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CLINICAL PRACTICE GUIDELINES

Diagnosis, assessment and management of constipation in advanced cancer: ESMO Clinical Practice Guidelines†

P. J. Larkin[1,2], N. I. Cherny[3], D. La Carpia[4], M. Guglielmo[5], C. Ostgathe[6], F. Scotté[7] & C. I. Ripamonti[5], on behalf of the ESMO Guidelines Committee*

[1]School of Nursing, Midwifery and Health Systems, University College Dublin, Dublin; [2]Our Lady's Hospice and Care Services, Dublin, Ireland; [3]Cancer Pain and Palliative Medicine Service, Department of Oncology, Shaare Zedek Medical Center, Jerusalem, Israel; [4]Centro Medicina Dell'Invecchiamento (Ce.M.I.), Fondazione Policlinico Agostino, Gemelli, Roma; [5]Oncology-Supportive Care Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy; [6]Palliative Care Department, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; [7]Department of Medical Oncology and Supportive Care, Foch Hospital, Suresnes, France

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, 6900 Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

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Introduction

Constipation is a common problem in patients with advanced cancer and a significant source of major morbidity and distress, which is often under-appreciated [1]. Constipation is subjectively experienced by the patient and diagnostic criteria do not always clearly express the diversity of factors, which may lead to constipation as a clinical problem [2]. Widespread use of opioid analgesics for cancer pain poses specific challenges for patients [3]. Despite its clinical impact, constipation is both poorly recognised and poorly treated. Oncologists must be familiar with the common causes of constipation among cancer patients and the strategies to evaluate and manage this distressing symptom. This European Society for Medical Oncology (ESMO) Clinical Practice Guideline (CPG) is directed towards adult cancer patients experiencing constipation as a consequence of their cancer diagnosis or treatment. The CPG makes specific reference to the context of opioid-induced constipation (OIC), highlights the impact of constipation and offers strategies for pharmacological and non-pharmacological management, as well as the specific challenges in the management of older patients with cancer at enhanced risk of constipation.

Definition

Constipation is defined as the slow movement of faeces through the large intestine, resulting in infrequent bowel movements (BMs) and the passage of dry, hard stools [4]. Constipation is a symptom, not a disease. Although usually temporary, it can impact significantly on quality of life.

The standard clinical definition of chronic (sometimes termed functional) constipation (CC), based on the Rome III criteria [5], requires the presence of any two of the following symptoms for at least 12 weeks in the previous 12 months (not necessarily consecutively):

- straining during BMs;
- lumpy or hard stool;
- sensation of incomplete evacuation;
- sensation of anorectal blockage or obstruction;
- manual evacuation procedures to remove stool;
- $<$ 3 BMs per week.

The description and definition of constipation given here reflects a broader patient cohort experiencing CC as a clinical problem, not solely a cancer population, although the assessment and treatment are similar across both chronic disease and cancer populations. The experience of constipation is highly subjective and, therefore, two further aspects should be taken into consideration: (i) measurable objective symptoms, including individual stool characteristics and frequency of defaecation; (ii) patient perception, level of discomfort and ease of defaecation [6].

The Rome IV criteria for functional gastrointestinal disorders (FGIDs) published in 2016 has seen the addition of OIC to the section on Bowel Disorders, defined as 'constipation triggered or worsened by opioid analgesics' [7]. The clinical presentation of OIC is similar to other FGIDs and requires differential diagnosis and management.

Table 1. Organic and functional factors relative to constipation in advanced disease

Organic factors	
Medications	Opioid analgesics, antacids, antitussives, anticholinergics, antidepressants, antiemetics, neuroleptics, iron, diuretics, chemotherapeutic agents
Metabolic problems	Dehydration, hypercalcaemia, hypokalaemia, uraemia, diabetes mellitus, hypothyroidism
Neuromuscular disorders	Myopathy
Neurological disorders	Autonomic dysfunction, spinal or cerebral tumours, spinal cord involvement
Structural issues	Abdominal or pelvic mass, radiation fibrosis, peritoneal carcinomatosis
Pain	Cancer pain, bone pain, anorectal pain
Functional factors	
Diet	Low fibre intake, anorexia, poor food and fluid intakes
Environment	Lack of privacy, need for assistance during toileting, cultural issues
Other factors	Inactivity, age, depression, sedation

Pathophysiology of constipation

Functioning normally, the colon absorbs fluids and transports waste to the rectum through the repetitive and periodic contractions of peristalsis, mediated principally by serotonin or 5-hydroxytryptamine (5-HT). Sodium is actively reabsorbed through active transport channels; water through osmosis. Colonic secretion is mediated through chloride channels and results in a net reabsorption of electrolytes and fluids. The rectum eventually distends, resulting in the urge to defaecate and associated contractions via the rectal sphincter. The average colonic transit time is 20–72 hours.

Constipation represents a disruption of these normal mechanisms. Causes may be primary (colonic or anorectal dysfunction) or secondary (disease- or medication-related). Factors contributing to constipation may include disruption of normal motility, excessive dryness of faecal content, diminished perception of rectal distension with loss of urge to defaecate and dysfunction of the rectal sphincter. The longer the stool remains in the colon, the drier it becomes. OIC occurs following titration or increased dosage of opioid medication affecting opioid receptors in the gastrointestinal tract.

Prevalence

The reported prevalence of constipation in advanced cancer patients ranges between 40% and 90% [2, 3]; more common in the opioid-treated population [8, 9]. Prevalence increases with age and the elderly are five times more prone to constipation than young people, due to polypharmacy, reduced mobility, reduced hydration and reduced urge to defaecate [10]. In older cancer patients receiving palliative care, constipation is one of the most prevalent symptoms, with prevalence rates ranging between 51% and 55% [11–13].

Impact and burden of care

Constipation is a major cause of distress for patients with cancer [14]. Constipation may be complicated by development of nausea, vomiting, haemorrhoids, anal fissure, bowel obstruction and urinary retention [8]. Untreated constipation places a burden on the healthcare system, with a need for increased nursing hours and a higher risk of hospitalisation. Prevention of constipation, screening for its presence and early intervention may reduce both patient distress and care costs [15, 16].

Causes and contributing factors

Among cancer patients, common precipitating factors may be classified as organic or functional. Organic contributing factors commonly include medications (especially opioids, vinca alkaloids, 5-HT3 antagonist antiemetics, iron and antidepressants), metabolic aberrations (particularly dehydration, hypercalcaemia, hypokalaemia and uraemia), neuromuscular dysfunction (autonomic neuropathy and myopathy), structural issues (abdominal or pelvic mass, radiation fibrosis) and pain. Functional factors would include, for example, age, poor food and fluid intake and lack of privacy when toileting (Table 1) [17, 18].

Information regarding the most frequent medications responsible for constipation among cancer patients derives from small-scale studies and expert review (Table 2).

