LEARNING OBJECTIVES
Upon completion of this activity, participants should be better able to:

- Evaluate baseline bowel habits, risk factors for opioid-induced constipation (OIC) development, and ongoing changes in bowel function in patients on long-term opioid therapy
- Implement a prophylactic treatment plan to address OIC concurrent with the initiation of opioid therapy
- Analyze current pharmacotherapies for OIC based on mechanisms of action and data on efficacy and safety
- Tailor treatment regimens for patients experiencing OIC according to symptom severity, past treatment responses, and patient preferences
- Discuss the essential elements of opioid pharmacology with specific focus on the effects of opioid receptor activation in the gastrointestinal tract
- Communicate with opioid-treated patients about treatment-emergent adverse events through open, patient-centered dialogue throughout the course of therapy

INTRODUCTION
Chronic pain is one of the most common reasons people seek medical care. In 2011, the Institute of Medicine reported that approximately 100 million adults in the United States have at least 1 chronically painful disorder. Not surprisingly, the consequences are often serious, including deleterious effects on overall health status, increased utilization of healthcare resources, and profound disability. Chronic pain interferes with patients’ abilities to perform
OPIOID-INDUCED CONSTIPATION

activities of daily living, maintain employment, and engage in social relationships.²³ Estimates for the economic burden of chronic pain exceed $500 billion annually, reflecting both the direct expenses of medical treatment and indirect costs of lost productivity.¹

Among the various treatment modalities for chronic pain, prescription opioid analgesics have received a great deal of attention over the last 2 decades, primarily due to concerns about misuse, abuse, and overdose.⁴ Nevertheless, opioids remain the mainstay treatment for cancer pain and other advanced illnesses.⁴⁵ Additionally, when prescribed as part of an appropriately structured treatment plan, these medications can also effectively and safely reduce pain levels, improve function, and enhance quality of life in carefully selected patients with chronic noncancer pain.⁹ Prescribers must be vigilant during ongoing monitoring, meticulous in their documentation, and knowledgeable about the risks of therapy, including common adverse events (AEs) and the potential for abuse.

The most frequent AE resulting from opioid treatment is constipation, which is reported by approximately half of opioid-treated patients in clinical trials and is probably even more common in day-to-day practice.⁴⁶⁷ Signs and symptoms of opioid-induced constipation (OIC) include infrequent, small, or incomplete bowel movements; abdominal or rectal pain; and the need to strain when having a bowel movement.⁷⁹Despite its prevalence, OIC is often overlooked and frequently unaddressed, in large part because patients are not eager to volunteer information about their bowel habits or discuss any symptoms of constipation with their clinicians.⁹ Patient embarrassment, lack of knowledge about the potential gastrointestinal effects of opioids, and fears that any complaints may result in a reduction in the opioid dose or discontinuation of opioid therapy altogether create hurdles to open dialogue with many patients.⁹ Consequently, clinicians who manage patients taking chronic opioid medications must be prepared to proactively ask their patients about changes in their bowel habits and discuss alternative treatment options should OIC develop.

In addition to significant burdens on patients’ quality of life and psychosocial status, poorly managed OIC can lead to a range of medical complications, including fecal impaction, hemorrhoids, and, in rare cases, bowel obstruction or rupture.¹⁰ Patients with OIC have also been known to skip their prescribed opioid doses, reducing any clinical benefit and subjecting themselves to symptoms of withdrawal.¹¹ Therefore, it is essential that clinicians anticipate, identify, and manage bowel dysfunction in patients on chronic opioid therapy. Semistructured and repeated inquiries into bowel habits can be used to individualize and tailor bowel regimens—potentially including medications that have been recently approved by the US Food and Drug Administration (FDA) for the treatment of OIC—when responses to dietary modifications and conventional laxative therapy are inadequate.¹²

EFFECTS OF OPIOIDS IN THE GASTROINTESTINAL TRACT

Endogenous opioid peptides (eg, endorphins) and prescription opioid analgesics (eg, mor-
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Pharmaceutical opioids, including morphine, oxycodone, exert their effects by binding to classic G-protein-coupled µ-opioid receptors expressed throughout the body. For example, activation of µ-opioid receptors located at the synapses between first-order pain-sensing neurons (nociceptors) and second-order neurons that carry signals up the spinal cord dampens the transmission of pain-related neural activity before it reaches the brain. Opioid receptors are also located peripherally in the gastrointestinal tract, where the binding of agonists modulates physiologic processes from the lower esophageal sphincter to the rectum. Outside of the central nervous system, the most clinically relevant effects of prescription opioids are mediated by µ-opioid receptors in the enteric nervous system, which regulate the activities of circular and longitudinal muscles located all along the gastrointestinal tract.

