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Constipation in people prescribed opioids

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ABSTRACT

INTRODUCTION: Constipation is reported in 52% of people with advanced malignancy. This figure rises to 87% in people who are terminally ill and taking opioids. Constipation may be the most common adverse effect of opioids. There is no reason to believe that people with chronic non-malignant disease who take opioids will be any less troubled by this adverse effect. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of: oral laxatives, rectally applied medications, and opioid antagonists for constipation in people prescribed opioids? We searched: Medline, Embase, The Cochrane Library, and other important databases up to August 2009 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 23 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: arachis oil enemas, bisacodyl, co-danthrusate/co-danthramer, docusate, glycerol suppositories, ispaghula husk, lactulose, liquid paraffin, macrogols plus electrolyte solutions, magnesium salts, methylcellulose, opioid antagonists, phosphate enemas, senna, sodium citrate micro-enema, and sodium picosulfate.

QUESTIONS

INTERVENTIONS

Key points

- Constipation is reported in 52% of people with advanced malignancy. This figure rises to 87% in people who are terminally ill and taking opioids. Constipation may be the most common adverse effect of opioids. There is no reason to believe that people with chronic non-malignant disease who take opioids will be any less troubled by this adverse effect.
- There is some RCT evidence, supported by consensus, that the oral laxatives lactulose, macrogol/electrolyte solutions, and senna are probably of similar efficacy in people with opioid-induced constipation.

  Macrogol/electrolyte solutions may have a better adverse effect profile than the other oral laxatives.

  We found no good-quality studies on other oral laxatives such as ispaghula husk and liquid paraffin. Liquid paraffin is associated with severe adverse effects and is not recommended for long-term use.

  Sodium phosphate enemas have a high incidence of adverse effects. We found no RCT evidence assessing other rectally applied agents (arachis oil enema, glycerol suppository, sodium citrate micro-enema).
- We found no RCT evidence assessing rectally applied agents (arachis oil enema, glycerol suppository, phosphate enema, sodium citrate micro-enema).
- There is consensus that the opioid antagonists alvimopan, methylnaltrexone, and naloxone can reverse not only the constipation but potentially the other gastrointestinal symptoms induced by opioids.

Naloxone may provoke reversal of opioid analgesia, but this is less likely with alvimopan or methylnaltrexone. Naloxone may also cause mild degrees of opioid withdrawal, but this has not been reported with methylnaltrexone or alvimopan.

- Further RCTs assessing all the currently available treatments are needed.

DEFINITION

Constipation is infrequent defecation with increased difficulty or discomfort and with reduced number of bowel movements, which may or may not be abnormally hard. It can have many causes, one of which is opioid use. Opioid-induced bowel dysfunction (OBD) encompasses a wide range of associated symptoms including abdominal distension and pain, gastric fullness, nausea, vomiting, anorexia, confusion, and overflow diarrhoea. [1] These symptoms may also be associated with constipation from other causes. This review focuses only on constipation in people prescribed opioids. For the purposes of this review, we have used the UK National Institute for Health and Clinical Excellence definition of supportive care as follows: supportive care "helps the patient and their family to cope with cancer and treatment of it — from pre-diagnosis, through the process of diagnosis and treatment, to cure, continuing illness or death and into bereavement. It helps the patient to maximise the benefits of treatment and to live as well as possible with the effects of the disease. It is given equal priority alongside diagnosis and treatment". [2] This definition was written in relation to people with cancer but is applicable to all people with chronic or terminal illness; for example, heart failure or lung disease. We have used the WHO definition of palliative care as follows: "Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual". [3] Although this definition of palliative care does not specify incurable or terminal illness, there is consensus that palliative care applies to people approaching the end of life; that is, people with a prognosis of less than 1 year. Thus, both supportive and palliative care embrace the same priorities of maximising quality of life; but supportive care aims to do this in people who may live longer, become cured, or who are living in remission from their disease.

INCIDENCE/ PREVALENCE

In one prospective cohort study (1000 people with advanced cancer), constipation was reported to occur in 52% of people. [4] In another prospective cohort study (498 people in hospice with advanced cancer) this figure rose to 87% in people who were terminally ill and taking opioids. [5] A survey (76 people) carried out by the American Pain Society found that, in people with chronic pain of non-cancer origin treated with opioids, the incidence of constipation was five times higher than in another US survey of 10,018 US controls (health status of controls not defined). [1] Fifty-eight percent of people who took opioids regularly required more than two types of treatment for constipation. [1] A British cohort study (274 people with cancer attending a tertiary referral cancer hospital) found that 72% of people taking oral morphine for pain had mild to severe grades of constipation. [6] The prevalence of constipation is not the same with all opioids. One RCT (212 people with cancer), assessing people who were taking opioids for 14 days or less, found that significantly more people taking modified-release oral morphine than taking transdermal fentanyl had constipation (27% with transdermal fentanyl *v* 45% with modified-release oral morphine; P less than 0.001). [7] One systematic review (search date 2004, 6 RCTs, 1220 people, 657 with cancer, 563 with chronic painful diseases taking opioids for 28 days or more) found that significantly more people had constipation when taking modified-release oral morphine than taking transdermal fentanyl (16% with transdermal fentanyl *v* 37% with modified-release oral morphine; P less than 0.001). [8] A more recent systematic review (search date 2007, 4 RCTs, 425 people with moderate–severe cancer pain) comparing oral morphine versus transdermal opioids (fentanyl and buprenorphine) found that both transdermal drugs were associated with a significantly reduced incidence of constipation (31/214 [14%] with transdermal opioids *v* 62 /211[29%] with oral morphine). [9]

