Pharmacological management of patients with opioid-induced constipation in primary and secondary care

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Pharmacological management of patients with opioid-induced constipation in primary and secondary care

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Opioids are widely used in the management of cancer and non-cancer pain. Data from the US suggest that opioids were prescribed in approximately 20% of non-cancer-related cases of patients presenting with symptoms or diagnoses of pain in 2010.1 Primary symptoms or diagnoses of pain also represented one-fifth of all patient visits to their healthcare provider.1 The prevalence of opioid use is likely to be even higher when over-the-counter (OTC) opioids are taken into account. Prescribing of opioids in the US is higher than in the UK, however, scripts for opioids in the UK have increased dramatically in recent years.2,3 In England in 2010, there were over 17 million prescriptions for opioid items.4 Concerns around the inappropriate use of opioids have led to the development of ‘Opioids Aware’—a resource to support safe and effective prescribing of opioids for the management of pain (www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware)—and to the initiation of a national parliamentary inquiry.5

Opioid-induced constipation

Opioids can cause adverse effects such as nausea, vomiting, sedation, dizziness and respiratory depression.7 Many people taking opioids experience constipation as it is the most common gastrointestinal adverse effect, and the incidence of opioid-induced constipation (OIC) increases with duration of opioid use.7 Estimates of prevalence vary, in part, because there is no uniform definition of OIC; however, it is estimated that the prevalence of OIC is around 41–57% in patients with non-cancer pain and at least 90% for patients with cancer-related pain.9 Use of OTC opioids such as codeine means that the prevalence of OIC is likely to be even higher than is reported in the literature, which focuses on opioids for moderate to severe pain. Opioid-induced constipation does not differ in clinical presentation from functional or idiopathic constipation7 (constipation that cannot be explained by any anatomical, physiological, radiological, or histological abnormality). Constipation is a disorder that can cause considerable morbidity; more than two-thirds of patients on opioid therapy experience constipation-related symptoms that affect their quality of life.10 Indeed, most patients with cancer ranked constipation as a greater distress than the pain for which they received treatment with opioids,11 and some would rather endure their pain than severe constipation.12 Some patients may become tolerant to some of the adverse effects of opioid treatment, such as nausea, vomiting, and sedation, but as patients are unlikely to develop tolerance to OIC,13 it can cause problems with treatment compliance. It is one of the most common reasons why patients stop taking opioid analgesia,14 resulting in a reduction in effective pain management.

In addition to the impact on patients, constipation also has economic implications. A study in the US found that total healthcare costs were more than double in patients with constipation compared with those who did not have constipation. Costs increased by more than 60% in all care settings—including inpatient departments, emergency departments, and nursing homes when patients had constipation.15

Rationale for this prescribing guideline

Guidance on the treatment pathway for OIC is generally lacking, which has resulted in variation in
the management of patients affected by this condition. The only current UK guidance on OIC is NICE Technology Appraisal 345 on the use of naloxegol, which recommends the use of naloxegol as an option for treating OIC in adults whose constipation has not adequately responded to laxatives. Technology Appraisal 345 defines ‘an inadequate response as symptoms of OIC of at least moderate severity in at least one of the four stool symptom domains (that is, incomplete bowel movement, hard stools, straining, or false alarms) while taking at least one laxative class for at least 4 days during the prior 2 weeks.’ Despite this recommendation, many patients are routinely offered more than one laxative treatment when other non-laxative treatments, including the peripherally acting mu-opioid receptor antagonists (PAMORAs), could be offered. There is, therefore, a need for clear guidance to support best practice in the pharmacological management of OIC, particularly when it has not adequately responded to first-line laxative treatment. This document represents an UK expert opinion guideline.

**Treatment options**

A variety of treatments are licensed for the management of constipation (see Box 1, right). However, although most have been used in patients with chronic idiopathic constipation, the evidence base for their specific use in OIC is lacking or of poor quality. The recommendations made in this guidance are, therefore, based on consideration of the clinical evidence on chronic idiopathic constipation, existing guidance (including recommendations from the European Association for Palliative Care, the European Consensus Group on Constipation in Palliative Care, and NICE and the clinical experience of the expert group. The choice of treatment should take into account patient preferences, side-effects, and ease of use.

