Paul Gauguin. *Making Merry,* 1892. Oil on canvas.

The characteristics and use of prophylactic laxatives to prevent and treat constipation in patients with cancer are reviewed.

Pharmacologic Treatment of Constipation in Cancer Patients

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Introduction

The high prevalence of constipation in patients with cancer has been described in the preceding article.[1] This condition can produce some of the most distressing symptoms of cancer and cancer treatment, thus appreciably affecting quality of life, daily living, and self-esteem.[2] Untreated constipation may contribute to increased abdominal pain and distention, urinary retention, nausea, vomiting, and anorexia, as well as the development of hemorrhoids, anal fissures, perianal abscesses, and intestinal obstruction.[2-4] Anal fissures and perianal abscesses can lead to systemic infections in neutropenic patients.[2] This review focuses on the pharmacologic management of constipation as it pertains to cancer patients.

Causes of Constipation in Cancer Patients

The causes of constipation range from primary (including decreased activity and decreased dietary intake) to secondary (eg, gastrointestinal [GI] obstruction from a tumor, spinal cord compression, and electrolyte abnormalities such as hypercalcemia or hypokalemia) to iatrogenic pharmacologic treatment) in nature.[5] Patients with cancer, especially those with advanced cancer, often have multiple factors at play, such as opioid analgesic use, reduced food and fluid intake, reduced mobility, advanced age, or malignancy-related conditions (eg, partial bowel obstruction, tumor-related hypercalcemia, and chemotherapy-induced constipation).[6] Constipated cancer patients may have poor performance status, which implies decreased mobility, as well as poor nutritional status, and they may be taking medications that contribute to constipation. Besides opioids, which comprise the most common class to induce constipation, many drug classes may result in constipation including chemotherapy agents, anticholinergics (tricyclic antidepressants, phenothiazines), calcium or aluminum-containing antacids, iron preparations, and antiemetics (5-HT_3 antagonists) (Table 1). Constipation is probably the most prevalent side effect of opioid use, and it is also the side effect that is least likely for tolerance to develop.[3] Thus, prophylactic laxatives should be used when administering such agents on a regular basis.[2]

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Management of Constipation

A discussion on the evaluation and assessment of patients with constipation is included in the previous article, and general measures such as mobilization and hydration are presented.[1] The effective management of constipation in cancer patients often times requires the appropriate use of laxatives. This article focuses on the appropriate use of laxatives and other pharmacologic agents. In addition, it is important to review all the medications being taken by a patient in order to consider discontinuing nonessential constipating drugs such as phenothiazines, iron sulfate, and constipating antacids.[3] Table 1 lists several drugs other than opioids that can contribute to the onset of constipation.

Table 1. — Reported Approximate Incidence of Constipation for Drugs Other Than Opioids

Drug/Classification	Incidence of Constipation (%)
Vinca Alkaloids:	
Vinblastine	>10
Vincristine	33
Vinorelbine	35
Antidepressants and Anxiolytics:	
Alprazolam	9–15
Citalopram	13
Desipramine	10
Doxepin	4
Fluoxetine	5
Fluvoxamine	18
Imipramine	20
Paroxetine	5–16
Trazodone	8
Oral Iron Preparations	**5–20**
Cardiovascular Drugs, Antihypertensives, Hypolipidemics:	
Atorvastatin	1.1–2
Cholestyramine	>10
Clonidine	10 (oral), 1 (transdermal)
Fluvastatin	3.1
Lovastatin	2–4
Prazosin	1–10
Simvastatin	5.7
Verapamil	12–42
NSAIDs:	
Diclofenac sodium	3–9
Fenoprofen	7–14
Ketoprofen	3–9
Naproxen sodium	3–9
Sulindac	1–10
Antispasmodics:	
Atropine	>10
5-HT_3 Antagonists:	
Dolasetron	3.2
Granisetron	3 (IV), 14–25 (PO)
Ondansetron	2–11
Antacids:	
Calcium supplements	1–10
Famotidine	1.2–1.4
Omeprazole	1.1–1.5
Others:	
Anastrazole	up to 8
Arsenic trioxide	27–86
Baclofen	2–6
Bicalutamide	22
Bortezomib	43
Busulfan	38 (IV)
Carboplatin	6
Carmustine	2 (wafers)
Doxorubicin liposome	12.7
Fulvestrant	12
Letrozole	9
Mycophenolate mofetil	18–23
Pamidronate	12
Tacrolimus	23–35
Temozolomide	up to 40
Thalidomide	3–30
Tretinoin	17
Zoledronic acid	26

Mechanism of Action

Laxative drugs can be classified by their mechanism of action. This classification includes bulk-forming, emollient, osmotic/saline, stimulant, and lubricant laxatives. Other pharmacologic agents, including prokinetic agents and opioid antagonists, are also used in the armamentarium against the constipating effects of cancer therapy (Tables 2 and 3).