AETIOLOGY/ RISK FACTORS

The constipating effect of opioids is through their action on mu opioid receptors in the submucosal plexus of the gastrointestinal tract. [10] This decreases gastrointestinal motility by decreasing propulsive peristalsis (at the same time increasing circular contractions), decreases secretions (pancreatic and biliary), and increases intestinal fluid absorption. [10] There is also a central descending opioid-mediated effect so that even spinally administered opioids cause decreased gastric emptying and prolonged oral–caecal transit time. The opioid-induced increase in circular muscle contractions causes colicky pain. There is good evidence from RCTs [8] [7] and animal studies [11] that, compared with water-soluble opioids such as morphine and oxycodone, the more lipid-soluble opioids such as fentanyl and buprenorphine are less likely to cause constipation while maintaining the same degree of analgesic effect. This is probably caused by their much reduced time in the systemic circulation. Other risk factors for constipation and bowel dysfunction in people taking opioids for advanced cancer include hypercalcaemia, reduced mobility, reduced fluid and food intake, dehydration, anal fissures, and mechanical obstruction. [12] Lack of privacy for defecation may also play a part for people in hospital. [12] Drugs that can cause or exacerbate constipation include an-

ticholinergics. In the treatment of cancer, thalidomide, vinca alkaloids, and $5HT_3$ antagonists can all cause constipation. [12] Additionally there is an increased risk of constipation in people with autonomic neuropathy caused by diabetes mellitus, for example, and in people with neuromuscular problems such as spinal cord compression. [12]

PROGNOSIS

One single-centre observational study (50 people) found a correlation between persistent constipation and poorer performance status (94% of people with Eastern Cooperative Oncology Group [ECOG] score 3 or 4 were constipated). [13] This study found no relationship between total opioid dose and degree of constipation. However, a more recent single-centre observational study (50 people with advanced cancer) found increased constipation in people taking opioids, but found no relationship between constipation and a more sophisticated measure of physical functioning such as the Barthel Index. [14]

AIMS OF INTERVENTION

To reduce constipation in people prescribed opioids, with minimal adverse effects of treatment.

OUTCOMES

Bowel movements/laxation frequency, completeness of evacuation, **stool consistency**, **abdominal pain and discomfort**, cramping, nausea, small bowel (oral–caecal) transit time assessed by hydrogen breath test, adverse effects, including reversal of opioid analgesia and opioid withdrawal symptoms.

METHODS

Clinical Evidence search and appraisal July 2009. The following databases were used to identify studies for this review: Medline 1966 to July 2009, Embase 1980 to July 2009, and The Cochrane Library and Cochrane Central Register of Controlled Clinical Trials, Issue 3, 2009. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE). Abstracts of the studies retrieved were assessed independently by two information specialists using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language. Open or blinded studies were included, containing at least 20 people, with a maximum loss to follow-up of 30% a year. There was no minimum length of follow-up required to include studies. We also included prospective or retrospective comparative cohort studies in any language for harms data. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the review as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 14). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of oral laxatives for constipation in people prescribed opioids?

OPTION LACTULOSE

Stool consistency

Compared with placebo Lactulose may be more effective at reducing the number of hard stools in people taking opioids (low-quality evidence).

Compared with polyethylene glycol 3350/electrolyte solution Lactulose may be as effective at reducing the number of hard stools (low-quality evidence).

Compared with senna Lactulose seems to be as effective at reducing the number of days without defecation in people prescribed opioids (moderate-quality evidence).

For GRADE evaluation of interventions for constipation in people prescribed opioids, see table, p 14 .

Benefits:

We found two systematic reviews (search dates not reported) of lactulose, which both identified the same studies, none of which met our inclusion criteria. [15] [16]

Lactulose versus senna:
We found no systematic review but found one open-label RCT (91 people with terminal cancer taking codeine [mean dose 123–177 mg] or morphine [mean dose 71–79 mg], mean age 67.8 years) comparing lactulose versus senna. [17] The RCT found no significant difference between lactulose and senna in defecation-free intervals over 3 days or in the mean number of days with defecation over 7 days (mean defecation-free interval: 0.9 hours in both groups; P = 0.85; mean number of days with defecation: 0.9 days with lactulose *v* 1.1 with senna; P = 0.72; analysis of 75/91 [82%] people who completed the trial).

Lactulose versus polyethylene glycol 3350/electrolyte solution and placebo:
We found no systematic review, but we found one crossover RCT (57 people aged 18–50 years with opioid-induced constipation) in people participating in a methadone maintenance programme (see comment below). The RCT compared three interventions: lactulose, polyethylene glycol 3350/electrolyte solution (PEG), and placebo for 2 weeks. [18] It found that both PEG solution and lactulose significantly reduced hard stools compared with placebo at 6 weeks after crossover (mean hard stools: 1.06 with PEG *v* 0.98 with lactulose *v* 1.75 with placebo; P less than 0.01 for either treatment *v* placebo). It found no significant difference in hard-stool formation between PEG and lactulose (reported as not significant; P value not reported). [18]

Harms:

Lactulose versus senna:
The RCT found that three people taking lactulose and three taking senna had adverse effects, including diarrhoea, vomiting, and cramps (no further data reported). [17]

Lactulose versus polyethylene glycol 3350/electrolyte solution and placebo:
The RCT found no significant difference between either PEG or lactulose and placebo in rates of excess flatulence or severe cramping a week (mean excess flatulence: 4.06 episodes/week with PEG *v* 3.60 episodes/week with lactulose *v* 2.96 episodes/week with placebo; mean severe cramps: 2.09 episodes/week with PEG *v* 1.49 episodes/week with lactulose *v* 2.13 episodes/week with placebo; reported as not significant; P value not significant). [18]

Comment:

Clinical guide:
Lactulose is an osmotic laxative. The two RCTs we found suggest that the outcomes after lactulose are similar to those with senna or PEG. The agent of choice therefore depends on patient preference and local cost. [19] Although lactulose is commonly used in people taking opioids, clinical experience suggests that it is only moderately effective, and often has to be combined with another stimulant or surface-wetting agent. In people with faecal impaction, the gas produced by bacterial breakdown of lactulose may aggravate discomfort. Blinded RCTs of lactulose would be difficult because of its taste, but large-scale open trials comparing it with other agents are needed. One of the RCTs we found was undertaken in participants in a methadone maintenance programme. This would not be regarded as representing a typical supportive or palliative-care population, but we have included this RCT as these people would be expected to suffer the same adverse effects of opioids as people taking opioids for symptom control. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION MACROGOLS (POLYETHYLENE GLYCOLS) PLUS ELECTROLYTE SOLUTIONS

Stool consistency
Compared with placebo Macrogols may improve stool consistency compared with placebo in people prescribed opioids (low-quality evidence).

