

Putting Evidence Into Practice[®]: Evidence-Based Interventions for the Prevention and Management of Constipation in Patients With Cancer

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Constipation is a major source of distress for patients with cancer, significantly affecting quality of life. It can be secondary to disease sequelae, side effects of treatment, or preexisting conditions. It often is unrecognized, underassessed, and ineffectively managed. Nurses play a key role in the prevention and management of constipation and need evidence-based interventions. This article summarizes the existing research evidence for constipation interventions and identifies gaps. Many of the strategies have been evaluated in nononcology populations; researchers should evaluate their effectiveness in oncology populations.

Constipation is a common issue in patients with cancer and a source of major distress. Although the exact incidence in the adult oncology population is not known, it has been reported as ranging from 50%–95%, with the highest incidence observed in patients receiving opioids (Cimprich, 1985; McShane & McLane, 1985; Smith, 2001). Among patients with cancer at the end of life, the prevalence of constipation may be as high as 60% and increases to 87% in such patients taking opioids (Wirz & Klaschik, 2005). Constipation is not unique to oncology. In nononcology populations, constipation is one of the most common digestive complaints in the United States and the primary reason for approximately 2.7 million ambulatory care visits annually. The total cost to the healthcare system is \$235 million annually, and about 55% of costs are incurred from inpatient hospitalization (Martin, Barghout & Cerulli, 2006).

Patients with cancer can experience constipation for a variety of reasons. Five common causes have been identified: (a) the cancer itself, which can obstruct the bowel, affect the autonomic nervous system, or cause spinal cord compression; (b) disease effects from illness such as dehydration, spinal cord compression, immobility, or changes in normal bowel habits; (c) previous laxative abuse; (d) cancer therapies such as the vinca alkaloids; and (e) interventions for symptom management such as opioids or tricyclic antidepressants (Wilkes & Barton-Burke, 2006). Figure 1 summarizes potential causes of constipation in the oncology population, underscoring the complexity of the issue.

Management of constipation can be complex and challenging because it often has more than one etiology in patients with cancer. The prevention and management of constipation should be essential components of oncology nursing practice and should

At a Glance

- ◆ Many expert opinions are available on the prevention and management of constipation in patients with cancer, but no high-level evidence supports the recommendations.
- ◆ Strategies likely to be effective in patients with cancer include instituting a prophylactic bowel regimen, switching from oral morphine to fentanyl (transdermal) or methadone, and using osmotic laxatives such as polyethylene glycol.
- ◆ Further research is needed to determine optimal strategies for preventing and managing constipation.

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Primary or Extrinsic Factors

- Advanced age
- Poor nutritional status
- Inadequate fluid intake
- Decreased mobility
- Inadequate privacy

Secondary Causes

- Structural abnormalities
 - Bowel obstruction
 - Pelvic tumor
 - Radiation fibrosis
 - Painful anorectal conditions
 - Surgical complications (e.g., adhesions)
- Metabolic effects
 - Hypercalcemia
 - Hyperglycemia
 - Hypothyroidism
 - Dehydration
 - Hypokalemia
- Neurologic disorders
 - Spinal cord compression
 - Sacral nerve infiltration
 - Cerebral tumors

Iatrogenic Causes (Pharmacologic Therapies)

- Cytotoxic agents (e.g., vinca alkaloids, oxaliplatin, thalidomide)
- Antiemetic therapy (5-HT₃ antagonists)
- Opioid therapy
- Angiotensin converting enzyme inhibitors
- Aluminum antacids
- Antiarrhythmics
- Anticholinergic drugs
- Anticonvulsants
- Antihistamines
- Antihypertensive drugs
- Anti-Parkinsonian agents
- Antispasmodics
- Barbiturates
- Calcium channel blockers
- Diuretics
- Iron
- Tricyclic antidepressants

Figure 1. Causes of Constipation in Patients With Cancer

Note. Based on information from Locke et al., 2000; Mancini & Bruera, 1998; McMillan, 2004; National Cancer Institute, 2006; Smith, 2001.

include evidence-based interventions. If constipation is not managed proactively, patients can experience negative consequences, such as anorexia, nausea, bowel impaction, or bowel perforation, all of which can have an impact on quality of life. Furthermore, primary tumor burden in the abdomen, metastatic disease in the liver, and peritoneal or mesenteric spread increase the risk and potential for discomfort as well as complications associated with constipation. A variety of pharmacologic and nonpharmacologic interventions are used for the management of this distressing symptom. The purpose of this article is to identify evidence-based interventions for the prevention and management of constipation in patients with cancer.

Methods

An initial step in the Oncology Nursing Society (ONS) Putting Evidence Into Practice® (PEP) process was identifying a definition for constipation. A review of the literature revealed no consistently accepted definition. The most developed definitions were related to chronic constipation. After carefully critiquing the literature, the researchers adopted a definition for constipation and used it to guide the literature search. For purposes of this project, constipation was defined as a decrease in the passage of formed stool characterized by stools that are hard and difficult to pass. Patients with constipation typically have fewer than two to three stools per week and may strain to have a bowel movement. Constipation can be accompanied by abdominal pain, nausea, vomiting, abdominal distention, loss of appetite, headache, and dry, hard stools (Bisanz, 2005; Cope, 2001; Petticrew, Rodgers, & Booth, 2001; Thompson, Boyd-Carson, Trainor, & Boyd, 2003). The various pharmaceutical and nonpharmaceutical interventions used in the prevention and treatment of constipation also were defined. Figure 2 includes some of the definitions used for this project. The full table of definitions may be found at <http://ons.org/outcomes/volume2/constipation.shtml>.

Search Strategy

In consultation with a medical librarian, the researchers conducted computerized searches of a variety of databases in July 2006 to identify meta-analyses, systematic reviews, research studies, and practice guidelines for interventions related to the prevention and management of constipation. The search was limited to English publications. Databases searched included Wiley's Cochrane Database of Systematic Reviews, Ovid's MEDLINE® (1966-July 2006), the National Guideline Clearinghouse, the National Cancer Institute's PDQ®, the National Comprehensive Cancer Network, and the *Cumulative Index to Nursing and Allied Health Literature (CINAHL®)* (1982-July 2006). To identify randomized, controlled trials (RCTs) in MEDLINE, the researchers used Cochrane's Highly Sensitive Search. In addition, a search for critically appraised topics was conducted in Ovid's Clinical Evidence and the American College of Physician's Information and Education Resource. Search terms included *constipation, defecation, fecal incontinence, bowel function, colonic transit, stool impaction, colonic inertia, and cancer, neoplasms, oncology*. Additional search terms included specific pharmacologic (e.g., laxatives, polyethylene glycol [PEG], senna) and nonpharmacologic (e.g., diet changes, biofeedback) interventions related to constipation.

The search then was refined and expanded to include specific interventions, using the term *constipation* combined with *vinca alkaloids, fluids, biotherapy, biofeedback, or acupuncture*. Additional searches were conducted through October of 2006 in the Cochrane Library; MEDLINE (1966-September Week 2 2006); CINAHL (1982-September 4, 2006) SCOPUS, and International Pharmaceutical Abstracts. The Institute of Scientific Information's Science Citation Index (1975 to present) also was used for cited references from key references and references in reviewed articles.

Laxative

Laxative agents are used to treat constipation and are classified by their mechanism of action: bulk forming, emollient, osmotic/saline, stimulant, and lubricant (Avila, 2004). Other pharmacologic agents used to treat constipation include prokinetic agents and opioid antagonists.

Laxative (emollient or surfactant)

Often referred to as stool softeners, these laxatives primarily as detergents, facilitating the mixing of aqueous and fatty substances, which soften feces. Examples include docusate sodium (Colace®) and docusate calcium (Surfak®) (Avila, 2004; Brandt et al., 2005).

Laxative (lubricant)

Providing lubrication for the passage of feces, this laxative group includes mineral oil and magnesium hydroxide combined with mineral oil (Phillips' Milk of Magnesia®). Long-term use is contraindicated because of the risk of malabsorption of fat-soluble vitamins (Avila, 2004).

Laxative (medicinal bulk-forming fiber)

Bulking agents add water and additional solid material to stool in the intestinal lumen. The swelling of the stool stimulates peristalsis and decreases stool transit time (Avila, 2004; Brandt et al., 2005). Examples of bulking agents include methylcellulose (Citrucel®); psyllium, also known as ispaghula husk (Metamucil® and Konsyl®); and calcium polycarboxophil (Konsyl® Fiber, Fibercon®, and Perdiem Fiber Therapy®). Most bulk laxatives need to be taken with 200–300 ml of fluid (Miaskowski et al., 2005). Caution: Bulk-forming laxatives should be avoided in patients who do not have adequate physical activity or fluid intake or who have severe constipation because it may worsen manifestations of constipation (Avila et al., 2004; Klaschik et al., 2003; Mancini & Bruera, 1998; Petticrew et al., 2001; Tamayo & Diaz-Zuluaga et al., 2004).

Laxative (medicinal soluble fiber)

These laxatives are nonprescription soluble-fiber supplements available over the counter. Soluble fiber nourishes the normal bacteria in the gut, resulting in fermentation and gas production, which stimulates laxation. Examples of this laxative type include partially hydrolyzed guar gum (Benefiber®), insulin (Fiber Choice®), and Liquefiber™.

Laxative (osmotic/saline)

Osmotic laxatives contain poorly absorbed ions or molecules, which create a local osmotic gradient within the intestinal lumen. Fluid and electrolytes are drawn osmotically from the surrounding tissue into the colon, which creates pressure-stimulating peristalsis (Avila et al., 2004; Brandt et al., 2005; Kot & Pettit-Young, 1992). Examples of this laxative type include lactulose and sorbitol (Brandt et al.). Adverse effects include electrolyte abnormalities, diarrhea, abdominal bloating, flatulence, and colic (Avila et al.; Brandt et al.).

An iso-osmotic laxative is physiologically inert and so is not absorbed or metabolized in the gut (Arora & Srinivasan, 2005). Polyethylene

Laxative (osmotic/saline) (continued)

glycol (PEG) is an example of this type of laxative. Standard-dose PEG with electrolytes is known in the United States as Golytely® and Colyte®. Low-dose PEG, referred to as PEG 3350, is available without electrolytes in the United States and is marketed as Miralax®. It is available with or without electrolytes in the United Kingdom and Netherlands. Nulytely® is a sodium-free mixture for specific patient populations. Regardless of the ingredients, PEG acts by opposing water absorption from stool in the large bowel, increasing the water content and volume of the stools, thus making them softer and easier to pass (Avila, 2004).

