To assist pharmacists and pharmacy technicians in understanding the role of linaclotide, lubiprostone, methylnaltrexone, and naloxegol in the treatment of constipation after traditional nonpharmacologic interventions and conventional laxatives such as bulking agents, osmotic laxatives, and stimulant laxatives have failed.

After participating in this activity, pharmacists will be able to:
> Discuss the different causes of constipation, including opioid induced constipation (OIC), chronic constipation, and constipation predominant irritable bowel syndrome (IBS-C)
> Define constipation according to Rome III and the American Gastroenterological Association criteria
> Identify the risk factors for constipation
> Review available OTC and prescription drug therapies for constipation, including mechanism of action, indications, side effects, onset of effect, duration of therapy, and clinical usage considerations
> Outline the pharmacist's role in providing recommendations to treat constipation, referral to a physician for inadequate response to OTC therapies and counseling patients to prevent the development of constipation

After participating in this activity, pharmacy technicians will be able to:
> Recall the basic definition of constipation
> Recall the risk factors for constipation
> List available OTC and prescription drug therapies for constipation
> Recognize when to refer patients to the pharmacist for recommendations on constipation management.

Educational Objectives

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in the knowledge-based activity, and will receive up to 0.2 CEUs (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor within 72 hours of submission.

AO#C: To assist pharmacists and pharmacy technicians in understanding the role of linaclotide, lubiprostone, methylnaltrexone, and naloxegol in the treatment of constipation after traditional nonpharmacologic interventions and conventional laxatives such as bulking agents, osmotic laxatives, and stimulant laxatives have failed.

During the development of this activity, all relevant financial relationships were reviewed and managed to ensure there was no actual or potential conflict of interest. The faculty have disclosed that they have no significant conflicts of interest, including no relevant financial interest in, or ownership of, any commercial products, supplies, equipment or devices discussed in this program and no并在使用此类药物时存在的并发症。

Disclosure of Discussions of Off-Label and Investigational Uses of Drugs: This activity may contain discussion of unlabeled/unapproved use of drugs in the United States and will be noted if it occurs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of Drug Topics or University of Connecticut School of Pharmacy. Please refer to the official information for each product for discussion of approved indications, contraindications, and warnings.

Faculty: Trinh Pham, PharmD, BCOP
Dr. Pham is an associate clinical professor at the University of Connecticut, School of Pharmacy, Storrs, Conn.

Abstract

Constipation is a common medical problem that can affect patients’ quality of life and ability to function. Patients who are constipated most likely seek treatment first by using over-the-counter products and then by visiting their physician if self-treatment was not effective. In recent years, a number of drugs with novel mechanisms of action have been made available for the treatment of constipation, including linaclotide, lubiprostone, methylnaltrexone, and naloxegol. This review will discuss the role of these new agents after treatment failure with conventional laxatives for the treatment of the three most common types of constipation: chronic idiopathic constipation, irritable bowel syndrome with constipation, and opioid-induced constipation.
Constipation is a common medical problem that affects patients’ quality of life and interferes with daily functioning and well-being. Patients with constipation suffer physical and mental discomfort, they are frustrated from lack of effective therapies, and fear their symptoms will relapse. Furthermore, constipation affects their well-being and interferes with activities of daily living. Chronic idiopathic constipation (CIC), irritable bowel syndrome with constipation (IBS-C), and opioid-induced constipation (OIC) are the three most common types of constipation diagnoses. The estimated prevalence rates of CIC and IBS-C in the United States are 14% (~42 million individuals) and 5% (~15 million individuals), respectively. For OIC, it is estimated that 40% to 90% of patients who use opioids to treat pain experience constipation as a side effect of the opioid. Approximately 4% (~12 million people) of adults in the United States take chronic opioids; thus, 5 to 11 million individuals may have OIC. Approximately 29% to 34% of patients with constipation seek medical care for self-reported constipation, and 7.2% seek care from pharmacists.

Constipation-related symptoms account for 2.5 million physician office visits annually, with 85% of these visits resulting in a drug prescription. More than $500 million is spent on laxatives each year. These numbers underscore the fact that drugs contribute significantly to the healthcare costs of treating constipation. The past 10 years have seen significant developments in the treatment of CIC, IBS-C, and OIC, and several new drugs with novel mechanisms of action have received approval from the Food and Drug Administration (FDA) over the past five years. These new agents include linaclootide, lubiprostone, naxegol, and methylnaltrexone. This article will review the mechanisms of action and side effects of these agents and discuss when these agents should be used to treat patients diagnosed with CIC, IBS-C, or OIC.

**Definition of constipation**

Appropriate treatment of constipation relies on the accurate diagnosis since the pathophysiology determines how the constipation may best be treated. For example, the mechanism of OIC is distinctly different from that of CIC and IBS-C, and so drugs that work for OIC may not be effective for CIC and IBS-C.

Constipation can result from disturbances in colonic motility and/or problems related to defecating. Constipation can be classified as primary or secondary constipation. Primary constipation may be idiopathic or functional and is divided into three categories: normal-transit constipation, slow-transit constipation, or pelvic floor disorder.

Secondary constipation can be caused by an organic disease (i.e., stroke, colorectal cancer, hypothyroidism) or medications (e.g., anticholinergics, antidepressants, anticonvulsants).