Compared with lactulose Macrogols may be as effective at reducing the number of hard stools in people prescribed opioids (low-quality evidence).

Adverse effects
Macrogols may have similar rates of adverse effects compared with lactulose.

For GRADE evaluation of interventions for constipation in people prescribed opioids, **see table, p 14 .**

Benefits:

Polyethylene glycol 3350/electrolyte solution versus placebo or lactulose:
We found no systematic review in English. One systematic review (search date 2003), published in Swedish, found that, compared with lactulose, there were no convincing data regarding the superiority of polyethylene glycol 3350/electrolyte (PEG; see comment below). However the people included in the review were not specifically people receiving opioid medication. [20] We found one additional RCT comparing PEG solution versus lactulose (see benefits of lactulose, p 3). [18]

Harms: **Polyethylene glycol 3350/electrolyte solution versus placebo or versus lactulose:**
See harms of lactulose, p 3 .

Comment: The review is being translated and will be reported in full in future updates of this review. [20]

Clinical guide:
PEG as described in this RCT from the USA is preparations available in the UK (minor differences are in type of glycol, electrolytes used, and concentrations of these). Macrogols plus electrolytes act as osmotic agents. The RCT we found suggested that the outcomes after PEG are similar to those of lactulose. The agent of choice therefore depends on patient preference and local cost. [19] Although macrogols are commonly used in people taking opioids, clinical experience suggests that they are only moderately effective, and they often have to be combined with another stimulant or surface-wetting agent. Because of their formulation, blinded RCTs of macrogols plus electrolytes would be difficult, but large-scale open trials against other agents should be performed. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION SENNA

Stool consistency
Compared with lactulose Senna and lactulose seem similarly effective for reducing the frequency of hard stools in people prescribed opioids (moderate-quality evidence).

Adverse effects
Senna seems to have a similar adverse-effect profile to lactulose.

For GRADE evaluation of interventions for constipation in people prescribed opioids, see table, p 14 .

Benefits: **Senna versus lactulose:**
See benefits of lactulose, p 3 .

Harms: **Senna versus lactulose:**
See harms of lactulose, p 3 .

Comment: **Clinical guide:**
Senna is a stimulant laxative. The RCT we found suggested that the outcomes after senna are similar to those of lactulose. The agent of choice therefore depends on patient preference and local cost. [19] Despite the lack of strong RCT evidence, senna is used commonly in the UK in people taking opioids. Senna is recommended in the UK over lactulose as it is similar in terms of benefits and adverse effects but is less expensive. Further RCTs are needed. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION BISACODYL

We found no clinically important results from RCTs about the effects of bisacodyl on constipation in people prescribed opioids.

For GRADE evaluation of interventions for constipation in people prescribed opioids, see table, p 14 .

Benefits: We found no systematic review, RCTs, or cohort studies of sufficient quality.

Harms: We found no studies.

Comment: **Clinical guide:**
As tablets (and suppositories) bisacodyl is marketed as Dulcolax (see also comment on sodium picosulfate, p 7 , marketed as Dulcolax perles). This only applies in the UK. Bisacodyl tablets are used in people with constipation after taking opioids, but there is no evidence of benefit. Clinical experience suggests that they should ideally be combined with an osmotic or bulk-forming agent. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION CO-DANTHRUSATE/CO-DANTHRAMER

We found no clinically important results from RCTs about the effects of co-danthrusate/co-danthramer for constipation in people prescribed opioids.

For GRADE evaluation of interventions for constipation in people prescribed opioids, **see table, p 14 .**

Benefits: We found no systematic review, RCTs, or cohort studies of sufficient quality.

Harms: We found no studies.

Comment: **Clinical guide:**
Co-danthrusate is a combination of danthron plus the surface-wetting agent docusate. Co-danthramer is a combination of danthron plus polaxamer. As danthron has been found to be carcinogenic in rats, agents containing it are licensed in the UK only for use in terminally ill people. Both co-danthrusate and co-danthramer are used in clinical practice in people taking long-term opioids, and clinical experience suggests that these combinations are moderately effective. Further RCTs are needed. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION DOCUSATE

Frequency of bowel movements
Compared with placebo Docusate may be no more effective than placebo at increasing stool frequency in people prescribed opioids (very low-quality evidence).

For GRADE evaluation of interventions for constipation in people prescribed opioids, **see table, p 14 .**

Benefits: We found one systematic review (search date 1997, 4 RCTs [21] [22] [23] [24]), which assessed people with chronic illness and either "chronic functional constipation" or dependency on laxatives. [25] The review did not state whether people were taking opioids. It did not perform a meta-analysis. Three of the RCTs it identified had weak methods: they did not ascertain what they meant by constipation or its evaluation before recruitment, did not state how randomisation occurred, and did not analyse people by intention to treat. [21] [22] [23] We therefore do not report further data from them. The fourth RCT (22 people aged 65–96 years in a nursing home, opioid dose unclear) compared docusate sodium 240 mg twice daily for 3 weeks versus placebo for 3 weeks in a crossover design with a washout of 2 weeks between treatment periods. [24] It found no significant difference between docusate and placebo in stool frequency or stool consistency at 8 weeks after crossover in 15/22 (68%) people who completed the trial (mean number of bowel movements/week: 4.25 with docusate *v* 4.12 with placebo; percentage of soft and normal stools: 97% with docusate *v* 93% with placebo; reported as not significant for both outcomes; P values not reported).

Harms: The review [25] and RCTs [21] [22] [23] [24] gave no information on adverse effects.