Hyperosmotic laxatives have a more rapid onset of action compared to other osmotic laxatives. An example of this type of laxative is a glycerin suppository, which also has lubricating properties (Avila, 2004).

Laxative (saline) or magnesium salts

These salt mixtures contain magnesium or sulfate ions and act by drawing fluid into the gut osmotically, softening the stool and causing increased intraluminal pressure and stimulation of peristalsis (Avila, 2004). Dehydration can occur with repeated use of saline laxatives, so they should not be prescribed in patients who cannot tolerate fluid loss (Curry, 1993) or in patients who cannot maintain adequate daily fluid intake. Examples include sodium phosphate enemas (Fleet Enema®), magnesium citrate, and magnesium hydroxide (milk of magnesia).

Laxative (stimulant)

Stimulant laxatives irritate the nerve endings in the colonic mucosa, stimulating peristalsis. They also may limit water absorption by altering fluid and electrolyte transportation within the intestinal mucosa (Brandt et al., 2005). Side effects of these agents include abdominal discomfort, electrolyte imbalances, allergic reactions, and hepatotoxicity. Melanosis coli (a benign pigmentation disorder of the colon) also has been reported with senna-containing compounds (Avila et al., 2004; Brandt et al.). Examples include senna (Senokot® and ExLax®) and bisacodyl (Dulcolax® and Correctol®) (Brandt et al.).

Milk and molasses enema

The sugar in milk and molasses enemas irritates the intestinal lining and produces gas, which distends the intestines and causes pressure, peristalsis, and subsequent evacuation. A low-volume enema less than 300 cc, when given high (12 inches) and held for 20 minutes, produces the best results. Caution: Evaluate intravascular volume status before using enemas with hypertonic solutions (Walker et al., 2003).

Directions: Mix 3 oz powdered milk in 6 oz cup warm water; add 4 oz molasses and mix. Insert enema tube approximately 12 inches into the rectum or until resistance is met, and administer less than 300 cc. After solution is given, clamp the enema tube and leave it in place while the patient lies on his or her right side for 20 minutes to allow solution to go into transverse and ascending colon. Repeat as many as four times per day until the impaction is relieved (Bisanz, 2005).

Figure 2. Definitions of Interventions for Constipation

Abstracts of the literature search were reviewed to determine whether articles met the inclusion criteria. Articles were retrieved and critiqued if they included constipation as an outcome variable or contained guidelines for the prevention and management of constipation.

Additional data sources were identified from manual searches in article bibliographies. Published references before Oc-

tober 2006 were retrieved. An updated literature search was conducted in June 2007 for this article and found an American Society of Clinical Oncology (ASCO) abstract reporting the findings of two phase III RCTs of methyl naltrexone and an updated version of the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHN) guidelines.

Synthesis and Evaluation

Two dyads of advanced practice nurses (APNs) and staff nurses extracted data in a systematic way from the selected publications as related to the prevention and management of constipation. An APN in the researcher role and a nurse researcher provided guidance in data extraction. Information was collected in a standardized format according to the type of publication (i.e., meta-analysis, systematic review, individual research study, guideline, or expert opinion). Data were extracted and a level of evidence was assigned for each category of intervention (e.g., stool softeners, osmotic laxatives). Most of the meta-analyses, systematic reviews, literature reviews, and guidelines contained information on a variety of interventions. Individual studies were rated and assigned an ONS level of evidence based on their type and quality (Ropka & Spencer-Cisek, 2001) (see Table 1). Studies then were grouped by intervention. The strength of evidence supporting each intervention was weighted based on seven categories of evidence identified by ONS, ranging from *recommended for practice* to *not recommended for practice*. The final category, *expert opinion*, included consensus panel reviews and publications by clinicians addressing bowel management in oncology and nononcology populations. A description of each of the weighted evidence categories is described in Table 1.

Most of the research identified was not conducted specifically in the oncology population. Because little to no evidence was found for interventions commonly used in practice and because

patients with cancer can have comorbid reasons for constipation, the project team decided to review the research related to constipation in the nononcology population. For interventions studied only in nononcology populations, the highest level of categorization assigned based on the strength of the evidence was likely to be effective. All of the summarized data were documented in standardized tables and reviewed for accuracy by the project team, by a second PEP project team, and by outside reviewers. Revisions were made based on feedback. In addition, the PEP short resource card and detailed card were reviewed by outside reviewers and revised based on feedback. The resources are available at www.ons.org/outcomes/constipation/shtml.

Highlights of Reviewed Literature: Constipation in Adult Patients With Cancer

Only eight studies were found that examined the management of constipation in patients with cancer. Two studies addressed nonopioid-induced constipation; one was a descriptive study looking at vincristine-induced constipation (Harris & Jackson, 1977), and the second was a poorly controlled trial examining the use of dietary fiber after radical hysterectomy (Griffenberg, Morris, Atkinson, & Levenback, 1997). The remaining six studies, which addressed opioid-induced constipation (OIC), were of mixed quality and evaluated different questions related to the

Table 1. Putting Evidence Into Practice® Weight-of-Evidence Classification Schema		
WEIGHT-OF-EVIDENCE CATEGORY	DESCRIPTION	EXAMPLES
Recommended for practice	Effectiveness is demonstrated by strong evidence from rigorously designed studies, meta-analyses, or systematic reviews. Expected benefit exceeds expected harms.	At least two multisite, well-conducted, randomized, controlled trials (RCTs) with at least 100 subjects Panel of expert recommendation derived from explicit literature search strategy; includes thorough analysis, quality rating, and synthesis of evidence
Likely to be effective	Evidence is less well established than for those listed under recommended for practice.	One well-conducted RCT with fewer than 100 patients or at one or more study sites Guidelines developed by consensus or expert opinion without synthesis or quality rating
Benefits balanced with harms	Clinicians and patients should weigh the beneficial and harmful effects according to individual circumstances and priorities.	RCTs, meta-analyses, or systematic reviews with documented adverse effects in certain populations
Effectiveness not established	Data currently are insufficient or are of inadequate quality.	Well-conducted case control study or poorly controlled RCT Conflicting evidence or statistically insignificant results
Effectiveness unlikely	Lack of effectiveness is less well established than those listed under not recommended for practice.	Single RCT with at least 100 subjects that showed no benefit No benefit and unacceptable toxicities found in observational or experimental studies
Not recommended for practice	Ineffectiveness or harm clearly is demonstrated, or cost or burden exceeds potential benefit.	No benefit or excess costs or burden from at least two multisite, well-conducted RCTs with at least 100 subjects Discouraged by expert recommendation derived from explicit literature search strategy; includes thorough analysis, quality rating, and synthesis of evidence
Note. Based on information from Mitchell & Friese, n.d.		

management of the side effect. They were an RCT comparing senna and lactulose (Agra et al., 1998); two studies evaluating the efficacy of opioid rotation from morphine to fentanyl (Ahmedzai & Brooks, 1997; Radbruch et al., 2000); one small, controlled study examining the use of oral naloxone (Meissner, Schmidt, Hartmann, Kath, & Reinhart, 2000); and two small, descriptive studies: one examining the relationship between opioid dose, bowel function, and activity and the other examining the use of fresh baker's yeast (Wenk et al., 2000). A summary of the studies can be found in Tables 2 and 3.

Recommended for Practice

As of September 30, 2006, the literature revealed no interventions that could be recommended for nursing practice in the oncology population. "Interventions which are recommended for practice are those for which effectiveness has been demonstrated by strong evidence from rigorously conducted studies, meta-analysis, or systematic reviews and for which expectation of harms is small compared with the benefits" (ONS, n.d.).

Likely to Be Effective

Several interventions for the prevention and management of constipation in patients with cancer were considered *likely to be effective* based on less well-established evidence. Examples include a well-conducted RCT, "consistent supportive evidence from well-designed controlled trials using small samples," or guidelines developed by a consensus panel of experts (ONS, n.d.) such as *Guideline for the Management of Cancer Pain in Adults and Children* (Miaskowski et al., 2005) and *Clinical Practice Guidelines in Oncology: Palliative Care* (National Comprehensive Cancer Network [NCCN], 2006a). The interventions considered *likely to be effective* include strategies for addressing OIC and those for managing refractory constipation in adult patients with cancer.

Opioid-induced constipation: OIC also is referred to as opioid bowel dysfunction and opioid-induced bowel dysfunction. Opioids bind to the *mu* receptors of the gastrointestinal tract, delaying gastric emptying and causing symptoms of constipation (Friedman & Dello Buono, 2001; Tamayo & Diaz-Zuluaga, 2004). In addition to the symptoms associated with constipation, OIC is thought to include abdominal cramping, bloating, and gastrointestinal reflux (Pappagallo, 2001). OIC is the most commonly occurring gastrointestinal side effect of chronic opioid use. About 41% of patients with cancer and more than 50% of all opioid-treated patients experience symptoms associated with OIC (Kalso, Edwards, Moore, & McQuay, 2004; McNicol et al., 2003; Tamayo & Diaz-Zuluaga). Strong evidence and expert opinion support the initiation of a prophylactic bowel management regimen and monitoring when opioids are prescribed (Bisanz, 2005; Kalso et al.; McNicol et al.; Miaskowski et al., 2005; National Cancer Institute, 2006; NCCN, 2006a; Robinson et al., 2000). However, the literature has a paucity of research indicating the most effective regimen to prevent OIC.

Opioid rotation is another strategy thought to decrease the incidence of constipation. Opioid rotation takes advantage of the different properties of opioids to maximize analgesia and minimize adverse effects (McNicol et al., 2003). Several researchers have studied whether switching opioids can decrease the consti-

pating side effects associated with opioid administration in oncology and nononcology populations. Research, including three crossover studies rotating sustained-released oral morphine to fentanyl transdermal patch, demonstrated a significant decline in laxative use or episodes of constipation after the switch to fentanyl (Ahmedzai & Brooks, 1997; Allan et al., 2001; McNicol et al.; Miaskowski et al., 2005; Radbruch et al., 2000).

