

Special Article

Consensus Recommendations for the Management of Constipation in Patients with Advanced, Progressive Illness

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Abstract

Constipation is a highly prevalent and distressing symptom in patients with advanced, progressive illnesses. Although opioids are one of the most common causes of constipation in patients with advanced, progressive illness, it is important to note that there are many other potential etiologies and combinations of causes that should be taken into consideration when making treatment decisions. Management approaches involve a combination of good assessment techniques, preventive regimens, appropriate pharmacological treatment of established constipation, and frequent monitoring. In this vulnerable patient population, maintenance of comfort and respect for individual preferences and sensitivities should be overriding considerations when making clinical decisions. This consensus document was developed by a multidisciplinary group of leading Canadian palliative care specialists in an effort to define best practices in palliative constipation management that will be relevant and useful to health care professionals. Although a wide range of options exists to help treat

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constipation and prevent its development or recurrence, there is a limited body of evidence evaluating pharmacological interventions. These recommendations are, therefore, based on the best of the available evidence, combined with expert opinion derived from experience in clinical practice. This underscores the need for further clinical evaluation of the available agents to create a robust, evidence-based foundation for treatment decisions in the management of constipation in patients with advanced, progressive illness. J Pain Symptom Manage 2010;40:761–773. © 2010 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Constipation, palliative care, advanced illness, laxatives, mu-opioid antagonists, management, guidelines

Introduction

The primary goal of palliative care is the relief of suffering to optimize quality of life and the quality of dying for patients and their families.¹ Collaborative and informed discussions between health care clinicians, the patient, and family are essential to develop strategies that will both promote comfort and maintain dignity.²

Constipation is a highly prevalent and distressing symptom in patients with advanced, progressive illnesses. Depending on the population of patients studied, constipation is especially common, with symptom surveys showing a prevalence of 23%–70% of those with terminal illnesses.^{3,4} Considering also the high prevalence of pain in terminally ill patients both cancer and noncancer patients and the prevalent treatment of these patients with opioids, constipation, a major adverse effect of opioids, is very common.^{5,6}

For constipation in patients with advanced, progressive illness, management approaches involve a combination of good assessment techniques, preventive regimens, appropriate pharmacological treatment of established constipation, and frequent monitoring.

Process of Consensus Recommendations Development

The following Canadian consensus recommendations are the result of an effort to define best practices in the management of constipation in patients with advanced, progressive illness. As there is a limited body of evidence evaluating pharmacological interventions in constipation, these recommendations are

based on the best of the existing evidence, combined with expert opinion derived from experience in clinical practice. They are intended to serve as a base for further research and further guideline development.

These recommendations were developed according to the ADAPTE protocol, an internationally validated generic guideline adaptation process designed to foster high-quality guidelines relevant for use in specific regions.⁷ A comprehensive literature search (1990 to present) was conducted in PubMed and the Cochrane Library using the following key words: constipation, palliative care, advanced illness, laxatives, management, guidelines, and recommendations. Based on the current literature identified in the search, a preliminary content outline was developed and circulated for approval by the core members of the Canadian Consensus Group. This multidisciplinary group consists of seven leading Canadian specialists in palliative care. The group reviewed the first draft of these recommendations in detail at a Steering Committee Meeting, which took place on June 26, 2009. Subsequent drafts were circulated to six secondary reviewers for editorial comment and further development. In a third developmental stage, the article was subjected to national review through a web-based survey sent to 300 multidisciplinary health care providers (including palliative care specialists, oncologists, nurses, and pharmacists) across Canada, whose input was considered in producing the final document.

In addition to publication in this journal, we will be disseminating these recommendations through local, provincial, and national conferences. Also, they will be highlighted in the

e-newsletters of various organizations, including the Canadian Society of Palliative Care Physicians and the Canadian Hospice Palliative Care Association.

Definition of Constipation in the Setting of Advanced, Progressive Illness

Two aspects that should be considered when defining constipation in patients with advanced illness are as follows¹:

- Measurable symptoms (defecation frequency and characteristics).
- Individual patient's perception of constipation and their level of discomfort.