Under normal circumstances, coordinated contractions in these muscles promote the mixing of ingested material and propel the intestinal contents forward from the stomach and through the large and small intestines. Local activation of µ-opioid receptors induces nonpropulsive contractions in circular muscles, resulting in increased absorption of fluid out of the intestinal lumen. In addition, reduced tone in longitudinal muscles decreases propulsive contractions, leading to increased transit time for ingested material. Other gastrointestinal effects of µ-opioid agonists include slowed gastric emptying; increased tone in the pylorus between the stomach and small intestine and in the ileocecal sphincter between the small and large intestines; and decreased secretions from the gallbladder, small intestine, and colon. Together, these downstream effects of opioid receptor activation increase the risk of bowel dysfunction, which most commonly manifests as constipation. To improve outcomes for opioid-treated patients with chronic pain, recent research has focused on developing medications that counteract the effects of prescription opioids. This includes agents designed to prevent the active drug from crossing the blood–brain barrier, thereby limiting antagonistic effects to peripheral systems without compromising the centrally mediated pain relief provided by an analgesic opioid medication.

ASSESSING BOWEL HABITS IN PATIENTS ON LONG-TERM OPIOID THERAPY

The diagnosis and treatment of opioid-induced bowel dysfunction were recently discussed by an expert panel comprising gastroenterologists, neurologists, and pain and palliative care specialists. In the resulting consensus statement, the multidisciplinary working group recommends that OIC be defined as a change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following: (1) reduced bowel movement frequency, (2) development or worsening of straining to pass bowel movements, (3) a sense of incomplete rectal evacuation, or (4) harder stool consistency. When considering this definition, it is important to take note of the range of potential clinical manifestations of OIC. Although a reduction in bowel movement frequency is a clear and commonly reported symptom of OIC, many affected individuals will only be identified if their baseline bowel habits are assessed, documented, and compared with information obtained during periodic follow-up appointments throughout the course of the opioid-based care.

When initiating opioids, clinicians should also take note of clinical characteristics that increase the risk of opioid-induced bowel dysfunction (eg, female sex or advanced age).
People with diets low in fiber and high in fat are also at greater risk for OIC development, highlighting an important topic for ongoing patient education. Additional clinical scenarios that may require more vigilant monitoring of bowel habits include relatively immobile patients, individuals who experience nausea or vomiting soon after starting opioids, people who have been recently hospitalized, and patients in whom a mechanical obstruction or malignancy has been identified.

When the decision is made to move forward with an opioid trial for chronic pain, patients should be educated on the gastrointestinal effects of opioids and risks of OIC and evaluated for baseline bowel habits. These conversations and subsequent discussions on therapeutic options are most effective when clinicians work to forge partnerships with their patients, listening to concerns, empathizing with challenges, considering preferences, and encouraging efforts to achieve agreed-upon goals. When assessing bowel habits, avoiding “yes/no” questions for quantitative queries will often result in more informative answers from patients. Examples of appropriate questions include “How many bowel movements do you have each week?” and “Can you describe what your stool usually looks like?” The same questions can then be asked at each follow-up appointment after opioids are prescribed, with additional inquiries into how bowel patterns have changed since therapy commenced or since the last appointment.