There is no standardized definition for OIC. A multidisciplinary consensus group of experts proposed defining OIC as a change from baseline bowel habits upon initiation of opioids. OIC is characterized by reduced bowel movement frequency, development of constipation symptoms will relapse. Furthermore, constipation affects patients’ quality of life and interferes with activities of daily living.1 Chronic idiopathic constipation (CIC), irritable bowel syndrome with constipation (IBS-C), and opioid-induced constipation (OIC) are the three most common types of constipation diagnoses. The estimated prevalence rates of CIC and IBS-C in the United States are 14% (~42 million individuals) and 5% (~15 million individuals), respectively.2,3 For OIC, it is estimated that 40% to 90% of patients who use opioids to treat pain experience constipation as a side effect of the opioid. Approximately 4% (~12 million people) of adults in the United States take chronic opioids; thus, 5 to 11 million individuals may have OIC.4,5 Approximately 29% to 34% of patients with constipation seek medical care for self-reported constipation, and 7.2% seek care from pharmacists.1 Constipation-related symptoms account for 2.5 million physician office visits annually, with 85% of these visits resulting in a drug prescription. More than $500 million is spent on laxatives each year. These numbers underscore the fact that drugs contribute significantly to the healthcare costs of treating constipation. The past 10 years have seen significant developments in the treatment of CIC, IBS-C, and OIC, and several new drugs with novel mechanisms of action have received approval from the Food and Drug Administration (FDA) over the past five years. These new agents include linaclootide, lubiprostone, naxegol, and methylnaltrexone. This article will review the mechanisms of action and side effects of these agents and discuss when these agents should be used to treat patients diagnosed with CIC, IBS-C, or OIC.

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Similarly, the Rome III diagnostic criteria are used to define CIC and IBS-C, which are also considered to be functional constipation. CIC is defined as the presence of ≥ 2 of the following for ≥ 25% of defecations for ≥ 3 months with symptom onset ≥ 6 months before diagnosis: straining, lumpy or hard stools, sensation of incomplete evacuation, sense of anorectal obstruction/blockage, manual maneuvers to facilitate defecation. Additionally, loose stools are rarely present without laxatives and criteria for IBS-C is not fulfilled. IBS-C is defined as recurrent abdominal pain or discomfort ≥ 3 days per month in the last 3 months, with symptom onset ≥ 6 months before diagnosis, and with ≥ 2 of the following: improvement with defecation, onset associated with a change in stool frequency, onset associated with a change in stool form.

**The BSFS is a useful visual tool that describes stool consistency and form and can facilitate the discussion on bowel function.**

The Bristol Stool Form Scale (BSFS) is a useful visual tool that describes stool consistency and form and can facilitate the discussion with patients. 

**Assessment of constipation**

Because constipation is generally a symptom-based diagnosis, in addition to performing a physical examination, clinicians should obtain a thorough history to diagnose and treat patients appropriately. The ideal history includes the patient’s perception of his or her bowel pattern and a description of stool frequency, stool form, and ease of stool passages. Educating patients so that they understand how to describe their normal bowel patterns and changes in bowel patterns is an essential first step in discussing how to recognize constipation. For patients who take opioids for pain management, this discussion by all healthcare providers, including pharmacists, should occur when opioids are first prescribed. This establishes a baseline of current bowel function and can be used as a reference for any changes in bowel pattern after initiation of the opioid.

A discussion of bowel patterns and habits may be embarrassing and uncomfortable for some patients. The Bristol Stool Form Scale (BSFS) is a useful visual tool that describes stool consistency and form and can facilitate this discussion with patients. 

Similarly, the Bowel Function Index (BFI) is a practical, rapid, validated tool that was developed to facilitate assessment of OIC. This tool asks patients three questions regarding the ease of defecation, feeling of...
incomplete bowel evacuation, and personal judgment regarding constipation. Each question is rated on a visual analog scale from 0 to 100, with 0 representing no difficulty and 100 representing severe difficulty. The overall score is an average of the response to the three questions. A change in score of ≥12 points suggests a clinically meaningful change in constipation symptoms. A multidisciplinary panel of 10 experts with extensive knowledge of opioid-associated adverse events convened to discuss and evaluate an optimal symptom-based tool for assessing OIC for the American Academy of Pain Medicine.\textsuperscript{13} This panel recommended the use of the three-item BFI because of its simplicity and its validated threshold of clinically significant constipation.\textsuperscript{13} Based on this consensus, the expert panel recommends that patients on opioids for pain management should complete the BFI.\textsuperscript{13} Further, it suggests that prescription treatments for OIC should be considered for patients with BFI scores of ≥30 points and an inadequate response to first-line interventions for OIC.\textsuperscript{13}

**Efficacy and safety data of new agents for the treatment of constipation**

**Prosecretory agents that act on chloride channels**

Linaclotide and lubiprostone are newer secretory laxatives that activate chloride channels. These agents have distinct mechanisms of action, thus offering two unique new drug classes for the treatment of constipation.

Linaclotide is a first-in-class drug that activates the guanylate cyclase-C (GC-C) receptor on the lumen of intestinal epithelial cells. This opens the cystic fibrosis transmembrane regulator (CFTR) chloride channel to secrete chloride ions and water into the lumen, which leads to increased colonic transit.\textsuperscript{14} FDA approval of linaclotide for the treatment of CIC was based on the results of two phase 3 randomized, placebo-controlled trials.\textsuperscript{15} The primary endpoint in the clinical trials was defined as both ≥3 complete spontaneous bowel movements (CSBM) per week and an increase from baseline of at least one CSBM per week for ≥9 of 12 weeks. Patients received daily doses of 145 mcg versus 290 mcg versus placebo. The results of the two trials showed that the primary endpoints were achieved in 16% and 21% of patients receiving 145 mcg linaclotide daily and 19.4% and 21.3% of patients receiving 290 mcg daily compared to only 3.3% and 6% of patients receiving placebo. Improvements in stool consistency (P < 0.001), straining severity (P < 0.001), abdominal discomfort (P < 0.001 to 0.04), bloating (P < 0.001 to 0.006), and constipation severity (P < 0.001) were significantly greater with both doses of linaclotide than with placebo. Discontinuation of linaclotide did not worsen CIC symptoms.\textsuperscript{15}

