An evidence review on managing constipation in palliative care

Key points

- Constipation in palliative care is so common it should almost be expected
- Opioids – the treatment of choice for cancer pain – are known to cause constipation
- There is insufficient evidence to determine the best way of managing constipation in palliative care
- Worsening constipation may be a sign of impending death
- When managing constipation in palliative care, the focus should be on quality of life

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**Abstract** Constipation – particularly opioid-induced constipation – in patients who are receiving palliative care is extremely common, but there is uncertainty about how to best manage it. There are many pharmacological treatments, but their efficacy is variable and the evidence inconclusive. There are many assessment tools to measure the severity of constipation, but no universal one, and although prophylactic laxatives are recommended, they are often not given. There is a plethora of research in this field, but most is quantitative; further research focusing on quality of life and an international consensus are needed to improve patient care. This article synthesises the latest evidence on the management of constipation in adults receiving palliative care.

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Patients receiving palliative care often have constipation, whether from a primary or secondary cause, with opioid-induced constipation being particularly problematic. So what are the best approaches to use when assessing, diagnosing and treating it? This article explores the latest research and concludes that the evidence base is not robust enough to answer that question. It argues in favour of more research, better information and training of health professionals, as well as a greater focus on patients’ quality of life.

**Constipation in palliative care**

Palliative care can be defined as care in advanced disease, with a focus on relieving symptoms. Its goal is to achieve the best possible quality of life for patients and families. Palliative care is holistic, as it encompasses psychological, social and spiritual support (Bit.ly/WHO PalliativeDefinition). The palliation of symptoms such as pain, agitation or breathlessness often requires the administration of drugs, but these can create adverse side-effects, including constipation.

Constipation is a common heterogeneous condition. The National Institute for Health and Care Excellence (2015) defines it as a symptom-based disorder, in which defecation is unsatisfactory because of infrequent stools, difficulty passing stools, and/or the sensation of incomplete bowel emptying. Physical symptoms include pain on defecation, bloating, abdominal pain and cramping due to reduced water in the stool. Slow transit time and/or low fibre intake mean the stool retains insufficient water. Untreated constipation can lead to distressing symptoms and bowel obstruction.

**Opioid-induced constipation**

One reason constipation is so frequent in palliative care is that the opioids used to relieve cancer pain are known to cause constipation.
dysfunction. Opioid-mediated effects on the central nervous system cause a reduction in gut motility which, in turn, decreases transit time (Kumar et al, 2014). Adverse effects on the gastrointestinal (GI) system are commonly reported with opioids given for pain relief; they relate to the whole gut and, beyond constipation, also include nausea, reflux and bloating.

Opioid-induced constipation is costly for the healthcare system and decreases patients’ quality of life. Common barriers to diagnosing it include:
- Lack of clinician awareness;
- Lack of communication with patients;
- Patients not disclosing their symptoms because they feel ashamed;
- The absence of a universal diagnostic tool (Camilleri et al, 2014).

In a meta-analysis, Sridharan and Sivaramakrishnan (2018) looked at 23 randomised controlled trials (RCTs), the primary end-point being an increase in spontaneous bowel movements. All studies showed that medication for opioid-induced constipation performed significantly better than placebo, but that some medication produced an increased risk of adverse side-effects that affect patients’ quality of life. The authors suggested that preventing constipation would support adherence to treatment.

Opioid-induced constipation is just one of many adverse effects patients may experience when receiving treatment for cancer or other life-limiting conditions that may cause physical and emotional pain (Star and Boland, 2018). Beyond the use of opioids, many other factors compound the risk of constipation, including hospitalisation, physical illness and reduced fluid intake (Larkin et al, 2008).

### Assessment

Constipation is a subjective experience, which partly explains why efforts to design assessment tools have not yet produced one that is definitive and universal.

In research, the criteria used to diagnose constipation vary from the number of bowel movements to the use and efficacy of laxatives. Different evaluation tools, definitions and stages of disease produce widely variable prevalence figures (Mercadante et al, 2018; Clark et al, 2012). Nazarko (2018) highlights the difficulty of ascertaining the prevalence of constipation, as studies use different criteria and methods, such as patient self-reports. She breaks down the causes of constipation into three types – propulsion, evacuatory and sensory – any of which can lead to slow transit, evacuation problems and faecal incontinence.