**Laxatives**

Similar to non-OIC, laxatives are advocated as a first-step approach to OIC and include fibre; stool softeners such as arachis oil and liquid paraffin; stimulants such as bisacodyl, sodium picosulfate, senna, and dantron; and osmotic laxatives such as lactulose and macrogol. Although sodium docusate is widely used in clinical practice, there is a lack of published literature supporting its efficacy.

In terms of the various laxatives, evidence from a systematic review of functional constipation supports the use of macrogol, which is indicated for the treatment of chronic constipation.

Macrogol induces a laxative effect through its osmotic action in the gut and contains electrolytes to ensure no overall gain or loss of water, potassium, or sodium. It is administered as an oral solution, with a maintenance dose of 1–2 doses per day (as 1–2 sachets, or 25 ml concentrate). One of the benefits of macrogol is that it acts both as a softener and a stimulant, a combination that is recommended by existing guidance on palliative care. If constipation persists despite macrogol, a stimulant laxative such as bisacodyl or sodium picosulfate can be added. Bisacodyl is indicated for the short-term relief of constipation (chronic or recent onset, whenever a stimulant laxative is required), and sodium picosulfate is indicated for the short-term relief of constipation and management of constipation of any aetiology. Both bisacodyl and sodium picosulfate have been shown to be more effective than placebo in the short term. Both of these laxatives have the same dual action, stimulating the mucosa of the large intestine and the rectum after hydrolysis in the large intestine. This results in colonic peristalsis with promotion of accumulation of water, and consequently electrolytes, in the colonic lumen. This softens the stool, and also stimulates defaecation. Bisacodyl is taken orally, with a recommended dose of one or two tablets (5–10 mg) daily before bedtime. Sodium picosulfate is taken orally, with a recommended dose of one to two 5 ml spoonfuls (5–10 mg) per day.

There are insufficient data to make a recommendation about the efficacy of stool softeners or senna in the management of idiopathic constipation, and there is a lack of data on their use in OIC. Dantron has a restricted licence in the UK because of its potential mutagenic effects. The side-effects of lactulose tend to preclude chronic use.

A 2001 survey of patients with OIC found that only 46% of patients prescribed laxative therapy achieved the desired treatment outcome.

**Non-laxative pharmacological options**

A variety of non-laxative options are available for the treatment of constipation, but few are specifically indicated in OIC due to lack of evidence.

**Lubiprostone**

The chloride-channel activator lubiprostone is indicated for the treatment of chronic idiopathic constipation.
constipation in adults when response to diet and other non-pharmacological measures are ineffective. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby facilitating the passage of stool and alleviating symptoms associated with chronic idiopathic constipation. Lubiprostone is taken orally (24 mcg) twice daily for 2–4 weeks. Lubiprostone has been recommended by NICE as a possible treatment option for chronic idiopathic constipation. Although it is not licensed for use in the treatment of OIC, there is evidence that it is effective in improving symptoms in patients with OIC and is generally well tolerated.

**Prucalopride**
The prokinetic prucalopride is indicated for symptomatic treatment of chronic constipation in adults in whom laxatives fail to provide adequate relief. Prucalopride is a selective, high-affinity serotonin (5-HT4) receptor agonist with gastrointestinal prokinetic effects. Prucalopride is taken orally—2 mg once daily. NICE has recommended prucalopride as an option for the treatment of chronic constipation only in women and its use is subject to specific criteria. Although it is not licensed for use in the treatment of OIC, there is evidence that it improves bowel movement frequency and is well tolerated in patients with OIC.

**Peripheral acting mu-opioid receptor antagonists**
Methylnaltrexone and naloxegol are PAMORAs, which act by binding to mu-opioid receptors in the gastrointestinal tract, targeting the underlying causes of OIC. They decrease the constipating effects of opioids without affecting the opioid-mediated analgesic effects on the central nervous system. These therapies are indicated for the treatment of OIC in adults who have had an inadequate response to laxatives.

