Overview of the PRN:

The Pain and Palliative Care PRN of ACCP is an organization of pharmacy practitioners, clinical scientists, pharmacy educators, and others. Its mission is to advance pain and palliative care–related pharmacy practice, education, and treatment. Its objectives are as follows. (1) Provide a supportive network for all practitioners with patient care concerns in pain and palliative care. (2) Provide quality education for practitioners, students, and those in postgraduate training. (3) Build leadership skills in young practitioners by encouraging their involvement in this PRN. (4) Provide an information source and expertise for outside organizations seeking expert opinions for publications or public policy.

Opportunities and Resources for Resident and Fellow Members of the PRN:

Each year, the Pain and Palliative Care PRN sponsors two travel awards to the ACCP Annual Meeting. Awards may be granted to pharmacy residents, fellows, or students. In addition, residents and fellows are allowed to sit on the PRN subcommittees, including the Programming and Membership committees.

Current Clinical Issue: Opioid-Induced Constipation

Opioid-induced constipation (OIC) is a common distressing symptom in patients with cancer taking opioids, with an estimated prevalence of 70%–100%.[1] Although definitions vary, the term *constipation* collectively refers to the subjective impression of a decrease in the frequency of passing formed stools; difficulty and discomfort passing stools; passing stools of inadequate volume; or passing hard stools.[1-3] Unlike other common opioid-induced adverse effects, minimal to no tolerance develops to OIC.[2] Ongoing, untreated constipation may lead to further symptoms, including nausea and vomiting, abdominal distention, anorexia, and obstruction or fecal impaction. Thus, untreated OIC may be very distressing for the patient. Targeted pharmacologic prophylaxis and management is fundamental to the prevention or progression of opioid-induced complications.

Opioids exert pharmacologic effects on binding primarily to the peripheral mu-opioid receptors within the gastrointestinal (GI) mucosa.[3,4] Many pharmacologic options, including those aimed at reversing actions on the mu-opioid receptors in the GI mucosa, are available for preventing and treating OIC.

The cornerstone of OIC management includes initiating an oral standing laxative bowel regimen at the time of opioid initiation, unless contraindicated. Although laxative suppositories and enemas offer the additional benefit of stimulating the anocolonic reflex, they are not used as prophylaxis or first-line treatment because of patient preference and potential for electrolyte disturbances, as well as to minimize the potential for complications that may be caused by introducing foreign bodies into the rectum.[3] Typically, one or two of the agents listed in Table 1[5,6] are used on a scheduled basis, with supplemental dosing of an additional agent as needed, depending on bowel symptoms.

Table 1. Agents for Prophylaxis and First-line Treatment of OIC				
Drug Class	**Examples**	**Dosing**	**Onset of Action**	**Comments**
Stimulant	Senna	17.2 mg PO daily, maximum dose 34.4 mg twice daily	6–12 hr	Adverse effects may include intestinal colic or diarrhea
	Bisacodyl	10–20 mg PO daily; available as 10-mg suppository	Tablet: 6–12 hr Suppository: 20 min to 3 hr	
Stool softener	Docusate sodium	100 mg PO daily, maximum dose 400 mg twice daily	12 hr to 3 days	Ineffective if given as monotherapy
Osmotic agents	Polyethylene glycols	17 g of powder PO daily mixed with 4–8 oz of beverage	1–4 days	Consider if patient has a history of cramping with use of stimulant laxatives
	Magnesium salts	Magnesium hydroxide: 400–800 mg PO daily Magnesium citrate: 195–300 mL or oral solution daily	30 min to 6 hr	Can give in divided doses Capable of systemic absorption; caution in preexisting heart failure, hypertension, and renal failure
	Lactulose	10–20 g PO daily, maximum dose 40 g daily	1–2 days	Caution in patients with diabetes (contains lactose and galactose) Potential adverse effects include abdominal discomfort, belching, flatulence
	Glycerin suppository	1 suppository once daily, as needed	15–30 min	May cause cramping pain, rectal discomfort
Enema	Mineral oil	5–45 mL of mineral oil given as a single dose (total enema	2–15 min	Correct electrolyte abnormalities before administering a sodium phosphate enema

		volume 60–150 mL)		Despite lack of sufficient evidence, it has been suggested to avoid use of enemas in neutropenic patients as a precautionary measure, given the increased risk of infection in this population
	Sodium phosphate	One 4.5-oz enema as a single dose	2–5 min	
OIC = opioid-induced constipation; PO = orally. Lexi-Comp, Inc. (Lexi-Drugs®). Hudson, OH: Lexi-Comp, March 3, 2015; Twycross R, Sykes N, Mihalyo M, et al. Stimulant laxatives and opioid-induced constipation. J Pain Symptom Manage 2012;43:306-13.				