Clark et al (2014) suggested exploring four domains to aid diagnosis, including evaluating/assessing:
- Physical changes that could cause constipation;
- Subjective sensations (such as bloating or incomplete evacuation);
- Objective changes (such as consistency of stools);
- Any history of constipation.

Opioid-induced constipation is listed among the Rome IV functional GI disorders (Box 1) (Drossman and Hasler, 2016), compiled by a panel of over 100 GI experts. Box 2 shows the Rome IV criteria for, or indicators of, constipation; these help clinicians diagnose constipation, but do not measure treatment response.

### Box 1. Rome IV functional gastrointestinal disorders
- Irritable bowel syndrome (IBS)
- IBS with predominant constipation (IBS-C)
- IBS with predominant diarrhoea (IBS-D)
- IBS with mixed bowel habits (IBS-M)
- IBS unclassified (IBS-U)
- Functional constipation
- Functional diarrhoea
- Functional abdominal bloating/distension
- Unspecified functional bowel disorder
- Opioid-induced constipation

Source: Drossman and Hasler (2016)

### Box 2. Rome IV indicators of constipation

Constipation is present if a person has experienced ≥ 2 of the following for at least 12 weeks in the previous 12 months:
- Straining in more than half of all defecations
- Lumpy or hard stools in more than a quarter of all defecations
- Sensations of incomplete evacuation in more than half of defecations
- Sensation of anorectal obstruction or blockage in more than half of defecations
- Manual manoeuvres (for example, digital evacuation or perineal support) to facilitate more than half of defecations
- Bowel frequency of less than three per week

Source: Adapted from Drossman and Hasler (2016)

The Bowel Function Index (BFI, Box 3) is a three-item questionnaire that has been peer validated for use in opioid-induced constipation and assesses:
- The ease of defecation;
- Whether there is incomplete evacuation;
- The patient’s view on their constipation (Box 3).

The higher the score, the more severe the bowel dysfunction (Emmanuel et al, 2017a).

The simple visual tool known as the Bristol Stool Chart (Fig 1) is widely used to help patients and/or relatives describe stool consistency. It is useful to help them characterise their bowel movements at the start of the assessment process. However, it may not be a reliable measuring tool: in a study of 225 patients receiving palliative care who had constipation, Cheng et al (2013) found that even those classified as having severe constipation reported ‘normal’ stool types on the Bristol Stool Chart.

Data collected from over 7,000 patients showed that, at the time of referral to a palliative care unit, 42.4% of people had disturbed bowel scores as measured using the Symptom Assessment Scale (Clark et al, 2012). This validated symptom tool uses a numeric rating score of 0 (no problems) to 10 (worst imaginable symptoms). In that study, only 13% of patients never described bowel dysfunction during their time in palliative care.

Using three validated scoring tools, Mercadante et al (2018) measured the prevalence of constipation in 246 patients on admission to a palliative care unit and after receiving palliative care for one week. They found that patients with a higher BFI score on admission had a statistically significant increase in laxative use after one week,
suggesting their bowel dysfunction was not being treated before admission.

Management
Research suggests constipation in palliative care is not always managed effectively, despite the range of treatments available; uncertainty remains on how to best manage it (Muldrew et al, 2018). It can be difficult to do so effectively because it is multifactorial: illness, medications, reduced fluid intake and loss of appetite all affect the gut. Management is also complicated because:

● Patients may have secondary constipation caused by a range of disorders, such as:stenosis, endocrine or metabolic disorders; neurological disorders; enteric neuropathies; myogenic disorders; anorectal disorders;
● Constipation can be induced by a variety of common drugs (Box 4);
● Laxatives have a non-specific action (Emmanuel et al, 2017a).

Pharmacological treatments
The pharmacological treatment of opioid-induced constipation can entail:

● The systemic use of laxatives;
● Treatment with agonist or antagonist substances;
● Both of the above.

At times, rectal interventions in the form of enemas or suppositories will be needed, but there is very little research on these approaches. Local formularies will guide the prescribing of the different drugs described below.

Laxatives include:

● Osmotic laxatives – these retain fluid in the bowel and increase bulk by bacterial fermentation;
● Stimulants – these induce a bowel movement in 8-12 hours by increasing peristalsis. Stimulants should be taken at night and should not be used if there is a risk of intestinal obstruction;
● Faecal softeners – these soften the stool, easing passage through the bowel;
● Bulk-forming laxatives – these increase the bulk of the stool, easing its passage through the bowel.