Persistent constipation: Polyethylene glycol 3350 (PEG 3350), an iso-osmotic laxative without electrolytes (Miralax®, Schering-Plough), is recommended as a treatment option for persistent constipation by the NCCN (2006a). It is used frequently in the oncology population, although no published meta-analyses, systematic reviews, or RCTs were found to support its use in that population. The categorization of PEG 3350 as *likely to be effective* is further supported by a high level of evidence concerning its safety and efficacy in nononcology populations.

Stimulant or osmotic laxatives also are *likely to be effective* in improving bowel function in patients with cancer who have persistent constipation at the end of life. In addition, some patients may need both types of laxatives to achieve optimal results (Agra et al., 1998; NCCN, 2006a). Although the NCCN recommends the use of senna and docusate, this review of the literature did not identify any trials to recommend the use of a specific stimulant laxative with or without the addition of a stool softener in the management of constipation in any population. One RCT of patients with terminal cancer (N = 91) comparing senna to lactulose found no significant difference in efficacy or tolerability (Agra et al.).

Benefits Balanced With Harms

The *benefits balanced with harms* category is designated for interventions "for which clinicians and patients should weigh the beneficial and harmful effects according to individual circumstances and priorities" (ONS, n.d.). The current review identified one intervention in this category.

Naloxone, an opioid receptor antagonist, has shown mixed efficacy and inconsistent reliability in reversing OIC. With naloxone, benefits must be balanced with potential harms. Its effects on central and peripheral opioid receptors can cause loss of analgesia and withdrawal symptoms such as nausea, sweating, restlessness, and abdominal cramps (Freidman & Dello Buono, 2001; McNicol et al., 2003). Multiple dosing and titration schedules have been studied (Choi & Billings, 2002; Friedman & Dello Buono; McNicol et al.; Meissner et al., 2000; Miaskowski et al., 2005).

Effectiveness Not Established

The pharmacologic and nonpharmacologic interventions classified as *effectiveness not established* are used commonly in the oncology population to prevent or treat constipation. They were not associated with any clear indication of harm; however, the data related to their efficacy were conflicting or of insufficient quality (i.e., inadequate power, limited sample sizes, or major flaws in study design or procedure) (ONS, n.d.). See Figure 3 for pharmacologic and nonpharmacologic interventions categorized as *effectiveness not established*. In addition, two promising investigational agents for the management of OIC

Table 2. Summary of Literature Addressing the Management of Nonopioid-Induced Constipation in Adult Patients With Cancer

STUDY	STUDY TYPE	SUMMARY
Harris & Jackson, 1977	Research evidence	A descriptive study examining the efficacy of lactulose as a treatment for vincristine-induced intractable constipation or for prevention of vincristine-associated constipation in eight patients with lymphoma or leukemia. Doses of lactulose ranged from 20 ml BID to 25 ml TID, and all patients obtained relief of constipation within two days of initiating lactulose.
Griffenberg et al., 1997	Research evidence	A randomized, controlled trial (RCT) (N = 35) evaluating the effect of increased fiber on bowel function in patients with cervical cancer who had a radical hysterectomy. The treatment group received dietary counseling and instructions to increase dietary intake to 30–40 g per day; the control group maintained a regular diet. Participants were given bran cereal (unmarked) with 15 g of fiber per bowl and were encouraged to increase intake of insoluble fiber. No significant change was found in bowel function between the groups, except the control group had a significant increase in the amount of medications used to achieve regularity. In addition, those with more fiber had significantly less abdominal cramping, fewer reports of straining, less retention of bowel movements, and more bowel movements with gas made in less than three minutes.
Fellowes et al., 2004	Systematic review/ meta-analysis	A comprehensive systematic review was performed to determine whether massage or aromatherapy decrease psychologic morbidity, lessen symptom distress, or improve quality of life in patients with cancer in the short or long term. No evidence was found related to constipation.
National Comprehensive Cancer Network (NCCN), 2006a	Guidelines	All recommendations in the NCCN palliative care guidelines were categorized as 2A based on a low level of evidence, including clinical experience and uniform consensus indicating the appropriateness of intervention in the oncology population. Preventive measures recommended include using prophylactic medications such as titration of a stimulant laxative plus stool softener with a goal of one nonforced bowel movement every one or two days, increasing fluid intake, and increasing dietary fiber if a patient has adequate fluid intake and physical activity and exercise, if appropriate. Interventions recommended if constipation is present include a thorough assessment of the cause and severity, ruling out impaction and obstruction, treatment of secondary or iatrogenic causes, adding and titrating another stimulant laxative such as bisacodyl, and clearing impaction via the rectal route if indicated. If constipation persists, reassess the patient for cause and severity; consider adding other oral or rectal treatment options such as osmotic laxatives, polyethylene glycol, enemas or prokinetic agents. If constipation persists, consult or refer to specialized palliative care services or hospice.
Avila, 2004	Expert opinion	This article reviewed the causes of constipation in patients with cancer, including decreased activity, decreased dietary intake, gastrointestinal obstruction from a tumor, spinal cord compression, electrolyte abnormalities such as hypercalcemia or hypokalemia, opioid analgesic and other constipating medication use, advanced age, and malignancy-related conditions. Options offered for the prevention and management of constipation included a variety of pharmacologic agents, including bulk-forming laxatives, emollient laxatives, osmotic saline laxatives, stimulant laxatives, lubricant laxatives, prokinetic agents, opioid antagonists, and investigational agents.
Bisanz, 2005	Expert opinion	The chapter addresses the management of diarrhea, constipation, and impaction in patients with cancer. The author stressed the importance of patient involvement in the plan of care, a preventive approach rather than temporary relief of symptoms, and an interdisciplinary approach in optimizing problem solving, and quality-of-life issues related to bowel management. Six steps to good bowel management were described: assessment and diagnosis of bowel dysfunction, normalization of the bowel, expectations for bowel movement frequency dependent on amount of food intake, development of a bowel management program, assessment of outcomes, and adjustment of the bowel management program through problem solving. A nutrition consult was recommended as a component of developing a bowel management program. Recommendations for the management of low and high impactions also were reviewed.
Cope, 2001	Expert opinion	An overview of management of chemotherapy-induced diarrhea and constipation, including the etiology and incidence of constipation in patients with cancer, discussed the importance of a comprehensive history and physical examination, including current cancer therapy, current medications, defecation history, abdominal examination, rectal examination, metabolic panel, and abdominal films if obstruction or paralytic ileus is suspected. A summary table described each type of pharmacologic agent (bulk, lubricant, saline, osmotic, detergent, and large bowel stimulants), their action, onset, drug examples, and comments. In addition, the author wrote about the nursing role in developing a bowel program for those on vinca alkaloids, teaching dietary modifications and increased fluid intake, educating patients about pharmacologic interventions, encouraging physical activity, and ensuring private time for defecation. Early intervention was stressed.

(Continued on next page)

Table 2. Summary of Literature Addressing the Management of Nonopioid-Induced Constipation in Adult Patients With Cancer (*Continued*)

STUDY	STUDY TYPE	SUMMARY
Mancini & Bruera, 1998	Expert opinion	A comprehensive review of the pathophysiology of bowel motility and constipation, causes of constipation in patients with advanced cancer, and the clinical manifestations and complications of constipation. In addition, the author offered a comprehensive review of management strategies, especially pharmacologic approaches to constipation. No specific dosing guidelines or algorithms regarding starting doses or escalation of laxatives were provided.
Smith, 2001	Expert opinion	Three sets of guidelines were described based on the results generated by a literature search and a survey conducted by the author. 1. Guidelines for prophylactic use of laxatives in patients receiving opioids and certain chemotherapeutic agents (morphine, codeine, vinca alkaloid, and other) 2. Guidelines for the management of acute constipation 3. Guidelines for the management of chronic constipation The guidelines included the use of codanthramer or equivalent (stimulant laxative), senna, docusate sodium, lactulose, bisacodyl suppository, micro enema, glycerin suppositories, phosphate enema, and arachis oil enema for various indications and in different combinations. The author described a small study (N = 6) conducted on an inpatient adolescent oncology unit in the United Kingdom, which concluded that the implementation of guidelines related to the prevention and management of constipation prevent acute hospital admissions related to constipation in adolescents with osteosarcoma.
Sykes, 1994	Expert opinion	This article from an oncology publication discussed approaches to constipation management in adults with advanced cancer. The author reviewed guidelines for prevention, including exercise and timing of meals to promote evacuation, fiber with fluid, and provision of comfort, privacy, and toilet accessibility. The value of adequate assessment was discussed, including history of bowel function, expectations, and physical examination. Recommendations and guidelines included the rectal management of constipation using bisacodyl suppositories, oil versus water enemas, and manual disimpaction; and the use of oral laxatives, including stimulant laxatives, stool softeners, osmotic laxatives, and magnesium hydroxide to maintain adequate bowel function. The use of paraffin, dexamethasone, and naloxone also were discussed.

are categorized under *effectiveness not established* because they have not been approved by the U.S. Food and Drug Administration (FDA): methylnaltrexone and alvimopan. Finally, many nonpharmacologic interventions, such as dietary fiber, physical activity, aromatherapy, massage, and biofeedback, are discussed in the literature addressing chronic constipation; however, they lack significant study using RCTs.

Pharmacologic interventions: Psyllium, a bulk laxative, often is prescribed to patients with cancer despite a lack of research evaluating its efficacy in the population. Evidence for its use in chronic constipation is conflicting (Brandt et al., 2005; Frizelle & Barclay, 2005; Ramkumar & Rao, 2005). Of the three systematic reviews that examined data related to psyllium, one concluded, “based on low-intermediate quality RCTs, psyllium appears to improve stool frequency and consistency” (Brandt et al.); one concluded that moderate evidence supports its use (Ramkumar & Rao); and another reported finding numerous RCTs of mixed quality (Frizelle & Barclay). Several publications have identified potential harms associated with psyllium, which may have implications for the oncology population. To prevent adverse events, patients must have good functional status, such as engaging in physical activity (Brandt et al.; Frizelle & Barclay; Petticrew et al., 2001; Ramkumar & Rao) and being able to consume adequate fluids (Miaskowski et al., 2005). For adults, psyllium should be taken with at least 200–300 ml of water (Miaskowski et al.; Sykes, 1994). Expert opinion recommends an additional 200–300 ml of water to prevent adverse events.