Evidence

A search of databases (last search, March 2018) including Medline (through Pubmed), Cochrane CENTRAL, EMBASE, CINHAL and SCOPUS was undertaken. No date restriction was applied. Search terms, using Boolean operators were: 'constipation' AND 'cancer' OR 'advanced cancer' OR 'palliative care' OR 'hospice care' AND 'opioid-induced constipation' AND 'management' AND 'pharmacology' AND 'non-pharmacology'. The search prioritised evidence from systematic reviews of randomised, controlled trials (RCTs), including meta-analyses and RCTs in cancer populations. However, as there is limited evidence in this area, as appropriate, we considered evidence derived from other study designs and from studies in other populations. A manual screening of retrieved articles was then undertaken to

Table 2. Specific treatment-related causes of constipation in cancer patients

Medication	Rationale
Opioid analgesics	All opioids cause constipation. Tolerance is not observed over time. Dose–response relationship to this effect is flat, and severity is not strongly dose-related. Some data indicate minor severity with fentanyl and, possibly, methadone [3, 83] and with oral oxycodone/naloxone combined formulation [41, 84]
Serotonin 5-HT3 receptor antagonists	5-HT3 receptor antagonist antiemetics slow colonic transit, increase fluid absorption and increase left colon compliance [85]. Laxative therapy is often indicated
Vinca alkaloids	All vinca alkaloids have pronounced neuropathic effects and prolonged gastrointestinal transit time. The most severe AEs are with vincristine and vindesine; less with vinblastine and the least reported with vinorelbine. AEs with vincristine are dose-related and more common and severe among patients receiving doses > 2 mg total dose [86]
Thalidomide	Other than sedation, constipation is the most common AE of thalidomide [87]
Other medications	Constipating drugs commonly used in cancer care include those with anticholinergic actions (antispasmodics, antidepressants, phenothiazines, haloperidol, antacids), anticonvulsants or antihypertensive drugs, iron supplements and diuretics

5-HT3, 5-hydroxytryptamine; AE, adverse event.

identify further studies to inform the guideline. Studies were reviewed by two authors for quality inclusion and agreed by the expert panel. High quality studies which focused on constipation but not cancer were reviewed and only included if clear extrapolation of findings to a cancer population were evident in the expert opinion of the authors. Studies from 2015 to present day reported an increased focus on new and innovative pharmacological treatments and the search was then extended to include these new treatments ('methylnaltrexone' AND 'naloxegol' AND 'naldemedine') in combination with original search terms. These were then included in the overall review of evidence.

Range of evidence. Although there is a significant body of literature which looks to the pharmacology of CC management, best clinical practice, and more recently cost-effectiveness [17–20], the focus on cancer is limited. The scope of studies identified either provided descriptive pharmacological management of constipation related to a specific treatment or the comparison of pharmacological treatments versus placebo. There is a growing body of literature to support the use of peripherally acting mu opioid receptor antagonists (PAMORAs) in the efficacy of laxation reported here [21–25]. In some studies, the constipation was a secondary focus for the study (where, for example, the primary outcome was pain management). There is evidence of high quality reviews with multiple trials regarding CC [26] from which recommendations for oncology practice may be derived. However, extrapolating these results to an advanced cancer or palliative care population is problematic, where comorbidity, frailty and trajectory towards decline may impact negatively on outcomes and effectiveness. The evidence presented here reflects that context in terms of the CPG and recommendations made arising out of evidence reviewed. Overall, based on the limited scope of high-quality trials and meta-analyses in advanced cancer, the expert group considered the quality of evidence for the management of constipation in patients with cancer to be low and largely based on expert opinion, pharmacological reviews and clinical case reports.

Review of evidence. A 2011 Cochrane systematic review [21] building on an earlier review from 2006 looked at the effectiveness of laxatives versus methylnaltrexone in the management of constipation in palliative care patients. Seven studies with 616 participants were identified. Two had a crossover design, and three were multicentre. All patients had advanced disease, and most (but not all) had cancer. Four studies looked at the use of lactulose, senna, co-danthramer, misrakasneham and magnesium hydroxide with liquid paraffin. Three reported on methylnaltrexone use. Comparisons were between laxative therapy and methynaltrexone versus placebo. The evidence for the use of laxatives was inconclusive. Studies on methylnaltrexone reported on 227 patients and demonstrated that, in comparison to placebo, patients had significantly improved laxation within 4 hours, with only one serious adverse event (AE) reported. Good quality RCTs were poor and, although subcutaneous methylnaltrexone was considered efficacious, further larger and more rigorous independent trials were needed.

A development of this review in 2015 [22] only considered the laxatives noted above but included docusate in the evaluation. The primary outcome was laxation response and secondary outcomes were patient preference and relief of other symptoms associated with cancer. Five studies (N = 370) were reviewed; all focused on an advanced cancer population, and two had a crossover study design. Laxatives were either compared or reported as a placebo versus laxative. Studies reviewed had small samples sizes and, in some cases, weak methodology, including being under-powered and no clear evidence of blinding. Attrition was high (> 50%) but not unusual given the population. As there were very few RCTs, it was not possible to show effectiveness or benefit of one treatment over another. A noted recommendation is that data from populations beyond palliative care cannot easily be extrapolated and that the nature of palliative care treatment and care may impact on laxative effect.

Opioid-induced constipation: OIC is the most common AE of opioid analgesic therapy in all populations including those with cancer. OIC incidence ranges between 40% and 60% and is variable due to dose and type of opioid used. Opioid analgesics act on mu receptors widely distributed in the gastrointestinal tract, resulting in reduced peristalsis and fluid secretion, increased fluid

reabsorption and increased sphincter tone. Symptoms would mirror those of a normal constipation pattern. Reducing the opioid dose is ineffective. Unless contraindicated by pre-existing diarrhoea, all patients receiving opioid analgesics should be prescribed a concomitant laxative [V, B]. Laxative therapies include first-line treatment options [V, B]. In unresolved OIC, new targeted therapies (i.e. PAMORAs) may be of value [II, B].

We also identified one very recent mixed-treatment comparison network meta-analysis of RCTs across a range of interventions to manage OIC [23]. The primary outcome was the number of patients reporting a rescue-free bowel movement (RFBM). Secondary outcomes were time to first laxation, AEs and changes to opioid analgesic activity. They identified 23 studies which formed part of a qualitative synthesis and 21 which were quantitatively examined using a network meta-analysis approach. In the meta-analysis, no clinical trial that specifically targeted cancer patients was identified, although six studies [24–29] included a cancer population with other groups and one study focused on constipation in cancer [30]. Medications reviewed included lubiprostone, naldemedine, naloxegol, alvimopan and oral and subcutaneous methylnaltrexone. All were more effective than placebo for RFBM. Subcutaneous methylnaltrexone was more effective than oral preparations and in relation to other medications reported, and showed no improvement regarding background pain using opioids. Although the quality of evidence is reported as low or very low, the meta-analysis concluded that subcutaneous methylnaltrexone was safe and effective for OIC.