Agonists and antagonists used to treat constipation include:

● 5-HT4 agonists – these stimulate the 5-HT receptors of the intestine, causing an increase in peristalsis. They are usually prescribed by specialists;
● Opioid receptor antagonists – these work selectively by antagonising peripheral opioid receptors to relieve constipation.

A new drug has emerged in recent years – the chloride channel activator lubiprostone – which NICE recommended for chronic idiopathic constipation. However, lubiprostone is not currently available as the manufacturer discontinued it in December 2018 for commercial reasons.

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Phosphate enemas are osmotic enemas that increase the water content of the stool, thereby stimulating rectal motility (Davies, 2004). They should be used with caution in:

● Older people who are frail;
● Patients with electrolyte disturbance, renal impairment, congestive heart failure, ascites or uncontrolled hypertension;
● Constipation can be induced by a variety of common drugs (Box 4);
● Laxatives have a non-specific action (Emmanuel et al, 2017a).

Evidence
A closer look at the evidence base raises the following questions:

● Is there enough robust evidence to support practice?
● When should treatment be stopped?

Some researchers point to the possibility that worsening constipation actually goes hand in hand with approaching death. Research focuses on objective measures of treatment success (such as frequency of bowel movements, efficacy and
Laxatives

Among the 225 patients with advanced cancer analysed by Cheng et al (2013), 92% used one or more treatments for constipation, including laxatives (such as lactulose, senna and bisacodyl), suppositories, enemas, digital evacuation and Chinese herbal medicine. A statistically significant correlation was noted between the use of strong opioids and worsened constipation. Those who had no constipation were taking significantly higher doses of Chinese herbal medicines and over-the-counter drugs, suggesting a preventative element. The study did not assess the severity of constipation before and after laxative use, which was acknowledged as a limitation.

Laxatives are prescribed on the assumption that there is a direct correlation between their use and the frequency and/or ease of bowel movements. This was tested by Clark et al (2011) in a retrospective, observational study of 211 patients admitted to a palliative care unit. The authors failed to correlate the use of laxatives with the frequency of bowel movements. All study participants were prescribed laxatives: 48% one type only; 42% two types; and 10% three or more. Docusate plus senna was the most common combination prescribed, followed by those two drugs plus a macrogol. There was no relationship between the number of laxatives prescribed and documented bowel movements, which suggests over-prescribing may have occurred.

Mercadante et al (2018) conducted a prospective multicentre study of 246 patients entering a palliative care unit. On day 7, there was a statistically significant increase in the use of laxatives (senna, lactulose and polyethylene glycol) in participants with a high BFI score on admission. Participants with a low BFI score on admission received higher doses of opioids than those with a high BFI. On day 7, they showed a statistically significant worsening of constipation. It could be that their initial lower score meant they were not perceived as requiring laxatives. This highlights the importance of ongoing daily assessment of patients receiving opioids.

The idea that all laxatives have some efficacy was challenged by Emmanuel et al (2017) in a cross-sectional survey of 198 patients taking opioids for at least one month. The BFI was used alongside questions regarding laxative use, efficacy and side-effects. Of the participants, 77% reported no constipation before starting opioids. After having started taking opioids, 73% of those who reported no constipation pre opioid use had, at some point, taken a laxative since using opioids. Higher BFI scores were not linked to higher opioid doses.

Laxatives ranged from osmotic, stimulant and softening laxatives, and were used as well as rectal interventions such as enemas; the survey did not, however, collect data on adherence. The use of laxatives was linked with a higher BFI score, and constipation was worse in participants who took laxatives than those who did not. Laxatives caused many side-effects including gas, bloating, a sudden urge to defecate and nausea. The authors concluded that laxative use was often ineffective and negatively affected quality of life.

In an RCT by Tarumi et al (2013), 39 patients were randomised to a 10-day trial of oral docusate and senna, and 39 patients to just senna. Docusate is a stool softener and this was the first RCT of this drug in a hospice setting. The primary outcome measures were stool frequency, consistency and volume. Opioid use was almost identical in the two treatment arms, but docusate and senna were not more efficacious than senna alone. This highlights that individual and ongoing assessment is vital.

According to Kyle (2011), there is little research regarding the timing of cessation of laxatives when treating patients with opioid-induced constipation at the end of life. This can cause uncertainty among health professionals.