FDA approval of linaclotide for the treatment of IBS-C was also based on the results of two phase 3 randomized, double-blind, placebo-controlled trials.\textsuperscript{16,17} One trial was a 12-week study and the other was 26 weeks. These trials assessed responses to primary endpoints that lasted for nine out of 12 weeks. These primary endpoints included improvements in abdominal pain intensity (reduction of ≥30% from baseline in average daily worst pain score) and stool frequency (increase of at least one CSBM per week from baseline), as specified by an FDA guidance issued in 2012 for the evaluation of drug efficacy in treating IBS-C.\textsuperscript{16} A CSBM is defined as a BM that occurs in the absence of any laxative, enema, or suppository and accompanied by a feeling of complete evacuation.\textsuperscript{16} In these two trials, 33.6% and 33.7% of patients treated with linaclotide achieved the primary endpoints compared with 21% and 13.9% of patients in the placebo group (P < 0.0001).\textsuperscript{16,17} The attrition rate for all patients was 19.4% and 25.6% at weeks 12 and 26, respectively, for both studies. The percentage of patient attrition attributed to side effects was 7.8% and 10.1% for patients receiving linaclotide compared to 2.5% in both studies for patients on placebo. Attrition due to perceived lack of efficacy was 1.2% and 3.7% for patients on linaclotide compared to 1% and 8% for patients on placebo. In the 12-week treatment trial, patients were also randomized to a 4-week withdrawal period at the end of the 12 weeks.\textsuperscript{17} Discontinuation of linaclotide did not cause worsening of IBS-C symptoms compared to baseline; however, abdominal pain did recur, and CSBM decreased to levels similar to the placebo group in the initial 12-week treatment period.

Lubiprostone is an analog of prostaglandin E1 that binds to and directly activates the chloride channel type 2 (ClC-2), which are cell-membrane bound protein pores involved in chloride secretion, in addition to activating CFTR chloride channels. This increases chloride secretion and leads to passive secretion.

**TABLE 1**

<table>
<thead>
<tr>
<th>Bristol Stool Form Scale</th>
<th>Slow transit</th>
<th>Type 1</th>
<th>Separate hard lumps</th>
<th>Hard, impacted stool; constipation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type 2</td>
<td>Sausage-like but lumpy</td>
<td>Considered normal stool; optimal because stool is easy to pass</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type 3</td>
<td>Sausage-like but with cracks in the surface</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type 4</td>
<td>Smooth and soft</td>
<td>May indicate diarrhea and urgency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type 5</td>
<td>Soft blobs with clear-cut edges</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type 6</td>
<td>Fluffy pieces with ragged edges, a mushy stool</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type 7</td>
<td>Watery, no solid pieces; entirely liquid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fast transit

Type 1

Type 2

Type 3

Type 4

Type 5

Type 6

Type 7

Form available at http://bowelcontrol.nih.gov/Bristol_Stool_Form_Scale_508.pdf. Source: Ref 11

**Prescription treatments for OIC should be considered for patients with BFI scores ≥30 and an inadequate response to first-line interventions.**
of sodium, water, and isotonic fluid into the intestinal lumen.\textsuperscript{18} Lubiprostone is poorly absorbed by the gut, and the serum concentration of this agent is too low to quantify. The drug has been evaluated in patients with CIC, IBS-C, and OIC.

The efficacy and safety of lubiprostone in adults with CIC were evaluated in two 4-week, phase 3, double-blind, randomized, placebo-controlled trials.\textsuperscript{19,20} The primary endpoint defined by the study was the number of SBMs during the first week of therapy. The primary endpoint was achieved in 5.69% and 5.89% of patients receiving lubiprostone 24 mcg twice daily compared to 3.46% and 3.99% of patients on placebo. The secondary endpoints were significantly improved with lubiprostone at all weeks compared to placebo and include: SBMs at weeks 2, 3, 4, stool consistency (P < 0.001), straining (P = 0.0003 to < 0.0001), and constipation severity (P < 0.0003 to 0.0265). Nausea was more common in patients receiving lubiprostone compared to placebo group (38% and 25% vs 4% and 5%). Headache was the second most common side effect for the lubiprostone group (14% and 6%) compared to placebo (7% and 3%).

The FDA approval of lubiprostone for the treatment of IBS-C in women was based on the combined results of two phase 3 randomized, placebo-controlled clinical trials and one 36-week, open-label extension study.\textsuperscript{21,22} The FDA did not deem that efficacy was demonstrated in men because only 8% of patients in the clinical trials were male. The primary endpoint of the two phase 3 studies was overall responder status calculated from weekly assessments of symptom relief. A patient was considered a monthly responder if: the symptoms were at least moderately relieved for all 4 weeks within the month, or significantly relieved for at least 2 weeks within the month. Patients receiving lubiprostone 8 mcg twice daily had a significantly higher overall response compared to placebo (17.9% vs 10.1%) over 12 weeks of treatment (P=0.001). The primary objective of the open-label extension study was assessment of long-term safety and tolerability.\textsuperscript{22} Diarrhea (11%) and nausea (11%) were the most common treatment-related adverse effects.\textsuperscript{22}

The efficacy of lubiprostone 24 mcg twice daily versus placebo in patients with OIC and chronic noncancer pain was established in two randomized clinical trials.\textsuperscript{23,24} Lubiprostone was shown to lead to a significantly greater mean change in the frequency of spontaneous bowel movements (SBM) from baseline (P=0.001 to 0.004) and a shorter median time to first SBM compared to placebo (P=0.004). The most common side effects with lubiprostone were diarrhea (9.6% - 11.3%), abdominal pain/distention (7.1% - 8.2%), and vomiting (4.2%).\textsuperscript{23,24}

**Peripherally acting mu-opioid receptor antagonists**

The peripherally acting mu-opioid receptor antagonists (PAMORAs) methylnaltrexone (MNTX) and naloxegol require a prescription and are not laxatives by definition. These agents reverse constipation caused by the binding of opioid receptor agonists to enteric neuron mu receptors widely expressed throughout the gastrointestinal tract; this binding between opioid receptor agonists and neuron mu receptors impairs peristalsis and intestinal secretions and increases luminal fluid reabsorption, leading to constipation.