Bulk-Forming Laxatives

Bulk-forming laxatives most closely approximate the physiologic mechanisms involved in promoting evacuation. They are available as natural or semisynthetic hydrophilic polysaccharides, cellulose derivatives, or polyacrylic resins. They include methylcellulose, psyllium, and polycarbophil. These agents either dissolve or swell in the intestinal fluid, forming a viscous liquid that facilitates the passage of intestinal contents, stimulates peristalsis, and reduces transit time.[7] They are not absorbed systemically and do not seem to disrupt nutrient absorption, although administration with other medications such as warfarin, digoxin, and potassium-sparing diuretics may decrease the effects of these medications.[8] Bulk-forming agents begin to exert their effects in 2 to 4 days. Since they take effect in approximately 72 hours, it is not ideal for the initial management of symptomatic constipation.

Bulk-forming agents are typically recommended as initial therapy for most forms of mild constipation.[7] Increasing dietary fiber intake, whether through diet or with bulk agents, often can reverse mild or transient cases of constipation.[9] These agents may be beneficial in cancer patients who have a good performance status or who are not concurrently receiving constipating medications such as narcotics, antiemetics, or vinca alkaloids. They may also be useful in patients with colostomies.[7] However, these agents are not ideal for most indications involving constipation in cancer patients. The powder

Table 2. — Commonly Used Laxative Agents: Classification, Dosage, and Mechanism of Action

Type of Laxative	Route(s)/Onset of Action	Dosage Forms	Usual Dosage
Bulk-Forming:			
Methylcellulose	PO: 12-72 hrs	Powder	1 tbsp up to TID mixed in 8 fl oz
Psyllium	PO: 12-72 hrs	Powder	1 tsp-1 tbsp QD to QID mixed in 8 fl oz
Polycarbophil	PO: 12-72 hrs	Powder	1 g QID or PRN (no more than 6 g/24 hrs)
Emollient:			
Docusate sodium	PO: 12-72 hrs	Capsules/tablets	50-300 mg daily
Docusate calcium	PO: 12-72 hrs	Syrup/capsules	240 mg daily till normal
Lubricant:			
Mineral oil	PO: 6-8 hrs Rectal: 5-15 min	Liquid Enema	15-45 mL at bedtime 118 mL (4.5 oz) in single daily dose
Osmotic:			
Lactulose	PO: 24-48 hrs	Solution	30-45 mL QD to QID
Sorbitol	PO: 24-48 hrs Rectal: 15 min-1 hr	Solution Enema	30 mL at bedtime 120 mL as 25-30% solution
Glycerin	Rectal: 15 min-1 hr	Suppository	1 as needed, retain 15-30 min
PEG with electrolytes	PO: 1-4 hrs (bowel-cleansing dose)	Powder (oral solution)	200-500 mL QD
PEG without electrolytes	PO: 2-4 days (constipation dose)	Powder (oral solution)	17 g daily in 8 fl oz
Saline:			
Magnesium hydroxide	PO: 30 min-3 hrs	Suspension (400 mg/5mL)	30-60 mL daily
Magnesium citrate	PO: 30 min-3 hrs	Solution (1.75 g/30 mL)	5-10 fl oz daily
Sodium phosphate	PO: 30 min-3 hrs Rectal: 2-5 min	Solution Enema	20-45 mL daily 118 mL QD
Stimulant:			
Bisacodyl	PO: 6-10 hrs Rectal: 15-60 min	Tablets Suppositories	5-15 mg QD at bedtime 10 mg QD
Senna	PO: 6-12 hrs	Tablets Liquid	8.6 mg sennosides: 1 BID to 2 QID 5-15 mL daily, preferably at bedtime
Cascara	PO: 6-12 hrs	Tablets Liquid	325 mg per day 5 mL per day, preferably at bedtime
Castor oil (ricinoleic acid)	PO: 2-6 hrs	Liquid, emulsion	15-60 mL per day
Casanthranol (with docusate)	PO: 6-12 hrs	Capsules (combined with docusate)	1-4 capsules per day
Prokinetic:			
Metoclopramide	PO: 15-60 min IV: 1-3 min IM: 10-15 min	Tablets Syrup Solution	10 mg QID 10 mg QID 10 mg QID