Comment: **Clinical guide:**
Although docusate is prescribed in people taking opioids, there is no good evidence to support its use. Some clinicians use it in combination with other laxatives, such as a stimulant, osmotic, or bulk-forming agent (see comment on co-danthrusate, p 6). Further high-quality RCTs are needed. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION ISPAGHULA HUSK

We found no clinically important results from RCTs about the effect of ispaghula husk on constipation in people prescribed opioids.

For GRADE evaluation of interventions for constipation in people prescribed opioids, **see table, p 14 .**

Benefits: We found no systematic review or RCTs of sufficient quality.

Harms: We found no studies.

Comment: **Clinical guide:**
Ispaghula husk forms a bulk-forming laxative. In people who have a low fibre intake in their diet, it may be helpful, but most clinicians would use it in combination with a stimulant agent. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION MAGNESIUM SALTS

We found no clinically important results from RCTs about the effects of magnesium salts on constipation in people prescribed opioids.

For GRADE evaluation of interventions for constipation in people prescribed opioids, **see table, p 14 .**

Benefits: We found no systematic review or RCTs of sufficient quality.

Harms: We found no studies.

Comment: **Clinical guide:**
Magnesium salts are osmotic laxatives. They are commonly used as non-prescription laxatives. They are infrequently prescribed for people taking long-term opioids; but, in this situation, clinical experience suggests that they are more effective when used in combination with a stimulant laxative. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION METHYLCELLULOSE

We found no clinically important results from RCTs about the effects of methylcellulose on constipation in people prescribed opioids.

For GRADE evaluation of interventions for constipation in people prescribed opioids, **see table, p 14 .**

Benefits: We found no systematic review or RCTs of sufficient quality.

Harms: We found no studies.

Comment: **Clinical guide:**
Methylcellulose is a bulk-forming agent. In people who have a low fibre intake in their diet, it may be helpful, but most clinicians would use it in combination with a stimulant agent. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION SODIUM PICOSULFATE

We found no clinically important results from RCTs about the effects of sodium picosulfate on constipation in people prescribed opioids.

For GRADE evaluation of interventions for constipation in people prescribed opioids, **see table, p 14 .**

Benefits: We found no systematic review or RCTs of sufficient quality.

Harms: We found no studies.

Comment: **Clinical guide:**
It is not possible to make a recommendation for sodium picosulfate in people with opioid-induced constipation. Sodium picosulfate is licensed in the UK for constipation and for bowel preparation before bowel imaging and surgery. As capsules, it is marketed as Dulcolax perles (see comment on bisacodyl, p 5). Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION LIQUID PARAFFIN

We found no clinically important results from RCTs about the effects of liquid paraffin on constipation in people prescribed opioids.

For GRADE evaluation of interventions for constipation in people prescribed opioids, **see table, p 14 .**

Benefits: We found no systematic review or RCTs of sufficient quality.

Harms: We found no studies. This agent is associated with serious adverse effects, including anal irritation, lipoid pneumonia, and interference with absorption of lipid-soluble vitamins.

Comment: **Clinical guide:**
Liquid paraffin probably acts as an osmotic agent. It has been extensively used in the past and may still be in the care of older people. There is, however, no good evidence that it is effective, and it may cause serious adverse effects, especially in people with stroke or other disorders of swallowing who may be at risk of aspiration. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

QUESTION What are the effects of rectally applied medications in people for constipation in people prescribed opioids?

OPTION ARACHIS OIL ENEMA

We found no clinically important results from RCTs about the effects of arachis oil enemas on constipation in people prescribed opioids.

For GRADE evaluation of interventions for constipation in people prescribed opioids, **see table, p 14 .**

Benefits: We found no systematic review or RCTs of sufficient quality.

Harms: We found no studies.

Comment: **Clinical guide:**
Arachis oil is a lubricant agent given rectally. It is also called "arachis oil enema"; it is derived from peanut. Arachis oil is infrequently prescribed in people taking long-term opioids. It should be avoided in people with known peanut allergy. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION GLYCEROL SUPPOSITORY

We found no clinically important results from RCTs about the effects of glycerol suppositories on constipation in people prescribed opioids.

For GRADE evaluation of interventions for constipation in people prescribed opioids, **see table, p 14 .**

Benefits: We found no systematic review or RCTs of sufficient quality.

Harms: We found no studies.

Comment: **Clinical guide:**
Glycerol acts as an osmotic agent and lubricant in the rectum. Glycerol suppositories are commonly prescribed for people with constipation taking long-term opioids, especially if there are hard rectal stools or faecal impaction. Their use is not supported by clinical trials but clinical experience suggests that they are not associated with any harm. Further RCTs are needed. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION PHOSPHATE ENEMA

We found no clinically important results from RCTs about the effects of phosphate enemas on constipation in people prescribed opioids.

For GRADE evaluation of interventions for constipation in people prescribed opioids, **see table, p 14 .**

Benefits: We found no systematic review or RCTs of sufficient quality.

Harms: We found no studies.

Comment: **Clinical guide:**
Phosphate enemas probably work as stimulant agents. They are commonly used in palliative care and clinical experience suggests that they are relatively free of harm. However, one systematic review (search date 2007, 39 studies covering both children and adults) assessing the use of sodium phosphate enema for a variety of indications found a high incidence of adverse effects. [26] The review identified a significant risk of harms, possibly through water and electrolyte disturbances, particularly in older people (age over 65 years) and in those with comorbidities. Thus it is likely that palliative-care patients may fall into this risk group and multiple applications of sodium phosphate enemas should be avoided in these people. [26] Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION SODIUM CITRATE MICRO-ENEMA

We found no clinically important results from RCTs about the effects of sodium citrate micro-enemas on constipation in people prescribed opioids.

For GRADE evaluation of interventions for constipation in people prescribed opioids, **see table, p 14 .**

Benefits: We found no systematic review or RCTs of sufficient quality.

Harms: We found no studies.

