Constipation in people prescribed opioids

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INTERVENTIONS

ORAL LAXATIVES

- Lactulose * New 3
- Macrogols (polyethylene glycols) plus electrolyte solutions * New 4
- Senna * New 4
- Bisacodyl New 4
- Co-danthrusate/co-danthramer New 5
- Ispaghula husk New 5
- Magnesium salts New 6
- Methylcellulose New 6
- Sodium picosulfate New 6

RECTAL PREPARATIONS

- Arachis oil enema New 6
- Glycerol suppository New 7
- Liquid paraffin 7
- Phosphate enema New 7
- Sodium citrate micro-enema New 8

RECTAL PREPARATIONS

- Unknown effectiveness

- 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.
- 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 also 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. These symptoms may also be associated with constipation because of 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
### Incidence/Prevalence

In one prospective cohort study (1000 people with advanced cancer), constipation was reported to occur in 52%. 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. 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). Fifty-eight per cent of people who took opioids regularly required more than two types of treatment for constipation. The prevalence of constipation is not the same with all opioids. One systematic review (search date 2004, 6 RCTs, 1200 people, 657 with cancer, 563 with chronic painful diseases taking opioids for 28 days) found that significantly more people had constipation when taking modified release oral morphine than taking transdermal fentanyl (16% with transdermal fentanyl vs 37% with modified release oral morphine; \( P < 0.001 \)). 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 (27.2% with transdermal fentanyl vs 44.5% with modified release oral morphine; \( P < 0.001 \)).

### Aetiology/Risk Factors

The constipating effect of opioids is through their action on mu opioid receptors in the submucosal plexus of the gastrointestinal tract. 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. 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 and animal studies 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. Lack of privacy for defecation may also play a part for people in hospital. Drugs that can cause or exacerbate constipation include anticholinergics. In the treatment of cancer, thalidomide, vinca alkaloids, and 5HT\(_2\) antagonists can all cause constipation. 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.

### 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). This study failed to show a correlation between total opioid dose and degree of constipation.

### 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

*BMJ Clinical Evidence* search and appraisal August 2006. The following databases were used to identify studies for this review: Medline 1966 to August 2006, Embase 1980 to August 2006, and
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The Cochrane Library and Cochrane Central Register of Controlled Clinical Trials, Issue 3, 2006. 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, RCTs, and prospective or retrospective comparative cohort studies in any language. Open or blinded studies were included, containing 20 or more people, with a maximum loss to follow up of 30% a year. There was no minimum length of follow up required to include studies. 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.

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

**OPTION**  LACTULOSE  New

Two RCTs found that lactulose reduced constipation in people prescribed opioids, with similar efficacy and adverse effect profile to both senna and polyethylene glycol 3350/electrolyte solution. These results are supported by clinical consensus that lactulose is moderately effective.

**Benefits:** We found two systematic reviews (search date not reported) of lactulose, which both identified the same studies, none of which met our inclusion criteria. [12] [13]

**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. [14] 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 in English. One systematic review (search date 2003), published in Swedish, found that lactulose and polyethylene glycol were equally effective in reducing constipation (see comment below). [15] 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. [16] 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 < 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). [16]

**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). [14]

**Lactulose versus polyethylene glycol 3350/electrolyte solution and placebo:**
The RCT found no significant difference between 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). [16]

**Comment:**
The review is being translated and will be reported in full in future updates of this review. [15]

**Clinical guide:**
Lactulose is an osmotic laxative. The two RCTs we found suggest that the outcomes after lactulose are similar to senna or PEG. The agent of choice therefore depends on patient preference and local cost. [17] 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
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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, but 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  New

RCTs suggest that polyethylene glycol 3350/electrolyte solution may improve constipation in people prescribed opioids compared with placebo and may result in similar improvements to lactulose, with similar rates of adverse effects. These results are supported by clinical consensus that macrogols are moderately effective.