To help structure evaluations of bowel patterns and document findings in the medical record, clinicians can turn to 1 of several brief and easy-to-use bowel assessment tools. For example, using the visually guided Bristol Stool Form Scale can help patients overcome embarrassment about describing the appearance of their stool; the most common form of stool is

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Separate hard lumps, like nuts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2</td>
<td>Sausage-like but lumpy</td>
</tr>
<tr>
<td>Type 3</td>
<td>Like a sausage but with cracks in the surface</td>
</tr>
<tr>
<td>Type 4</td>
<td>Like a sausage or snake, smooth and soft</td>
</tr>
<tr>
<td>Type 5</td>
<td>Soft blobs with clear-cut edges</td>
</tr>
<tr>
<td>Type 6</td>
<td>Fluffy pieces with ragged edges, a mushy stool</td>
</tr>
<tr>
<td>Type 7</td>
<td>Watery, no solid pieces</td>
</tr>
</tbody>
</table>

Figure 1. Bristol Stool Form Scale.
identified from type 1 to type 7 using short descriptive text with associated images (Figure 1).22 The Bowel Function Index (BFI) is a 3-item questionnaire that produces an average score (0-100) for ratings during the past week of the ease of defecation (“no difficulty” to “severe difficulty”), feelings of incomplete bowel evacuation (“not at all” to “very strongly”), and the clinician’s opinion about the degree of constipation (“no constipation” to “very heavily constipated”).23 The 12-item Patient Assessment of Constipation questionnaire examines the presence and severity of patient-reported symptoms over the prior 2 weeks using 3 individually scored subscales for stool symptoms, rectal symptoms, and abdominal symptoms.24 Communication among patients, clinicians, and other members of the healthcare team can facilitate ongoing, semistructured evaluations of bowel function to ensure opioid-based regimens are tailored to maximize analgesia and functional gains while minimizing AEs.

PROPHYLACTIC BOWEL REGIMENS FOR OPIOID-TREATED PATIENTS
Most clinical practice guidelines covering long-term opioid therapy for chronic pain include recommendations on the prescription of prophylactic bowel regimens when patients are initiating treatment.4 General preventive strategies include encouraging adequate intake of dietary fiber (15-30 g daily), regular exercise, and, for some patients, treatment with traditional laxatives.4 Results of clinical studies have shown that prophylactic laxative therapy reduces the likelihood of constipation in patients who have decided to move forward with an opioid trial.25,26 On the other hand, although many clinicians recommend that patients increase their water intake, there is little evidence to support this approach for OIC unless an individual is significantly dehydrated.4

Available classes of laxatives include stool softeners, stimulants, osmotics, lubricants, and bulking agents (Table 1).27-29 However, most of these medications have not been examined in high-quality clinical trials, and when they have, they have only been evaluated for relatively short periods of time. The mechanisms of action of traditional laxatives vary. Stimulants generally work by altering electrolyte transport in the intestinal mucosa, producing results within a few hours of administration.30 Osmotic laxatives include saline agents that induce the secretion of water into the intestines.30 Other members of this class include lactulose, a poorly

<table>
<thead>
<tr>
<th>Type of Laxative</th>
<th>Specific Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool softener</td>
<td>Docusate sodium, docusate calcium</td>
</tr>
<tr>
<td>Stimulant</td>
<td>Senna, bisacodyl, castor oil</td>
</tr>
<tr>
<td>Osmotic</td>
<td>Polyethylene glycol, lactulose</td>
</tr>
<tr>
<td>Lubricant</td>
<td>Mineral oil</td>
</tr>
<tr>
<td>Bulking agent</td>
<td>Psyllium, bran, methylcellulose</td>
</tr>
</tbody>
</table>
absorbed carbohydrate that becomes a substrate for colonic bacterial fermentation, and polyethylene glycol, a large polymer that draws water into the intestinal lumen. Bulking agents and medicinal fiber, such as psyllium, should be avoided in patients with OIC; there is a paucity of positive data supporting the use of bulking agents to treat constipation, and these compounds can worsen abdominal pain, increase bloating, and further harden the stool. Clinicians should educate patients on the potential AEs of the chosen laxative, including nausea, vomiting, diarrhea, and abdominal pain. Although most of these unpleasant effects will dissipate after a bowel movement, they may interfere with adherence to bowel regimens, particularly when high doses are required to achieve clinical benefit.