PEG = polyethylene glycol

	Mechanism of Action	Comments
	Causes absorption of water into the intestine to form a viscous liquid, which promotes peristalsis and reduces transit time	To be taken with adequate amount of fluid daily
	Facilitates the admixture of fat and water, resulting in the softening of stool	To be taken with adequate amount of fluid daily
	Slows colonic absorption of fecal water and emulsifies into the stool; also coats the rectum to provide lubrication for passage of stool	Precautions need to be taken to avoid aspiration; may cause leakage through anal sphincter; may consider dividing dose
	Lactulose and sorbitol are hydrolyzed into organic acids, causing retention of fluid in the colon and increasing peristalsis; glycerin promotes fluid retention to stimulate peristalsis; PEG induces catharsis by strong electrolyte and osmotic effects	Lactulose: hourly doses of 30-45 mL may be used to induce rapid laxation at initiation of therapy; may mix with fruit juice to mask taste; sorbitol: hourly doses of 30 mL may be used to induce rapid laxation; PEG with electrolyte: dosage for bowel cleansing 240 mL every 10 min until diarrhea fluid is clear or until 4-5 L consumed; PEG without electrolytes: tasteless
	Promotes bowel evacuation by causing osmotic retention of fluid, which distends the colon and increases peristaltic activity	Magnesium citrate: chill solution prior to administration; sodium phosphate enema: generally should not be used > 1 wk
	Cascara: causes direct action on intestinal mucosa/nerve plexus and alters water and electrolyte secretion	Bisacodyl PO: not to be taken within 1 hr of antacids or milk, up to 30 mg daily has been used for complete bowel evaluation; senna: maximum of 8 tablets per day, maximum of 30 mL senna liquid per day
	Improves gastric tone and peristalsis; increases resting esophageal sphincter tone; relaxes pyloric sphincter; augments duodenal peristalsis, leading to increased gastric emptying and decreased transit time through duodenum, jejunum, and ileum	

and granule products need to be mixed with fluids and taken in a full 8-ounce dosage. The daily dosage is then titrated based on response.[10] Due to the hydration requirement needed to appropriately administer these products (the usual goal of fluid intake being 30 mL/kg per day), many patients with advanced cancer, particularly elderly patients, are not suitable candidates for bulk-forming laxatives. Administering these laxatives to this population may predispose them to fecal impaction and bowel obstruction. These products are used with caution in patients with esophageal strictures, ulcers, stenosis, or intestinal adhesions and are contraindicated in patients who have obstructive symptoms or fecal impaction. In addition, patients who have slow GI transit (eg, secondary to opioid use) or other defecation disorders are less likely to respond to bulk-forming agents than patients without these conditions.[11]

The two most common adverse effects of increasing fiber intake (either through diet or bulk-forming products) are abdominal pain and bloating.[11] However, these symptoms are expected during the first few weeks of therapy and decrease in severity over time.[10] They can be avoided by gradually increasing the dosage.[10] Bloating is less common with cellulose derivatives because they do no undergo bacterial fermentation.[10]

Bulk-forming agents are considered an appropriate first-line therapy for those patients who meet adequate fluid-intake requirements; they should be avoided in those who are unable to maintain adequate fluid intake and should not be used as single-agent therapy for those patients receiving opioid analgesics.

Emollient Laxatives

Emollient laxatives increase the wetting efficiency of intestinal fluid and facilitate the mixing of aqueous and fatty substances that soften feces. Docusate is known as a stool softener and comes in various forms: docusate calcium, docusate sodium, and docusate potassium. The onset of action is usually seen after 1 to 2 days but may take as long as 3 to 5 days. Like the bulk-forming laxatives, emollient laxatives require increased fluid intake to facilitate stool softening. In prescribing these agents, practitioners should avoid concurrent administration of poorly absorbed drugs such as mineral oil. Administering these drugs together may increase the absorption of the mineral oil, thereby increasing the risk of toxicity.[7]

Emollient laxatives serve little value by themselves in the treatment of long-term constipation. They may be beneficial when given concurrently with bulk-forming agents so as to reduce straining.[12] Traditionally, these agents are indicated in cases of acute perianal disease in order to soften and avoid painful defecation or to avoid straining. Stool softeners are beneficial when the addition of dietary fiber or bulk-forming agents and fluids is insufficient to produce a soft stool.[3] They can also be

used as first-line therapy in the prevention of iatrogenic or drug-related constipation.[2] They do not stimulate peristalsis and evacuation; however, they can be used in combination with stimulant laxatives to provide a softer stool that is easier to evacuate.