Psyllium should not be administered in large amounts because it has been associated with increased flatulence, abdominal distension, bloating, mechanical obstruction of the esophagus and colon, and anaphylactic reactions (Brandt et al.; Frizelle & Barclay). Therefore, the intervention should be used with caution in patients with severe constipation (Petticrew et al.) and, according to expert opinion, in patients with advanced cancer (Klaschik, Nauck, & Ostgathe, 2003; Mancini & Bruera, 1998) because its use may worsen symptoms.

Osmotic laxatives, such as lactulose and sorbitol, are associated with significant improvements in stool consistency, fecal impaction, straining of stool, and other symptoms of chronic constipation (Brandt et al., 2005; Kot & Pettit-Young, 1992; Petticrew et al., 2001). The two osmotic laxatives contain the same main ingredients but are manufactured by different pharmaceutical companies, with lactulose costing more than sorbitol (Agra et al., 1998). Several RCTs support their use for constipation management in nononcology patients. Systematic reviews have found mixed-quality studies indicating no significant differences in efficacy between sorbitol and lactulose (Kot & Pettit-Young; Lederle, Busch, Mattox, West, & Aske, 1990), between senna and lactulose (Agra et al.), and between lacticol (not available in the United States) and lactulose (Frizelle & Barclay, 2005). Of note, the cited adverse effects of lactulose are cramping and flatus, which may be considered harmful in the oncology population (Kot & Pettit-Young; Petticrew et al.; Ramkumar & Rao, 2005).

Table 3. Summary of Literature Addressing the Management of Opioid-Induced Constipation in Adult Patients With Cancer

STUDY	STUDY TYPE	SUMMARY
Agra et al., 1998	Research evidence	A randomized, open, parallel group design study (N = 75) comparing senna to lactulose in relation to efficacy and adverse events in patients with terminal cancer in Madrid, Spain. Dosing of senna was started at 0.4 ml (12 mg) BID and titrated up in 0.4 ml increments to a maximum dose of 1.6 ml (48 mg) every three days. Dosing of lactulose was started at 15 ml BID and increased in increments of 15 ml every three days to a maximum of 60 ml (40 g). When a patient reached the ceiling of his or her respective laxative and had three days without defecation, he or she was maintained on that dose and, in absence of side effects, was started on initial dose of other laxative, which could then be increased at three-day intervals until reaching the experimental maximum. Enema and/or mechanical bowel evacuation was prescribed after a three-day period without defecation (for ethical reasons), and this was recorded as a failure with increase in laxative dose. If no results from mechanical evacuation after six hours, the patient was held on stand-by outside the study until defecation. No difference was found between senna and lactulose in efficacy as measured by defecation-free intervals, days with defecation, or adverse effects. Opioid dose did not determine laxative efficacy, and 37.5% of patients required both laxatives by the end of the study.
Ahmedzai & Brooks, 1997	Research evidence	A randomized, open, two-period, crossover study (N = 110) compared the efficacy and tolerability of transdermal fentanyl to sustained-released morphine in patients with cancer receiving palliative care in the United Kingdom. The results indicated that fentanyl was associated with significantly less constipation than morphine ($p < 0.001$). This was confirmed through multiple assessment mechanisms, and the authors concluded that opioid rotation to transdermal fentanyl results in less constipation compared to morphine.
Bennett & Cresswell, 2003	Research evidence	A descriptive study (N = 50) examining the relationship between opioid dose, bowel function, and activities of daily living in patients with advanced cancer admitted to a hospice in the United Kingdom. Interviews conducted over a two-month period showed a reduced bowel score (particularly stool frequency) in patients taking opioids but no dose-dependent relationship; no relationship was found between bowel score and physical functioning for any given dose of opioid. Fitter patients were treated with larger doses of laxatives. The authors concluded that constipation in patients with advanced cancer likely is more strongly related to other variables (e.g., food, fluid intake, abdominal tumor involvement, depression, cognitive impairment, use of antimuscarinic drugs) and advised clinicians not to base laxative prescribing on opioid dose but to titrate laxatives according to bowel function.
Meissner et al., 2000	Research evidence	This was a controlled study (N = 17) with a control period not a control group whose purpose was to evaluate the use of oral naloxone to treat opiate-associated constipation in patients with cancer in a hospital in Germany. Patients were observed for six days without intervention, then oral naloxone was titrated starting at 3 mg TID and increasing to a maximum of 12 mg TID in 3 mg increments. Titration stopped with laxation or increased peristalsis. The study found that nausea, restlessness, and sweating were the most common side effects; laxation increased in 14 of 17, and laxative use decreased in 9 of 17 patients; pain ratings were unchanged between the periods; and naloxone dose was not based on morphine dose but on opioid tolerance level. In conclusion, the authors recommended starting with low-dose naloxone and titrating up based on efficacy and tolerance.
Radbruch et al., 2000	Research evidence	An open, sequential, multicenter study (N = 46) investigated constipation and compared the use of laxatives in patients with chronic cancer pain treated with oral morphine and transdermal fentanyl in Germany. The frequency of bowel movements did not change significantly between patients on fentanyl and morphine, but the use of laxatives was reduced in 23 of 28 patients on transdermal fentanyl and increased in 2 of 28 patients on transdermal fentanyl. Quality-of-life questionnaire symptom scores showed significant decreases for constipation only.
Wenk et al., 2000	Research evidence	A small descriptive study (N = 15) explored whether the consumption of fresh baker's yeast reduces constipation in opioid-treated patients with advanced cancer in Argentina. Results were inconclusive. Although the author concluded that fresh baker's yeast was effective, nine patients used additional laxatives or enemas.
Choi & Billings, 2002	Systematic review/ meta-analysis	A systematic review examined the use of opioid antagonists in palliative care, particularly for managing opioid-induced constipation. A Medline search (1990–2000) was conducted using the terms <i>opioids</i> and <i>constipation</i> . Additional articles were pulled from the reference sections of the articles. Two hundred and seven articles were referenced. The majority of the studies examined the efficacy and tolerability of opioid antagonists that act centrally and peripherally (i.e.,

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Table 3. Summary of Literature Addressing the Management of Opioid-Induced Constipation in Adult Patients With Cancer (Continued)

STUDY	STUDY TYPE	SUMMARY
		naloxone, naltrexone, and nalmefene), and most of them looked at naloxone. The studies were small and of mixed quality. Many of the studies reported side effects, including loss of analgesia and symptoms of withdrawal. Parenteral and oral dosing was studied, with one author recommending starting at 0.8 mg BID, with a maximum of 5 mg per day, titrated up to 12 mg per day, monitoring for toxicity and loss of analgesic effect. Caution should be used in physically dependent patients. In addition, guidelines indicate that doses less than 10% of the daily morphine dose may be ineffective, whereas most patients respond to a dose equivalent of 20% of the total daily morphine dosage. However, the recommendations were based primarily on clinical experience. Limited studies of naltrexone and oral nalmefene were found. The research, looking at peripherally acting opioid antagonists (i.e., methylnaltrexone (MTNX) and ADL 8-2698 [alvimopan]), indicated that the agents do not affect analgesia or prevent the gastrointestinal side effects of opioids and that they are generally well tolerated. Six studies were found on MTNX. It is available IV or PO, and enteric coating of PO MTNX optimizes effect on small and large intestines. Increased sensitivity to MTNX was noted to occur in subjects receiving long-term opioid treatment, including those with cancer. Alvimopan is an investigational, peripherally selective <i>mu</i> opioid antagonist shown to increase gastrointestinal motility and stool weight significantly without antagonizing analgesia. It also has been shown to speed the recovery of bowel function and shorten the duration of hospitalization for patients receiving opioids for postoperative pain relief after undergoing partial colectomy or abdominal hysterectomy. Peripheral opioid receptor antagonists may be clinically useful for the prevention and treatment of opioid-induced constipation; however, studies are ongoing regarding their appropriate use and dosing.
McNicol et al., 2003	Systematic review/ meta-analysis	A critical review of the management of opioid side effects, including constipation, studied 17 articles. The authors noted that a bowel program should be initiated at the start of opioid therapy; however, recommended regimens were based on anecdotal experience. "It is commonly accepted that a stool softener and a stimulant are required" (p. 345). Docusate sodium and senna are often the agents of choice. Psyllium may be used, but fluid balance must be maintained. Metoclopramide helps patients with slow gastric mobility. Numerous articles favored the use of naloxone titration for amelioration of constipation in opioid-dependent people; however, various dosing regimens were found. In addition, several studies, including some randomized, controlled trials, showed laxation after MTNX administration. Some reports reported mild to severe abdominal cramps after laxation with MTNX. Opioid rotation also was discussed; in particular, switching to methadone or transdermal fentanyl appeared to offer some benefit in preventing constipation. However, the studies were small.
Miaskowski et al., 2005	Guidelines	This guideline addressed constipation in the setting of cancer pain management in adults and children. Constipation occurs in 40%–70% of patients who receive morphine for chronic cancer pain (Miaskowski et al., 2005). The need for prevention and routine assessment of bowel function was stressed. Recommendations were made for prevention and management regimens, including a stimulant laxative (senna or bisacodyl) and a stool softener (docusate sodium). In addition, the authors provided suggested regimens for intermittent exacerbation of constipation for patients already receiving stimulant laxatives: lactulose, sorbitol, magnesium citrate, milk of magnesia, and polyethylene glycol. Other interventions discussed were bulk-forming laxatives (with 200–300 ml of water), oral naloxone (6–14 mg daily), and opioid rotation to transdermal fentanyl or methadone.
National Comprehensive Cancer Network (NCCN), 2006a	Guidelines	All recommendations in the NCCN palliative care guidelines were categorized as 2A based on a low level of evidence, including clinical experience and uniform consensus indicating the appropriateness of intervention in the oncology population. Preventive measures recommended were the use of prophylactic medications such as titration of a stimulant laxative plus stool softener with a goal of one nonforced bowel movement every one or two days. If constipation persists, consider adding other oral or rectal interventions such as osmotic laxatives, PEG, enemas, or prokinetic agents. If constipation persists, consult or refer to specialized palliative care services or hospice.
Robinson et al., 2000	Expert opinion	The author described a quality-assurance/quality-improvement project to develop a research-based protocol to prevent constipation in patients with cancer at a large urban teaching hospital. A bowel protocol using Senokot-S®, Milk of Magnesia®, and Dulcolax® tablets was developed to prevent opioid-induced constipation in patients with cancer based on a literature review for research-based bowel protocols. Measurable outcomes were selected, and nurses were educated before implementation of the program. The authors concluded that adopting a bowel protocol may reduce nursing time related to impaction removal and treatment for constipation.