Although the ROME III criteria for constipation are widely accepted and useful in research protocols, they are rarely used in clinical practice as not all patients who need treatment fit the criteria.⁸

Constipation is primarily associated with infrequent (relative to the patient's normal bowel habits), difficult passage of small, hard stools.^{1,8,9} Individuals may report associated symptoms, such as the inability to defecate at will, pain, and discomfort when defecating, straining, unproductive urges, flatulence or bloating, or a sensation of incomplete evacuation.¹

It cannot be overemphasized that the normal frequency of bowel movements is highly individualized. Frequency of bowel movements alone as a criterion may not capture some of the other aspects of constipation as defined by the patient. However, as a general principle, if a patient is defecating less than three times per week, constipation may be a problem and an appropriate assessment should be conducted.

Burden of Constipation

Constipation significantly increases the burden on the severely ill patient, their family, and the health care system. Table 1 summarizes this burden.

Etiology of Constipation in Patients with Advanced, Progressive Illness

Patients with advanced illness are at greater risk of constipation because of a wide variety of causes, not just opioids as is often assumed. Table 2 lists the causes of constipation.

Table 1
The Burden of Constipation on Patient, Family, and Health Care System^{10,17-19}

Patient	<ul style="list-style-type: none"> • Decreased quality of life • Increased discomfort, pain, and distress • Nausea and vomiting • Hemorrhoids • Anal fissures • Spurious diarrhea • Fecal impaction • Need for additional medications • Increased emergency visits and hospitalization
Family	<ul style="list-style-type: none"> • Increased stress • Increased health care costs
System	<ul style="list-style-type: none"> • Increased health care resource utilization <ul style="list-style-type: none"> ○ Nursing time ○ Emergency visits ○ Hospital admissions ○ Medication costs

Assessment and Diagnosis of Constipation in Patients with Advanced, Progressive Illness

Constipation is just one of the many symptoms and conditions the clinician must take into consideration when evaluating patients with advanced illness. A clinical assessment must be comprehensive and tailored to respond to each patient's unique needs and preferences. All patients with advanced progressive illnesses should be monitored frequently (at least every three days) with inquiry and with a validated assessment scale.

Components of Assessment and Investigation^{1,2}

Global History. Evaluate constipation in the context of the patient's overall context: the primary illness; its complications and treatments; and physical, psychological, social, functional, and spiritual needs. The history should include a systematic assessment of all of the elements listed in Table 2.

Constipation History. Take a constipation history from the patient, establishing:

- "Normal" bowel pattern (for individual baseline assessment).
- Current bowel performance:
 - Onset, duration, frequency, pattern
 - Aggravating and alleviating factors
 - Stool volume and appearance (consistency, color, odor, blood, mucous)

Table 2
Common Causes of Constipation in Patients with Advanced, Progressive Illness¹

Common Causative Factors	
Pharmacologic agents (often used in combination for symptomatic relief in patients requiring palliative care)	Opioid analgesics, antacids, antiepileptics, antiemetics (5-HT ₃ antagonists), antidepressants, cancer chemotherapeutic agents, iron (orally administered), and others
Metabolic disturbances	Dehydration, hypercalcemia, hypokalemia, uremia, hypothyroidism, diabetes
Weakness/fatigue	Proximal and central myopathy
Neurological disorders	Cerebral tumors, spinal cord involvement, sacral nerve infiltration, autonomic dysfunction
Structural abnormalities	Pelvic tumor mass, radiation fibrosis, painful anorectal fissures
Anorexia	Reduced fluid and food intake, poor appetite, and low fiber intake
Environmental/cultural	Lack of privacy, comfort, or assistance with toileting Cultural sensitivities regarding defecation
Uncontrolled pain associated with defecation	Anorectal pain Bone pain and other cancer pain
Other factors	Advanced age, inactivity, decreased mobility, confined to bed, depression, sedation

- Bloating, flatus
- Diarrhea
- Tenesmus

Constipation should still be considered even in patients who are anorexic and have limited oral intake as stools continue to be produced even in the absence of good oral intake (fecal content also consists of unabsorbed gastrointestinal secretions, shed epithelial cells, and bacteria).¹⁰

Constipation Evaluation Scale. Confirm the presence and severity of constipation using a validated constipation assessment scale. The Victoria Hospice Society Bowel Performance Scale (below) is one of several scales currently used in Canada. The use of images to describe stool consistency has been shown to be meaningful to patients. Other recommended scales include the Bristol Stool Form Scale and the Constipation Assessment Scale (CAS) scale.^{2,11,12}

The group supported the inclusion of a portion of the Victoria Hospice Bowel Performance Scale (BPS) (Fig. 1).