- Methylnaltrexone bromide is administered by subcutaneous injection; the recommended dose is dependent on the patient’s weight, and the administration schedule differs for treatment of OIC in patients with chronic pain and patients receiving palliative care.
- Naloxegol is a PEGylated derivative of the mu-opioid receptor antagonist naloxone, which is administered orally at a usual dose of 25 mg.

It should be noted that naloxone is available in a compound preparation with oxycodone, but that this formulation has a limited role in the management of OIC.

**Alternative strategies**
One option for managing OIC while maintaining analgesia is by rotating one opioid with another (i.e. change either the drug or route of administration of the drug). Although such an approach is often used in clinical practice there is limited supportive literature. However, there are some data to suggest that transdermal fentanyl, and transdermal buprenorphine may cause less constipation (than oral opioids).

**Non-pharmacological options**

**Complementary therapies**
There is insufficient evidence to recommend probiotics in patients with chronic idiopathic constipation and no evidence to support their use in patients with OIC. Many other complementary therapies have been used in the management of idiopathic constipation, but the evidence to support them is entirely anecdotal.

**Prophylaxis**
In anticipation of potential development of constipation with long-term opioid use, treatment guidelines recommend initiation of a prophylactic bowel regimen that may involve increased fluid and fibre intake, stool softeners, and/or laxatives.

**Guideline for patients with opioid-induced constipation**

**Identification of patients**
An algorithm to help identify patients at risk of, or with OIC is shown in Figure 1 (p.5). The following screening question can be used to assess for the presence of OIC: ‘Has there been any change in frequency and/or difficulty/ease of bowel movement since starting opioids?’

- Patients fall into three groups:
  - patients without a previous history of constipation starting opioids (who are at risk of OIC)
  - patients with a history of constipation starting opioids
  - patients taking opioids presenting with constipation

- If OIC is unlikely in a patient presenting with abnormal bowel habit because aetiological risk factors are absent, examine the patient, and arrange investigations to exclude other causes, and refer as appropriate:
  - ask about changes in diet and mobility
  - review medications for concomitant constipating agents such as drugs with anticholinergic effects (e.g. antidepressants)
  - OIC is unlikely if the patient has episodes of diarrhoea and is not taking laxatives
  - rule out other systemic issues such as rectal bleeding, unintentional weight loss, abdominal distension, and faecal impaction

- If OIC is likely, assess baseline Bowel Function Index (BFI) score and Bristol Stool Chart (BSC) score to allow monitoring

- If the patient does not have OIC, monitor for constipation for the duration of opioid treatment.

The BFI was chosen as the key assessment tool as it is a validated condition-specific instrument, which is easily administered, responsive to change and widely utilised in clinical studies.
Management of patients with OIC

An algorithm covering the treatment of patients with OIC is shown in Figure 2 (p.6).

› Review the need for ongoing opioid analgesics
› Explain to the patient that opioids may lead to, or exacerbate, constipation (as stated in Clinical Guideline 14021)
› Offer lifestyle advice (see Box 2, below)
› Assess baseline BFI (constipation is controlled if BFI <30) and BSC scores to allow monitoring
› Prescribe macrogol for use on a regular basis while taking opioids:
   – other laxatives may be prescribed based on, for example, patient preference, ease of use, and potential side-effects
   – do not offer a repeat prescription until the patient has had a follow-up contact
   – consider offering a delayed prescription for a ‘step-up’ drug (i.e. alternative laxative) that the patient can use if constipation persists