Osmotic/Salines Laxatives

Osmotic laxatives work by attracting and retaining fluid into the bowel to form softer stool. Many medications, including lactulose, sorbitol, polyethylene glycol (PEG) compounds, and saline laxatives (eg, magnesium hydroxide), fall under the classification of osmotic laxatives. Lactulose and sorbitol are nonabsorbable sugars that are hydrolyzed into organic acids, drawing fluid osmotically into the intestinal lumen to stimulate propulsion and motility.[11] The onset of effect is usually seen 24 to 72 hours once the drug has reached the colon. However, adverse effects such as abdominal pain or distention may arise shortly after ingestion. These adverse effects subside after a few days. Larger doses of lactulose tend to result in bloating and colic.[13]

Both lactulose and sorbitol have been shown to be equally effective in relieving idiopathic constipation in elderly patients.[11] Their sweet tastes and the production of flatulence may cause problems with compliance in cancer patients. Mixing lactulose with fruit juice, water, or milk may increase palatability, but if the patient is already nauseated, these medications may exacerbate complaints. Sorbitol may be less nauseating than lactulose,[11] and some guidelines have suggested that lactulose should be used only for the treatment of encephalopathy and not for constipation.[2]

Polyethylene glycol-electrolyte solution is an osmotic laxative that traditionally has been used for GI lavage solutions prior to procedures. It is designed to rapidly cleanse the GI tract without disturbing the patient's water and electrolyte balance. Long-term use of this colon lavage solution (200 to 500 mL per day) has been studied and suggested as an option for patient's bowel regimens.[9,14,15] Both GoLYTELY and NuLYTELY solutions appear to be equally efficacious for colonoscopy preparation, but the latter does not contain sodium sulfate. A 500-mL dose of GoLYTELY would provide more than half of the US recommended daily sodium allowance.[15] Since NuLYTELY does not contain sodium sulfate, this may be an advantage for use in patients who have sodium restrictions.[9] PEG 3350 (MiraLax) contains no electrolytes and may be used for cancer patients who fail to respond to bulk-forming agents and saline laxatives.[10] It may be preferred over lactulose or sorbitol since these agents are associated with increased gas production, cramping, and abdominal distention,[10] and PEG 3350 is tasteless and has low toxicity. The recommended starting dose of PEG 3350 without electrolytes is 17 g per day. These agents typically produce a bowel movement within 24 to 48 hours.

Glycerin, a trihydroxy alcohol, is considered a hyperosmotic laxative. It is administered rectally as a suppository or an enema. It helps to promote water retention to stimulate peristalsis. Unlike other osmotic laxatives, the onset of action is fairly rapid; a bowel movement usually occurs within 30 minutes of administration. Suppository dosage forms may cause bleeding, rectal discomfort, and a burning sensation.[11] Although rectally administered drugs offer a viable route of administration for cancer patients, particularly those with advanced cancer, some specific precautions are required. The rectal route is generally avoided in patients who are neutropenic because of the increased risk of bleeding/tearing and thus creating a source of ingress for blood-borne pathogens.[2]

Saline osmotic laxatives include agents such as sodium phosphate (Fleets), magnesium citrate (Citroma), and magnesium hydroxide (Milk of Magnesia). These products mediate water retention osmotically, and they also stimulate peristalsis. The small intestine, acting as a semipermeable membrane to ions (magnesium, sulfate, phosphate, citrate), retains these osmotic ions in the gut. These ions with high osmotic activity draw fluid into the gut, causing an increase in intraluminal pressure.[7] This increased pressure exerts a mechanical stimulus, increasing intestinal motility. In addition, magnesium compounds can mediate water retention osmotically to stimulate peristalsis.[11]

Saline laxatives can produce undesirably strong purgative actions.[13] Dehydration may occur with repeated use of saline laxatives, so they should not be prescribed in patients who cannot tolerate fluid loss.[7] Also, due to their ability to cause hypomagnesemia and their high sodium content, saline laxatives should also be used with caution in cancer patients with comorbid conditions such as cardiac failure, renal insufficiency, or electrolyte disturbances. A typical oral dose of phosphate salts contains 96.5 mEq of sodium; therefore, they should be administered with caution to patients needing sodium restriction. When given via the rectal dosage form, up to 10% more sodium is absorbed.[9] Up to 20% of the magnesium ions may be absorbed from the magnesium salts administered for constipation. If a patient has impaired renal function or is elderly, toxic concentrations of magnesium can accumulate. Liquid preparations of saline laxatives may be more palatable to cancer patients if they are chilled prior to administration.[7] Citrate of magnesia is available as a carbonated liquid and may be preferred by some patients.