Comment: **Clinical guide:**
Sodium citrate micro-enemas probably work by osmotic action in the rectum. Although there is no good RCT evidence for their use, sodium citrate micro-enemas are frequently used in palliative care of people taking long-term opioids. They can be useful in people with hard stools in the rectum or with faecal impaction. RCTs assessing their effects are needed. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

QUESTION What are the effects of opioid antagonists for constipation in people prescribed opioids?

OPTION OPIOID ANTAGONISTS (ALVIMOPAN, METHYLNALTREXONE, NALOXONE)

Frequency of bowel movements
Compared with placebo The oral opioid antagonist alvimopam is more effective at increasing frequency of defecation at 3 to 6 weeks in people taking opioids (moderate-quality evidence).

Compared with placebo Subcutaneous methylnaltrexone is more effective at increasing rate of bowel movements at 4 to 24 hours in people taking opioids (moderate-quality evidence).

Compared with placebo Naloxone combined with prolonged release oxycodone is more effective at increasing rate of bowel movement at 2 to 6 weeks in people taking opioids (moderate-quality evidence).

For GRADE evaluation of interventions for constipation in people prescribed opioids, **see table, p 14 .**

Benefits: **Alvimopan versus placebo/no treatment:**
We found one systematic review (search date 2007) [27] and one subsequent RCT, [28] which compared alvimopan versus placebo. The review [27] included one RCT (168 people with opioid-induced bowel dysfunction, 148 of whom were taking opioids for chronic pain, primarily back pain) comparing oral alvimopan (0.5 or 1 mg once daily) versus placebo for 21 days. [29] The RCT found that significantly more people taking alvimopan at either dose had a bowel movement within 8 hours (54% with alvimopan 1 mg *v* 43% with alvimopan 0.5 mg *v* 29% with placebo; P less than 0.001 for either dose *v* placebo). Alvimopan at the higher dose also significantly reduced median times to first bowel movement compared with placebo (3 hours with alvimopan 1 mg *v* 7 hours with alvimopan 0.5 mg *v* 21 hours with placebo; P less than 0.001 for alvimopan 1 mg *v* placebo; P = 0.12 for alvimopan 0.5 mg *v* placebo). Alvimopan 1 mg also significantly increased the frequency of bowel movements and overall patient satisfaction compared with placebo (frequency of bowel

movements: P less than 0.001; overall patient satisfaction: P = 0.046). Alvimopan did not antagonise opioid analgesia in that opioid consumption remained constant in all groups throughout the study (absolute results presented graphically).

The subsequent four-armed RCT (522 people with fewer than 3 spontaneous bowel movements/week [SBMs/week]; with over 25% accompanied by sensation of incomplete evacuation, straining, or lumpy hard stool requiring analgesia of morphine 30 mg/day or greater) compared oral alvimopan (0.5 mg twice daily, 1 mg once daily, or 1 mg twice daily) versus placebo for 6 weeks. [28] The RCT found that, compared with placebo, all three doses of alvimopan significantly increased the mean weekly rate of spontaneous bowel movements at 3 and 6 weeks (mean at 3 weeks; 0.5 mg twice daily: 1.71 SBMs/week, 95% CI 0.83 SBMs/week to 2.58 SBMs/week; 1 mg once daily: 1.64 SBMs/week, 95% CI 0.88 SBMs/week to 2.40 SBMs/week; 1 mg twice daily: 2.52 SBMs/week, 95% CI 1.40 SBMs/week to 3.64 SBMs/week; P less than 0.001 for all comparisons, placebo data not reported; at 6 weeks: P less than 0.001 for all comparisons, no further data reported). The RCT also reported that, compared with placebo, all three doses of alvimopan significantly reduced the rate of incomplete evacuation, improved stool consistency, and reduced the rate of straining at 6 weeks (reduction in rate of incomplete evacuation: P less than 0.009 for all comparisons; improved stool consistency: P less than 0.006 for all comparisons; reduction in rate of straining: P less than 0.001, for all comparisons; absolute numbers not reported for any comparison). [28]

Methylnaltrexone versus placebo/no treatment:
We found one systematic review (search date 2007) [27] and two subsequent RCTs [30] [31] of the parenterally administered peripherally acting opioid antagonist methylnaltrexone.The review included four RCTs of opioid antagonists for constipation caused by opioids, and one of the included RCTs assessed the effects of methylnaltrexone but not in the population of interest for this review, and therefore will not be discussed further. [27]

The first subsequent double-blind RCT (154 people with advanced illness and opioid-induced constipation in hospice and palliative care centres) compared single subcutaneous injections of methylnaltrexone (0.15 or 0.3 mg/kg) versus placebo. [30] The RCT found that, compared with placebo, methylnaltrexone significantly increased the rate of laxation response at 4 and 24 hours (4 hours: 29/47 [62%] with methylnaltrexone 0.15 mg/kg *v* 32/55 [58%] with methylnaltrexone 0.3 mg/kg *v* 7/52 [14%] with placebo; P less than 0.0001 for both comparison; 24 hours: 32/47 [68%] with methylnaltrexone 0.15 mg/kg *v* 35/55 [63%] with methylnaltrexone 0.3 mg/kg *v* 14/52 [27%] with placebo; P less than 0.0001 for both comparisons). Approximately half of the methylnaltrexone responders defecated within 30 minutes of dosing. The RCT also included an open-label phase (up to 4 months). It found that response rates mirrored those for methylnaltrexone during the double-blind phase (no further data reported). [30]

The second subsequent double-blind RCT with a 3-month open-label extension (133 people who received opioids for 2 or more weeks and who had received stable doses of opioids and laxatives for 3 or more days without relief of opioid-induced constipation) compared subcutaneous methylnaltrexone 0.15 mg/kg versus placebo every other day for 2 weeks. [31] The RCT found that methylnaltrexone significantly increased the rate of laxation (without the use of rescue laxatives) within 4 hours after the first study dose (48% with methylnaltrexone *v* 15% with placebo; P less than 0.001; absolute numbers not reported) and after two or more of the first four doses (52% with methylnaltrexone *v* 8% with placebo; P less than 0.001; absolute numbers not reported). There was a 3-month, open-label extension to the RCT. It found that the response rate remained consistent throughout the extension trial (no further data reported). [31]