Inadequate treatment

› Inadequate treatment is defined as persistent constipation (BFI >30), or continued side-effects from laxatives
› If constipation persists despite adherence to treatment with macrogol monotherapy:
   – add in a stimulant such as bisacodyl or sodium picosulfate, taking into account patient preference, for use on a regular basis:
   • do not offer a repeat prescription until the patient has had a follow-up contact
   • ask the patient to make contact if symptoms worsen, new symptoms develop, or side-effects develop before follow-up contact
   • initiate a PAMORA (e.g. naloxegol) for use on a regular basis:
   • do not offer a repeat prescription until the patient has had a follow-up contact
   • ask patient to make contact if symptoms worsen, new symptoms develop, or side-effects develop before follow-up contact

Box 2: Patient education/lifestyle advice

• Patients should be given tailored education and lifestyle advice
• Advise patients that opioids may lead to constipation
• Patients should be advised to:
  – increase exercise/keep mobile
  – increase consumption of fibre to 25–35 g/day
  (www.bladderandbowel.org/bowel/bowel-resources/fibre-contents-of-food-chart)
  – use footstools during toileting to attain correct position
  – avoid sleep deprivation
  – increase fluid intake to >1.2 l/day
• Ensure privacy and dignity during toileting (in all care settings).
PHARMACOLOGICAL MANAGEMENT OF OPIOID-INDUCED CONSTIPATION

(very common side-effects of PAMORAs include abdominal pain and diarrhoea)

If constipation persists despite treatment with a PAMORA:
- add in a laxative for use on a regular basis (an osmotic or stimulant or laxative will complement the action of a PAMORA)
- refer to secondary care or seek secondary care opinion to consider other treatments (these may include prokinetics, secretagogues, suppositories/enemas, and transanal irrigation).

Figure 2: Management of opioid-induced constipation

Follow-up
- Arrange for follow-up contact within 2 weeks, unless OIC is severe in which case follow-up contact should occur sooner
- Reassess BFI and BSC scores to identify changes since baseline
- Assess adherence.

Prophylaxis
- In patients starting opioids:
  - explain that opioids may lead to or exacerbate constipation

*Take into account factors such as patient preference, ease of use, and side-effects.
†Review ideally within 1–2 weeks but the patient should return sooner if symptoms worsen, new symptoms develop, or side-effects develop.
OIC=opioid-induced constipation; BFI=Bowel Function Index; BSC=Bristol Stool Chart; PAMORA=peripherally acting mu-opioid receptor antagonist
- offer lifestyle advice (see Box 2, p.5)
- prescribe macrogol as prophylaxis for use on a regular basis while taking opioids:
  - other laxatives may be prescribed based on, for example, patient preference, ease of use, and potential side-effects.

Referral

> Refer patients with the following red-flag symptoms for further investigation and specialist opinion (secondary care, either gastroenterology or colorectal team, depending on local guidelines):

- bleeding
- unintentional weight loss
- abdominal distension
- faecal impaction:
  - history over preceding fortnight of bowel infrequency, faecal leakage, loose stools, passive soiling (‘overflow’), palpable abdominal mass, slack anal tone with hard faeces on rectal examination
- bowel obstruction in patients with a history of bowel cancer.

A list of useful resources can be found in Box 3 (right).

Conclusion

Opioid-induced constipation affects a large proportion of patients receiving opioid therapy, regardless of the route of administration or dosing. This report describes the output from a UK expert group meeting comprising primary and secondary care with both cancer and non-cancer pain specialists. Case finding for OIC is strongly advocated. There is little evidence to support a response to lifestyle measures or probiotics, and equally, while laxatives are mostly used as first-line therapy, there is no body of medical evidence to support efficacy for such an approach. Peripherally acting mu-opioid receptor antagonists have been shown to be effective when used in an approach. Box 3: Useful resources

- Bristol Stool Chart—medical aid to classify the form of human faeces into seven categories: goo.gl/9o7f37 (accessed 24 August 2017)
- Dietetic information sheet for irritable bowel syndrome (www.bda.uk.com/foodfacts/IBSfoodfacts.pdf)
- Opioids Aware—resource to support safe and effective prescribing of opioid medicines for pain in the UK: www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware

Key points

- OIC is widely prevalent in people with non-cancer pain and one of the most common reasons for discontinuing opioid analgesia
- Proactive identification of OIC using the screening question is recommended in all individuals taking opioid-based analgesia: ‘Has there been any change in frequency and/or difficulty/ease of bowel movement since starting opioids?’
- OIC is usually treated with laxatives, and an inadequate response is common
- Peripheral acting mu-opioid receptor antagonists such as naloxegol are indicated for adults with inadequate response to laxatives.

