology*. 2013;144:218-238.
4. Bharucha AE, Dorn SD, Lembo A, Pressman A. American Gastroenterological Association medical position statement on constipation. *Gastroenterology*. 2013;144(1):211-217.
5. Camilleri M, Drossman DA, Becker G, Webster LR, Davies AN, Mawe GM. Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. *Neurogastroenterology and motility: the official journal of the European Gastrointestinal Motility Society*. 2014;26(10):1386-1395.
6. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis research & therapy*. 2005;7(5):R1046-1051.
7. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *The journal of pain: official journal of the American Pain Society*. 2009;10(2):113-130.
8. Pharmacist's Letter Detail-Document: Treatment of Constipation in Adults. Pharmacist's Letter/Prescriber's Letter. June 2015.
9. Naloxegol (Movantik) prescribing information. <https://www.movantikhcp.com/home.html>. Accessed January 20, 2016.
10. Lubiprostone (Amitiza) prescribing information. <http://www.amitiza.com/>. Accessed January 20, 2016.
11. Methylnaltrexone (Relistor) prescribing information. <http://www.relistor.com/>. Accessed January 20, 2016.
12. Badke A, Rosielle DA. Opioid Induced Constipation Part I: Established Management Strategies #294. *J Palliat Med*. 2015;18(9):799-800.