Naloxone versus placebo/no treatment:
We found one systematic review (search date 2007), which identified no RCTs of sufficient quality. [27] We found two subsequent RCTs. [32] [33]

The first subsequent double-blind, double-dummy, parallel-group RCT (265 people on a stable dose of oxycodone prolonged release (OXN/PR, 60–80 mg/day) for chronic non-cancer pain) comparing new prolonged-release formulation oxycodone plus naloxone (OXN/PR) versus standard oxycodone (OXY/PR) for 12 weeks. [32] The primary outcome for the RCT was improvement in symptoms of constipation as measured by the Bowel Function Index (BFI). The RCT found that OXN/PR significantly improved bowel function compared with OXY/PR at 4 weeks (mean difference BFI scores: –14.9, 95% CI –17.9 to –11.9; P less than 0.0001). This result was seen after 1 week of treatment continuing to the end of the study. The RCT found that, compared with OXY/PR, OXN/PR increased the median number of complete spontaneous bowel movements a week at 4 weeks (3.0 with OXN/PR *v* 1.0 with OXY/PR; P value not reported). The RCT also reported that OXN/PR significantly reduced the use of laxatives at 4 weeks (55/130 [43%] with OXN/PR *v* 86/135 [64%] with OXY/PR). [32]

The second subsequent RCT (202 people with chronic pain, mainly non-cancer related, under stable oxycodone therapy 40, 60, or 80 mg/day) compared naloxone combined with prolonged-release oxycodone (10, 20, or 40 mg/day) versus prolonged-release oxycodone plus naloxone placebo for 10 weeks. [33] The RCT found that naloxone 40 mg daily significantly improved bowel function (measured by BFI) at 2 weeks (P less than 0.05), and that both 20 and 40 mg daily significantly improved bowel function at 6 weeks compared with placebo (absolute results presented graphically). [33]

Harms:

Alvimopan:

The RCT included in the review found similar rates of adverse effects, including abdominal cramping, nausea, vomiting, diarrhoea, and flatulence, among people taking alvimopan at either dose and placebo (proportion of people who reported mild to moderate adverse effects: 48% with alvimopan 1 mg *v* 37% with alvimopan 0.5 mg *v* 33% with placebo). [29]

The subsequent RCT found the most frequently reported adverse effects to be abdominal pain, nausea, and diarrhoea occurring more frequently in the higher-dosage groups; however, between-group significance assessments were not performed (abdominal pain: 22/130 [17%] with alvimopan 0.5 mg twice daily *v* 29/133 [22%] with alvimopan 1 mg once daily *v* 36/130 [28%] with alvimopan 1 mg twice daily *v* 19/129 [15%] with placebo; nausea: 9/130 [7%] with alvimopan 0.5 mg twice daily *v* 12/133 [9%] with alvimopan 1 mg once daily *v* 13/130 [10%] with alvimopan 1 mg twice daily *v* 12/129 [9%] with placebo; diarrhoea: 9/130 [7%] with alvimopan 0.5 mg twice daily *v* 14/133 [11%] with alvimopan 1 mg once daily *v* 18/130 [28%] with alvimopan 1 mg twice daily *v* 7/129 [5%] with placebo). [28]

Methylnaltrexone:

The first subsequent RCT reported no change in pain scores or evidence of central opioid withdrawal (median change in pain score: 0 in all treatment groups; median central opioid withdrawal change score: 0 in all treatment groups). The RCT found that the most common adverse effects were abdominal pain and flatulence, but it did not perform significance assessments between groups. However, three people suffered serious adverse effects attributed to methylnaltrexone. [30]

The second subsequent RCT reported no evidence of withdrawal mediated by central nervous system opioid receptors, or changes in pain scores. It found that abdominal pain and flatulence were the most common adverse effects but did not perform significance assessments between groups. [31]

Naloxone:

The first subsequent RCT reported that improvements in bowel function were achieved without loss of analgesic efficacy; pain intensity scores were comparable between the groups and consistent for duration of the study. The RCT reported that a higher proportion of people in the oxycodone-plus-naloxone group suffered from any adverse effects (82/130 [63%] with OXN/PR *v* 71/135 [53%] with OXY/PR) compared with oxycodone alone; however, the RCT did not perform significance assessments between groups. [32]

The second subsequent RCT reported similar rates of mild and moderate adverse effects across groups, but a slight increase in the proportion of people with serious adverse effects in the higher-dosage naloxone groups (2/50 [4%] with oxycodone *v* 8/51 [16%] with naloxone 10 mg/day *v* 8/51 [16%] with naloxone 20 mg/day *v* 11/50 [22%] with naloxone 40 mg/day; significance assessment not performed). [33]

We found one retrospective observational study in people in intensive care who received enteral naloxone for management of opioid-induced constipation over 4 months. [34] Twenty-four people provided 88 doses of naloxone for data analysis. The study found that administration of enteral naloxone to people on intravenous opiates in the ICU setting was not associated with changes in pain, sedation score, vital signs (heart rate, blood pressure, and respiratory rate), or with fentanyl, midazolam, or propofol dose. [34]

Comment:

Clinical guide:

Constipation occurs when opioids are being used therapeutically because the drugs are acting on peripheral opioid receptors in the gastrointestinal (GI) tract, as well as in the nervous system where their main drug benefits arise. It therefore makes good sense to try to block the action of opioids on these peripheral GI receptors. The main drawback to this approach has been the difficulty of retaining the central beneficial effects — and of avoiding the precipitation of opioid withdrawal syndrome — while preventing the unwanted GI effects. This could be achieved either by the patient taking an opioid antagonist orally, thus minimising absorption and working only on the GI mucosa, or with antagonists that do not cross the blood–brain barrier. The only drug currently available in the UK that can perform this function is naloxone. Taken orally, it can block GI opioid receptors,

but it is partly absorbed and, as it can penetrate the central nervous system, it can potentially reverse the therapeutic action of opioids. It is not available as an oral preparation, so the injectable form has to be prepared for oral use. Some small studies have shown that it can reverse opioid-induced constipation; but the therapeutic window is narrow, so that it is easy to lose pain control or to cause opioid withdrawal. [35] [36] [37] A new formulation of combined prolonged-release oxycodone together with prolonged-release naloxone in a fixed 10:1 ratio has become available in the UK after many years of being available in Germany. Although it restricts the choice of opioid being used for pain to oxycodone, the limited evidence so far is that it can prevent the development of troublesome opioid-induced constipation without reversal of analgesia. [32] Two other opioid antagonists have recently been investigated, although neither is yet licensed for opioid-induced constipation in the UK. Methylnaltrexone can be given orally or by intravenous or subcutaneous injection. Methylnaltrexone has recently been licensed for opioid-induced constipation in the UK. Methylnaltrexone is licensed to be given by subcutaneous injection in one of two fixed doses, depending on the patient's weight. It has been shown to be effective and safe in several RCTs for the indication of opioid-induced constipation, including in palliative-care patients in a hospice setting. [30] [38] [31] Alvimopan can be taken orally. Neither of these can cross the blood–brain barrier and so they are inherently safer than naloxone in not reversing therapeutic central nervous system effects of opioids. In small studies of postoperative and opioid-induced constipation, both of these have been successful in blocking the peripheral constipating effect of opioids without compromising pain relief. [39] [40] [41] [42]

GLOSSARY

Barthel index The Barthel scale or Barthel ADL index is a scale used to measure performance in basic activities of daily living (ADL). It uses 10 variables describing ADLs and mobility. A higher number is associated with a greater likelihood of being able to live with a degree of independence.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Opioid antagonists: One systematic review [27] and five subsequent RCTs [28] [30] [31] [32] [33] added. The review and subsequent RCTs found that oral alvimopam, subcutaneous methylnaltrexone, and naloxone combined with prolonged-release oxycodone improved bowel movements compared with placebo or no treatment. Categorisation unchanged (Beneficial).

REFERENCES

1. Pappagallo M. Incidence prevalence, and management of opioid bowel dysfunction. *Am J Surg* 2001;182:11S–18S.[PubMed]
2. National Institute for Health and Clinical Excellence (NICE). Definitions of supportive and palliative care. In: Improving supportive and palliative care for adults with cancer. NICE 2004. Introduction C, 17–22.
3. World Health Organization. WHO definition of palliative care. Available online at: http://www.who.int/cancer/palliative/definition/en/ (last accessed 11 March 2010).
4. Walsh D, Donnelly S, Rybicki L. The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. *Support Care Cancer* 2000;8:175–179.[PubMed]
5. Sykes NP. The relationship between opioid use and laxative use in terminally ill cancer patients. *Palliat Med* 1998;12:375–382.[PubMed]
6. Droney J, Ross J, Gretton S, et al. Constipation in cancer patients on morphine. *Support Care Cancer* 2008;16:453–459.[PubMed]
7. Ahmedzai S, Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. *J Pain Symptom Manage* 1997;13:254–261.[PubMed]
8. Clark AJ, Ahmedzai SH, Allan LG, et al. Efficacy and safety of transdermal fentanyl and sustained-release oral morphine in patients with cancer and chronic noncancer pain. *Curr Med Res Opin* 2004;20:1419–1428. Search date 2004.[PubMed]
9. Tassinari D, Sartori S, Tamburini E, et al. Adverse effects of transdermal opiates treating moderate-severe cancer pain in comparison to long-acting morphine: a meta-analysis and systematic review of the literature. *J Palliat Med* 2008;11:492–501.[PubMed]
10. De Luca A, Coupart IM. Insights into opioid action in the intestinal tract. *Pharmacol Ther* 1996;69:103–115.[PubMed]
11. Meert TF, Vermeirsch HA. A preclinical comparison between different opioids: antinociceptive versus adverse effects. *Pharmacol Biochem Behav* 2005;80:309–326.[PubMed]
12. Tamayo AC, Diaz-Zuluaga PA. Management of opioid-induced bowel dysfunction in cancer patients. *Support Care Cancer* 2004;12:613–618.[PubMed]
13. Fallon MT, Hanks GW. Morphine, constipation and performance status in advanced cancer patients. *Palliat Med* 1999;13:159–160.[PubMed]
14. Bennett M, Cresswell H. Factors influencing constipation in advanced cancer patients: a prospective study of opioid dose, dantron dose and physical functioning. *Palliat Med* 2003;17:418–422.[PubMed]
15. Kot TV, Pettit-Young NA. Lactulose in the management of constipation: a current review. *Ann Pharmacother* 1992;26:1277–1282. Search date not reported.[PubMed]
16. McNicol E, Horowicz-Mehler N, Fisk RA, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. *J Pain* 2003;4:231–256. Search date not reported; primary sources Medline and the Cochrane Controlled Trials Register.[PubMed]
17. Agra Y, Sacristan A, Gonzalez M, et al. Efficacy of senna versus lactulose in terminal cancer patients treated with opioids. *J Pain Symptom Manage* 1998;15:1–7.[PubMed]
18. Freedman MD, Schwartz HJ, Roby R, et al. Tolerance and efficacy of polyethylene glycol 3350/electrolyte solution versus lactulose in relieving opiate induced constipation: a double-blinded placebo-controlled trial. *J Clin Pharmacol* 1997;37:904–907.[PubMed]
19. Christie AH, Culbert P, Guest JF. Economic impact of low dose polyethylene glycol 3350 plus electrolytes compared with lactulose in the management of idiopathic constipation in the UK. *Pharmacoeconomics* 2002;20:49–60.[PubMed]
20. Ohlen K. The effect of polyethylene glycol in chronic constipation is not sufficiently evaluated. A systematic literature review. *Lakartidningen* 2004;101:2568–2572. Search date 2003. [In Swedish] [PubMed]
21. Cass LJ, Frederik WS. Doxinate in the treatment of constipation. *Am J Gastroenterol* 1956;26:691–698.[PubMed]
22. Goodman J, Pang J, Bessman AN. Dioctyl sodium sulphosuccinate – an ineffective prophylactic laxative. *J Chronic Dis* 1976;29:59–63.[PubMed]
23. Fain AM, Susat R, Herring M, et al. Treatment of constipation in geriatric and chronically ill patients: a comparison. *South Med J* 1978;71:677–680.[PubMed]
24. Castle SC, Cantrell M, Israel DS, et al. Constipation prevention: empiric use of stool softeners questioned. *Geriatrics* 1991;46:84–86.[PubMed]
25. Hurdon V, Viola R, Schroder C. How useful is docusate in patients at risk for constipation? A systematic review of the evidence in the chronically ill. *J Pain Symptom Manage* 2000;19:130–136. Search date 1997.[PubMed]