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Table 3. Summary of Literature Addressing the Management of Opioid-Induced Constipation in Adult Patients With Cancer (Continued)

STUDY	STUDY TYPE	SUMMARY
Tamayo & Diaz-Zuluaga, 2004	Expert opinion	<p>This was a comprehensive review of opioid-induced bowel dysfunction, including etiology, incidence, assessment, and treatment recommendations. A prophylactic regimen was recommended to prevent constipation in patients taking opioids. Recommendations included the following.</p> <ol style="list-style-type: none"> 1. Walking and activity should be encouraged. 2. Provide a comfortable, intimate environment for defecating. 3. The benefits and harms of different classes of laxatives and other interventions were reviewed, including bulking agents, osmotic agents, stimulating agents, lubricants, prokinetic agents, opioid antagonists, and colchicine. 4. Other treatments, including digital disimpaction, suppositories, enemas, and mechanical handling, were discussed. 5. Opioid rotation was discussed.

PEG 3350 was mentioned previously in relation to persistent constipation. In the United States, standard-dose PEG with electrolytes is known as Golytely® (PEG-3350 and electrolytes for oral solution, Braintree Laboratories, Inc.) and Colylytely® (Schwartz Pharma, Inc.). Low-dose PEG 3350 is available in the United States without electrolytes, marketed as Miralax, and with or without electrolytes in the United Kingdom and the Netherlands. Of note, PEG with electrolytes should be avoided in patients with renal compromise. Because of the lack of high-quality evidence supporting its use in the management of other forms of constipation in patients with cancer, all forms of PEG are categorized as *effectiveness not established*, excluding PEG 3350 for persistent constipation. In nononcology populations, evidence supports the use of all forms of PEG in patients with idiopathic chronic constipation. Four systematic reviews, including seven RCTs, two with populations of more than 100 participants, found that PEG (in various forms) has significant effects on stool frequency and consistency over placebo and lactulose (Brandt et al., 2005; Frizelle & Barclay, 2005; Petticrew et al., 2001; Ramkumar & Rao, 2005).

Tegaserod (Zelnorm®, Novartis) has not been investigated in patients with cancer, so its efficacy has not been established. However, it was approved by the FDA for the treatment of irritable bowel syndrome with constipation in women and for the treatment of chronic constipation in men and women younger than 65 (Brandt et al., 2005). On March 30, 2007, the FDA notified healthcare professionals and patients that Novartis had agreed to discontinue marketing tegaserod for the short-term treatment of women with irritable bowel syndrome with constipation and for patients younger than 65 years of age with chronic constipation. FDA analysis of safety data pooled from 29 clinical trials involving more than 18,000 patients showed an excess number of serious cardiovascular adverse events, including angina, heart attacks, and strokes, in patients taking tegaserod compared to patients taking placebo (FDA, 2007; Novartis, 2007). In July 2007, the FDA approved restricted use of tegaserod for patients for whom other treatment options were considered unsafe or ineffective. Use is now limited by strict criteria to patients without heart disease. Each individual patient is evaluated by Novartis under FDA supervision to ensure that he or she meets the criteria for treatment. In addition, patients who receive tegaserod are fully informed of the potential risks and

benefits of using tegaserod. Updated information can be found at www.fda.gov/bbs/topics/NEWS/2007/NEW01673.html.

Investigational agents: Alvimopan and methylnaltrexone, two peripherally selective *mu* opioid receptor antagonists, are under investigation for FDA approval. The drugs are promising in the prevention and treatment of OIC because they do not cross the blood-brain barrier and therefore do not inhibit the desired analgesic effects of opioids or cause symptoms of withdrawal.

Alvimopan compared to placebo has shown significant improvements in stool frequency in nononcology chronic opioid users (Webster et al., 2006) and in earlier return of bowel function and food tolerance in patients after abdominal surgery (Neary & Delaney, 2005). Side effects noted during the phase III trial of alvimopan include nausea, vomiting, and hypotension (Neary & Delaney). In June 2007, the FDA suspended the approval of alvimopan pending complete analysis of safety data (GlaxoSmithKline, 2007). In February 2008, the FDA extended the new drug application for alvimopan to May 2008 pending evaluation of the revised Risk Management Program.

Three phase III trials comparing parenteral MTNX with placebo for OIC had been completed as of June 2006. One RCT (N = 154) comparing two dosages of MTNX in patients with advanced illness (80% with cancer) found a significant decrease in time to laxation (60% within one hour); no significant difference was found between the two doses, but both were significantly more effective than placebo ($p < 0.0001$) (Yuan & Israel, 2006). Two phase III trials (N = 124 and N = 78) in patients with cancer found that laxation occurred within the first 24 hours of administration without increased pain or opioid withdrawal symptoms (Karver, Slatkin, Thomas, Israel, 2007). Cramping was the most common adverse event discussed in the literature (Choi & Billings, 2002; Yuan & Israel); flatulence, nausea, and dizziness were reported with higher doses (Yuan & Israel).

Nonpharmacologic interventions: Although dietary fiber often is recommended for the prevention and management of constipation, the research evidence is inconclusive. A synthesis of empirical research studies found mixed-quality studies and conflicting findings, primarily in subjects with chronic constipation (Brandt et al., 2005; Muller-Lissner, 1988; Ramkumar & Rao, 2005; Richmond & Wright, 2004). Of note,

Pharmacologic Interventions

- Laxatives
 - Bulk-forming laxatives
 - ♦ Methylcellulose (Brandt et al., 2005; Frizelle & Barclay, 2005; Ramkumar & Rao, 2005)
 - Lubricants
 - ♦ Glycerin suppositories (Frizelle & Barclay, 2005)
 - ♦ Mineral oil (Brandt et al., 2005)
 - Osmotic laxatives
 - ♦ Magnesium salts (Frizelle & Barclay, 2005)
 - ♦ Magnesia hydroxide (Phillips' Milk of Magnesia® (Brandt et al., 2005; Ramkumar & Rao, 2005))
 - Stimulant laxatives
 - ♦ Bisacodyl (Frizelle & Barclay, 2005)
 - ♦ Senna (Brandt et al., 2005; Frizelle & Barclay, 2005)
 - Non-bulk-forming fiber laxatives (Petticrew et al., 2001)
 - Stool softeners (Brandt et al., 2005; Frizelle & Barclay, 2005; Ramkumar & Rao, 2005)
 - ♦ Docusate sodium and calcium (Frizelle & Barclay, 2005)
- Prokinetic agent: erythromycin (Ramkumar & Rao, 2005)
- Enemas: phosphate enema and sodium citrate enema (Frizelle & Barclay, 2005)

Nonpharmacologic Interventions

- Activity and increased mobility (Bennett & Cresswell, 2003; Frizelle & Barclay, 2005; Richmond & Wright, 2004; Tamayo & Diaz-Zuluaiga, 2004)
- Aromatherapy, massage therapy, and aromatherapy massage (Fellowes et al., 2004)
- Biofeedback (Brandt et al., 2005; Coulter et al., 2002).
- Dietary fiber (Griffenberg et al., 1997; McEligot et al., 2002; Muller-Lissner, 1988; National Comprehensive Cancer Network, 2006a; Richmond & Wright, 2004)
- Fresh baker's yeast (Wenk et al., 2000)
- Herbal supplements (Brandt et al., 2005)
- Paraffin (Frizelle & Barclay, 2005)
- Seeds dils/arachisoil (Frizelle & Barclay, 2005)
- Stercullia (type of fiber) (Frizelle & Barclay, 2005)

Figure 3. Interventions for Constipation in Adult Patients: *Effectiveness Not Established*

fiber is not recommended in patients with advanced disease or those with inadequate fluid intake (NCCN, 2006a). A small, poorly controlled RCT of women with cervical cancer (N = 35) who had radical hysterectomies (type II or III) compared a high-fiber diet and dietary instruction (treatment group) versus regular diet (control group); women in the treatment group reported less abdominal cramping and positive bowel function changes compared to those on a regular diet. Limitations of the study included lack of regulation of the amount of fiber intake in the control group (Griffenberg et al., 1997). Further research is needed.

Increased activity and exercise have been considered beneficial in preventing and managing constipation by increasing blood flow to the digestive organs, leading to improved motility (Richmond & Wright, 2004). However, research findings are conflicting and few RCTs have supported the hypothesis (Frizelle & Barclay, 2005). A small, descriptive, prospective

study (N = 50) examining factors influencing constipation in patients with advanced oncology found no relationship between bowel scores and physical functioning (Bennett & Cresswell, 2003).

One small study suggested a potential benefit in using fresh baker's yeast (FBY) in patients with cancer; however, the intervention was not well tolerated and storage is an issue (Wenk et al., 2000). Furthermore, FBY is a fungus and would not be recommended for use in neutropenic patients with cancer.

Aromatherapy is the use of essential oils that produce odors thought to affect physiologic functions. A Cochrane review looked at the effects of aromatherapy with or without massage. The findings of the systematic review yielded eight RCTs of aromatherapy and/or massage in 357 patients with cancer and found no data to support their use in the management of constipation in the oncology population (Fellowes, Barnes, & Wilkinson, 2004).

Biofeedback is a mechanism used to train the body and mind to change a particular bodily function, bowel management for example. The majority of biofeedback RCTs included patients with pelvic floor dysenergia and excluded those with cancer. The findings of most of the studies were inconclusive; further research is needed to determine whether biofeedback is an effective intervention (Brandt et al., 2005; Coulter et al., 2002; Frizelle & Barclay, 2005).

Not Recommended for Practice

The category *not recommended for practice* describes "interventions for which lack of effectiveness or harmfulness has been demonstrated by strong evidence from rigorously conducted studies, meta-analyses, or systematic reviews or interventions for which the costs, burdens, or harms associated with the intervention exceed anticipated benefit" (ONS, n.d.).

