Targeted Treatment Options for Opioid Induced Constipation: Update for the Pharmacist

EDUCATIONAL OBJECTIVES
Upon completion of this activity, participants will be better able to:

1. Classify and define opioid-induced constipation (OIC);
2. Describe how opioids act centrally and peripherally to cause gastrointestinal symptoms;
3. Identify the role of lifestyle interventions and laxatives in managing OIC;
4. Identify how certain treatment options can reduce OIC by targeting opioids’ effects on opioid receptors in the gastrointestinal tract; and
5. Recommend effective management options for OIC for patients who fail traditional therapies.

Post-Test/Rationale:
1. Opioids induce constipation primarily through gastrointestinal stimulation of what receptor?
   A. Delta-opioid receptor
   B. Kappa-opioid receptor
   C. Mu-opioid receptor***
   D. Opioid receptor-like 1

   Correct answer: C

   Rationale (Objective #2): All 4 of the receptor subtypes listed are involved centrally in the analgesic effects of opioids. Mu, kappa, and delta receptors are all present in the gastrointestinal (GI) tract, as well. Mu-opioid receptor stimulation within the GI tract is primarily responsible for reduced GI motility and subsequent constipation.

2. A patient has been taking sustained-release morphine 15 mg orally 3 times daily for 2 months for chronic back pain. She completes the Bowel Function Index (BFI) and reports her scores as follows: ease of defecation, 44 out of 100 points; feeling of incomplete bowel evacuation, 30 out of 100 points; and an overall judgment of constipation, 52 out of 100 points. Her average score is 43 out of 100 points. Which of the following statements is correct regarding this patient’s presentation?
   A. This patient is experiencing opioid-induced constipation (OIC) because her average score is above 28.8 points***
   B. An improvement of 3 points in her score would signify a clinically meaningful difference in her symptoms
   C. The BFI was validated in patients with chronic idiopathic constipation and is, therefore, not a valid tool for the assessment of OIC
   D. An increase in her score over time indicates improvement in her symptoms

   Correct answer: A
Rationale (Objective #1): The BFI is a tool that was validated for use in patients with OIC. Three parameters are scored on a scale of 0 to 100, and an average score is reported. An average score greater than 28.8 indicates the presence of OIC, and a change in the average score by at least 12 points indicates a clinically meaningful difference. Worse symptoms are indicated by higher scores.

3. Which lifestyle change can help prevent constipation?
   A. Eat a bland, high-fat diet
   B. Increase physical activity***
   C. Increase intake of coffee
   D. Wait until there is adequate time to have a complete bowel movement

Correct answer: B

Rationale (Objective #3): Patients with low levels of physical activity have been shown to have improvements in constipation symptoms when they increase their levels of physical activity. If dietary measures are introduced, it is recommended that patients increase their intake of fiber, not fat, and increase their intake of water, not coffee. Patients should be encouraged to act upon the initial urge to defecate and not to wait until they have adequate time to have a complete bowel movement.

4. Which of the following is a peripherally acting mu-opioid receptor antagonist?
   A. Lubiprostone
   B. Senna
   C. Psyllium
   D. Naloxegol***

Correct answer: D

Rationale (Objective #4): Naloxegol is a peripherally acting mu-opioid receptor antagonist (PAMORA), which treats opioid-induced constipation without antagonizing opioid analgesic effects or inducing opioid withdrawal symptoms. Lubiprostone is a chloride channel activator, which increases fluid content within the gastrointestinal tract, minimizing constipation. Senna is a stimulant laxative, and psyllium is a fiber supplement that serves as a bulk-forming laxative.

5. All of the following therapies are approved by the U.S. Food and Drug Administration for the treatment of opioid-induced constipation EXCEPT:
   A. Naloxegol
   B. Lubiprostone
   C. Alvimopan***
   D. Methylaltrexone

Correct answer: C
Rationale (Objective #4): The agents that are approved for the treatment of opioid-induced constipation (OIC) are the peripherally acting mu-opioid receptor antagonists (PAMORAs) naloxegol and methylnaltrexone. Lubiprostone, a chloride channel activator, is also approved for treatment of OIC. Alvimopan is a PAMORA approved for use following bowel surgery to prevent or treat post-operative ileus; it is not approved for the treatment of OIC.

6. A 47-year-old male is currently receiving extended-release oxycodone 20 mg orally twice daily for chronic pain plus oxycodone 5 mg orally every 6 hours as needed for breakthrough pain and senna 2 tablets (17.2 mg) orally at bedtime. He has been on this regimen for 8 weeks. Today he complains of continued constipation. His Bowel Function Index mean score is 42. Which of the following options is the best recommendation for this patient's constipation based on efficacy, safety, and convenience?

A. Reduce extended-release oxycodone dose to 10 mg orally twice daily
B. Add methylnaltrexone 12 mg subcutaneously every morning
C. Add docusate 200 mg orally once daily at bedtime
D. Add naloxegol 25 mg orally once daily***

Correct answer: D

Rationale (Objective #5): Naloxegol 25 mg orally once daily, a peripherally acting mu-opioid receptor antagonist (PAMORA), is the best option for this patient because he is already receiving a stimulant laxative without adequate relief of his constipation. Reducing his opioid dose would not be expected to significantly improve his constipation since peripheral mu-opioid receptor effects such as constipation may occur at lower doses than those required to achieve adequate analgesia. Methylnaltrexone could be used, but the subcutaneous route of administration is less convenient than an oral dosing option. Methylnaltrexone 450 mg orally once daily could be an oral option. The addition of docusate to senna therapy has not been shown to significantly improve opioid-induced constipation.