### ADDITIONAL MANAGEMENT OPTIONS FOR PATIENTS WITH OIC

When patient education and other prophylactic efforts fail to prevent the development of constipation in patients on chronic opioid therapy, additional management options are available. Clinicians should start by ruling out other potential causes, such as hypothyroidism or side effects of concomitantly prescribed medications (eg, calcium channel blockers or certain classes of antidepressants). If OIC is the most likely cause of the bowel dysfunction, some

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**Table 2. Medications Currently Approved by the FDA for the Treatment of OIC**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Lubiprostone</th>
<th>Methylnaltrexone</th>
<th>Naloxegol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Chloride channel activator</td>
<td>PAMORA</td>
<td></td>
</tr>
<tr>
<td><strong>Mode of administration</strong></td>
<td>Oral</td>
<td>Subcutaneous</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Recommended dose</strong></td>
<td>24 µg</td>
<td>12 mg/0.6 mL</td>
<td>25 mg/12.5 mg</td>
</tr>
<tr>
<td><strong>Dosing frequency</strong></td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Once daily</td>
</tr>
</tbody>
</table>
| **Clinical considerations** | • Take with food and water  
• May be used concomitantly for length of opioid treatment  
• May be less effective in patients taking methadone | • Discontinue laxative therapy prior to use  
• Need close proximity to toilet once administered  
• May be used concomitantly for length of opioid treatment  
• Monitor for signs of opioid withdrawal | • Discontinue laxative therapy prior to use  
• Take on an empty stomach and avoid grapefruit consumption  
• May be used concomitantly for length of opioid treatment  
• Monitor for signs of opioid withdrawal |
patients may benefit from opioid rotation—switching to an alternative µ-opioid agonist to take advantage of intraindividual variability in the analgesic and/or nonanalgesic effects of opioid medications.36,37 To ensure patient safety when substituting one opioid for another, prescribers must be well versed in best-practice recommendations, including appropriate reductions in the dose of the new agent to account for incomplete cross-tolerance, limitations inherent to equianalgesic dosing tables, overall health status, and the specific complexities of certain medications, especially methadone.36,38 Differences in the gastrointestinal risks of various opioid analgesics should also be considered; some evidence suggests that OIC is less common with more lipophilic molecules, such as fentanyl and buprenorphine, compared with other commonly prescribed opioids, such as morphine and oxycodone.19

Clinicians can also turn to new pharmacologic options for OIC therapy, especially when patient responses to the prescribed opioid are otherwise positive.39-43 There are currently 3 agents that have been approved by the FDA for the treatment of OIC: lubiprostone, methylnaltrexone, and naloxegol (Table 2).39-43 Lubiprostone activates chloride channels in gastrointestinal epithelial cells to promote fluid secretion into the intestinal lumen, whereas methylnaltrexone and naloxegol specifically target the cause of OIC by antagonizing the activation of peripherally localized µ-opioid receptors without interfering with the effects of opioid agonists in the central nervous system.42-44

The first peripherally-acting µ-opioid receptor antagonist (PAMORA) available in the United States was methylnaltrexone. This subcutaneously injected agent was originally approved by the FDA for the treatment of OIC in patients with noncancer pain who had not responded to standard nonpharmacologic treatment.45 The primary end point was the percentage of patients with ≥3 spontaneous bowel movements (SBMs) per week, during a 4-week period. Results from a double-blind, randomized, placebo-controlled, phase 3 clinical trial involving 312 patients showed that methylnaltrexone 12 mg once daily (n = 150) achieved the primary end point in 59% of patients compared with 38% of placebo-treated patients (n = 162) (Table 2).70

Table 2. Methylnaltrexone for the treatment of OIC.70

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients Achieving Primary End Point, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylnaltrexone 12 mg Once Daily</td>
<td>59%</td>
</tr>
<tr>
<td>Placebo</td>
<td>38%</td>
</tr>
</tbody>
</table>

4-week, double-blind, randomized, placebo-controlled, phase 3 clinical trial

Primary end point: Percentage of patients with ≥3 SBMs/wk, during 4-week period

Figure 2. Methylnaltrexone for the treatment of OIC.70,45

*Included all randomized patients who received ≥1 dose of double-blind study medication; bP < .001 vs placebo; N = 312 patients with chronic noncancer pain.