Nalmefene and naltrexone, two opioid receptor antagonist medications similar to naloxone but with longer half-lives, have been studied for the management of OIC and were found to have harms that outweigh their benefits. The drugs are lipid soluble and cross the blood-brain barrier, acting on the central and peripheral opioid receptors. As a result, they have a propensity to inhibit the desired effect of analgesia as well as decrease the constipating effects of opiates (Choi & Billings, 2002). Because of that finding, few studies of nalmefene have been conducted in humans. Furthermore, naltrexone is not recommended for use in the oncology population because of reports of psychological dependence and dose-related elevations in serum transaminase levels, resulting in discontinuation of the drug (Choi & Billings).

Cisapride and Dantron™ (Hexal Pharma) are *not recommended for practice* in the management of constipation in adult patients, not specific to opioids. Cisapride, a prokinetic drug known to increase gastrointestinal motility, has been effective in managing constipation (Ramkumar & Rao, 2005). However, access to cisapride is restricted in some countries because of adverse cardiac effects and was taken off the market in the United States in 2000 by the FDA (Coggrave, Wiesel, & Norton, 2006). Dantron, a stimulant laxative, has not been approved by the FDA for use in the United States because it has been associated with rodent cancer.

Expert Opinion

Numerous articles and guidelines from experts have addressed the management of constipation in oncology and nononcology populations. A proactive approach to preventing constipation is recommended strongly in at-risk patients with cancer, particularly those receiving medications such as vinca alkaloids, which slow colonic transit times, or opioids (Bisanz, 2005; Harris & Jackson, 1977; NCCN, 2006a; NCI, 2006; Smith, 2001; Tamayo & Diaz-Zuluaga, 2004). Thorough assessment, including normal bowel pattern, medication history including use of laxatives, and a physical examination, also is widely recommended (Bisanz; Coggrave et al., 2006; Cope, 2001; Klaschik et al., 2003; Mancini & Bruera, 1998; NCCN, 2006a; NCI; Richmond & Wright, 2004; Sykes, 1994). Bisanz stressed the importance of normalizing the bowel (i.e., clearing the build-up of stool or impaction) before instituting a maintenance bowel regimen, as well as the importance of establishing goals for the frequency of bowel movements. She also recommended an interdisciplinary approach, including a nutrition consultation, in developing the plan of care. The importance of teaching patients about bowel function and involving them in the development of a bowel regimen also is stressed in the adult oncology literature (Bisanz; McCallum, Walsh, & Nelson, 2002).

Several general recommendations related to optimizing bowel function were noted in the literature. Expert opinion recommends a good bowel management program that includes increasing fluids and fiber and decreasing constipating medications or providing medications to offset constipating side effects of medications (Bisanz, 2005; Cope, 2001; NCCN, 2006a; NCI, 2006). Other recommendations include the following.

- Provide a comfortable, quiet, private environment for defecating (Folden, 2002; NCI, 2006; Smith, 2001; Sykes, 1994).
- Provide a toilet, bedside commode, and any necessary assistive devices and avoid the use of a bedpan whenever possible (Folden, 2002; NCI, 2006).
- Encourage adequate fluid intake (eight 8 oz glasses of fluid per day). Warm or hot liquids may be of some benefit (Consortium for Spinal Cord Medicine, 1998; NCI, 2006).
- Perform valsalva maneuver in patients with neurogenic problems (Consortium for Spinal Cord Medicine, 1998).
- Use mealtimes for bowel routines to capitalize on the gastrocolic reflex (Day, 2001).
- Maintain a diary of bowel movements (NCI, 2006).

After three days without a bowel movement, a patient should initiate a bowel management program (Bisanz, 2005; NCI, 2006). Insufficient high-quality evidence exists to recommend a systematic approach in the titration of a bowel program in patients with long-term effects of constipation. A systematic review, including 10 RCTs of patients with neurologic diseases (Coggrave et al., 2006) and expert opinion (NCCN, 2006a; NCI, 2006; Robinson et al., 2000), recommended an individualized approach based on outcomes to reach the desired goal for bowel management. Because insufficient evidence exists to guide a bowel management program, a trial-and-error approach with nursing guidance is common. The NCCN recommends titrating prophylactic medications, including a stimulant laxative plus a stool softener, to achieve one nonforced bowel movement every one or two days; increasing fluid intake; increasing dietary fiber if a patient has an

adequate fluid intake and physical activity; and increasing exercise if appropriate. Although the NCCN recommends the use of senna and docusate, this review of the literature did not identify any adequately powered trials to recommend the use of a specific stimulant laxative in the prevention of constipation.

Experts have identified several agents that are not recommended for practice or that should be used with caution.

- Castor oil is not recommended because it causes severe cramping (Mancini & Bruera, 1998).
- Prokinetic medications such as metoclopramide should be reserved for use in individuals with severe constipation and those resistant to bowel programs (Mancini & Bruera, 1998; NCCN, 2006a; Consortium for Spinal Cord Medicine, 1998). In addition, prokinetic agents should be avoided in patients with large abdominal tumors or bowel obstruction (Wilkes & Barton-Burke, 2006).
- Oral mineral oil is effective for hard stool but should not be used for routine prevention of constipation because it may interfere with absorption of some nutrients; it should not be used in patients at risk for aspiration (Bisanz, 2005; Mancini & Bruera, 1998).
- In myelosuppressed patients, rectal agents and manipulation (i.e., rectal examinations, suppositories, and enemas) are discouraged because they can lead to development of bleeding, anal fissures, or abscesses, which are portals for infection. In addition, the stoma of a neutropenic patient should not be manipulated (NCI, 2006).

Lastly, patients with impactions should be evaluated to determine whether impaction is high or low. With high impactions, stool remains in the ascending and transverse colon, causing nausea and vomiting, loss of appetite, abdominal distention, and cramping. In some cases, liquid stool oozing around an impaction can appear to be diarrhea but can be a sign of high impaction (Bisanz, 2005). High impactions are relieved comfortably with low-volume (less than 300 mL) milk and molasses enemas given high (12 inches) as many as four times per day along with an oral laxative (Bisanz; Thorpe, 2001). The recipe for a molasses enema is described in Figure 2. With low impactions, stool is detected by digital examination in the rectum. Patients with low impactions have the urge to defecate but are unable to expel stool. Patients may describe it as, "I can't sit because I feel like I'm sitting on something." For low impactions, oil retention enemas soften hard stool. In non-myelosuppressed patients, stool can be disimpacted manually followed by enemas of choice (Bisanz).

Highlights of Reviewed Literature: Pediatric Constipation

Constipation in the general pediatric population is predominantly functional constipation, also known as idiopathic constipation, functional fecal retention, and fecal withholding. The North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHN) (2006) described the evolution of functional constipation from painful defecation related to such things as toilet training, changes in routine, and stressful events to the development of retentive behavior and accompanying symptoms of constipation. Normal bowel

function (stool frequency) in children is dependent on age, with a gradual decline in mean stools per day until about 4 years of age (NASPGHN, 2006).

Only a small percentage of children have a pathologic cause of constipation. Children with cancer may have comorbid or coexisting etiologies, and one may exacerbate the other. The only literature that specifically addressed pediatric constipation in the oncology population was the *NCCN Clinical Practice Guidelines: Pediatric Cancer Pain* (NCCN, 2006b), which review interventions for the management of OIC. The guidelines are supported by uniform NCCN expert panel consensus based on lower-level evidence, including clinical experience. Numerous guidelines, research studies, and expert opinions addressing a variety of interventions for constipation and encopresis (voluntary or involuntary passage of stools causing soiling of clothes) in children without a diagnosis of cancer were found, and many of the interventions are used in pediatric oncology. However, because of the lack of any data in the pediatric oncology population, interventions were categorized under *effectiveness not established* or *expert opinion*. Interventions described in this article address constipation in children, with only a few recommendations for infants. The NASPGHN guidelines for constipation in infants and children referenced in the original project (Baker et al., 1999) were updated and available online after September 2006, the last search date for the PEP constipation project. The updated guidelines (NASPGHN, 2006) are endorsed by the American Academy of Pediatrics. Because no significant changes were found in recommendations between the older and revised versions, the newer version is referenced. The complete NASPGHN guidelines are available online at www.naspghn.org.

As of September 30, 2006, no interventions found in the literature could be categorized as *recommended for practice*, *likely to be effective*, or *benefits balanced with harms* for pediatric oncology.

Effectiveness Not Established

Pharmacologic interventions: Although studies have not been conducted in the oncology population, a high level of evidence was found for the safety, effectiveness, and tolerability of PEG 3350 in pediatric patients for the short-term and long-term management of chronic or functional constipation as well as fecal impaction (Arora & Srinivasan, 2005; NASPGHN, 2006). PEG 3350 was associated with fewer side effects and better laxation outcomes in at least four RCTs as well as numerous lower-level studies (Arora & Srinivasan; Bell & Wall, 2004; Kinservik & Friedhoff, 2004). A number of the studies found that compliance with PEG 3350 was better than with other laxatives such as lactulose and magnesium hydroxide (milk of magnesia) (Arora & Srinivasan). Additional RCTs are needed to determine the optimal dosing and most effective form of PEG 3350 in children as well as its role in constipation management in pediatric oncology.

The other pharmacologic intervention categorized as *effectiveness not established* is stimulant laxatives; their use in the general pediatric population is not supported by a high level of evidence (Bell & Wall, 2004; NASPGHN, 2006; Rubin, 2004). NASPGHN recommended only short-term use of stimulant laxatives as rescue therapy in selected patients to prevent fecal im-

paction or in patients who are difficult to manage with mineral oil, magnesium hydroxide, lactulose, or sorbitol. NASPGHN did not recommend the use of stimulant laxatives for maintenance therapy in the general pediatric population.

Nonpharmacologic interventions: Support for the use of dietary fiber in the management of pediatric constipation is mixed and requires additional investigation (Bell & Wall, 2004; NASPGHN, 2006; Rubin, 2004). The evidence supporting the use of biofeedback in children with defecation disorders, including encopresis, is inconsistent (Brazzelli & Griffiths, 2006; Coulter et al., 2002; Rubin).