Physical Examination.^{8,9} Conduct a physical examination for signs of constipation. Privacy and cultural sensitivities should be taken into consideration before performing a rectal examination.

The important elements include the following:

- Abdominal examination:
 - Abdominal distension
 - Visible peristalsis
 - Increased bowel sounds
 - Fecal masses (indentable, mobile, rarely tender)
 - Signs of bowel obstruction
- Rectal examination:
 - Anal sphincter tone
 - Presence/absence of stool
 - Stool consistency, color, presence of mucous
 - Possible masses obstructing the rectum
 - Hemorrhoids
 - Anal fissures or abscesses
 - A dilated rectum may indicate higher constipation in the sigmoid area

-4	-3	-2	-1	BPS Score 0
← Constipation				Normal
Impacted or Obstructed +/- small leakage 	Formed Hard with pellets 	Formed Hard 	Formed Solid 	Characteristics Formed Semi-solid 
No stool produced	Delayed ≥ 3 days	Delayed ≥ 3 days	Patient's Usual	Pattern Patient's Usual
Unable to defecate despite maximum effort or straining	Major effort or straining required to defecate	Moderate effort or straining required to defecate	Minimal or no effort required to defecate	Control Minimal or no effort to defecate

Fig. 1. Bowel Performance Scale (BPS). Only the left side is shown including constipation; the right side being diarrhea. © Victoria Hospice Society.”

Caution should be exercised if performing rectal examinations in immunocompromised patients; rectal examination may lead to the development of anal fissures or abscesses, which are portals of entry for infection.¹⁰

*Investigations.*⁸ Potential lab investigations are limited, but may include calcium and CBC (complete blood count, including white count) to assess the cause of constipation or risk of complications.

In cases of severe constipation or constipation unresponsive to treatment, an abdominal flat plate (plain X-ray with patient lying in supine position) should be performed in all patients who are well enough to have one performed.⁹ This tends to be an underused diagnostic tool, but it can be useful to help quantify constipation and exclude fecal impaction.

Patients with signs of obstruction should be evaluated for potential surgical intervention (if it is consistent with their goals of care).

Management

General Principles

When constipation is confirmed in the patient with advanced, progressive illness, the degree of intervention required should be determined based on patient status and preference, where they are in the trajectory of their illness, and the amount of distress that constipation is causing. Maintenance of patient comfort and dignity should be the clinician's paramount concern.

General Goals^{1,2}

The goals of effective management of constipation include:

- Relieve pain and discomfort of constipation, increasing patient's quality of life
- Re-establish bowel habits to the patient's comfort and satisfaction
- Restore optimal level of independence regarding bowel habits
- Consider individual patient preferences
- Prevent or treat related gastrointestinal symptoms such as nausea, vomiting, abdominal distension, and abdominal pain

Nonpharmacological Interventions

Oral Intake—Fluid and Fiber. Adequate fluid intake is important to promote normal bowel function, but the ability to consume fluids often diminishes with disease progression. Fluid intake may be increased with food containing a large amount of water such as soups, fruits, gelatin desserts, yoghurt, mousses, sauces, milky desserts, and fortified supplements.¹⁰

Patients with advanced progressive illnesses often have anorexia, with an associated reduction in fiber intake. The effective and safe use of dietary fiber supplements requires at least 1.5 L of water per day, which may often be beyond the capabilities of the patient with advanced disease. Fiber may not be an appropriate choice to prevent or treat constipation in this population.¹⁰

Mobility. Patients are often beset by weakness and fatigue, which significantly compromises the capacity for physical activity.

When possible and appropriate, increasing patient activity and range of motion should be encouraged as a means of alleviating constipation.

Optimized Toileting. The most powerful gastrocolic reflex occurs in the morning. Health care providers should encourage the patient to sit on the toilet 20 minutes after breakfast.¹⁰

Privacy (visual, auditory, and olfactory) is essential to encourage defecation. Bedpans should be avoided if possible as they inhibit privacy and make it difficult for patients to generate enough intra-abdominal pressure to pass stool.⁸

Correct positioning while toileting can help patients raise their intra-abdominal pressure and facilitate the opening of the bowels. A footstool may help patients to sit in the optimal position.¹⁰ In very weak patients, a toilet seat with arms may help the patient bear down.