SBM was defined as a bowel movement with no laxative use within the prior 24 hours.
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approved by the FDA to treat OIC in patients with advanced illnesses, and has since received an expanded indication to include the management of OIC in opioid-treated adult patients with chronic noncancer pain.39,44 In a 4-week phase 3 trial, methylnaltrexone significantly increased the percentage of patients who experienced at least 3 spontaneous bowel movements (SBMs) per week without the help of traditional laxatives (Figure 2).39,45 The prescribing information for methylnaltrexone states that laxative therapy should be discontinued prior to injecting the medication.39,45 Methylnaltrexone can be administered once daily throughout the course of opioid therapy, provided it produces the desired results.39,44 Although as many as 4 methylnaltrexone doses may be required to produce clinically significant improvements in bowel function, the drug should only be injected when the patient has access to a nearby toilet because it may induce a bowel movement almost immediately after administration.39

Naloxegol is the other PAMORA approved by the FDA for the treatment of patients with OIC.40,43,46 This orally administered agent was examined in 2 identically designed, 12-week phase 3 clinical trials using a particularly rigorous primary end point—at least 3 SBMs per week and an increase in the number of SBMs compared with baseline for a minimum of 9 of the 12 study weeks and for at least 3 of the final 4 weeks.43 In both of these trials, the groups treated with naloxegol 25 mg daily achieved the primary end point, whereas the desired composite outcome was observed in patients taking naloxegol 12.5 mg daily in 1 of the 2 studies (Figure 3).43 As with methylnaltrexone, laxative therapy should be discontinued prior to naloxegol treatment, and the drug can be used as long as opioid therapy is required.40 Patients should be advised to take this oral PAMORA on an empty stomach. Moreover, because naloxegol is

![Response Rates in the Intent-to-Treat Population](image)

**Primary end point:** 12-week response rate (≥3 SBMs/wk and increase over baseline of ≥1 SBM for ≥9 of 12 weeks and ≥3 of the final 4 weeks)

*Naloxegol for the treatment of OIC.*43

*P <.05 vs placebo in each study; Study 04, N = 652; Study 05, N = 700 patients with noncancer pain. SBM was defined as a bowel movement with no laxative use within the prior 24 hours.
metabolized via the cytochrome P450 (CYP) pathway, patients should avoid drinking grapefruit juice or taking strong CYP3A4 inhibitors. If moderate CYP3A4 inhibitors (eg, diltiazem or erythromycin) are required, the naloxegol dose should be decreased to 12.5 mg once daily and patients should be closely monitored for AEs and withdrawal symptoms.40

The oral chloride-channel activator lubiprostone is approved by the FDA for patients with constipation-predominant irritable bowel syndrome, chronic idiopathic constipation, or OIC.41,42 In a 14-week phase 3 trial, lubiprostone was shown to be superior to placebo based on the change at week 8 from baseline in the weekly frequency of SBMs without the recent use of laxatives (Figure 4).42 Lubiprostone should be taken twice daily with food and water, and, if effective, can be used for the duration of opioid therapy.41 There is some evidence to suggest that lubiprostone is less effective for bowel dysfunction associated with methadone use; therefore, alternative therapies should probably be employed in patients treated with methadone.41

The 3 FDA-approved agents generally have favorable safety and tolerability profiles. Diarrhea, nausea, and abdominal distention were reported in at least 5% of patients treated with lubiprostone and more often with lubiprostone than with placebo.42 The most common AEs with methylnaltrexone (>5% of patients) include cramping and abdominal pain (typically mild to moderate), followed by nausea and diarrhea.39 AEs of naloxegol at the 25-mg dose included abdominal pain, diarrhea, nausea, flatulence, and upper abdominal pain (≥5% of patients). Most AEs were mild to moderate and occurred shortly after initiating naloxegol therapy.43 Safety data from a 52-week, open-label, parallel-group, phase 3 study were similar to the results
from the 12-week trials. Notably, because PAMORAs have been designed to prevent active drugs from entering the central nervous system, they should not induce centrally mediated opioid withdrawal in most patients. However, this may not hold true under special conditions or at particularly high dosages. No AEs indicative of opioid withdrawal were observed in the clinical trials, but conditions that compromise the blood–brain barrier such as epilepsy, Alzheimer disease, and traumatic brain injury may allow the medications to bind to central opioid receptors, antagonize the desired analgesic effects, and precipitate other symptoms of opioid withdrawal.