Not Recommended for Practice

The use of cisapride as an effective laxative in the pediatric population was supported by high levels of evidence from several systematic reviews (Baker et al., 1999; Rubin, 2004). However, as previously noted, cisapride was taken off of the market and therefore is not recommended for practice. In addition, soap suds, tap water, and magnesium enemas are not recommended for rectal disimpaction in children because of their potential toxicity, and enemas are not recommended for use in infants (Bell & Wall, 2004; NASPGHN, 2006). Lastly, information is conflicting related to the use of corn syrup as a stool softener based on concerns that it is not sterilized when packaged and may be a source of *Clostridium botulinum* spores (Bell & Wall). The spores have been isolated in samples of corn syrup; however, since changes in corn syrup processing were initiated, no further spores have been identified (Risko, 2006). The NASPGHN (2006) guidelines state that "light and dark corn syrup are not considered to be potential sources of *Clostridium botulinum* spores" (p. E11) and thus can be used as stool softeners in infants and children. Any pasteurized corn syrup is considered safe for use in infants and children. Corn syrup was categorized under *not recommended for practice* on the constipation PEP cards, based on the 2004 article by Bell and Wall citing the potential risk of *Clostridium botulinum*, because the pediatric cancer population often is immunocompromised.

Expert Opinion

In the literature addressing constipation in children without cancer, many strategies for prevention and management were the same as for adults. The importance of providing education and counseling for parents and children regarding the etiology of constipation and the need for a consistent and positive approach to the issue was stressed by the NASPGHN in its 2006 guidelines. Consistent with expert opinion regarding adults, the guidelines also support the need to disimpact children before initiation of a maintenance bowel regimen. Pharmacologic interventions for disimpaction include oral and rectal medications, such as enemas when age appropriate. No high-level evidence has clarified which route is more effective, and clinicians should consider each case individually when determining the choice of treatment. Disimpaction with the oral administration of high-dose PEG, mineral oil, or both has been found to be effective in the clinical setting. Phosphate soda, saline, and mineral oil enemas are considered acceptable rectal therapies, and bisacodyl suppositories for children and glycerin suppositories for infants younger than one year also may be used (Bell & Wall, 2004; NASPGHN).

Maintenance therapy aimed at preventing recurrence includes dietary and behavior modifications as well as laxatives. The evidence related to dietary fiber is conflicting; however, numerous experts support increasing whole grains, fruits, and vegetables as part of the treatment for constipation (Bell & Wall, 2004; NASPGHN, 2006; NCCN, 2006b; Rubin 2004). In addition, Baker et al. (1999) noted that sorbitol found in some juices (prune, pear, and apple juices) can cause an increase in frequency and water content of stool. In addition, modifying behaviors and establishing routine toilet habits are important adjuncts in the treatment of pediatric constipation (Bell & Wall; NASPGHN). For children one year of age or older, mineral oil, magnesium hydroxide, PEG, lactulose, sorbitol, or a combination may be used for maintenance bowel regimens (Bell & Wall; NASPGHN; Rubin). For children, mineral oil may be more effective than senna-based laxatives but less effective than osmotic laxatives (Brandt et al., 2005). As noted previously, stimulant laxatives are not recommended for maintenance therapy but can be used for acute constipation, for patients who have failed other protocols, and for children receiving opioids (Bell & Wall; NASPGHN; NCCN, 2006b).

Implications for Practice and Research

Nurses are in a unique position to impact the quality of life of patients with cancer through the assessment, prevention, and management of constipation. Clinicians should understand individual characteristics that predispose patients to developing constipation and guidelines that are effective for managing it in the oncology population. Constipation is a common gastrointestinal symptom, and the lack high-quality evidence to support the pharmacologic and nonpharmacologic interventions often recommended in the literature is surprising. Most interventions identified were categorized as *effectiveness not established* because the interventions were not studied in patients with cancer. Expert opinion forms the foundation of current practice because of the lack of evidence. When implementing evidence-based practice for the management of constipation, consider the strength of the evidence, clinical expertise, and patient preferences (Melnik & Fineout-Overholt, 2005).

A limitation in synthesizing findings for this project was the lack of consistent definitions used to describe the issue, the interventions, and the measurement of outcomes across studies. Researchers must define study variables clearly and, when possible, build on existing definitions so that a standardized definition can be established. This will facilitate the ability to synthesize research findings in the future. Nurse scientists in collaboration with clinical experts can contribute to evidence-based practice by identifying areas for research and developing research protocols to study this phenomenon. Some authors propose the use of mixed-methods research, combining qualitative, experiential, and intuitive aspects of nursing knowledge with the quantitative methods of RCTs to broaden the base for evidence-based practice (Flemming, 2007). Answering high-priority clinical questions using the PICO format is advised. The process identifies: (a) the *patient population* of interest, (b) the *intervention* to be evaluated, (c) the *comparison* intervention, and (d) the *outcomes* of the study (Melnik & Fineout-Overholt, 2005). Combining clinical expertise and patient input

- Research every category of laxatives and determine which have the most comfort and best outcome for patients with cancer, adult and pediatric, at various stages of the disease process (e.g., mineral oil, lactulose, magnesium hydroxide, docusate sodium, senna-S, Dulcolax® tabs, Miralax®, prokinetic drugs)
- Which treatment protocols need a proactive approach to preventing constipation?
- Prove through research the value of low volume, hyperosmolar enemas given high and retained for 20 minutes while lying on the right side, leaving the enema tube in place to negate the defecation reflex.
- Prove through research that treatment is available for an impacted, myelosuppressed patient.
- Assess the prevalence of constipation in patients receiving treatment protocols, including ondansetron.
- What is the value of cleaning out the colon before starting patients on treatment protocols that cause constipation and myelosuppression?
- What do patients need to know to prevent constipation when taking opioids and constipating treatment regimens?
- Compare the use of nutritional versus medicinal fiber in the prevention of constipation in patients with cancer, adult and pediatric, at various stages of disease.
- How effective is prune juice followed by a hot liquid in patients with cancer after surgery and in patients on other treatment protocols?
- What are the options for treating impactions in patients with renal disease and who are myelosuppressed?
- How can treatments for constipation be made palatable for pediatric patients (food, fluid, fiber, and medications)?
- What do mothers need to know about prevention of constipation in their children?

Figure 4. Areas for Potential Research

in the research design will produce clinically relevant research outcomes. When studying pharmaceutical agents, researchers should determine whether observed side effects are attributable to the drug or the disease process. Figure 4 contains a list of suggested research areas based on the gaps identified.

Conclusions

Constipation continues to be overlooked and under-reported. When not addressed proactively in patients with cancer, it often results in increased discomfort and negative consequences, some of which can be life threatening (e.g., impaction, bowel perforation). Oncology nurses should identify patients at risk and implement evidence-based interventions. The goal for managing constipation should be prevention, accomplished through patient education and proactive treatment to decrease associated discomfort. Selection of interventions should be individualized for patients according to history, disease process, and plan of care. Despite the variety of interventions used commonly for the prevention and management of constipation, a surprising lack of research has evaluated the effectiveness of interventions in the oncology population. Although a breadth of research exists in some areas related to constipation in nononcology populations, many gaps in the evidence remain. As a result, the

prevention and management of constipation in patients with cancer is based on tradition, theoretical considerations, clinical practice experience, and findings extrapolated from nononcology populations. Further studies are needed in patients with cancer and should include controls, larger samples, and clearer explanations of outcomes measured. As research evolves, oncology nurses should synthesize the information and update the evidence underlying various interventions.

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Put Evidence Into Practice

The Putting Evidence Into Practice® (PEP) resource card for constipation appears on the following pages. For more information about evidence-based interventions for constipation, including different versions of the card, definitions, evidence tables, and a complete list of references, visit www.ons.org/outcomes/volume2/constipation.shtml. PEP resources for several other nursing-sensitive patient outcomes are available at www.ons.org/outcomes.

The *Clinical Journal of Oncology Nursing* wants to hear how you use the PEP resources to improve the quality of cancer care that you deliver. E-mail CJONEditor@ons.org to share your experiences with nurses everywhere.

Appendix. Putting Evidence Into Practice® Card on Constipation in Patients With Cancer

What interventions are effective for preventing and treating constipation in patients with cancer?

RECOMMENDED FOR PRACTICE

Interventions for which effectiveness has been demonstrated by strong evidence from rigorously conducted studies, meta-analyses, or systematic reviews and for which expectation of harms is small compared with the benefits

No intervention can be recommended for nursing practice as of September 30, 2006.

LIKELY TO BE EFFECTIVE

Interventions for which effectiveness has been demonstrated by supportive evidence from a single rigorously conducted controlled trial, consistent supportive evidence from well-designed controlled trials using small samples, or guidelines developed from evidence and supported by expert opinion

Opioid-Induced Constipation: Prophylactic Regimen

A proactive approach, including initiation of a prophylactic regimen, is needed to prevent constipation when taking opioids.¹⁻³ However, not enough evidence exists to identify the most effective regimen (see Expert Opinion section).

Opioid-Induced Constipation: Opioid Rotation

Research has demonstrated that some opioids have less constipating effect than others, and rotating opioids would decrease the associated side effects.^{1,4}

- Switching opioids from sustained-release oral morphine to transdermal fentanyl patches may decrease constipation.^{1,2,4-6}
- Switching opioids to methadone may result in a reduction in laxative use.^{1,2}

Refractory Constipation in Adults

The National Comprehensive Cancer Network recommends the use of polyethylene glycol (PEG) as a treatment alternative for patients with cancer with persistent constipation.⁷ Standard-dose PEG with electrolytes in the United States is known as Golytely® (Braintree Laboratories) and Colyte® (Schwarz Pharma). Low-dose PEG, referred to as PEG 3350, is available without electrolytes in the United States and is marketed as Miralax® (Schering-Plough). Stimulant or osmotic laxatives are effective in improving bowel function in patients with cancer with persistent constipation and/or at the end of life, and some patients may need both types of laxatives to achieve optimal results.^{3,7}

BENEFITS BALANCED WITH HARMS

Interventions for which clinicians and patients should weigh the beneficial and harmful effects according to individual circumstances and priorities

Opioid-Induced Constipation: Oral Naloxone

Oral naloxone, an opioid receptor antagonist, has shown mixed results for managing opioid-induced constipation, potentially causing adverse reactions, including loss of analgesia and withdrawal symptoms.^{1,2,8-10}

EFFECTIVENESS NOT ESTABLISHED

Interventions for which there are currently insufficient or conflicting data or data of inadequate quality, with no clear indication of harm

Pharmacologic Interventions for Constipation in Adults

These interventions are based on high-level evidence in nononcology populations and need to be studied in the oncology population.