26. Mendoza J, Legido J, Rubio S, et al. Systematic review: the adverse effects of sodium phosphate enema. *Aliment Pharmacol Ther* 2007;26:9–20.[PubMed]
27. McNicol ED, Boyce D, Schumann R, et al. Mu opioid antagonists for opioid induced bowel dysfunction. In: The Cochrane Library, Issue 2, 2008. Chichester, UK: John Wiley & Sons, Ltd. Search date 2008.
28. Webster L, Jansen JP, Peppin J, et al. Alvimopan, a peripherally acting mu-opioid receptor (PAM-OR) antagonist for the treatment of opioid-induced bowel dysfunction: results from a randomized, double-blind, placebo-controlled, dose-finding study in subjects taking opioids for chronic non-cancer pain. *Pain* 2008;137:428–440.[PubMed]
29. Paulson DM, Kennedy DT, Donovick RA, et al. Alvimopan: an oral, peripherally acting, mu-opioid receptor antagonist for the treatment of opioid-induced bowel dysfunction – a 21-day treatment-randomized clinical trial. *J Pain* 2005;6:184–192.[PubMed]
30. Slatkin N, Thomas J, Lipman AG, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. *J Support Oncol* 2009;7:39–46.[PubMed]
31. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med* 2008;358:2332–2343.[PubMed]
32. Lowenstein O, Leyendecker P, Hopp M, et al. Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: a randomised controlled trial. *Expert Opin Pharmacother* 2009;10:531–543.[PubMed]
33. Meissner W, Leyendecker P, Mueller-Lissner S, et al. A randomised controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation. *Eur J Pain* 2009;13:56–64.[PubMed]
34. Arpino PA, Thompson BT, Arpino PA, et al. Safety of enteral naloxone for the reversal of opiate-induced constipation in the intensive care unit. *J Clin Pharm Ther* 2009;34:171–175.[PubMed]
35. Sykes NP. An investigation of the ability of oral naloxone to correct opioid-related constipation in patients with advanced cancer. *Palliat Med* 1996;10:135–144.[PubMed]
36. Latasch L, Zimmermann M, Eberhardt B, et al. Treatment of morphine-induced constipation with oral naloxone. *Anaesthetist* 1997;46:191–194. [In German]
37. Meissner W, Schmidt U, Hartmann M, et al. Oral naloxone reverses opioid-associated constipation. *Pain* 2000;84:105–109.[PubMed]
38. Portenoy RK, Thomas J, Moehl Boatwright ML, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study. *J Pain Symptom Manage* 2008;35:458–468.[PubMed]
39. Yuan CS, Foss JF, O'Connor M, et al. Methylnaltrexone for reversal of constipation due to chronic methadone use: a randomized controlled trial. *JAMA* 2000;283:367–372.[PubMed]
40. Yuan CS, Foss JF. Oral methylnaltrexone for opioid-induced constipation. *JAMA* 2000;284:1383–1384.[PubMed]
41. Thomas J, Portenoy R, Moehl M, et al. A phase II randomized dose-finding trial of methylnaltrexone for the relief of opioid-induced constipation in hospice patients. *Proc Am Soc Clin Oncol* 2003;22:abstract 2933.
42. Schmidt WK. Alvimopan (ADL 8-2698) is a novel peripheral opioid antagonist. *Am J Surg* 2001;182:27S–38S.

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Competing interests: SHA has been reimbursed by Janssen–Cilag, the manufacturer of the opioid fentanyl, for undertaking research, speaking at conferences, and running educational meetings. SHA has been reimbursed by GlaxoSmithKline, the manufacturer of the opioid antagonist alvimopan, for undertaking research and consultancy. SHA is the lead author of one RCT and a co-author of one systematic review referenced in this review. SHA has received payment from Wyeth, the manufacturer of methylnaltrexone, for giving lectures, and has received funding from Mubdipharma, the manufacturer of Targinact, for undertaking research and consultancy. JB declares that he has no competing interests.

Disclaimer

TABLE 1 **Constipation in people prescribed opioids**

Important outcomes	**Bowel movement frequency, stool consistency, abdominal pain, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of oral laxatives for constipation in people prescribed opioids?									
1 (57) [18]	Stool consistency	Lactulose *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (57) [18]	Stool consistency	Macrogol/electrolyte solution *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (57 [18]	Stool consistency	Lactulose *v* polyethylene glycol 3350/electrolyte solution	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (91) [17]	Frequency of bowel movements	Lactulose *v* senna	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (22) [24]	Frequency of bowel movements	Docusate sodium *v* placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertainty about population group
What are the effects of rectally applied medications in people for constipation in people prescribed opioids?									
No clinically important studies found									
What are the effects of opioid antagonists for constipation in people prescribed opioids?									
2 (690) [29] [33]	Frequency of bowel movements	Alvimopan *v* placebo/no treatment	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (287) [30] [31]	Frequency of bowel movements	Methylnaltrexone *v* placebo/no treatment	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (732) [32] [33]	Frequency of bowel movements	Naloxone *v* placebo/no treatment	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies. Directness: generalisability of population or outcomes.