7. Based on survey results of patients who use opioids to treat chronic pain and experience opioid-induced constipation (OIC), which of the following statements describes patients’ and their health care providers’ experiences?

A. The majority of patients will not adjust their opioid therapy in response to adverse effects
B. The majority of patients who reported altering opioid therapy did so due to sedative effects
C. Health care providers are likely to discuss OIC with patients when initiating opioid therapy***
D. Health care providers accurately estimate their patients’ OIC, but underestimate the amount of pain experienced

Correct answer: C

Rationale (Objective #1): Health care providers are likely to discuss OIC with patients when initiating opioid therapy, but only about half of surveyed health care providers discuss OIC at subsequent visits. The majority of patients surveyed (57%) reported taking less than their
prescribed opioid doses or discontinuing their opioid therapy altogether due to opioid-related adverse effects. While 90% of patients who altered their opioid dosing did so in response to constipation, only 22.27% reported doing so due to sedation. Health care providers were found to underestimate the presence of OIC, with only 61% agreement among patients and health care providers; the agreement regarding degree of pain was very high.

8. A 67-year-old woman is experiencing opioid-induced constipation (OIC). Her current medications include: hydrocodone 10 mg/acetaminophen 300 mg orally every 4 hours, extended-release venlafaxine 150 mg orally daily, senna 2 tablets orally at bedtime, and polyethylene glycol 3350 17 gm orally once daily. Her diet is high in fruits, vegetables, and whole grains, and she drinks 8 to 10 glasses of water per day. Her past medical history is significant for depression, irritable bowel syndrome with constipation, and a motor vehicle accident 6 months ago with subsequent chronic pain. She is enrolled in a physical therapy program that requires her to be physically active within her ability for approximately 30 minutes per day. Which of the following approaches would be most appropriate to initiate to treat OIC in this patient?

A. Discontinue venlafaxine as this may exacerbate her constipation
B. Initiate lubiprostone 24 mcg orally twice daily***
C. Increase water intake
D. Increase physical activity

Correct answer: B

Rationale (Objective #5): Lubiprostone is indicated for the treatment of OIC and irritable bowel syndrome with constipation, making this a reasonable option for this patient. Venlafaxine is associated with diarrhea and would not be expected to worsen constipation. This patient is likely not dehydrated, as she drinks 8 to 10 glasses of water per day, so increasing water intake would not be expected to have a significant effect on her OIC. She is also physically active within her ability; therefore, increasing her physical activity would not be expected to affect her OIC, and it may not be a feasible recommendation given her pain.

9. A 54-year-old man with chronic pain is being initiated on chronic opioid therapy. Which of the following recommendations is best for this patient?

A. Initiate naloxegol 25 mg orally once daily concurrently with chronic opioid therapy
B. Assess patient after 3 months of opioid therapy and initiate lubiprostone 24 mcg orally twice daily if opioid-induced constipation is present
C. Conduct a Bowel Function Index assessment prior to starting opioid therapy and initiate fiber supplementation only if the mean score is above 28.8
D. Initiate bisacodyl 10 mg orally once daily concurrently with the initiation of opioid therapy***

Correct answer: D

Rationale (Objective #3): When initiating chronic opioid therapy, it is necessary to educate the patient regarding opioid adverse effects such as constipation. An appraisal of the patient’s
lifestyle and the potential for lifestyle modifications such as increased physical activity and increased fluid and fiber intake should be considered. Patients who will receive chronic opioids should receive a conventional laxative such as a stimulant laxative like bisacodyl concurrently. Naloxegol, a peripherally acting mu-opioid receptor antagonist, should be reserved for patients who continue to experience opioid-induced constipation (OIC) despite conventional laxative use. Patients should receive 1 or more conventional laxatives and be assessed on a regular basis rather than waiting 3 months before initiating OIC treatment. The use of the Bowel Function Index or other assessment tool at baseline and periodically during opioid therapy is important, but all patients should receive conventional laxative therapy when initiating chronic opioid treatment, not only those who are constipated at baseline with a score above 28.8.

10. Which of the following statements is correct regarding the prolonged-release oxycodone and naloxone combination product?

A. Orally administered naloxone undergoes first-pass metabolism, but high doses can achieve concentrations that antagonize analgesic effects centrally***

B. Prolonged-release oxycodone and naloxone is only effective for opioid-induced constipation (OIC) treatment when used in combination with a peripherally acting mu-opioid receptor antagonist such as naloxegol

C. The naloxone in the combination product is present only to induce withdrawal to deter abuse and will not result in improvement in OIC

D. Patients treated with the combination product for 12 weeks reported an average reduction of 48.5 points on the Bowel Function Index, which was statistically significant but not clinically significant

Correct answer: A

Rationale (Objective #5): Orally administered naloxone does undergo first-pass metabolism, limiting the amount of naloxone that reaches systemic circulation and crosses the blood-brain barrier. However, at higher doses, naloxone achieves high enough systemic concentrations to antagonize central analgesic effects. This is the reason for a fixed 2-to-1 oxycodone-to-naloxone ratio in the combination product. Prolonged-release oxycodone and naloxone has not been evaluated in combination with a peripherally acting mu-opioid receptor antagonist (PAMORA). Its effects on reducing OIC are based on its use without a concurrent PAMORA. While it is true that the U.S. Food and Drug Administration’s focus is the abuse-deterrent potential, the combination product has been shown to reduce OIC as well. In a 12-week study of prolonged-release oxycodone and naloxone for patients who were previously treated with oxycodone and experienced OIC despite laxative use, average Bowel Function Index scores decreased by an average 48.5 points, which was statistically significant (p < 0.001). A reduction of at least 12 points indicates a clinically meaningful difference.