Methylnaltrexone: Methylnaltrexone is a quaternary derivative of naltrexone, approved by the European Medicines Agency (EMA) for use in the treatment of OIC in advanced illness and palliative care patients whose response to usual laxative therapy has been insufficient. It does not cross the blood–brain barrier and, as a result, it antagonises only peripherally located opioid receptors while sparing centrally mediated analgesic effects of opioid pain medications. There is evidence of predictable effectiveness after subcutaneous administration (initially once every other day), with most patients achieving defaecation within 90 minutes of administration [II, B] [24, 25, 31, 32]. The frequency of administration can be increased, if needed, to once daily.

A review and meta-analyses of methylnaltrexone in OIC [33] for both objective and subjective efficacy and safety outcomes identified seven trials [N = 1860], four specifically with cancer patients, where methylnaltrexone was the drug studied and OIC the primary outcome. Secondary outcomes included time to laxation, patient-reported outcome measures (PROMs) and impact of burden and distress. In each case, methylnaltrexone was compared with placebo. The meta-analyses demonstrated a higher stool frequency and less time to laxation in patients receiving methylnaltrexone. Better patient outcomes and less distress were also associated with methylnaltrexone use. AEs were minimal with only a 0.2% incidence reported. The review concluded that methylnaltrexone is a safe and effective treatment in OIC.

This supports a later exploratory single arm, single dose phase II trial; subcutaneous methylnaltrexone to address severe OIC in cancer patients [34] was given to 12 patients presenting with a prognosis of ≥ 3 months and OIC with ≤ 3 laxations in the preceding week. The primary endpoint was a rescue-free laxation ≤ 4 hours after single dose treatment. Secondary endpoints included rescue-free laxation within 24 hours following treatment, laxation with or without laxatives at 48 hours, overall pain scores, assessment of laxation and patient satisfaction scores. Four patients (33.3%) had an RFBM after 4 hours, five (41.7%) after 24 hours and 10 (83.5%) achieved laxation within 48 hours. Despite reported recruitment difficulties which led to the small sample, authors conclude that methylnaltrexone is effective and well-tolerated by patients.

An earlier double-blind RCT of fixed-dose methylnaltrexone [35] was conducted in patients with advanced illness and OIC. Patients were randomised to subcutaneous injection of methylnaltrexone (8 mg or 12 mg by body weight, $n = 116$) or placebo ($n = 114$) every other day for two weeks. Those completing the RCT were eligible to go on to an open label extension of the study ($n = 149$). The primary endpoint of interest was the percentage of patients with an RFBM with ≤ 2 of 4 doses in the first week. Of the methylnaltrexone group, 62.9% achieved the primary endpoint versus 9.6% of those taking placebo. Median laxation of the methylnaltrexone group was 0.8 hours as opposed to 23.6 hours in the placebo group. The open label study results were consistent with the RCT in terms of safety and efficacy, and methylnaltrexone was considered effective and well-tolerated by the patient cohort.

One study already noted [24] specifically focused towards cancer reported 133 patients described as having advanced illness, currently stable on their opioid and laxative regime and randomly assigned to receive a subcutaneous injection of methylnaltrexone at 0.15 mg/kg of body weight versus placebo, every other day for 2 weeks. Co-primary endpoints were defined as laxation within 4 hours after first dose and laxation within 4 hours after ≥ 2 of the first 4 doses. Of the intervention group, 48% experienced laxation within 4 hours as opposed to only 15% in the placebo group, while 52% reported laxation within 4 hours of ≥ 2 of the first 4 doses, with only 8% reporting the same response in the placebo group. Treatment did not appear to impact analgesic response or to precipitate opioid withdrawal.

Naloxegol: Naloxegol was the first orally dosed PAMORA indicated for the treatment of OIC [36, 37]. It is approved by the EMA for adults who have not responded adequately to previous treatment with laxatives. Based on the mechanism of action, the benefit for cancer patients with OIC is not expected to be different, and the EMA licence for naloxegol includes cancer patients. The recommended dose is 25 mg once daily which can be reduced to 12.5 mg daily in case of abdominal cramps or other AEs [29].

This phase II double-blind, randomised, placebo-controlled, dose-escalation study [29] evaluated efficacy, tolerability and safety of naloxegol in patients with OIC. Two-hundred and seven patients with ≤ 3 BMs per week were randomised to a 4-week trial of naloxegol (5, 25 or 50 mg in sequential cohort following 1-week placebo) versus placebo. The primary endpoint was median change in spontaneous BMs (SBMs) in 1 week. A positive response to dosage at 25 and 50 mg versus placebo was reported. Increase in SBMs was maintained over 4 weeks. AEs were described as transient (e.g. nausea, abdominal pain and diarrhoea), although these did increase in severity relative to higher doses. The outcome of the study was that naloxegol improves the frequency of SBMs with minimal AEs.

A large study undertaken with a non-cancer population (but with relevance to advanced cancer and palliative care) [38] presented two identical phase III double-blind studies (termed studies 4 and 5) to evaluate the efficacy and safety of naloxegol for the treatment of OIC. Using a population of opioid-dependent, non-cancer patients (N = 652; study 4 and N = 700; study 5), patients were assigned to receive 12.5 or 25 mg of naloxegol or placebo over a period of 12 weeks. The primary endpoint was noted as ≥ 3 BMs for ≥ 9 out of 12 weeks and for ≥ 3 BMs in the last 4 weeks of the intention-to-treat group. The study also reported response rate in the subpopulation of those who had inadequate laxative response before being enrolled to the study, time to first SBM and number of days per week, with ≥ 1 SBMs as secondary endpoint.

Results demonstrated a significantly higher response with 25 mg of naloxegol than with placebo. The studies concluded that naloxegol led to a higher rate of treatment response compared with placebo, with no loss of opioid-mediated analgesia. As such, outcomes of this study are relevant to a palliative care population, given the likelihood of need for opioid analgesia and concomitant constipation treatment to manage symptoms.

This study was later further reported in a pharmaceutical industry report on the pooled analysis of data from the two studies that supported the assertion of the benefit of naloxegol in the treatment of OIC [39].

Naldemedine: Naldemedine, a more recent PAMORA, has been the subject of phase II and III trials. Two recent studies [30, 40] report on a phase IIb and III trials, respectively, to determine the dose and safety of naldemedine with cancer patients experiencing OIC.

The phase IIb study [30] involved a randomised double-blind multicentre trial to assess efficacy and safety of naldemedine. Two-hundred and twenty-seven patients were randomly assigned to once daily oral naldemedine (at 0.1, 0.2 or 0.4 mg) or placebo ($n = 56$ in each group). The primary endpoint was a change in SBMs per week from baseline including response rate, change from baseline, change in straining at stool and evidence of complete evacuation. A positive change in SBMs was reported at all doses of naldemedine in comparison with placebo. Change of SBMs with respect to reduction of straining was noted to be significant when doses of 0.2 and 0.4 mg were taken. Diarrhoea was a notable AE reported in the naldemedine group.