Saline laxatives play a limited role in the long-term management of constipation in cancer patients due to the potential for adverse effects in this population. They are beneficial in situations where acute evacuation of the bowel is desired.[11] They may also be temporarily useful in cases where symptomatic constipation is still occurring despite increased doses of stimulant laxatives and stool softeners. Saline laxatives, as well as all other osmotic laxatives, should be avoided when there is suspicion of obstruction or impaction.[12]

The daily use of osmotic agents, excluding the saline laxatives, is indicated either as second-line or third-line agents. They may be added as second-line agents after further softening of stool and stimulation of peristalsis is needed despite using bulk-forming agents and stool softeners, or they may be added as third-line agents if stimulant laxatives, softeners, and bulk agents are insufficient to maintain normal stool elimination.[3]

Stimulant Laxatives

Stimulant laxatives include diphenylmethanes (bisacodyl) and the anthraquinones (senna and cascara). These laxatives have a more potent laxation effect than bulk-forming and osmotic laxatives and seem to be more effective than enemas.[11,16] Diphenylmethanes and anthraquinones act by altering electrolyte transportation within the intestinal

Table 3. — Advantages, Disadvantages, and Therapeutic Role of Commonly Used Laxative Agents

Type of Laxative	Advantages	Disadvantages	Suggested Role in Therapy
Bulk-Forming: Methylcellulose Psyllium Polycarbophil	Most closely mimics the physiologic mechanism in promoting evacuation; useful in patients with colostomies	May take up to 3 days for effect; increased gas and bloating during initiation of therapy; potential for drug-drug interaction when coadministered with other medications; significant hydration requirement; contraindicated in patients who have obstructive symptoms or fecal impaction	Ideal as first-line agents in cases of mild or transient constipation not associated with opioid-induced constipation
Emollient: Docusate	Effective stool softener, particularly in cases where pain defecation and straining need to be avoided; available in tablets or liquid formulations	Increased fluid intake requirement; increased risk of absorption of poorly absorbed drugs when given concurrently; unpleasant taste of liquid formulation	First-line agent concomitantly with stimulant laxatives in the prevention of iatrogenic constipation; beneficial when given with bulk-forming agents to reduce straining
Lubricant: Mineral oil	Useful in situations of excessive straining	Chronic use may lead to malabsorption of fat-soluble vitamins; risk of possible aspiration when given orally; enhanced toxicity when given with docusate	Not routinely recommended
Osmotic: Lactulose Sorbitol Glycerin PEG with electrolytes PEG without electrolytes	Useful in liquefying stools to allow for defecation; sorbitol less nauseating than lactulose	May cause abdominal pain and distention shortly after ingestion; excessive bloating and colic with larger doses of lactulose; sweet taste may exacerbate underlying nausea	Second-line therapy when a stimulant laxative and stool softener do not relieve constipation
Saline: Magnesium hydroxide Magnesium citrate Sodium phosphate	Fewer doses needed of magnesium formulations for effect compared to phosphate formulations; magnesium citrate available in carbonated liquid	Can produce undesirably strong purgative actions; chronic use may lead to dehydration; use with caution in patients with comorbid conditions (eg, cardiac disease, renal insufficiency); risk of accumulation of magnesium in renal failure	Indicated when acute evacuation of the bowel is desired; third-line treatment if previous therapy is ineffective in producing evacuation
Stimulant: Bisacodyl Senna Cascara Castor oil (ricinoleic acid) Casanthranol (with docusate)	Useful in liquefying stools to allow for defecation; sorbitol less nauseating than lactulose	Long-term use associated with development of melanosis coli, cathartic colon, and potentially cancer; discoloration of urine; may need to titrate to higher doses (multiple daily tablets for adequate control; may cause abdominal cramping and hypokalemia	First-line (senna) for prevention of opioid-induced constipation; may be used first-line in combination with stool softener; useful in iatrogenic constipation (vincas, 5-HT_3 antagonists)
Prokinetic: Metoclopramide	Fairly rapid onset	Adverse effects including restlessness, drowsiness; potential for development of extrapyramidal symptoms	May be beneficial in refractory cases or when first- or second-line agents not tolerated
Opioid Antagonists: Naloxone	Low bioavailability, thus concentrating antagonism or opioid receptors in the GI tract; can produce laxative effect without reversing analgesic effect	May induce withdrawal symptoms	Currently being investigated to reverse opioid-induced constipation only

PEG = polyethylene glycol

mucosa, thus stimulating peristalsis. Activity begins in 6 to 12 hours when given orally and in 15 to 60 minutes after rectal administration. The dose should be titrated to effect. Side effects include abdominal cramping, hypokalemia, and melanosis coli (a reversible pigmentation of the colonic mucosa most commonly seen with the anthraquinones). Patients who experience abdominal cramping may benefit from a divided daily dose.[13] In general, stimulant laxatives are recommended for short-term treatment of constipation that is refractory to other laxatives. However, they have a more central role in the treatment of constipation in cancer patients.