In 2008, MNTX subcutaneous injection was the first PAMORA to be approved by the FDA for the treatment of OIC in patients with advanced illness in whom laxative therapy failed. In 2014, this agent was also approved for the treatment of OIC in patients with chronic noncancer pain. Two multicenter, randomized, controlled trials of MNTX evaluated the occurrence of laxation within four hours after the first dose in patients with advanced illness.\textsuperscript{25,26} These patients had received opioids for at least two weeks and laxatives for at least three days without relief of OIC. Laxation was achieved within four hours in 48% of patients receiving 0.15 mg/kg of subcutaneous MNTX versus 15% of patients receiving placebo and in 62% and 58% of patients receiving MNTX 0.15 mg/kg and 0.3 mg/kg, respectively versus 14% of patients receiving placebo. The efficacy of MNTX for OIC in patients with chronic noncancer pain was assessed in a phase 3, placebo-controlled, four-week study. Patients received either subcutaneous MNTX 12 mg once daily or every other day or placebo. Within the first four hours, 34% of patients treated with either dosing regimen of MNTX achieved a rescue medication-free bowel movement (RFBM) versus 10% of patients treated with placebo.\textsuperscript{27}

Naloxegol is a polymer conjugate of naloxone. In 2014, naloxegol became the first orally administered PAMORA approved by the FDA for the treatment of OIC in patients with noncancer pain. Two identical phase 3 randomized controlled trials evaluated naloxegol 12.5 mg and 25 mg versus placebo in patients with chronic, noncancer pain.\textsuperscript{4} The primary endpoint was the 12-week response rate of at least three SBM per week, an increase from baseline of at least one SBM per week for at least nine of 12 weeks and for at least three of the final four weeks. The response rate was higher with the 25 mg dose (40% and 44% for the two trials) versus placebo (29.4%). Naloxegol 12.5 mg daily was significantly greater in only one of the studies with a response of 40.8% (P < 0.05); whereas the study with a response of 34.9% did not show statistical significance compared to placebo.

Alvimopan, another PAMORA agent, is FDA approved to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis. It is not FDA approved for the treatment of OIC because of the high incidence of myocardial infarction with this agent in trials of patients receiving opioids for noncancer pain.\textsuperscript{28}
Side effects and administration considerations for new agents for the treatment of constipation Linacotide. Linacotide has minimal systemic exposure after oral administration. It is rapidly converted in the small intestine to a metabolite that has a half-life of 10 minutes, and 3% to 5% of the oral dose is excreted in the feces. This agent has demonstrated an antinoceptive or analgesic effect in various animal models of pain, which may translate to improvements in abdominal pain symptoms in patients with IBS-C. Among side effects occurring within the first four weeks of treatment initiation, diarrhea was the most frequently reported in phase 3 clinical trials (14.2% to 19.7% compared to 2.5% to 5% with placebo). Other side effects included abdominal pain and distention, flatulence, and headache. Linacotide has a boxed warning regarding its use in pediatric patients aged six to 17 years because of observed cases of dehydration and death in young juvenile mice. This agent is also contraindicated in children aged less than six years and in patients with mechanical gastrointestinal obstruction. Linacotide has a category C rating for pregnancy. It is not expected to enter breast milk, and renal and hepatic impairment does not affect dosing because of minimal systemic absorption. Linacotide should be taken 30 minutes before the first meal of the day, as the presence of food may result in looser stools. There are no drug interactions with linacotide.18

Lubiprostone. Nausea was the most common adverse event seen in patients treated with lubiprostone in phase 3 trials (32%). Other gastrointestinal symptoms included diarrhea (11%), abdominal distention (6%), abdominal pain (5%), and flatulence (4%). Administration of lubiprostone with a meal may reduce the risk of nausea. Mechanical gastrointestinal obstruction is the only contraindication to lubiprostone treatment. Even though this agent is similar to a prostaglandin analog that is considered to be an abortifacient, lubiprostone has a category C pregnancy rating because it has limited systemic exposure. Breastfeeding women should use lubiprostone with caution, and infants of breastfeeding mothers should be monitored for the occurrence of diarrhea. Lubiprostone is metabolized by the cytochrome P450 system, but drug interaction is unlikely because of its minimal systemic absorption. Methadone decreases ClC-2 activation and may reduce the efficacy of lubiprostone; therefore, lubiprostone should not be used in patients with OIC from methadone. Dose adjustment is recommended for patients with moderate or severe hepatic impairment (Child-Pugh class B or C) but not for patients with renal impairment.18,29

MNTX. This agent is a weak CYP2D6 inhibitor with no significant drug interactions. Abdominal pain (17%), flatulence (13%), vomiting (13%), nausea (11%), dizziness (8%), and diarrhea (6%) are the most common side effects with MNTX in phase 3 clinical trials.26-28 MNTX is contraindicated in patients with bowel obstruction, diarrhea, or acute abdominal conditions. This agent does not cross the blood-brain barrier and has not been observed to reverse analgesia or cause symptoms of opioid withdrawal. The recommended dose is 8 mg in patients weighing 38 to 61 kg and 12 mg in patients weighing 62 to 114 kg; a dose of 0.15 mg/kg should be used for patients outside of these weight ranges. After one dose of MNTX, a bowel movement occurs within four hours in 50% to 60% of patients. The dose may be given every other day if no therapeutic effect is observed with the first dose. No dose adjustment is required in patients with mild to moderate hepatic impairment, but the dose should be reduced by 50% in patients with creatinine clearance <30 mL/min. MNTX is not recommended for patients with end-stage renal impairment requiring dialysis or for those with severe hepatic impairment.29