Based on these results, a phase III study [40] was undertaken. This study included a 12-week open label extension study as well as a 2-week, randomised double-blind placebo-controlled trial termed COMPOSE-4 and COMPOSE-5. In the COMPOSE-4 study, 193 patients were randomly assigned to a once-daily dose of 0.2 mg naldemedine ($n = 97$) or placebo ($n = 96$). The primary endpoint was recorded as an increase in SBMs per week from baseline. The COMPOSE-5 study focused specifically on safety. The COMPOSE-4 study demonstrated a 74% SBM response rate in the intervention group as opposed to placebo (34.4%). The intervention group also reported a change from baseline in terms of SBMs and reduction of straining at stool. Higher levels of AEs (e.g. diarrhoea) were reported in the intervention group but were also reported frequently in the COMPOSE-5 study. It was concluded that 0.2 mg naldemedine was effective to manage OIC and was generally well-tolerated.

Prolonged-release oxycodone-naloxone: The use of a prolonged-release (PR) combination formulation of oxycodone and naloxone is also increasingly evident in practice [41]. Tertiary amines including naloxone have been shown to restore laxation when opioid therapy is used. The risk of reversal of centrally mediated analgesia and withdrawal may be reduced by the use of PR formulations. Combined opiate/naloxone medications have been shown to reduce the risk of OIC through a range of open label, phase II and III studies [II, B] [42].

PR oxycodone/naloxone versus PR oral oxycodone alone was reported in a double-blind placebo-controlled trial [41] evaluating both analgesia and bowel function. Two-hundred and two opioid-stable patients (mainly non-cancer), taking 40–60 mg oxycodone daily, were randomised to either naloxone (10–40 mg daily) or placebo. The Bowel Function Inventory (BFI) was used to assess constipation. Patients taking a combined oral therapy reported significant improvements in bowel function compared with those only taking PR oral oxycodone, with no loss of analgesic efficiency. This outcome has been supported in a more recent review of literature of clinical trials and observational studies into the evidence for PR oxycodone/naloxone treating moderate-to-severe pain and specific impact on opioid-induced bowel dysfunction (OIBD) [42]. Thirty-eight clinical trials and observation studies were reported of which seven were undertaken with a cancer population [43–50]. Other studies reported on patient groups with direct relevance to patients with cancer (e.g. those with neuropathic pain, pain in the elderly and patients with pain and refractory laxatives symptoms) [42]. Although the method of review is not explicit, the range of evidence presents PR oxycodone/naloxone as an effective treatment of moderate-to-severe pain and effective OIC bowel management for patients unresponsive to normal laxative therapy.

Although these studies demonstrate a growing body of evidence, particularly in relation to therapies to manage OIC, the overall impact remains relatively small in terms of application to clinical practice, and further studies are needed to support these early data. Some of the study outcomes reported here do include an advanced cancer population. However, although the use of PAMORAs is evident in practice, the recommendation would be that they should be used in patients who have not responded successfully to laxative intervention.

Table 3. Key factors in the assessment of constipation

Date of last defaecation
Frequency of bowel movements
Consistency of the stool
Recent changes in bowel patterns
Urge to defaecate (presence or absence)
Sensation of evacuation (complete or incomplete)
Faecal incontinence (presence or absence, including rectal leakage)
Evidence of blood or mucus on defaecation
Current and previous laxative use
Need for digital manipulation to assist or manage evacuation

Assessment and diagnosis

All cancer patients should be evaluated for constipation [V, B]. In patients with advanced cancer, underlying causative factors for

constipation are usually long-standing and may be modifiable. Frequent, regular assessment of bowel pattern is important to detect improvements or deterioration in bowel patterns, regardless of whether or not the patient is receiving treatment [2].

A full medical history will assist in identifying causes of constipation and should elicit key facts when constipation is suspected (Table 3) [2].

Assessment should include questions to determine possible causes for constipation including:

- eating and drinking habits;
- medication use (medically prescribed and purchased 'over the counter');
- level of physical activity (relative to stage of illness);
- pre-existing irritable bowel syndrome or diverticular disease;
- other comorbid disease (e.g. heart failure, chronic pulmonary airway disease);
- environmental factors (e.g. lack of privacy, assistance needed, bed bound).

The evidence for this arises from consensus expert review and national guidelines [2, 51] but is considered sufficient to make recommendations for best practice [V, B].

Physical assessment includes abdominal examination [auscultation, perineal inspection and digital rectal examination (DRE)] [V, B]. DRE is a safe and simple, diagnostic tool which may have particular benefit in advanced disease [52]. Table 4 presents the rationale for basic physical assessment.

If constipation is considered part of a spinal cord compression syndrome, full neurological examination is essential, including assessment of anal sphincter tone (lax with colonic hypotonia) and rectal sensation. Again, although derived from expert review, clinical examination including DRE is generally recommended in practice [2, 53].

Table 4. Basic physical assessment in case of suspected constipation

Abdominal examination including auscultation	Perineal inspection	Digital rectal examination
Distension	Skin tags	Inner haemorrhoids
Abdominal masses	Fissures	Sphincter tone
Liver enlargement	Prolapse	Tenderness
Tenderness	Anal warts	Obstruction/stenosis
Increased/decreased bowel sounds	Perianal ulceration	Impacted faeces
		Complete absence of stool
		Tumour masses
		Blood

Investigations

Investigations are not routinely necessary. If suspected clinically, corrected calcium levels and thyroid function should be checked. More extensive investigation is warranted for those with severe symptoms, sudden changes in number and consistency of BMs or blood in the stool, and for older adults relative to their health and stage of disease.

Assessment scales for constipation

A number of cancer and palliative care symptom assessment scales include a constipation intensity numerical rating scale [54–60]. Specific constipation assessment scales have been shown to have benefit in advanced disease, notably the Victoria Bowel Performance Scale (BPS) and the Constipation Assessment Scale (CAS) [61, 62] as well as those which use images, such as the Bristol Stool Form Scale, with good clinical utility [2, 63].

Consensus recommendations from a multidisciplinary exert panel of the American Academy of Pain Medicine [62] evaluated five validated assessment tools used in constipation management for an optimal OIC assessment model in clinical practice: the Patient Assessment of Constipation–Symptoms (PAC-SYM), Patient Assessment of Constipation–Quality of Life (PAC-QoL), Stool Symptom Screener (SSS), Bowel Function Index (BFI) and Bowel Function Diary (BF-Diary). BFI and SSS had best utility, although PAC-SYM and BFI were most commonly used. The BF-Diary had specific resonance to OIC, but the panel concluded that the psychometrically validated BFI was less complex and therefore more favourable to use in practice. Consensus was also reached on when to prescribe medication to address OIC, based on symptom severity as indicated by the tool. They concluded that prescription should be introduced for a patient with a BFI score ≥ 30 points and no response to initial laxative therapies.

In general, due its subjective nature, PROMs are a preferred aspect of clinical assessment of constipation [64, 65]. However, beyond the one study noted above [62], no large-scale studies were identified, and further studies are needed to determine optimal tools for practice. As noted in recommendations below, although evidence is limited, best practice would indicate strong clinical benefit to utilising constipation assessment tools in conjunction with PROMs for best outcome [V, B].