If initial, less expensive options fail to produce significant results after appropriate titration, a trial with an alternative agent, such as one of the newer targeted therapies for refractory OIC (as discussed next), may prove beneficial.[5-9]

Targeted Therapies for OIC:

***Naloxegol* (*Movantik*)**, a derivative of the mu-opioid receptor antagonist naloxone, is indicated for the treatment of OIC in patients with noncancer pain.[7] Its pegylated chemical structure prohibits it from crossing the blood-brain barrier, and it maintains a solely peripheral mechanism of action. Two identical, phase III, clinical, placebo-controlled trials of naloxegol were conducted in adult patients using stable regimens of opioids for noncancer pain.[10] Patients were randomly assigned to receive an oral daily dose of 12.5 mg or 25 mg of naloxegol, or placebo, for 12 weeks. Response rates were defined as three or more unplanned bowel movements each week and an increase from baseline of one or more spontaneous bowel movements for 9 or more of the 12 weeks and for 3 or more of the 4 final weeks. In both studies, patients taking 25 mg of naloxegol had a significantly greater response rate during 12 weeks than placebo (p=0.001 and p=0.02, respectively). In one study, patients taking 12.5 mg also had significant improvement compared with placebo (p=0.02). The most commonly reported adverse events were GI in nature (i.e., diarrhea, nausea, vomiting, and abdominal pain) and were more common in the group taking 25 mg. It is recommended to discontinue other laxatives when initiating naloxegol.[7] If the patient does not produce a bowel movement within 72 hours after starting naloxegol, other laxatives can be reinitiated.

***Methylnaltrexone bromide* (*Relistor*)** is a peripherally acting mu-opioid receptor antagonist that is U.S. Food and Drug Administration (FDA) approved for treating OIC in patients with advanced illness who are receiving palliative care when response to laxative treatment has been insufficient.[8] It is administered by subcutaneous injection every other day as needed. In a randomized, double-blind, placebo-controlled study, 133 patients who used opioids for 2 weeks or more, were at stable doses, and used laxatives for 3 days or more without relief were randomized to receive 0.15 mg/kg of methylnaltrexone subcutaneously every other day, or placebo, for 2 weeks.[11] Forty-eight percent of patients in the

methylnaltrexone group experienced laxation within 4 hours of receiving the first dose, compared with 15% in the placebo group ($p<0.001$). The average time to laxation after the first dose was 6.3 hours for patients receiving methylnaltrexone versus more than 48 hours for patients receiving placebo ($p<0.001$). Adverse reactions of abdominal pain, flatulence, nausea, increased body temperature, and dizziness were more prevalent in the methylnaltrexone group.

***Lubiprostone* (*Amitiza*)** is a locally acting chloride channel activator[9] that gained FDA approval for OIC in 2013.[12] Lubiprostone increases intestinal fluid secretion without altering serum sodium or potassium concentrations. The increased fluid secretion in the intestines serves to improve intestinal motility, allowing easier passage of stool. A randomized, double-blind, placebo-controlled study of 418 patients using stable doses of opioid for chronic noncancer pain found that oral lubiprostone 24 mcg twice daily was significantly better than placebo at improving the occurrence of spontaneous bowel movements (3.3 vs. 2.4 per week at 8 weeks; $p=0.005$).[12] Compared with placebo, more patients who received lubiprostone had their first spontaneous bowel movement within 24 hours ($p=0.018$) and 48 hours ($p=0.050$) of receiving the first dose of the study medication. Patients in the lubiprostone group reported significant improvements in symptoms of abdominal discomfort, straining, constipation severity, and stool consistency compared with placebo. Nausea, diarrhea, and abdominal distention were the most commonly reported adverse events, occurring more often in the lubiprostone group.

Opioid-induced constipation is a common problem in patients with cancer. When removal of the offending agent is not possible (i.e., need for analgesia), aggressive prophylactic measures should be taken. Regimens should be tailored to patient-specific needs depending on symptoms, adverse effects, cost, adherence, and contraindications. For refractory OIC, one of the newer targeted agents may prove beneficial to avoid further escalation of distressing symptoms and life-threatening complications. As additional targeted drugs are developed and further evidence from larger, high-quality trials becomes available, clinicians should expect to see the development of a more standardized approach to treating and preventing constipation.

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