Naloxegol. Abdominal pain (8.5% - 10%) and diarrhea (3.3% - 9.3%) were common in phase 3 trials of naloxegol.4 Opioid withdrawal occurred in less than 5% of patients in all studied groups and was comparable to the rates of withdrawal seen with placebo or usual care. For OIC caused by methadone, this agent is preferred over lubiprostone. Naloxegol 25 mg should be taken one hour before or two hours after the first meal of the day. The dose may be reduced to 12.5 mg if the 25-mg dose is not tolerated. Patients with creatinine clearance <60 mL/min and those who require treatment with moderate CYP3A4 inhibitors should begin naloxegol treatment at 12.5 mg and increase to 25 mg as tolerated. This agent is contraindicated in patients being treated with a strong CYP3A4 inhibitor.30

Stepwise approach to treating CIC, IBS-C, and OIC
Pharmacists must understand the possible causes and underlying mechanisms of constipation symptoms to determine the appropriate treatment approach and recommendation. Organic causes of secondary constipation such as colorectal cancer are managed by treating the underlying disease. The pharmacist should assess the patient for “red flags” that raise suspicion of an underlying organic disease. The patients should be asked the following questions: have you had a sudden change in bowel habits, do you have a family history of colon cancer, do you see blood in your stool or blood from your rectum after a bowel movement, do you have recent unexplained weight loss, do you have a fever, vomiting, rectal or abdominal pain? If the patient answers yes to any of these questions, he or she should be referred to a physician for further work-up and evaluation.2 The patient should also be asked how long he or she had the constipation symptoms, if the patient experiences straining, sensation of incomplete evacuation, or the need for digital removal of the stool. If the patient had the symptoms for more than 7 days or answers yes to these questions, he or she should also be referred to a physician. The pharmacist can introduce the patient to the BSFS at this point to help the patient describe the stool form and ease of stool passage. Drug-induced constipation is another major cause of constipation; therefore, the pharmacist should review the patient’s medication history. If the pharmacist identifies that the patient is on a drug or drugs that can cause constipation, the pharmacist can provide this list of constipating drugs to the patient to provide to his/her physician. The pharmacist should inform the patient that the physician may consider discontinuation of the offending agent if it is safe for the patient or another agent with fewer or no constipating effects may be substituted. The pharmacist can also request the patient to complete the BFI at the time of opioid initiation and/or at the time of assessment of constipation to establish the patient’s baseline bowel function and, in cases of opioid treatment, ensure that the
AN OVERVIEW OF TREATMENT OPTIONS FOR CONSTIPATION

PAUSE AND PONDER

Is there a role for over-the-counter laxatives for the treatment of IBS-C or CIC?

———

of stools per week compared with placebo in patients with CIC. The efficacy of fiber has not been demonstrated in patients with OIC. However, fiber is inexpensive, nontoxic, and readily available, making it worthwhile to attempt a brief trial period with fiber despite the lack of data for its efficacy in these patients, with the caveat that it may not be as effective and can worsen the problem for patients with slow-transit constipation. Educating patients to distinguish between soluble and insoluble fibers is useful, as soluble fiber causes less cramping and bloating and is more effective than insoluble fiber for constipation. Soluble fiber is found in barley, flax, oats, certain fruits and vegetables, and supplements such as psyllium, methylcellulose, and calcium polycarbophil. Examples of foods containing insoluble fiber include wheat bran, whole grains, corn fiber, skin on fruits and vegetables, seeds, and nuts. Fiber requires adequate water intake to be effective; otherwise, constipation symptoms can be exacerbated. A gradual increase of fiber supplement intake every seven to 10 days up to three times daily is recommended to minimize bloating. Patients should also be counseled that response will not be immediate and so they should remain on the regimen for several weeks before declaring therapy failure.

If patients do not respond to the conservative, nonpharmacologic approach after several months of therapy, it is reasonable to initiate treatment with an osmotic laxative and/or a stimulant as the next step. The American College of Gastroenterology conducted a series of systematic reviews of therapy in IBS and CIC and found no evidence for the efficacy of osmotic or stimulant laxatives for the treatment of IBS-C. The group did strongly recommend using polyethylene glycol (PEG), lactulose, and bisacodyl in patients with CIC, as these agents have been shown to be effective in improving symptoms from CIC even though the quality of evidence was low for lactulose and moderate for bisacodyl (but high for PEG). The American Gastroenterological Association Technical Review in Constipation recommended the use of PEG over lactulose because a Cochrane Database review of 10 randomized trials comparing PEG and lactulose found that PEG was superior for improving stool frequency, stool consistency, and abdominal pain. Furthermore, lactulose requires a prescription and may cause more bloating and cramping than PEG. The American Gastroenterological Association also prefers PEG over stimulant laxatives because of more evidence of short- and long-term efficacy for osmotic agents. Thus, the final recommendation is that an osmotic agent may be used regularly for CIC, with PEG being the preferred product, and a stimulant laxative may be used as a rescue or add-on agent if PEG is not effective.

Consensus statements for OIC and clinical guidelines for the use of opioids in chronic cancer or noncancer pain all recommend the use of nonpharmacologic conservative therapy and conventional laxatives for the prophylaxis and management of OIC, even though there is little evidence to support the efficacy of these treatment approaches. The National Comprehensive Cancer Network recommends the use of sennoside (laxative) with or without a stool softener or PEG while the patient maintains adequate intake of fluids and dietary fiber. The administration of docusate (stool softener) is optional because one study showed that the addition of docusate to the sennoside laxative was less effective than sennoside administered alone. Laxatives should be titrated to achieve one nonforced bowel movement every one to two days.