We identified one prospective cross-sectional study to assess the correlation between use of the CAS and a plain abdominal X-ray in an advanced cancer population ($N = 50$), in a palliative care unit. All patients were given an abdominal X-ray, and the extent of faeces was then scored on a scale of 0–12. Three palliative care physicians then independently scored the X-ray, and the Kendall Tau Correlation Coefficient was used to estimate and test correlations. No concordant correlation was found between physicians' CAS and independent radiological scores, nor their CAS score and combined physician radiology scores, with only a moderate correlation overall in physician radiological scores. Therefore, in the absence of any strong correlation, the authors of the study recommended that optimal clinical assessment should include radiological examination [V, C] [66]. However, we conclude that evidence currently remains limited, with only one small study and one expert opinion (as a Letter to the Editor) noted [67], and that further quality studies are needed.

Recommendations:

- All cancer patients should be evaluated for constipation [V, B].
- Assessment should include questions to determine possible causes for constipation [V, B].
- The use of PROMs is recommended [V, B].
- If constipation is identified, physical examination should include abdominal examination, perineal inspection and DRE [V, B].
- Investigations are not routinely necessary [V, B].

Table 5. Key factors for prevention and self-care in the management of constipation

Ensuring privacy and comfort to allow a patient to defaecate normally
Positioning (to assist gravity, a small footstool may help patient exert pressure more easily)
Increased fluid intake
Encourage activity and increased mobility within patient limits (even bed to chair)
Anticipatory management of constipation when opioids prescribed
Advise against home remedies or 'over the counter' or online products which may impact treatments

- If suspected clinically, corrected calcium levels and thyroid function should be checked. More extensive investigation is warranted for those with severe symptoms, sudden changes in number and consistency of BMs or blood in the stool, and for older adults relative to their health and stage of disease.
- Plain abdominal X-ray, although limited as a tool in itself, may be useful to image the extent of faecal loading and to exclude bowel obstruction [V, C].

Management

Overall principles for management

Best practice is based on a balance between strategies for prevention and self-care and prescribed oral and rectal laxative therapy [V, B]. Approaches may differ between those undergoing oncological therapy and those receiving palliative care alone. Care should be taken, where possible, to avoid drug interaction between anticancer therapy and constipation treatments [68, 69].

Prevention and self-care strategies (non-pharmacological approaches)

Healthcare professionals should encourage and promote changes in the patient's lifestyle or other underlying factors that may prevent or reduce constipation. Preventative measures should be ongoing throughout a patient's care. Key factors for prevention and self-care to prevent or reduce risk are listed in Table 5. Of note, lifestyle factors alone have a positive but limited influence on constipation and should not be the sole focus of management [2]. As disease progresses and health deteriorates, lifestyle factors may become less important in clinical management.

We did not identify any studies on non-pharmacological approaches with cancer populations. There is some evidence that abdominal massage can be efficacious in reducing gastrointestinal symptoms and improving bowel efficiency, particularly in those patients with concomitant neurogenic problems [II, B] [70] but not in a cancer population. A multicentre randomised superiority trial to compare abdominal massage against no massage was conducted in a sample of multiple sclerosis patients who had neurogenic bowel dysfunction (NBD). Patients ($N = 30$) were randomly assigned to an intervention group, where the caregiver carried out a daily abdominal massage over 4 weeks versus a control group of bowel management advice only. Patients were asked to complete the Constipation Scoring System (CSS), the NBD score and to keep a bowel diary. Scores were taken at baseline, at week 4 and at week 8; the NBD score was taken also at week 24.

Both groups showed a decrease in constipation between weeks 0 and 4 based on the CSS. However, the extent of improvement was significantly greater in the massage group than in the control group.

A more recent pilot RCT [II, B] [71] also looked at the use of massage in patients with Parkinson's disease, a patient group more recently seen by palliative care specialists. Thirty-two patients from three movement disorder clinics were randomised to either a 6-week daily abdominal massage plus a lifestyle constipation management programme ($n = 16$) or to a control group ($n = 16$) who received lifestyle management only. Data were collected at baseline, week 6 (post intervention) and at week 10 using a bowel diary, the Gastrointestinal Rating Scale and the scales used in the multiple sclerosis study described above (i.e. the NBD score and CSS) and qualitative analysis of patient and caregiver interviews. Massage was largely administered by a caregiver. Results demonstrated that those who received both massage and lifestyle support had a better laxation outcome than those receiving lifestyle advice alone. The practice of massage was considered efficacious and, therefore, of added benefit to patients. These are small-scale studies with no evident application to cancer patients. Without further evidence, they are currently considered to be of limited value to standard laxative management and lifestyle factors to manage constipation in those with advanced illness.

In terms of other non-pharmacological therapies, we did not find any studies with sufficient evidence relative to an advanced illness population.

Laxative use, choice and rationale

Judicious use of laxatives is often essential in the prevention and relief of constipation. There is limited evidence to support the use of one laxative over another [19, 20, 22, 32]. Recommendations for patients with advanced cancer regarding the selection of laxatives are proposed in Table 6, noting those which are generally preferred in clinical practice [V, B].

Use of suppositories and enemas

Suppositories and enemas are a preferred first-line therapy when DRE identifies a full rectum or faecal impaction [V, B] [2, 63]. Suppositories and enemas may be perceived as a more invasive option by patients. Enemas (such as hyperosmotic saline) and suppositories increase water content and stimulate peristalsis to aid in expulsion, and both work more quickly than oral laxatives.

Suppositories. Suppositories containing glycerine, bisacodyl oxyphenisatin (veripaque) and CO_2-releasing compounds are all stool softeners and stimulants for rectal motility. They are commonly used for short-term treatments and are often effective. We found no evidence that treatment of constipation with suppositories has been studied in patients with cancer. One Cochrane systematic review has reported on the effectiveness of CO_2-releasing

Table 6. Types of laxatives and rationale for use

Type	Rationale
Laxatives generally preferred in advanced disease	
Osmotic laxatives	Strongly endorsed in systematic reviews of chronic constipation [88, 89] • PEG (Macrogol): Virtually no net gain or loss of sodium and potassium • Lactulose: Not absorbed by the small bowel. Latency of 2–3 days before onset of effect. Intolerance to the sweet taste, nausea, abdominal distention or discomfort are common • Magnesium and sulfate salts: Commonly used laxatives. Mainly osmotic action. Excessive doses of oral magnesium salts can lead to hypermagnesaemia. Use cautiously in renal impairment [V, D] [90]
Stimulant laxatives	• Anthranoid plant compounds (senna, aloe, cascara): Hydrolysed by glycosidases of the colonic bacteria to yield the active molecules. Both motor and secretory effects on the colon. Best taken in the evening or at bedtime, with the aim of producing a normal stool next morning. Wide variation in clinical effectiveness. Stimulating effect too great for overtly weak or debilitated patients • Polyphenolic compounds: Bisacodyl and sodium picosulfate work similarly to anthranoid laxatives; short-term use in situations of refractory constipation recommended
Laxatives generally not recommended in advanced disease	
Bulk laxatives	Useful for patients who cannot take adequate dietary fibres. Requires fluid volume and impact wanes over time. Not recommended for OIC
Detergent/Stool softener	Stimulates fluid secretion by the small and large intestine. The use of docusate sodium in palliative care is based on inadequate experimental evidence [V, C] [91, 92]
Liquid paraffin	A mineral oil that softens and lubricates the stools. Aspiration may cause lipoid pneumonia [93], anal seepage, skin excoriation and a foreign body reaction if there is a break in the anorectal mucosa. Less effective than PEG

OIC, opioid-induced constipation; PEG, polyethylene glycol.

suppositories on adults with central neurological dysfunction citing two RCTs but not applicable in the context of cancer [72].