Bisacodyl, a diphenylmethane stimulant, is available as a tablet or a suppository. It may be beneficial in cases of refractory constipation and in the management of cancer patients with colostomies who have managed their colostomies with routine irrigation but now find it difficult to perform this procedure.[12] Chronic use of this stimulant may lead to complications such as metabolic acidosis or alkalosis, hypocalcemia, and malabsorption. The use of bisacodyl has become more common due to withdrawal of phenolphthalein in the United States. (Phenolphthalein, another diphenylmethane derivative, was taken off the market in 1999 due to its suggested carcinogenic risk.)

Castor oil (ricinoleic acid) is also used as a stimulant laxative. However, it is rarely used for the management of constipation, and instead is used for GI tract evacuation. Abdominal cramping limits the long-term use of castor oil.[9] Furthermore, its unpleasant taste makes this option less desirable for cancer patients.

Anthraquinones are useful in opioid-induced constipation since they stimulate the myenteric plexus to induce peristalsis and reduce net absorption of water and electrolytes in the colon. The available preparations of anthraquinones are crude and contain a mixture of chemicals.[9] They are activated by bacterial metabolism in the colon. Adverse effects associated with these medications include allergic reactions, electrolyte depletion, and melanosis coli. Patients should be informed that they might experience a discoloration (red-brown, yellow-brown, or black) of their urine while taking senna. Some concerns have arisen with long-term use of anthraquinones, including a possible predisposition to colon cancer and the development of colonic inertia or a "cathartic colon."[9] Lastly, stimulant laxatives should be avoided when there is suspicion of obstruction or impaction.[12]

Stimulant laxatives may be required when spontaneous defecation does not occur.[17] Stimulant laxatives, particularly senna, are often used for patients who are taking opioid narcotics, and they should also be considered for patients receiving other known constipating drugs such as vinca alkaloids. Since senna is a mild preparation with a well-controlled transit time, it is a preferred agent.[12] Agra et al[18] conducted a trial comparing the efficacy of senna (stimulant laxative) with lactulose (osmotic laxative) in 91 patients with terminal cancer who were taking either codeine or morphine. There was no difference between both agents in terms of defecation-free intervals or in days with defecation. The adverse effects produced by these laxatives were similar, leading to the conclusion that senna should be considered the laxative of choice in this setting since it is less expensive. Stimulant laxatives such as senna can be used in combination with a stool softener (eg, docusate). In fact, whenever a patient has opioid analgesics prescribed for the first time, a regular bowel regimen should be initiated, which includes a stimulant and stool softener.[17] The dosage of senna should be increased until the desired effect is achieved, up to 8 tablets a day if necessary. The doses may need to be increased if the doses of opioids are increased. Unfortunately, the quantity of tablets needed for a desired effect may rise, particularly in opioid-induced constipation, to a point that is undesirable to the patient. In this case, use of additional laxatives such as sorbitol or PEG 3350 is warranted.

Lubricant Laxatives

Lubricant laxatives alter the physical characteristics of feces by emulsifying themselves into the fecal mass. They coat the rectum as well as provide lubrication for the passage of feces.[9] Mineral oil can be used as a lubricant laxative when given either orally or as an enema. It may be useful for a patient who complains of excess straining to evacuate. Long-term use can cause malabsorption of fat-soluble vitamins. Also, foreign body reactions in the intestinal mucosa and lymph nodes may occur and aspiration of mineral oil is possible, leading to lipoid pneumonia.[9] For these reasons, mineral oil administered orally is not routinely recommended for long-term use. As mentioned earlier, the toxicity of mineral oil may be enhanced when given concurrently with docusate.

Rectal Laxatives

Rectal laxatives should not be a regular component of most cancer patients' constipation regimens.[13] However, rectal laxatives, along with digital stimulation, are necessary for treating fecal impaction, as well as treating constipation associated with spinal cord compression or neurogenic bowel dysfunction, in which case long-term use may be required. Rectal laxatives include bisacodyl (stimulant), sodium phosphate (saline), glycerin (osmotic), and mineral oil (lubricant). They are available as either suppositories or enemas, depending on the product. When evacuation of soft stools is needed, then the rectal suppository of choice is bisacodyl (stimulant). However, when a hard stool needs to be softened, then glycerin suppositories should be considered.[13] On occasion, an enema may be required for acute situations. Of note, the use of both rectal suppositories and enemas are usually contraindicated in neutropenic and thrombocytopenic patients.[3]