When conventional laxatives are not effective for treating constipation, after several months of trial period, the use of prescription agents such as lubiprostone and linaclotide is indicated for IBS-C and CIC. There is a strong recommendation from the American College of Gastroenterology for the use of linaclotide and lubiprostone for IBS and
KEEPS YOUR PATIENTS “MOVING”

**TABLE 2**

<table>
<thead>
<tr>
<th>Medications Commonly Used to Treat Constipation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HYPERSMOLAR AGENTS</strong></td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
</tr>
<tr>
<td><strong>Side effects/comments</strong></td>
</tr>
<tr>
<td>Lactulose</td>
</tr>
<tr>
<td>Undergoes bacterial enzymatic degradation in the colon to carbon dioxide, lactic acid, and acetic acid, which causes acidification of fecal pH, producing an osmotic and fermentative diarrhea</td>
</tr>
<tr>
<td>• 15-30 mL once or twice daily</td>
</tr>
<tr>
<td>• Solution may be more palatable when mixed with fruit juice, water, or milk</td>
</tr>
<tr>
<td>• Onset of effect: 24-48 hours</td>
</tr>
<tr>
<td>• Flatulence, abdominal discomfort, cramping</td>
</tr>
<tr>
<td>Polyethylene glycol 3350 (OTC) (Miralax®)</td>
</tr>
<tr>
<td>Osmotically increases intraluminal fluid</td>
</tr>
<tr>
<td>• 17 g (1 heaping tablespoon) once or twice daily (powder) in 8 ounces of water</td>
</tr>
<tr>
<td>• Onset of effect: 0.5-1 hour</td>
</tr>
<tr>
<td>• Flatulence, nausea, diarrhea</td>
</tr>
</tbody>
</table>

**STIMULANTS**

| Bisacodyl (OTC) (Dulcolax®)                  |
| Inhibits water resorption and stimulates secretion and motility of small intestine and colon through the sensory nerve endings of colon mucosa |
| • 10-15 mg by mouth and 10-mg suppository up to 3 times per week |
| • Onset of effect: 0.25-1 hour               |
| • Gastric or rectal irritation              |

| Semisides (OTC) (Senokot®)                  |
| Increases electrolyte transport into the bowel and stimulates intestinal motility |
| • 2 tablets once daily to 4 tablets twice daily |
| • Onset of effect: 8-12 hours               |
| • No association with myenteric nerve damage |

**STOOL SOFTENERS**

| Docusate (OTC) (Colace®)                    |
| Decreases the surface tension to lubricate and soften fecal matter |
| • 50-400 mg daily                          |
| • Onset of effect: 12-72 hours             |
| • Requires fluid intake; bitter taste     |

**PROSECRETORY AGENTS**

| Linaclotide                                  |
| Stimulates secretion of chloride into the intestinal lumen, resulting in increased intestinal fluid and accelerated transit |
| • IBS-C: 290 mcg by mouth once daily         |
| • CIC: 145 mcg by mouth once daily          |
| • Take on an empty stomach at least 30 minutes before the first meal of the day |
| • Diarrhea common                           |
| • Metabolism and excretion not affected in cases of hepatic or renal impairment |
| • No drug interactions                      |

| Lubiprostone                                 |
| Activates type 2 chloride channels in the intestine, causing fluid secretion and motility |
| • IBS-C: 8 mcg by mouth twice daily          |
| • CIC and OIC: 24 mcg by mouth twice daily |
| • Take with food and water to decrease risk of nausea |
| • Nausea common                             |
| • Requires dose adjustment in cases of hepatic impairment |
| • Effectiveness with methadone OIC not established |

**PERIPHERALLY ACTING MU OPIOID RECEPTORS**

| Methylnaltrexone                            |
| Blocks mu-opioid receptor peripherally in the gastrointestinal tract |
| OIC: Patients >50 kg: 12 mg SC every other day |
| Patients <50 kg: 8 mg SC every other day      |
| • Abdominal pain, flatulence, nausea, vomiting |

| Naloxegol                                   |
| Blocks mu-opioid receptor peripherally in the gastrointestinal tract |
| OIC: 25 mg daily on empty stomach ≥1 hour before or 2 hours after the first meal of the day |
| • Maintenance laxatives should be discontinued before initiation of naloxegol |
| • Laxative can be used as needed if there is a suboptimal response to naloxegol after 3 days |

Abbreviations: OIC, idiopathic opioid constipation; CIC, idiopathic constipation; IBS-C, irritable bowel syndrome with constipation; OTC, over-the-counter; SC, subcutaneous. Source: Ref 34,40-42

CIC based on high and moderate quality of evidence. However, linaclotide and lubiprostone were evaluated versus placebo; no comparative studies between the two agents or between these agents and the standard, conventional treatment have been performed, making it difficult to determine the place of each agent in the treatment algorithm for CIC and IBS-C. The American Gastroenterological Association states that for patients with IBS-C who place a high value on avoiding diarrhea or the high out-of-pocket expenses associated with linaclotide, an alternative agent to linaclotide should be considered. For patients who wish to avoid nausea or the high out-of-pocket expenses associated with lubiprostone, an alternative agent to lubiprostone should be considered.