Enemas. In general, enemas are used only if oral treatment fails after several days and in order to prevent faecal impaction [2, 63]. Small volume self-administered enemas are commercially available and are often adequate. Larger volume clinician-administered enemas should be administered by an experienced health professional [IV, C] [25]. The use of enemas involves risks of perforation of the intestinal wall (which should be anticipated and suspected if abdominal pain occurs), rectal mucosal damage and bacteraemia. Patients on therapeutic or prophylactic anticoagulation or who are affected by coagulation and platelet disorders are at risk of bleeding complications or intramural haematomas [73, 74].

Contraindications to enemas in the treatment of constipation are presented in Table 7.

Table 8 presents a range of enemas commonly used in practice and the rationale for use. Evidence to support choice of one type of enema over another is limited.

Recommendations for the management of constipation:

- Best practice is based on a balance between strategies for prevention and self-care and prescribed oral and rectal laxative therapy [V, B].

Table 7. Enemas: contraindications for use

Neutropaenia or thrombocytopaenia
Paralytic ileus or intestinal obstruction
Recent colorectal or gynaecological surgery
Recent anal or rectal trauma
Severe colitis, inflammation or infection of the abdomen
Toxic megacolon
Undiagnosed abdominal pain
Recent radiotherapy to the pelvic area

Adapted from [25].

- Key factors for prevention and self-care in the management of constipation include: ensuring privacy and comfort to allow a patient to defaecate normally; positioning (to assist gravity, a small footstool may help patient exert pressure more easily); increased fluid intake; increased activity and increased mobility within patient limits (even bed to chair); anticipatory management of constipation when opioids are prescribed [V, B].
- There is some evidence that abdominal massage can be efficacious in reducing gastrointestinal symptoms and improving

Table 8. Enemas, rationale for use and potential AEs

Enema type	Rationale	Risks/comments
Normal saline	Distend rectum and moisten stools/soften faeces with less irritating effects on rectal mucosa	Large volume watery enemas risk water intoxication if the enema is retained
Soap solution enema	1 mL of mild liquid soap per 200 mL of solution (1:200 ratio) Total volume 1000 mL	May cause chemical irritation of the mucous membranes
Osmotic micro-enema	Commercial preparations (e.g. enema containing sorbitol) contain a combination of agents, mainly sodium lauryl sulfoacetate (a wetting agent similar to docusate) and osmotic agents such as sodium citrate and glycerol. Sodium citrate creates an osmotic imbalance that brings water into the large bowel to soften the stool and stimulates the bowel to contract. Sodium lauryl sulfoacetate improves the penetrating abilities of the solution and glycerol helps to lubricate the stools	Works best if rectum is full on DRE
Hypertonic sodium phosphate enema	Both distend and stimulate rectal motility	AEs are uncommon
Docusate sodium enema	Docusate sodium softens stool by aiding water penetration of the faecal mass. Takes 5–20 min	Common AEs are anal or rectal burning and pain, short-lasting diarrhoea
Bisacodyl enema	Promotes intestinal motility by means of a passage of water into the intestinal lumen from vessels	Can cause abdominal discomfort (including cramps and abdominal pain) and diarrhoea
Retention enema	Retention enemas are held within the large intestine for a specified period, usually at least 30 min. Warm oil retention enemas (cottonseed, arachis or olive oil) lubricate and soften the stool so it can be expelled more easily	Arachis oil is derived from peanuts, so peanut allergy may prevent its use
Peristeen®	A relatively new anal irrigation system. Introduces water (500–700 mL) into the bowel using a rectal catheter and it is carried out while sitting on the toilet. Stimulates peristalsis and bowel emptying. Evidence for its use comes primarily from studies on neurogenic bowel dysfunction in patients with spinal cord injury and may not be practical in advanced disease [93]	Invasive procedure. Needs close supervision to ensure safe administration

AE, adverse event; DRE, digital rectal examination.

bowel efficiency, particularly in those patients with concomitant neurogenic problems [II, B].

- When laxatives are needed, preferred options include the osmotic laxatives [polyethylene glycol (PEG), lactulose or magnesium and sulfate salts] or stimulant laxatives (senna, cascara, bisacodyl and sodium picosulfate) [V, C].
- Magnesium and sulfate salts can lead to hypermagnesaemia and should be used cautiously in renal impairment [V, D].
- Suppositories and enemas are a preferred first-line therapy when DRE identifies a full rectum or faecal impaction [V, B].
- Enemas are contraindicated for patients with neutropaenia or thrombocytopaenia, paralytic ileus or intestinal obstruction, recent colorectal or gynaecological surgery, recent anal or rectal trauma, severe colitis, inflammation or infection of the abdomen, toxic megacolon, undiagnosed abdominal pain or recent radiotherapy to the pelvic area [V, D].

Recommendations for the management of OIC:

- Unless contraindicated by pre-existing diarrhoea, all patients receiving opioid analgesics should be prescribed a concomitant laxative [V, B].
- Osmotic or stimulant laxatives are generally preferred [V, B].
- Bulk laxatives such as psyllium are not recommended for OIC [V, D].
- In unresolved OIC, peripheral opioid antagonists such as methylnaltrexone or naloxegol may be of value [II, B] [23–40].
- Combined opiate/naloxone medications have been shown to reduce the risk of OIC through both open label, phase II and III studies [II, B] [41–50].