Prokinetic Agents

For patients who are refractory to typical first- and second-line bowel regimens (stimulant, emollient, and osmotic laxatives) or for those who do not tolerate the side effects of such medications, prokinetic agents may be useful.[3] Metoclopramide, a gastroprokinetic agent, may be effective for delayed gastric emptying when used prior to meals and at bedtime.[12] The onset of action is with 30 to 60 minutes after an oral dose and within 1 to 3 minutes when given intravenously. The typical dose for gastroparesis is 5 to 10 mg given 30 minutes before meals and a bedtime. Adverse effects include restlessness, drowsiness, and the potential for extrapyramidal symptoms. Extrapyramidal symptoms occur more often at higher doses (1 to 2 mg/kg), at which point diphenhydramine may be coadministered to reduce this risk.

Opioid Antagonists

Opioids reduce GI propulsion, which result in slower movement of intestinal contents. This in turn allows for a more efficient absorption of water and electrolytes. They also inhibit intestinal fluid secretion, thus leading to constipation.[4] Naloxone (Narcan) is a competitive antagonist of opioid receptors. It reverses both centrally and peripherally mediated opioid effects.[19] When naloxone is administered orally, it has a bioavailability of less than 3% due to extensive (first-pass) hepatic metabolism.[4] Because of minimal absorption into the systemic circulation, oral naloxone's action is related to antagonism of opioid receptors in the GI tract, thereby reversing certain cases of idiopathic constipation.[6] The naloxone dose required to produce a laxative effect without reversing pain control may be proportional to the oral morphine doses causing constipation.[6] Many small studies have investigated the role of naloxone in reversing opioid-induced constipation.[4] It has been noted that oral naloxone's therapeutic index is narrow and that the response to opioid antagonists is proportional to the degree of opioid tolerance and not opioid levels.

The recommended starting dose of naloxone for treating opioid-induced constipation is 0.8 mg twice daily, with a maximum of 5 mg per day. It can be titrated up to 12 mg per day; however, careful observation of toxicity and decreased pain control is required.[4] Particular caution is needed for patients who are physically dependent on opioids. Naloxone may induce opioid withdrawal symptoms (tachycardia, ventricular arrhythmias, anxiety, diaphoresis, nausea, dyspnea). Doses of at least 10% of the concurrent opioid have been found to effectively reverse constipation without reversing analgesia. However, these doses may not be effective in physically dependent patients, where doses up to 20% of the total daily opioid dosage may be necessary.[4] The use of naloxone for opioid-induced constipation is still considered investigational, and the unavailability of an oral dosage formulation for naloxone in the United States limits its current use. Other opioid antagonists — naltrexone and nalmefene — are currently being investigated for this indication.

Investigational Agents

Methylnaltrexone is a quaternary ammonium opioid receptor antagonist, which limits it from crossing the blood-brain barrier. It was developed to block the peripheral GI effects of opioids while not affecting analgesia and other central effects. Methylnaltrexone is currently unavailable commercially. Several studies of both intravenous and oral dosage forms have been shown to prevent opioid effects on gastric emptying, nausea, and transit time while not affecting its analgesic action in noncancer patients (chronic methadone users).[4] Thomas et al[20] evaluated the activity of methylnaltrexone in cancer patients with advanced disease with opioid-induced constipation. Thirty patients were randomized to 4 doses (1 mg, 5 mg, 12.5 mg, or 20 mg), which were given subcutaneously every other day for 3 doses. This was followed by an open-label phase, where patients could continue at 5 mg, followed by titration to laxation effect. Preliminary results showed a dose-related response, with most of the laxative effect occurring approximately 4 hours following dosing and an up to 70% response at the 12.5 mg dose. Adverse effects included abdominal cramping and flatulence, which were transient.[20] Another investigational agent, ADL 8-2698, is a peripherally selective μ-opioid antagonist that has potential to increase GI motility without antagonizing analgesia.[4]

Conclusions

A variety of laxatives can be used in the prevention and treatment of constipation in cancer patients. The need to treat constipation is usually a result of the failure to prevent this condition. Even though constipation may be considered preventable, it continues to occur commonly among cancer patients and is responsible for many hospital admissions.[2] Unfortunately, there are few evidence-based guidelines and published comparative studies to help guide a clinician as to the appropriate choice of laxative or dosage. Because of this, laxatives are often inappropriately prescribed, with treatment of constipation usually occurring after a significant problem arises.[2] Furthermore, maintaining an appropriate bowel regimen may be more challenging since many of the laxatives discussed can be easily acquired over-the-counter, without the advice of health professionals (Table 4). McNicol et al[19] studied the management of opioid-induced constipation and other side effects. They determined that the type, strength, and consistency of evidence for available inter-