Bulk Laxatives (Psyllium)

Psyllium is recommended for patients with a good functional status, including the ability to tolerate adequate fluids for the prevention and treatment of constipation.¹¹⁻¹³ Most bulk laxatives need to be taken with at least 200–300 ml of water.² Psyllium should be avoided in patients who do not have adequate physical activity or fluid intake and/or who have severe constipation, as it may worsen manifestations of constipation.¹² Psyllium administered in large amounts has been associated with increased flatulence, abdominal distension and bloating, mechanical obstruction of the esophagus and colon, and anaphylactic reactions.^{11,14}

Osmotic Laxatives (Sorbitol, Lactulose)

Osmotic laxatives such as sorbitol or lactulose are associated with significant improvements in stool consistency, fecal impaction, and other symptoms of chronic constipation, such as straining of stool.^{12,14} Adverse effects include abdominal cramping, flatulence, bowel distension, an unpleasant sweet taste, and diarrhea. In many cases, osmotic laxatives were no better than other laxatives such as senna.^{7,15} Lactulose often is used in combination with a stimulant laxative in difficult-to-treat constipation.¹⁴⁻¹⁶

Polyethylene Glycol With or Without Electrolytes

A high level of evidence was found in the nononcology population regarding the safety and efficacy of PEG with or without electrolytes.^{11-14,17} Caution: Do not administer electrolytes when kidney function is compromised.

Tegaserod

The effectiveness of tegaserod, a 5-HT₄ agonist, in patients with cancer has not been established because this population was excluded from published premarketing studies.¹⁸ However, in nononcology patients, tegaserod has been shown to be effective and safe in relieving symptoms of chronic constipation, with a recommended dosage of 6 mg orally twice a day.^{14,18,19}

Pharmacologic Intervention for Pediatric Patients With Chronic Constipation

This intervention is based on high-level evidence in nononcology populations and needs to be studied in the oncology population.

PEG 3350

Although studies have not been conducted in the oncology population, PEG 3350 has been found to be safe, effective, and well-tolerated in pediatric patients.²⁰⁻²²

Interventions for Constipation in Adults and Pediatric Patients Where Data Are Insufficient

The effectiveness of the interventions described below has not been established because they are based on studies that are inadequately powered, have limited sample sizes, or have flaws in study design or in study procedures. The majority of the research is in nononcology patients who have chronic constipation. Further study using randomized controlled trials is needed.

Pharmacologic Interventions (Adults)

- Laxatives
 - Bulk-forming laxatives
 - ♦ Methylcellulose^{11,13,14}
 - Lubricants
 - ♦ Glycerin suppositories¹¹
 - ♦ Mineral oil¹⁴
 - Osmotic laxatives (saline)
 - ♦ Magnesium salts¹¹
 - ♦ Magnesium hydroxide (Phillips' Milk of Magnesia®, Bayer Consumer Care)^{13,14}
 - Stimulant laxatives
 - ♦ Bisacodyl¹¹
 - ♦ Senna^{11,14}
 - Non-bulk-forming fiber laxatives¹²
 - Stool softeners: Systematic reviews of the chronic constipation population found insufficient data to make a recommendation, and the consensus was that stool softeners are minimally effective in improving symptoms of constipation.^{11,13,14}
 - ♦ Docusate sodium and docusate calcium^{11,23}
- Prokinetic agent: Erythromycin¹³
- Enemas: Phosphate enema and sodium citrate enema¹¹

For information on investigational drugs used in preventing and treating constipation, see the detailed ONS PEP card at www.ons.org/outcomes.

Nonpharmacologic Interventions (Adults)

- Activity/increased mobility^{11,24,25}
- Aromatherapy, massage therapy, and aromatherapy massage²⁶
- Biofeedback: Many studies excluded patients with cancer. Of the studies found, the data were inadequate to support its efficacy in treating chronic constipation.^{11,14,27}
- Dietary fiber: A relatively large body of mixed-quality evidence indicates positive effects of dietary fiber on bowel function in oncology and nononcology populations.^{25,28,29} Note: Fiber is not recommended in patients with inadequate fluid intake, such as patients with advanced disease.^{3,30}
- Fresh baker's yeast³¹
- Herbal supplements¹⁴

Pharmacologic Interventions (Pediatrics)

- Stimulant laxatives^{22,32}

Nonpharmacologic Interventions (Pediatrics)

- Biofeedback: The evidence supporting the use of biofeedback in children is inconsistent and primarily relates to defecation disorders.^{27,32,33}
- Dietary fiber^{22,32}
- Soy milk in children who are lactose intolerant³⁴

NOT RECOMMENDED FOR PRACTICE

Interventions for which lack of effectiveness or harmfulness has been demonstrated by strong evidence from rigorously conducted studies, meta-analyses, or systematic reviews or interventions for which the

costs, burdens, or harms associated with the intervention exceed anticipated benefit

- Cisapride: A prokinetic drug that is known to increase gastrointestinal motility¹³ (Caution: Restricted access exists in some countries because of adverse cardiac effects. Cisapride was taken off the market in the United States in 2000 by the U.S. Food and Drug Administration [FDA].)³⁵
- Corn syrup: No longer recommended as a stool softener because it is not sterilized when packaged and may be a source of *Clostridium botulinum* spores²²
- Dantron™ (Hexal Pharma)²⁴: This drug has not been approved by the FDA for use in the United States because it has been associated with rodent cancer.
- Enemas in children: Soap suds, tap water, and magnesium enemas²²
- Enemas in infants²²
- Nalmefene: Limited studies of the efficacy of oral nalmefene in humans are available because of its propensity to reverse analgesia or to induce withdrawal.¹⁰
- Naltrexone: A lipid soluble drug that crosses the blood-brain barrier and may negatively affect the analgesic effects of opioids.³⁶ It has been associated with dose-related elevations in serum transaminase levels, resulting in the discontinuation of the drug.¹⁰ (Note: This is different from methyl naltrexone.)

EXPERT OPINION

Low-risk interventions that are (1) consistent with sound clinical practice, (2) suggested by an expert in a peer-reviewed publication (journal or book chapter), and (3) for which limited evidence exists. An expert is an individual who has authored articles published in a peer-reviewed journal in the domain of interest.

Special Note: Myelosuppressed Patients

Avoid rectal agents and/or manipulation (i.e., rectal examinations, suppositories, and enemas) in myelosuppressed patients. These actions can lead to development of bleeding, anal fissures, or abscesses. In addition, avoid manipulation of the stoma of neutropenic patients.³⁷

General Constipation (Both Adult and Pediatric)

Prevention

- Take preventive measures in anticipation of constipation for those receiving medications, such as vincristine or other chemotherapies, that slow colonic transit times.^{38,39}

Assessment

- Perform a thorough history and physical examination in evaluation of constipation before determining the treatment plan, including assessment of individual risk factors.^{3,14,25,35,37,39-43}
- Obtain a nutritional consult.⁴¹
- Consider in-depth diagnostic workup for constipation after patient fails initial treatment.^{14,41}

Interventions

- Teach the patient about bowel function.^{40,41}
- Provide a comfortable, quiet, private environment for defecating.^{37,44,45}
- Provide a toilet, bedside commode, and any necessary assistive devices. Avoid the use of a bedpan when possible.^{37,45}
- Minimize use of constipating medications whenever possible.^{3,41}
- Involve the patient in development of a bowel regimen.⁴¹
- Encourage the intake of warm or hot liquids.^{37,46}
- Castor oil: Not recommended secondary to severe cramping⁴²

Opioid-Induced Constipation

Stimulant Laxatives Plus Stool Softener

This combination is recommended when initiating opioid therapy.^{2,3,37,41,47,48} A useful bowel regimen includes docusate sodium (100–300 mg per day) along with senna (two to six tablets twice a day).^{2,37} Bulk laxatives are not recommended for opioid-induced constipation because of the risk of bowel impaction in poorly hydrated patients.²

- The laxative dose should be individually titrated for effectiveness according to bowel function, not opioid dosing.^{2,9,24,49}

Constipation in Adults

Pharmacologic Interventions

- Prokinetic medication (i.e., metoclopramide) should be reserved for use in individuals with severe constipation and those resistant to bowel programs.^{3,42,46} Caution: Avoid in patients with large abdominal tumors or bowel obstruction.^{3,41}
- Oral mineral oil is effective for hard stool but should not be used for routine prevention of constipation because it may interfere with absorption of some nutrients.^{41,42}
- Expert opinion supports the use of a stimulant laxative plus a stool softener in preventing and managing constipation in patients at the end of life.³

Nonpharmacologic Interventions

- Recommended fluid intake per day is eight 8-oz glasses in adults.^{3,25,41}
- Treat high and low impactions differently.⁴¹
 - High impactions: These are comfortably relieved with low-volume (< 300 ml) milk and molasses enemas up to four times per day along with an oral laxative.⁴¹ For enema recipe, see definition table at www.ons.org/outcomes.
 - Low impactions: Oil-retention enemas soften hard stool. In nonmyelosuppressed patients, stool can be manually disimpacted followed by enemas of choice.⁴¹

Individualized Bowel Management Program

- After three days without a bowel movement, initiate a bowel management program.^{37,41}
- A good program includes fluids, fiber, and a decrease in constipating medications or provision of medications to offset constipating side effects of medications.^{3,37,39,41}

Constipation in Pediatric Patients

Pharmacologic Interventions

- Disimpaction can be achieved with either oral or rectal medications, including enemas in age-appropriate children.⁴⁰ For specifics, see detailed ONS PEP card at www.ons.org/outcomes.

Nonpharmacologic Interventions

- A balanced diet containing whole grains, fruits, and vegetables is recommended as part of the treatment of constipation.^{40,50}

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Definitions of the interventions and full reference lists are available at: www.ons.org/outcomes. Literature search completed through September 2006.

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