Management of faecal impaction

Faecal impaction is a complication of CC evidenced by a large mass of dry, hard stool in the rectum or proximal colon due to

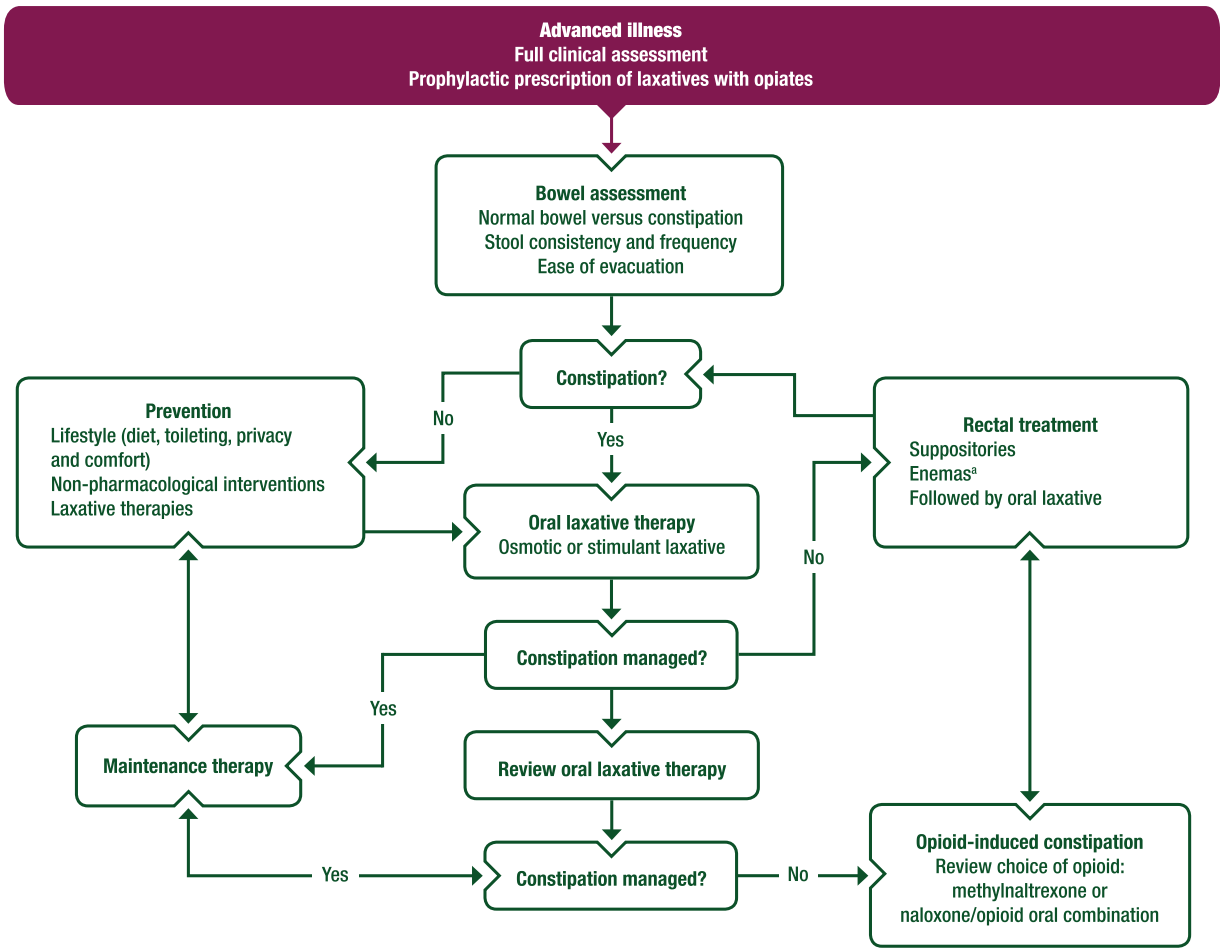

Figure 1. Management of constipation in advanced disease.
[a]Contraindicated for patients with neutropaenia (WBC < 0.5 cells/μL).
WBC, white blood cell count.

CC [75]. Watery stool from higher in the bowel may leak (overflow). Diagnosis of faecal impaction is confirmed by DRE. Where faecal impactions occur in the proximal rectum or sigmoid colon, DRE will be non-diagnostic. The treatment of a distal faecal impaction has not been the subject of clinical trials. Practice reports the utility of digital fragmentation of the stool, followed by enema (water or oil retention) or suppository to facilitate its passage through the anal canal. Once the distal colon has been partially emptied with disimpaction and enemas, PEG may be administered orally. In the case of proximal faecal impaction and in the absence of complete bowel obstruction, lavage with PEG solutions containing electrolytes may help to soften or wash out stool. Complications of faecal impaction, though uncommon, include urinary tract obstruction, perforation of the colon, dehydration, electrolyte imbalance, renal insufficiency, faecal incontinence, decubitus ulcers, stercoral ulcers and rectal bleeding [76, 77].

Recommendation:

- In the absence of suspected perforation or bleed, the management of faecal impaction involves disimpaction (usually through digital fragmentation and extraction of the stool), followed by the implementation of a maintenance bowel regimen to prevent recurrence [V, B] [75–78].

Management of constipation in the elderly cancer patient

Aetiology. Ageing causes a degenerative process in the enteric nervous system. The effect of cancer and oncological treatments can be magnified, leading to a greater risk of severe constipation, faecal impaction and complications such as intestinal obstruction.

Elderly patients with cancer represent a distinct subgroup at enhanced risk of constipation and its sequelae. The prevalence of constipation in the older adult ranges from 24% to 50% and laxatives are used daily by 10%–18% of community-dwelling older adults and 74% of nursing home residents [79, 80].

The evidence for the management of constipation in the older person is notably based on expert opinion and therefore, although appropriate for best practice, further high-quality studies are required to support clinical practice. There are two points to note with specific reference to ageing:

Assessment. Particular attention should be paid to the assessment of elderly patients [V, B]. Noting all comorbidities, a complete medication list should be obtained. Withdrawal of inappropriate or unnecessary medications is important. Key factors include:

- A social history particularly focused on the patient's current living situation (living with family or alone; in a nursing

Table 9. Summary of recommendations

Assessment and diagnosis

- All cancer patients should be evaluated for constipation [V, B]
- Assessment should include questions to determine possible causes for constipation [V, B]
- The use of PROMs is recommended [V, B]
- If constipation is identified, physical examination should include abdominal examination, perineal inspection and DRE [V, B]
- Investigations are not routinely necessary [V, B]
- If suspected clinically, corrected calcium levels and thyroid function should be checked. More extensive investigation is warranted for those with severe symptoms, sudden changes in number and consistency of BMs or blood in the stool and for older adults relative to their health and stage of disease
- Plain abdominal X-ray, although limited as a tool in itself, may be useful to image the extent of faecal loading and to exclude bowel obstruction [V, C]

Management

- Best practice is based on a balance between strategies for prevention and self-care and prescribed oral and rectal laxative therapy [V, B]
- Key factors for prevention and self-care in the management of constipation include: ensuring privacy and comfort to allow a patient to defaecate normally; positioning (to assist gravity, a small footstool may help patient exert pressure more easily); increased fluid intake; increased activity and increased mobility within patient limits (even bed to chair); anticipatory management of constipation when opioids are prescribed [V, B]
- There is some evidence that abdominal massage can be efficacious in reducing gastrointestinal symptoms and improving bowel efficiency, particularly in those patients with concomitant neurogenic problems [II, B]
- When laxatives are needed, preferred options include the osmotic laxatives (PEG, lactulose or magnesium and sulfate salts) or stimulant laxatives (senna, cascara, bisacodyl and sodium picosulfate) [V, C]
- Magnesium and sulfate salts can lead to hypermagnesaemia and should be used cautiously in renal impairment [V, D]
- Suppositories and enemas are a preferred first-line therapy when DRE identifies a full rectum or faecal impaction [V, B]
- Enemas are contraindicated for patients with neutropaenia or thrombocytopaenia, paralytic ileus or intestinal obstruction, recent colorectal or gynaecological surgery, recent anal or rectal trauma, severe colitis, inflammation or infection of the abdomen, toxic megacolon, undiagnosed abdominal pain or recent radiotherapy to the pelvic area [V, D]