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 was no convincing data regarding the superiority of polyethylene glycol 3350/electrolyte (PEG; see comment below). [15] We found one additional RCT (see benefits of lactulose, p 3). [16]

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. [15]

Clinical guide:
PEG as described in this RCT from the USA is similar to Movicol or Idrolax, which are 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 lactulose. The agent of choice therefore depends on patient preference and local cost. [13] Although macrogols are commonly used in people taking opioids, clinical experience suggests that they are only moderately effective, and 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, but do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION  SENNA  New

One RCT found that senna and lactulose were similarly effective for constipation in people prescribed opioids, both in terms of improving symptoms and adverse effect profile. These results are supported by clinical consensus that senna is moderately effective.

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 lactulose. The agent of choice therefore depends on patient preference and local cost. [12] 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, but do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION  BISACODYL  New

We found no systematic review, RCTs, or cohort studies of sufficient quality assessing the effect of bisacodyl on constipation in people prescribed opioids.

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

Comment: Clinical guide: As tablets (and suppositories) bisacodyl is marketed as Dulcolax (see also comment on sodium picosulfate, p 6 which is marketed as Dulcolax perles). Bisacodyl tablets are used in people with constipation after taking opioids, but there is no evidence for this. 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, but do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION CO-DANTHRUSATE/CO-DANTHRAMER New

We found no systematic review, RCTs, or cohort studies of sufficient quality assessing the effects of co-danthrusate/co-danthramer for constipation in people prescribed opioids.

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, but do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION DOCUSATE New

Docusate is a surface wetting agent, which should make it easier to pass stool. However, one systematic review of four weak RCTs provided insufficient evidence to assess docusate for constipation in people prescribed opioids.

Benefits: We found one systematic review (search date 1997, 4 RCTs ) that assessed people with chronic illness and either “chronic functional constipation” or dependency on laxatives. 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. 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. 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 and RCTs 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 5). Further high quality RCTs are needed. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation, but do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION ISPAGHULA HUSK New

We found no systematic review, RCTs, or cohort studies of sufficient quality assessing the effect of ispaghula husk on constipation in people prescribed opioids.

Benefits: We found no systematic review, RCTs, or cohort studies of sufficient quality.
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### 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, but do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

### OPTION MAGNESIUM SALTS

We found no systematic review, RCTs, or cohort studies of sufficient quality assessing the effects of magnesium salts on constipation in people prescribed opioids.

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

### Harms:
We found no studies.

### Comment:
**Clinical guide:**
Magnesium salts are osmotic laxatives. They are commonly used as over the counter 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, but do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

### OPTION METHYLCELLULOSE

We found no systematic review, RCTs, or cohort studies of sufficient quality assessing the effects of methylcellulose on constipation in people prescribed opioids.

### Benefits:
We found no systematic review, RCTs, or cohort studies 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, but do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

### OPTION SODIUM PICOSULFATE

We found no systematic review, RCTs, or cohort studies of sufficient quality assessing the effects of sodium picosulfate on constipation in people prescribed opioids.

### Benefits:
We found no systematic review, RCTs, or cohort studies 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, p5). Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation, but 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 systematic review, RCTs, or cohort studies of sufficient quality assessing the effects of arachis oil enemas on constipation in people prescribed opioids.
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Benefits: We found no systematic review, RCTs, or cohort studies of sufficient quality.
Harms: We found no studies.

Comment: Clinical guide:
Arachis oil is a lubricant agent given rectally. It is also called “Fletcher's 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, but do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION GLYCEROL SUPPOSITORY New

We found no systematic review, RCTs, or cohort studies of sufficient quality assessing the effects of glycerol suppositories on constipation in people prescribed opioids.

Benefits: We found no systematic review, RCTs, or cohort studies 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, but do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION LIQUID PARAFFIN

We found no systematic review, RCTs, or cohort studies of sufficient quality assessing the effects of liquid paraffin on constipation in people prescribed opioids.