Monitoring and Evaluation. Consistent and regular monitoring by patient, family, and health care providers is vital in the control of constipation.

Pharmacological Interventions

Although nonpharmacologic measures will help some patients, concomitant pharmacological treatment will often be required to

alleviate constipation in patients with advanced illness.¹

Laxatives. Most evidence for the use of laxatives has been demonstrated in patients with chronic constipation, not in those with advanced, progressive illnesses. In 2005, the American College of Gastroenterologists compiled a comprehensive review of the published data about the management of chronic constipation in North America. The results reveal that there is an overall lack of robust evidence in support of various pharmacotherapeutic interventions in patients with constipation, highlighting the need for well-designed trials to sufficiently evaluate the effectiveness of agents used in this population.¹³

Within the category of bulk forming laxatives, there was sufficient evidence (Level II; see Appendix)¹⁴ to support a Grade B recommendation for the use of psyllium to increase stool frequency in patients with chronic constipation. The College found insufficient evidence on which to base a recommendation about the efficacy of polycarbophil, methylcellulose, and bran in patients with chronic constipation.¹³

The College concluded that there also are insufficient data to permit making a recommendation about the efficacy of stool softeners such as the docusates, but speculate that, when used as single agents, they may be inferior to psyllium in the improvement of stool frequency (Grade B recommendation).¹³ Similarly, there are insufficient data to make a recommendation about the effectiveness of stimulant laxatives (senna or bisacodyl) in patients with chronic constipation (Grade B recommendation).¹³

The data (Level I) supporting the osmotic laxatives polyethylene glycol (PEG) and lactulose resulted in a Grade A recommendation being applied to both agents for their efficacy in improving stool frequency and consistency in patients with chronic constipation. There was insufficient data supporting the effectiveness of milk of magnesia.¹³

The American College of Gastroenterologists review was consistent with the findings of the Cochrane Collaboration, which explored the use of laxatives for the management of constipation in palliative care patients. Only four trials could be evaluated

according to the strict criteria of Cochrane reviews.¹⁴

The Cochrane authors identified that all laxatives demonstrated a limited level of efficacy, and a significant number of participants required rescue laxatives in each of the studies. They conclude that “treatment of constipation in palliative care is based on inadequate evidence, such that there are insufficient randomized, controlled trial (RCT) data. Recommendations for laxative use can be related to costs as much as to efficacy. There have been few comparative studies. Equally there have been few direct comparisons between different classes of laxative and between different combinations of laxatives. There persists an uncertainty about the “best” management of constipation in this group of patients.”¹⁴

Based on consensus best practices, the health care provider should select laxatives based on the individual patient’s symptoms, performance status, and preference. An enema or suppository may be required if constipation does not resolve.^{1,2}

Tables 3a and 3b summarize the properties of oral and rectal laxatives currently used by Canadian health care professionals.

Peripheral Opioid Receptor Antagonists. Opioid-induced constipation is predominantly mediated by gastrointestinal μ -opioid receptors. Selective blockade of these peripheral receptors might relieve constipation without compromising centrally mediated effects of opioid analgesia or precipitating withdrawal.

Only one specific peripheral opioid receptor antagonist, methylnaltrexone (MNTX) is available in Canada at the present time. In MNTX trials, the median time to laxation was significantly shorter in the MNTX group than in the placebo group, with most patients having a bowel movement within the first two hours after administration. Evidence of withdrawal mediated by central nervous system opioid receptors or changes in pain scores were not observed. The incidence of adverse events with MNTX was similar to placebo and generally reported as mild to moderate. Abdominal pain and flatulence were the most common adverse events.¹⁵

Relative to the laxatives, there is a small body of RCT evidence supporting the use of these