Table 4. — Availability of Commonly Used Laxative Agents

Over-the-Counter Drugs	Prescription Drugs
Bisacodyl (Dulcolax)	Lactulose
Cascara	PEG 3350 with no electrolytes (MiraLax)
Castor oil	PEG electrolyte solution (GoLYTELY, NuLYTELY)
Docusate (Colace, Surfak)	Sorbitol
Glycerin	
Magnesium citrate (Citro-Mag, Citroma)	
Magnesium hydroxide (Milk of Magnesia)	
Methylcellulose (Citrucel)	
Mineral oil	
Polycarbophil (FiberCon, Fiberall, Fiberlax)	
Psyllium (Metamucil)	
Senna (Senokot)	
Sodium phosphate (Fleet Enema, Fleet Phospho-Soda)	

PEG = polyethylene glycol

ventions to manage opioid side effects vary from strong to weak; well-designed trials are required to establish effective management techniques to successfully address these side effects. More studies are needed to identify the most beneficial bowel regimens for prophylaxis and treatment of constipation in cancer patients. In turn, this evidence-based literature could assist in the development of better treatment guidelines that would improve the supportive care of cancer patients.

References

1. McMillan SC. Assessing and managing narcotic-induced constipation in adults with cancer. *Cancer Control*. 2004;11(3 suppl 1): 3-9.
2. Smith S. Evidence-based management of constipation in the oncology patient. *Eur J Oncol Nurs*. 2001;5:18-25.
3. O'Mahony S, Coyle N, Payne R. Current management of opioid-related side effects. *Oncology (Huntingt)*. 2001;15:61-73,77.
4. Choi YS, Billings AJ. Opioid antagonists: a review of their role in palliative care, focusing on use in opioid-related constipation. *J Pain Symptom Manage*. 2002;24:71-90.
5. Wright PS, Thomas SL. Constipation and diarrhea: the neglected symptoms. *Semin Oncol Nurs*. 1995;11:289-297.
6. Sykes NP. An investigation of the ability of oral naloxone to correct opioid-related constipation in patients with advanced cancer. *Palliat Med*. 1996;10:135-144.
7. Curry CE, Tatum-Butler D. Laxative products. In: Covington TR, Lawson LC, Young LL, eds. *Handbook of Nonprescription Drugs*. 10th ed. Washington, DC: American Pharmaceutical Association; 1993:219-236.
8. Lacy CF, Armstrong LL, Goldman MP, et al, eds *Drug Information Handbook*. 11th ed. Hudson, Ohio: Lexi-Comp Inc; 2003.
9. Schiller LR. Clinical pharmacology and use of laxatives and lavage solutions. *J Clin Gastroenterol*. 1999;28:11-18.
10. Doughty DB. When fiber is not enough: current thinking on constipation management. *Ostomy Wound Manage*. 2002;48:30-41.
11. Scarlett Y. Medical management of fecal incontinence. *Gastroenterology*. 2004;126(1 suppl 1):S55-S63.
12. Gerber L, Hicks J, Shah J. Rehabilitation of the cancer patient. In: Devita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 6th ed. Baltimore, Md: Lippincott Williams & Wilkins; 2001:3089-3110.
13. Fallon M, O'Neill B. ABC of palliative care: constipation and diarrhea. *BMJ*. 1997;315:1293-1296.
14. Wong PW, Kadakia S. How to deal with chronic constipation: a stepwise method of establishing and treating the source of the problem. *Postgrad Med*. 1999;106:199-200,203-204,207-210.
15. Cleveland MV, Flavin DP, Ruben RA, et al. New polyethylene glycol laxative for treatment of constipation in adults: a randomized, double-blind, placebo-controlled study. *South Med J*. 2001;94:478-481.
16. Dosh SA. Evaluation and treatment of constipation. *J Fam Pract*. 2002;51:555-559.
17. Foley KM. Supportive care and quality of life: management of cancer pain. In: Devita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 6th ed. Baltimore, Md: Lippincott Williams & Wilkins; 2001:2997-3011.
18. Agra Y, Sacristan A, Gonzalez M, et al. Efficacy of senna versus lactulose in terminal cancer patients treated with opioids. *J Pain Symptom Manage*. 1998;15:1-7.
19. McNicol E, Horowicz-Mehler N, Fisk RA, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. *J Pain*. 2003;4:231-256.
20. Thomas J, Portenoy M, Moehl C, et al. A phase II randomized dose-finding trial of methylnaltrexone for the relief of opioid-induced constipation in hospice patients. *Proc Annu Meet Am Soc Clin Oncol*. 2003;22:729. Abstract 2933.