Conventional laxative therapy fails for 54% of patients with OIC. Lubiprostone, MNTX, and naloxegol are indicated for the treatment of OIC in these patients. The decision regarding which drug to choose is based on the route of administration, the side effect profiles of the agents, and whether the constipation is truly caused by the opioid or is constipation that predates opioid administration.
Lubiprostone is safer in patients with renal impairment or receiving therapy with a moderate or strong CYP3A4 inhibitor. Naloxegol is safer in patients with hepatic impairment. If opioid use is the most likely cause of constipation, MNTX or naloxegol is indicated as first-line therapy when contraindications are ruled out. Naloxegol may be preferred over MNTX because it is available for oral administration, and most patients may not want to self-inject with subcutaneous MNTX. If the PAMORA does not relieve constipation after a significant amount of time (1 to 2 months of therapy), lubiprostone may be tried next. On the other hand, if opioid use is ruled out as the cause for constipation in a patient who is taking opioids for pain management, then lubiprostone may be preferred as first-line therapy after failure of conventional laxatives. If a patient already had signs and symptoms of constipation prior to initiation of the opioid, it is reasonable to assume that the opioid may not necessarily be the cause of the constipation. Lubiprostone may not be effective in a patient with OIC caused by methadone; therefore, naloxegol or MNTX should be used in these patients. According to the multidisciplinary panel of 10 experts with extensive knowledge of opioid-associated adverse events who developed consensus recommendations on OIC assessment for the American Academy of Pain Medicine, the use of a PAMORA or lubiprostone is recommended in patients with BFI scores of ≥30 points and an inadequate response to first-line interventions.13 When lubiprostone or a PAMORA is initiated, preexisting scheduled as-needed laxatives should be discontinued, and other healthcare providers such as pharmacists. The treatment of constipation is multifaceted and requires the implementation of multiple strategies both concurrently and in a stepwise algorithmic approach. Pharmacists can play an integral role in helping patients with constipation by promoting lifestyle changes; counseling on the use of conventional and novel laxative products; and providing information on side effects, drug interactions, and when to expect a response to therapy. Pharmacists may also educate patients on how to recognize the signs and symptoms of constipation through the use of the BSFS and should remind patients to allow enough time for the laxative to work before declaring it ineffective. Most significantly, pharmacists can perform a comprehensive medication review with patients and provide documentation for drugs that may cause constipation; patients can share this information with their primary care provider to instigate consideration of changing to an alternative drug that does not cause constipation. Pharmacy technicians may facilitate the management of constipation by ensuring that the appropriate prescription drug with the appropriate dose is prescribed for patients with CIC, IBS-C, or OIC when reviewing the prescription presented by a patient. If the technician notices a significant discrepancy with the dose or the specific agent for type of constipation, the pharmacist should be alerted so that he or she can contact the prescriber to clarify the prescription. The pharmacy technicians may also refer patients to the pharmacist for constipation counseling if they notice patients are purchasing over-the-counter laxatives such as polyethylene glycol (Miralax®), sennosides (Senokot®), bisacodyl (Dulcolax®), docusate sodium (Colace®), or sennosides plus docusate (Senokot-S®, Peri-Colace®).

**When should the discussion of bowel function be initiated for a patient who is prescribed an opioid for pain management?**

**Take-home message**

Constipation is a common complaint that prompts individuals to seek medical care from primary care providers, gastroenterologists, and other healthcare providers such as pharmacists. The treatment of constipation is multifaceted and requires the implementation of multiple strategies both concurrently and in a stepwise algorithmic approach. Pharmacists can play an integral role in helping patients with constipation by promoting lifestyle changes; counseling on the use of conventional and novel laxative products; and providing information on side effects, drug interactions, and when to expect a response to therapy. Pharmacists may also educate patients on how to recognize the signs and symptoms of constipation through the use of the BSFS and should remind patients to allow enough time for the laxative to work before declaring it ineffective. Most significantly, pharmacists can perform a comprehensive medication review with patients and provide documentation for drugs that may cause constipation; patients can share this information with their primary care provider to instigate consideration of changing to an alternative drug that does not cause constipation. Pharmacy technicians may facilitate the management of constipation by ensuring that the appropriate prescription drug with the appropriate dose is prescribed for patients with CIC, IBS-C, or OIC when reviewing the prescription presented by a patient. If the technician notices a significant discrepancy with the dose or the specific agent for type of constipation, the pharmacist should be alerted so that he or she can contact the prescriber to clarify the prescription. The pharmacy technicians may also refer patients to the pharmacist for constipation counseling if they notice patients are purchasing over-the-counter laxatives such as polyethylene glycol (Miralax®), sennosides (Senokot®), bisacodyl (Dulcolax®), docusate sodium (Colace®), or sennosides plus docusate (Senokot-S®, Peri-Colace®).

**REFERENCES** are available online at www.drugtopics.com/cpe.

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**TABLE 3**

American College of Gastroenterology Recommendations and Quality of Evidence for IBS-C and CIC Therapy

<table>
<thead>
<tr>
<th>Statement for IBS-C/CIC</th>
<th>Recommended/quality of evidence for IBS-C</th>
<th>Recommended/quality of evidence for CIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiber provides overall symptom relief in IBS-C/Fiber increases stool frequency in CIC</td>
<td>Weak/Moderate</td>
<td>Strong/Low</td>
</tr>
<tr>
<td>No evidence that polyethylene glycol improves overall symptoms and pain in patients with IBS/Polyethylene glycol increases stool frequency and consistency in CIC</td>
<td>Weak/Low</td>
<td>Strong/High</td>
</tr>
<tr>
<td>NA/Lactulose increases stool frequency and consistency in CIC</td>
<td>NA/NA</td>
<td>Strong/Low</td>
</tr>
<tr>
<td>NA/Bisacodyl is effective in CIC</td>
<td>NA/NA</td>
<td>Strong/Moderate</td>
</tr>
<tr>
<td>Linaclotide is superior to placebo for IBS-C/Linaclotide is effective in CIC</td>
<td>Strong/High</td>
<td>Strong/High</td>
</tr>
<tr>
<td>Lubiprostone is superior to placebo for IBS-C/Lubiprostone is effective in CIC</td>
<td>Strong/Moderate</td>
<td>Strong/High</td>
</tr>
</tbody>
</table>

Abbreviations: CIC, chronic idiopathic constipation; IBS-C, irritable bowel syndrome with constipation; NA, not applicable. Source: Ref 8
**TEST QUESTIONS**

**For Pharmacists**

1. A 40-year-old woman is diagnosed with chronic idiopathic constipation. She has tried fiber, stimulant laxatives, and osmotic laxatives to relieve her symptoms, with no or limited success. Which of the following may be a reasonable next treatment step for this patient?
   a. Methylnaltrexone
   b. Lubiprostone
   c. Naloxegol
   d. All of the above

2. According to a 2014 meta-analysis conducted by the American College of Gastroenterology, which of the following has a high level of evidence supporting its use in the treatment of irritable bowel syndrome with constipation?
   a. Linaclotide
   b. Lubiprostone
   c. Probiotics
   d. All of the above

3. A 65-year-old woman has been taking oxycodeone extended release 10 mg twice daily for osteoarthritis pain in her fingers for the last three years. She now presents with constipation symptoms with an inadequate response to four tablets of Senokot and 300 mg of docusate once daily and addition of 17 g of polyethylene glycol. Assessment of the patient's constipation history did not reveal that the patient experienced constipation prior to administration of oxycodeone. What would be the best course of action to relieve her constipation symptoms?
   a. Recommend adding dietary fiber and four glasses of water daily to her current laxative regimen.
   b. Add lubiprostone to her current laxative regimen.
   c. Add naloxegol to treat opioid-induced constipation.
   d. Discontinue opioid therapy.