Table 3a
Oral Laxatives^{1,8,20}

Category	Mechanism of Action	Potential Side Effects	Example	Not Recommended	Oral Dosages (Daily)	Latency
Bulking agents	Increase in fecal bulk and fluid retained in the bowel lumen. Transit time through the colon is increased	May cause distension, bloating, or abdominal pain	Dietary fiber, bran, psyllium, methylcellulose, polycarbophil	Not recommended in weak, bedridden patients taking opioids because of the need for extra water	Variable 20–30 g/day	Initially 24–72 hours, later 8–24 hours
Surfactant laxatives/softeners	Increases water penetration and softens stool	Diarrhea, nausea, abdominal cramps, skin rash, bitter taste, oral liquid has an unpleasant taste		<p>Docusate sodium is not recommended based on consensus opinion</p> <p>Capsule, oral, as sodium: 100 mg, 250 mg [DSC]</p> <p>Liquid, oral, as sodium: 150 mg/15 mL</p> <p>Docusate calcium is not recommended based on consensus opinion</p> <p>Capsule, oral, 240 mg</p>	<p>60–300 mg twice a day</p> <p>100–200 mg three times a day</p>	24–48 hours
Lubricants/emollients	Lubricates and softens stool	May decrease absorption of fat-soluble vitamins, anal seepage and irritation, risk of lipid pneumonia		Mineral oil is not recommended as it may interfere with absorption of other medications and nutrients	10–30 mL	6–8 hours
Stimulant (irritant) laxatives	Alters intestinal mucosal permeability and reduces absorption of water from the gut, increases intestinal motility through direct stimulation of the nerve endings in the colonic mucosa	Watery diarrhea, may cause abdominal cramping, electrolyte imbalance, dermatitis	<p>Senna</p> <p>Syrup: Sennosides 8.8 mg/5 mL (240 mL)</p> <p>Tablet: Sennosides 8.6 mg</p> <p>Bisacodyl</p> <p>Tablet (enteric coated): 5 mg</p>		<p>Max: 15 mL twice a day</p> <p>Max: 4 tablets twice a day</p> <p>10–20 mg twice a day</p>	<p>6–10 hours</p> <p>6–12 hours</p>

(Continued)

Table 3a
Continued

Category	Mechanism of Action	Potential Side Effects	Example	Not Recommended	Oral Dosages (Daily)	Latency
Osmotic laxatives	Draws water into the intestine, increases fecal weight, promotes peristalsis by mechanical distention	Lactulose: flatulence or colic, abdominal distension and discomfort, monitor use closely in patients who are diabetic; sickly sweet taste may not be tolerated by some patients	Lactulose		15–60 mL twice to three times a day	24–48 hours
		Sorbitol: less nauseating than lactulose	Sorbitol		Oral: 30–150 mL (as 70% solution)	
Saline laxatives	Draws water into the intestine, stimulates peristalsis	Electrolyte and fluid imbalance (hypermagnesemia, hyperphosphatemia, hypocalcemia, sodium overload), caution in patients with cardiac and renal diseases	Magnesium hydroxide		30–45 mL—suspension	1–6 hours
			Magnesium sulfate		25–50 mL—emulsion	1–6 hours
			Magnesium citrate		240–300 mL—solution	3–6 hours
Polyethylene glycol-PEG 3350 (with and without electrolytes)	Increases stool water content and stool volume, triggers direct colonic propulsive activity and defecation	Abdominal distension and pain, borborygmi, nausea, mild diarrhea	MiraLAX/LAX-A-DAY powder, for oral solution: PEG 3350 17 g/packet (14s); PEG 3350 255 g (16 oz); PEG 3350 527g(32 oz)		17 g, two to three times per day	24–72 hours

Table 3b
Rectal Laxatives^{1,8,20}

Category	Mechanism of Action	Potential Side Effects	Example	Not Recommended	Oral Dosages (Daily)	Latency (Hour)
Lubricant laxative	Allows penetration of water into feces to soften stool	Local irritation	Mineral oil enema Vegetable oil enema		60–120 mL	Up to 1 hour
Osmotic laxative	Increases water in intestinal lumen and fecal weight	Local irritation	Glycerin suppository (softening and irritant properties)		1	15–60 minutes
Stimulant (irritant) laxative	Increases intestinal motility, directly stimulates the nerve endings in the colonic mucosa	Abdominal cramping and pain, diarrhea, local irritation	Bisacodyl suppository		1–2 (10 mg per suppository)	15–60 minutes must come into contact with the bowel wall to be effective
Saline laxative	Increases intestinal water secretion and stimulates peristalsis	Local irritation (phosphate enema)	Phosphate enema		1	15–30 minutes
		Excessive use may cause diarrhea and fluid loss	(Microlax-proprietary) Each mL contains: sodium citrate, sodium lauryl sulfoacetate, glycerin, sorbitol, sorbic acid, and purified water q.s. in a disposable plastic tube fitted with a flexible enema tip about 5 cm long. Tubes of 5 mL		1	30–60 minutes

agents in patients with advanced, progressive illness.¹⁵

MNTX is an option for patients who have failed to respond to optimal laxative therapy recognizing that there is not enough information to make firm conclusions about the safety or effectiveness of MNTX although the drug does show promise.¹⁵

*Monitoring and Evaluation.*¹ Consistent and regular monitoring by patient, family, and health care providers is vital in the control of constipation.