Conflicts of interests statements

Andrew Davies has acted as a paid advisor for AstraZeneca, Kyowa Kirin Ltd, and Wyeth Pharmaceuticals.

Andrew Dickman has received an honorarium from Kyowa Kirin Ltd for this meeting only.

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Sanjay Suman has received speaker and consultancy fees from Astellas Pharma Ltd, Boehringer Ingelheim Ltd, Internis Pharmaceuticals Ltd, Kyowa Kirin Ltd, Lilly, Pfizer Limited, Merck Sharp & Dohme Limited, and has participated in advisory boards for Astellas Pharma Ltd and Vifor Pharma UK Ltd.

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Prescribing Information (prepared October 2016.)

Moventig 12.5mg and 25mg film-coated tablets® (naloxegol oxalate) Consult Summary of Product Characteristics (SmPC) before prescribing. Indication: Opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s) (concurrent OIC symptoms of at least moderate severity while taking at least one laxative class for a minimum of four days during the previous 2 weeks). Dosage and administration: Recommended 25 mg once daily. Take on empty stomach at least 30 minutes prior to first meal of day or 2 hours after first meal of day. Crushed tablets can be mixed with water (120ml) and drunk immediately or administered via a nasogastric tube (CH8 or greater). Renal impairment: Moderate to severe renal impairment starting dose 12.5mg. Discontinue if side effects impact tolerability. Increase to 25mg if well tolerated. Hepatic impairment: Use in severe hepatic impairment not recommended. Moderate CYP3A4 inhibitors: Starting dose 12.5mg, can be increased to 25mg if well tolerated. Paediatric population (< 18 years): Safety and efficacy not yet established. Adverse effects: Consult SmPC for full list of side effects. Very Common: Abdominal pain, diarrhoea. Common: Nasopharyngitis, headache, flatulence, nausea, vomiting, hyperhidrosis. Uncommon: Opioid withdrawal syndrome. Contraindications: Hypersensitivity to active substance or any of the excipients or any other opioid antagonist. Patients with known or suspected gastrointestinal (GI) obstruction or patients at increased risk of recurrent obstruction. Patients with underlying cancer who are at heightened risk of GI perforation, such as those with underlying malignancies of gastrointestinal tract or peritoneum, recurrent or advanced ovarian cancer or vascular endothelial growth factor (VEGF) inhibitor treatment. Concomitant use with strong CYP3A4 inhibitors. Warnings and precautions: Use with caution in patients with any condition which might result in impaired integrity of the gastrointestinal tract wall. Advise patients to discontinue therapy and promptly report if unusually severe or persistent abdominal pain develops. Use with caution in patients with clinically important disruptions to the blood brain barrier and/or known CNS effects. Discontinue if interference with opioid-mediated analgesia or opioid withdrawal syndrome occurs. Use with caution in patients taking methadone. If opioid withdrawal syndrome is suspected the patient should discontinue Moventig and contact their physician. Use with caution in patients with a recent history of myocardial infarction, symptomatic congestive heart failure, overt cardiovascular (CV) disease or with a QT interval of ≥500msec. Use with caution in OIC patients with cancer-related pain. Use in pregnancy and lactation: Not recommended. Legal category: POM. Marketing Authorisation numbers: Moventig 12.5mg tablets EU/1/14/962/001; Moventig 25mg tablets EU/1/14/962/005. Further information available on request from the Marketing Authorisation holder: Kyowa Kirin Ltd. Galabank Business Park, Galashiels, Scotland TD1 1QH, UK.

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NHS cost: Moventig 12.5mg, 30 tablets, £55.20; Moventig 25mg, 30 tablets, £55.20

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