Opioid-induced constipation

- Unless contraindicated by pre-existing diarrhoea, all patients receiving opioid analgesics should be prescribed a concomitant laxative [V, B]
- Laxative therapies include first-line treatment options [V, B]; osmotic or stimulant laxatives are generally preferred [V, B]
- Bulk laxatives such as psyllium are not recommended for OIC [V, D]
- Combined opiate/naloxone medications have been shown to reduce the risk of OIC through both open label, phase II and phase III studies [II, B]
- In unresolved OIC, new targeted therapies (PAMORAs) may be of value [II, B]

Faecal impaction

- In the absence of suspected perforation or bleed, best practice involves disimpaction (usually through digital fragmentation and extraction of the stool), followed by the implementation of a maintenance bowel regimen to prevent recurrence [V, B]

Constipation in the elderly cancer patient

- Particular attention should be paid to the assessment of elderly patients [V, B]
- Key prevention measures include:
  - ensuring access to toilets, especially in all cases of decreased mobility [V, B]
  - dietetic support [V, B]
  - managing known decrease in food intake (anorexia of ageing, chewing difficulties) which negatively influence stool volume, consistence and, consequently, BMs [V, B]
  - optimised toileting, educating patients to attempt defaecation at least twice a day, usually 30 min after meals and to strain no more than 5 min [V, B]
- Laxatives must be individualised and targeted to the older person's medical history (cardiac and renal comorbid conditions), drug interactions and AEs [V, B]
- Regular monitoring of chronic kidney/heart failure when a concomitant treatment with diuretics or cardiac glycosides is prescribed (risk of dehydration and electrolyte imbalances) [V, B]
- PEG (17 g/day) offers an efficacious and tolerable solution for elderly patients (good safety profile) [V, B]
- Avoid liquid paraffin for bed-bound patients and those with swallowing disorders (due to risk of aspiration lipoid pneumonia) [V, D]
- Saline laxatives (e.g. magnesium hydroxide) have not been examined in older adults, they should be used with caution because of the risk of hypermagnesaemia [V, D]
- Non-absorbable, soluble dietary fibre or bulk agents should be avoided in non-ambulatory patients with low fluid intake because of the increased risk of mechanical obstruction [V, D]. Stimulant laxatives can be used, cognisant of risk for pain and cramps
- If swallowing difficulties or a repeated faecal impaction present, rectal measures (enemas and suppositories) can be the preferred choice of treatment [V, B]. Isotonic saline enemas are preferable in older adults because of the potential AEs of sodium phosphate enemas in this age group [V, B]

AE, adverse event; BM, bowel movement; DRE, digital rectal examination; OIC, opioid-induced constipation; PAMORA, peripherally acting mu opioid receptor antagonist; PEG, polyethylene glycol; PROM, patient-reported outcome measure.

Table 10. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, . . .), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [94].

home or in hospice) to understand timing and feasibility of ongoing assessment of bowel pattern and choice of best therapeutic strategy for the patient.
- Mobility and autonomy in activities of daily living [81] (risk for poor nutrition and lack of independence in toileting).
- Presence of cognitive impairment (caregiver involvement for reliable information and better patient cooperation and comfort during physical examination is crucial).

Recommendations for managing constipation in older people with cancer:

- Particular attention should be paid to the assessment of elderly cancer patients [V, B] [78, 79]
- For this age group, prevention approaches include:
  - ensuring access to toilets, especially in all cases of decreased mobility [V, B];
  - dietetic support [V, B];
  - managing known decrease in food intake (anorexia of ageing, chewing difficulties) which negatively influence stool volume, consistence and, consequently, BMs [V, B];
  - optimised toileting: educating patients to attempt defaecation at least twice a day, usually 30 minutes after meals and to strain no more than 5 minutes [V, B].
- Laxatives must be individualised and targeted to the older person's medical history (cardiac and renal comorbid conditions), drug interactions and AEs [V, B] [81].
- Regular monitoring of chronic kidney/heart failure when a concomitant treatment with diuretics or cardiac glycosides is prescribed (risk of dehydration and electrolyte imbalances) [V, B].
- PEG (17 g/day) offers an efficacious and tolerable solution for elderly patients (good safety profile) [V, B] [26, 81, 82].
- Avoid liquid paraffin for bed-bound patients and those with swallowing disorders (due to risk of aspiration lipoid pneumonia) [V, D].
- Saline laxatives (e. g. magnesium hydroxide) have not been examined in older adults and should be used with caution because of the risk of hypermagnesaemia.
- Non-absorbable, soluble dietary fibre or bulk agents should be avoided in non-ambulatory patients with low fluid intake because of the increased risk of mechanical obstruction [V, D]. Stimulant laxatives can be used, cognisant of risk for pain and cramps.
- If swallowing difficulties or a repeated faecal impaction present, rectal measures (enemas and suppositories) can be the preferred choice of treatment [V, B]. Isotonic saline enemas are preferable in older adults because of the potential AEs of sodium phosphate enemas in this age group.

Conclusions

Figure 1 provides an algorithm of diagnosis and treatment of constipation in advanced illness. Constipation is a major management issue for cancer clinicians. There is a clinical imperative for oncologists to be familiar with the common causes of this problem, its evaluation and management strategies. The lack of robust studies and over-reliance on expert review and consensus means that this clinical area requires further ongoing clinical research investigation.

Methodology

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 9.

Levels of evidence (LoEs) and grades of recommendation (GoRs) given in this clinical practice guideline have been applied using the system shown in Table 10. The LoEs and GoRs are adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System. LoEs are reported on a scale from I to V, where I is applied when evidence from at least one large RCT of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials

without heterogeneity is identified, and V is applied for studies without a control group, case reports and expert opinions. GoRs are described from A to E, where A represents strong evidence for efficacy with a substantial clinical benefit (and therefore strongly recommended) through to E, where there is strong evidence against efficacy or for adverse outcome and would never be recommended. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty.

The review of evidence and writing of sub-sections for this CPG was assigned to each author as follows: CO provided the section on assessment and clinical management; DLC and MG revised the section on palliative care and older people; PJL reviewed the sections on non-pharmacological management and faecal impaction; FS revised the section on new mu opioid receptor antagonists; NIC, FS and PJL reviewed and revised the LoE and GoR where appropriate. All authors reviewed and consolidated the CPG in its entirety. NIC provided an earlier draft ESMO guideline on the management of constipation for the group to review and utilise as a template for this CPG. PJL collated each author's revised section into a revised CPG, which was reviewed and agreed by the team. Each author identified and sourced the literature for their respective section. All authors approved the final CPG.

Disclosure

The authors have declared no conflicts of interest.

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