A retrospective study of patients receiving palliative care who had constipation, undertaken by Clark et al (2011), looked at patients in four validated phases of illness: stable, unstable, deteriorating and terminal. Senna and docusate were the most commonly prescribed laxatives. Nearly 45% of participants had bowel actions occurring less frequently than every third day. As they moved through the different phases of illness, they had fewer bowel movements despite the use of laxatives. This may indicate that worsening constipation could be a predictor of death and raises questions regarding the use and benefits of laxatives in this phase.

Clark et al (2012) conducted a second retrospective study to review the prescribing of laxatives in 92 patients towards the end of life. Only 20 participants were classified as being constipated on admission, yet 67 were prescribed one or more laxatives, and three who were documented as having constipation were not prescribed laxatives; this suggests failures in the assessment process. The study found no statistical differences between those who were and were not receiving laxatives in the time of the last recorded bowel movement before death. This, again, supports the theory that bowel actions become less frequent as death approaches.

Opioid receptor antagonists

Three types of opioid receptors are distributed in the central, enteric and peripheral nervous system, and analgesia occurs through stimulation of the central μ-opioid receptors. Naloxegol is a peripherally acting μ-opioid antagonist taken orally in tablet form. When it is initiated, all other laxatives should be stopped. Portenoy et al (2008) pointed out that naloxegol can lead to an increase in pain due to systemic absorption but, as it is in tablet form, it could be seen as preferable to subcutaneous injections of methylnaltrexone.

Methylnaltrexone was licensed for the treatment of opioid-induced constipation in 2008. Portenoy et al (2008) conducted a multicentre, double-blind, randomised dose-ranging study to assess the efficacy and safety of subcutaneous methylnaltrexone. Participants were randomised to three different drug doses, the primary endpoint being to have a bowel movement within four hours of initial administration. The authors concluded that:

- Methylnaltrexone at doses of 23mg reversed opioid-induced constipation;
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- The drug was well tolerated;
- Participants were satisfied with the treatment.

While not yet licensed for use in the UK, naldemedine has been selected for phase-III studies for the treatment of opioid-induced constipation. In Japan, Katakami et al (2017) undertook a phase-II randomised, double-blind, placebo-controlled study of naldemedine for opioid-induced constipation in patients with cancer. They randomly assigned 225 participants to three different doses of the drug or a placebo for a two-week period. The primary endpoint was a change in spontaneous bowel movements within a week. All three doses of the drug produced a statistically significant positive change compared with placebo.

Implications for practice

Assessing and managing constipation in palliative care is vital. Assessment should be individualised and ongoing, and opioid-induced constipation needs to be addressed in a timely fashion. However, the best strategies remain unclear. Research has not been able to establish a relationship between laxative use and frequency of bowel movement. In addition, so far, it has focused on pharmaceutical management, not on quality of life, privacy and dignity – which, arguably, are of the utmost importance at the end of life. Alternative therapies such as abdominal massage, probiotics and herbal remedies have not been well researched.

There seems to be a consensus that opioids should always be prescribed with laxatives but this is not reflected in practice. As opioids remain the treatment of choice for cancer pain, there is pressing a need to effectively assess and treat opioid-induced constipation. Not doing so risks compromising holistic, patient-centred care. Patients and families need to know the risks of opioid-induced constipation and when to seek help.

One solution could be to prescribe, after a thorough assessment, prophylactic laxatives to all patients receiving palliative care who are taking opioids. The cost of this would be negligible compared with the cost of hospital admissions and, more importantly, the impact of poorly managed constipation on quality of life.

Gaps in guidance on bowel care in the palliative and end-of-life stages have been highlighted as a challenge for nurses (Kyle, 2011). The need for a more research was highlighted by Larkin in 2008 but the evidence base to guide practice remains poor. The Royal College of Nursing’s (2012) guidance on the management of lower bowel dysfunction does not cover opioid-induced constipation, but this will hopefully be remedied in the document’s forthcoming update.

Daines et al (2013) conducted a qualitative study on nurses’ experiences of caring for patients and families in a palliative care unit. It outlined the emotional and physical challenges faced by nurses, patients and families when dealing with bowel obstruction. It also stressed that nurses needed to be equipped with the right knowledge and skills to diagnose and treat patients. A better understanding of opioid-induced constipation and its burden may promote better management.

Health professionals working in palliative care especially hospice and community nurses - are well placed to contribute to further research on constipation in their patients, not just in terms of their GI function but also of their experiences and quality of life. NT

References


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