SUMMARY
In a carefully selected subset of patients with chronic pain, long-term opioid therapy can reduce pain levels, help patients achieve predefined functional goals, and improve quality of life. As the most common AE of prescription opioid analgesics, OIC can be a significant hurdle to positive patient outcomes and can impair treatment adherence. It is essential that clinicians who treat pain collaborate with their patients and other members of the healthcare team to tailor long-term opioid therapy and any required bowel regimen. The comprehensive plan of care should be individualized based on ongoing evaluations of symptoms, responses to therapy, and patient preference. If constipation symptoms persist despite attempts at laxative therapy, clinicians should consider newer FDA-approved agents for OIC treatment. A strong patient-clinician partnership facilitates ongoing monitoring of opioid-treated patients, including reassessment of bowel habits and reinforcing education on the importance of adhering to both pain management and bowel regimens, with the goal of safely and effectively providing pain relief and helping patients achieve their functional goals.

CASE: A 61-Year-Old Man With OIC Due to Use of Opioids for Osteoarthritis Pain

PRESENTATION
Stanley is a 61-year-old, retired high school teacher with osteoarthritis and ongoing pain in his right knee. Three years ago, the pain began restricting his mobility and forced him to retire early. Over-the-counter and prescription nonsteroidal anti-inflammatory drugs were not effective for his pain. Eventually, Stanley agreed to an opioid trial, and he now takes oxycodone extended-release (ER) 20 mg twice daily, which has improved his mobility over the last 2 years.

He presents to a new primary care clinician today, after moving to the area. Despite reporting no AEs from his opioids, specific queries about his bowel habits reveal that he finds it difficult to defecate since he started opioid therapy. He did not discuss this issue with his previous
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clinician. His medical records show he has adhered to his opioid treatment plan without any aberrant behaviors, but also contain no evidence that he was prescribed a prophylactic bowel regimen.

Bowel Function Assessment
- BFI score: 71
- Bristol Stool Form Scale: type 1 and type 2
- Infrequent, hard, lumpy stools that are accompanied by straining and mild to moderate pain

Clinical Decision Point
At what point after Stanley was initially prescribed opioids should his bowel habits have first been assessed?
A. At the office visit when opioids were first prescribed
B. After 2 weeks of opioid treatment
C. After 1 month of opioid treatment
D. After 6 months of opioid treatment

COMMENT
Patients should be asked about their bowel habits at the office visit when opioids are first prescribed and then reassessed at regular intervals thereafter. Correct answer: A

CASE (cont’d)
Stanley reports that he has increased his dietary fiber and drinks more water. On most days, he puts 2 tablespoons of psyllium in his morning orange juice. When he is very uncomfortable or has not defecated in days, Stanley skips his oxycodone ER for 1 or 2 days. This usually helps produce a bowel movement, but also results in his knee pain becoming unbearable.

At today’s appointment, Stanley is prescribed a laxative regimen consisting of 3 docusate sodium 100-mg tablets after breakfast and 3 bisacodyl 5-mg tablets before bed. At a 6-week follow-up appointment, Stanley reports that his constipation symptoms have somewhat improved. His BFI score is now 63 and he reports mostly type 2 stools on the Bristol Stool Form Scale. Nevertheless, despite some increase in the frequency of his bowel movements, Stanley has to strain to defecate and still experiences mild to moderate pain.

Clinical Decision Point
What would be your next step to help Stanley improve his bowel function?
A. Discontinue opioid therapy
B. Add 4 glasses of water daily to his current regimen, reassess in 1 month
C. Add 2 servings of dietary fiber and 4 glasses of water daily to his current regimen, reassess in 1 month
D. Prescribe an FDA-approved agent for treating OIC
COMMENT
Because a multimodal laxative regimen did not sufficiently improve Stanley’s constipation, it would be appropriate to consider prescribing an FDA-approved agent for the treatment of OIC. Correct answer: D

CASE CONCLUSION
Stanley should have been prescribed a prophylactic bowel regimen at the time his opioid therapy was initiated. Subsequent assessments of his bowel habits would have uncovered the development of OIC sooner, allowing the clinician to intensify therapy with a multimodal laxative regimen or an FDA-approved medication for OIC.

REFERENCES


**CLICK HERE TO COMPLETE THE EVALUATION AND SELF-ASSESSMENT QUESTIONS.**