When treating constipation, the occurrence of a bowel movement sufficient to relieve the patient's symptoms without the occurrence of diarrhea or stool incontinence would indicate the success of the intervention. For ongoing evaluation of prevention strategies, a monitoring plan should include assessment of stool quantity and quality, length of time required for defecation, patient symptoms of constipation, fluid and food intake, and patient satisfaction.

Consensus Best Practice Recommendations and Summary

1. Assessment and Investigation
 - a. Regular screening for constipation should be part of the comprehensive assessment of all patients with advanced progressive illness.
 - b. The history of constipation should include more than just stool frequency; include questions about unsatisfactory urges and other patient complaints.
 - c. Use a validated assessment scale. The Victoria Hospice Society Bowel Performance Scale is often used and is recommended; it has been validated and its visual analogs are meaningful to patients. Other recommended scales include the Bristol Stool Form Scale and the CAS scale.
2. Physical Examination
 - a. An abdominal flat plate is recommended in patients well enough to undergo radiography in severe or poorly responsive constipation.
 - b. Rectal examinations should be conducted except in immunocompromised patients.
3. Management—Prophylaxis
 - a. Mobility can be a key stimulus to peristalsis and defecation—patients with advanced progressive illness should be encouraged to be as mobile as possible within their capabilities.
 - b. Encourage adequate fluid intake.
 - c. Clinicians should be aware of which drugs are likely to cause constipation and either:
 - i. Avoid them if possible.
 - ii. Make a laxative available at the time of first prescription, before constipation is established.
 - d. Opioids should not be decreased to manage constipation unless absolutely necessary. Doing so may expose the patient to significant pain.
4. Management—Nonpharmacological
 - a. Consideration of patient dignity, individual preferences and cultural sensitivities should precede any intervention.
 - b. Optimized toileting should be provided (privacy and avoidance of bedpan use where possible); regular toileting should be promoted and effective positioning.
 - c. Ongoing monitoring and evaluation by patient, family, and health care providers is essential to prevention and control.
 - d. Fiber should be used with caution in this population because inadequate fluid intake is often a problem.
5. Management—Pharmacological
 - a. Osmotic laxatives, lactulose, and PEG are supported by Grade A evidence and are recommended in the appropriate patient.
 - b. Use of docusates is not recommended.
 - c. Use of mineral oil is not recommended.
 - d. Stimulants such as senna base laxatives and bisacodyl can be used despite the insufficient evidence of efficacy.
 - e. If constipation persists, an enema or suppository may be needed.

- i. For constipation with hard feces, a mineral/vegetable oil or phosphate enema is recommended and may need to be followed by a higher saline enema,
 - ii. For constipation with softer feces, a suppository or phosphate enema may suffice.
- f. MNTX is recommended as an option for patients on opioids who have failed to respond to optimal laxative therapy.
6. Management—Monitoring
- a. All patients with advanced progressive illnesses should be monitored frequently (at least every three days) with inquiry and with a validated assessment scale.

quality of life. Opioids are one of the most common causes of constipation in this population; however, it is important to note that there are many other potential etiologies and combinations of causes that should be taken into consideration when making treatment decisions.

There is a wide range of options to help treat constipation and help prevent its development (Fig. 2). Laxatives are the mainstay of pharmacological intervention; however, the body of clinical evidence supporting their use is poor. The best levels of evidence are associated with the osmotic laxatives, lactulose, and PEG, but choices should be made based on the individual status and preference of each patient. MNTX has demonstrated effectiveness in RCTs conducted in palliative care patients with opioid-induced constipation. Pending further clinical experience to confirm safety and efficacy, MNTX is currently recommended in these recommendations as an option for patients with constipation secondary to opioid use, who have failed to respond to optimal laxative therapy.