Benefits: We found no systematic review, RCTs, or cohort studies of sufficient quality.
Harms: We found no studies. This agent is associated with serious adverse effects, including anal irritation, lipid 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 care of the elderly. 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, but do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

OPTION PHOSPHATE ENEMA New

We found no systematic review, RCTs, or cohort studies of sufficient quality assessing the effects of phosphate enemas on constipation in people prescribed opioids.

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

Comment: Clinical guide:
Phosphate enema is also called “Fletcher's phosphate enema”. 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. RCTs assessing their effects are needed. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation, but do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.
We found no systematic review, RCTs, or cohort studies of sufficient quality assessing the effects of sodium citrate micro-enemas on constipation in people prescribed opioids.

Benefits: We found no systematic review, RCTs, or cohort studies 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, but do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.

We found no systematic review, RCTs, or cohort studies of sufficient quality assessing methylnaltrexone or naloxone. Clinical experience suggests that oral naloxone may be effective in reducing the symptoms of opioid-induced constipation but may reverse analgesic efficacy, or cause opioid withdrawal. One RCT found that alvimopan reduced constipation compared with placebo. This RCT is supported by small studies of both alvimopan and methylnaltrexone, and by clinical consensus suggesting that these drugs may block the peripheral constipating effect of opioids without compromising pain relief.

Benefits: Alvimopan:

We found no systematic review but found 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. The RCT found that significantly more people taking alvimopan at either dose had a bowel movement within 8 hours (54% with alvimopan 1 mg vs 43% with alvimopan 0.5 mg vs 29% with placebo; P < 0.001 for either dose vs placebo). Alvimopan at the higher dose also significantly reduced median times to first bowel movement compared with placebo (3 hours with alvimopan 1 mg vs 7 hours with alvimopan 0.5 mg vs 21 hours with placebo; P < 0.001 for alvimopan 1 mg vs placebo; P = 0.12 for alvimopan 0.5 mg vs placebo). Alvimopan 1 mg also significantly increased the frequency of bowel movements and overall patient satisfaction compared with placebo (frequency of bowel movements: P < 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 (results presented graphically).

Methylnaltrexone, naloxone:

We found one systematic review (search date 2004), which identified no RCTs of sufficient quality.

Harms: Alvimopan:
The RCT 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 vs 37% with alvimopan 0.5 mg vs 33% with placebo).

Methylnaltrexone, naloxone:
We found no RCTs.

Comment: Clinical guide:
Constipation arises when opioids are being used therapeutically because the drugs are acting on peripheral opioid receptors in the gastrointestinal tract, as well as in the nervous system where their main drug benefits arise. It therefore makes good sense to try and block the action of opioids on these peripheral gastrointestinal 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 gastrointestinal effects. This could be achieved either by taking an opioid antagonist orally, thus minimising absorption and working only on the gastrointestinal mucosa, or by using antagonists that do not cross the blood–brain barrier. The only drug currently available in the UK which can perform this function is naloxone. Taken
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orally, it can block gastrointestinal 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. [24] [25] [26] In the UK, this is an off-label use and it is also clearly inconvenient for long term treatment to have to use ampoules of injectable drug orally. In Germany, a combination of oxycodone and naloxylo n in a 2:1 ratio has recently been licensed: clinical trial evidence for its benefits and adverse effects are yet to be published. 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. Alvimopan can be taken orally. Neither of these can cross the blood–brain barrier and so they are inherently safer than naloxylo n 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. [27] [28] [29] [30]

SUBSTANTIVE CHANGES

New option added Lactulose
New option added Macrogol (polyethylene glycols) plus electrolyte solutions
New option added Senna
New option added Bisacodyl
New option added Co-danthrusate/co-danthramer
New option added Docusate
New option added Ispaghula husk
New option added Magnesium salts
New option added Methylnaltrexone
New option added Sodium picosulfate
New option added Arachis oil enema
New option added Glycerol suppository
New option added Phosphate enema
New option added Sodium citrate micro-enema
New option added Opioid antagonists (alvimopan, methylnaltrexone, naloxylo n)

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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 (Ref 7) and a co-author of one systematic review (Ref 6). JB has no competing interests.