4. Choose the correct statement regarding FDA-approved treatments for opioid-induced constipation:
   a. Lubiprostone is a peripherally acting mu-opioid receptor antagonist.
   b. Methylnaltrexone and naloxegol are centrally acting mu-opioid receptor antagonists.
   c. Naloxegol is an oral peripherally acting mu-opioid receptor antagonist.
   d. Lubiprostone is an oral chloride channel 2 activator, and methylnaltrexone and naloxegol are oral peripherally acting mu-opioid receptor antagonists.

5. Assessment of bowel habits in a patient who is initiating opioid therapy should begin:
   a. After a patient has good pain control
   b. After one month of opioid treatment
   c. When the patient starts complaining of constipation symptoms
   d. At the time when the opioid is prescribed

6. The consensus-based definition of opioid-induced constipation proposed by an expert panel includes all of the following criteria EXCEPT:
   a. Fewer than three spontaneous bowel movements per week
   b. Decreased bowel movement frequency
   c. Harder stool consistency
   d. Sense of incomplete rectal evacuation

7. Which of the following agents does not have an FDA-approved indication for opioid-induced constipation?
   a. Linaclotide
   b. Lubiprostone
   c. Naloxegol
   d. None of the above

8. Which of the following FDA-approved agents are indicated for chronic idiopathic constipation and irritable bowel syndrome with constipation?
   a. Linaclotide
   b. Lubiprostone
   c. Naloxegol
   d. A and B

9. Terry is a 37-year-old woman with a 10-month history of chronic constipation that has not improved with change in diet, exercise, fluid intake, or use of over-the-counter laxatives. The potential diagnoses include irritable bowel syndrome, constipation, and irritable bowel syndrome with constipation. Which of the following factors from her history indicates that she is likely suffering from irritable bowel syndrome with constipation?
   a. Use of manual maneuvers to facilitate evacuation
   b. Fewer than three bowel movements per week
   c. Recurrent abdominal pain or discomfort that improves with bowel movement
   d. Sense of incomplete evacuation

10. Choose the correct statement:
   a. There is a strong recommendation from the American College of Gastroenterology and a high level of evidence for the use of bisacodyl and lactulose in patients with irritable bowel syndrome with constipation.
   b. There is strong evidence for the efficacy of prophylactic conventional laxatives such as polyethylene glycol and sennosides for opioid-induced constipation.
   c. There is a strong recommendation from the American College of Gastroenterology for the use of lubiprostone for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation.
   d. There is strong evidence for the use of linaclotide for the treatment of opioid-induced constipation after failure of conventional laxatives.

**For Pharmacy Technicians**

1. Which of the following agents is not available over the counter for treating constipation?
   a. Polyethylene glycol 3350 (Miralax®)
   b. Lactulose
   c. Docusate (Colace®)
   d. Sennoside (Senokot®)

2. Which of the following agents is not FDA approved for the treatment of opioid-induced constipation?
   a. Linaclotide
   b. Lubiprostone
   c. Naloxegol

3. Which of the following is the definition for opioid-induced constipation?
   a. A change from baseline bowel habits upon initiation of opioids
   b. Symptoms of straining and abdominal pain for more than 6 months
   c. Recurrent abdominal pain or discomfort for 3 months that improves with defecation

4. Which of the following agents has FDA-approval indications for all of the following types of constipation: chronic idiopathic constipation, irritable bowel syndrome with constipation, and opioid-induced constipation?
   a. Linaclotide
   b. Lubiprostone
   c. Naloxegol

5. Which of the following options are considered to be conservative, nonpharmacologic therapy for the treatment of constipation?
   a. Sennosides (Senokot®) and docusate sodium (Colace®)
   b. Polyethylene glycol 3350 (Miralax®)
   c. Bisacodyl (Dulcolax®)
   d. Fiber supplements, fluid intake, and exercise

6. Which of the following agents is not FDA approved for the treatment of chronic idiopathic constipation?
   a. Linaclotide
   b. Methylnaltrexone
   c. Naloxegol
   d. B and C

7. Which of the following is a definition for irritable bowel syndrome with constipation?
   a. A change from baseline bowel habits upon initiation of opioids
   b. Reduced bowel frequency and movement
   c. Recurrent abdominal pain or discomfort for 3 months that improves with defecation and change in stool form
   d. All of the above

8. Which of the following products is available as powder form and needs to be mixed in 8 ounces of water prior to administration?
   a. Lactulose
   b. Polyethylene glycol 3350 (Miralax®)
   c. Bisacodyl (Dulcolax®)
   d. Sennoside (Senokot®)

9. When a patient presents to your pharmacy complaining of constipation, which is your best approach?
   a. Refers to the patient’s primary care physician
   b. Refers the patient to the pharmacist for further assessment of constipation symptoms
   c. Recommends that the patient try eating more fiber and drinking more fluids

10. Which of the following agents is administered by subcutaneous injection?
    a. Linaclotide
    b. Lubiprostone
    c. Methylnaltrexone
    d. Naloxegol
A REVIEW OF NEW TREATMENT OPTIONS FOR CONSTIPATION

References