Summary

Patients with advanced, progressive illness are at high risk for constipation, a distressing condition, which can significantly compromise

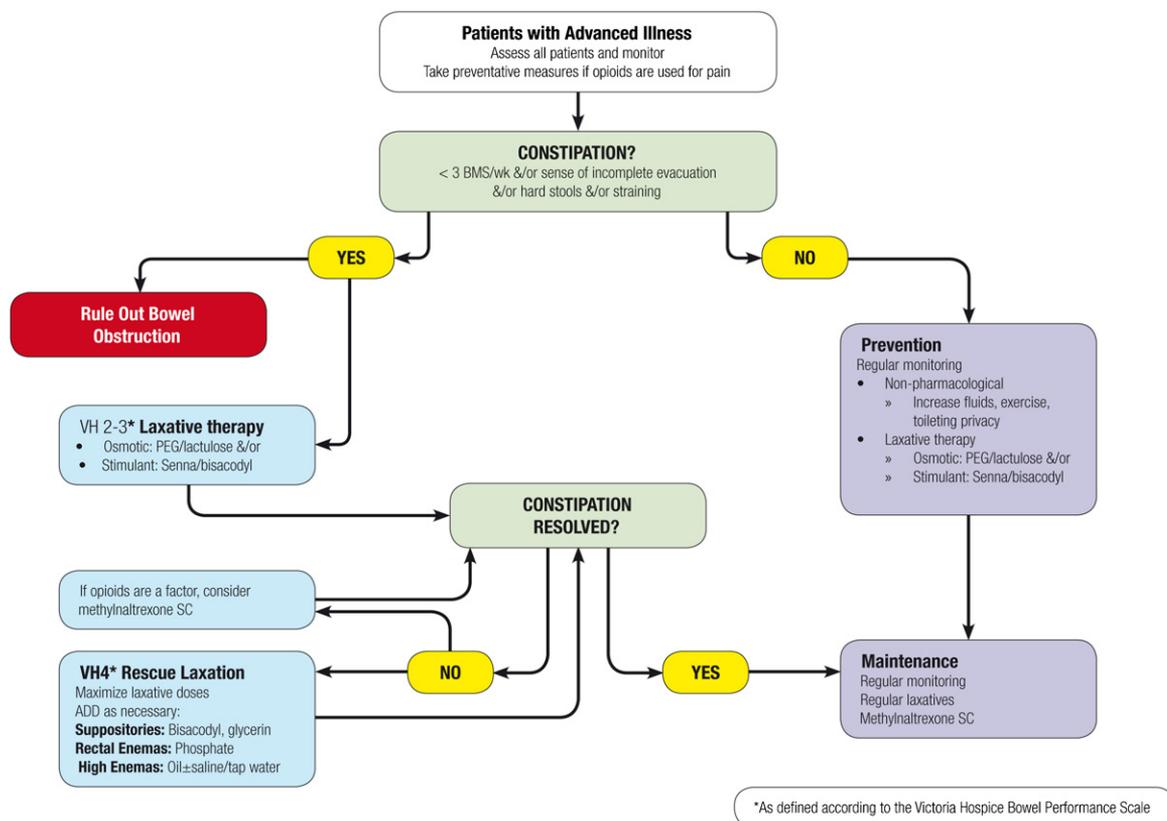


Fig. 2. Decision points in the management of constipation in patients with advanced, progressive illness.

In conclusion, it is worth bearing in mind that the treatment recommendations in this guideline are primarily derived from best practices. This underscores the need for further clinical evaluation of the available agents to create a robust, evidence-based foundation for treatment decisions in the management of constipation in patients with advanced, progressive illness.

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Appendix

Levels of Evidence and Grading of Recommendations^a

Level I Evidence: RCTs with $P < 0.05$, adequate sample sizes and appropriate methodology.

Level II Evidence: RCTs with $P > 0.05$, or inadequate sample sizes and/or inappropriate methodology.

Level III Evidence: Nonrandomized trials with contemporaneous controls.

Level IV Evidence: Nonrandomized trials with historical controls.

Level V Evidence: Case series.

Grade A Recommendations: Recommendations supported by two or more Level I trials without conflicting evidence from other Level I trials.

Grade B Recommendations: Recommendations based on evidence from a single Level I trial OR recommendations based on evidence from two or more Level I trials with conflicting evidence from other Level I trials OR supported by evidence from two or more Level II trials.

Grade C Recommendations: Recommendations based on Level III–V evidence.

RCT = randomized, controlled trial.

^aModified from Reference 16.