ClinicalEvidence

Constipation: opioid antagonists in people prescribed opioids

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ABSTRACT

INTRODUCTION: Constipation is a common adverse effect of opioids. As an example, constipation is reported in 52% of people with advanced malignancy, and this figure rises to 87% in people who are terminally ill and taking opioids. There is no reason to believe that people with chronic non-malignant disease who are prescribed opioids will be any less troubled by this adverse effect. METHODS AND OUTCOMES: We conducted a systematic overview and aimed to answer the following clinical question: What are the effects of opioid antagonists for constipation in people prescribed opioids? The population we studied included people with any condition, although most studies were in people with cancer pain. We searched Medline, Embase, The Cochrane Library, and other important databases up to May 2014 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). RESULTS: At this update, searching of electronic databases retrieved 162 studies. After deduplication and removal of conference abstracts, 84 records were screened for inclusion in the review. Appraisal of titles and abstracts led to the exclusion of 47 studies and the further review of 37 full publications. Of the 37 full articles evaluated, two systematic reviews and one RCT were included at this update. We performed a GRADE evaluation for three PICO combinations. CONCLUSIONS: In this systematic overview we categorised the efficacy for three interventions based on information relating to the effectiveness of alvimopan, methylnaltrexone, and naloxone.

QUESTIONS

INTERVENTIONS

Key points

- Constipation is one of the most common and persistent effects of opioids. As an example, constipation is reported in 52% of people with advanced malignancy, and this figure rises to 87% in people who are terminally ill and taking opioids. Although most of the data on opioid-induced constipation comes from studies on cancer patients, 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.

  Traditionally, laxatives have been used to try and manage constipation when it occurs as a side-effect of opioid therapy. These act by relieving the symptoms and effects of opioid-induced constipation (i.e., palliation) by stimulating bowel movement or softening the stools. They do not address the cause of opioid-induced constipation, and the evidence base for their efficacy is poor (see previous version of this topic). The relatively new use of opioid antagonists represents a targeted approach to stopping the cause of opioid-induced constipation at the bowel opioid receptor level.

- 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, given as a normal-release drug, may provoke reversal of opioid analgesia, but this is less likely with prolonged-release naloxone, alvimopan, or methylnaltrexone. Normal-release naloxone may also cause opioid withdrawal, but this has not been reported with methylnaltrexone, alvimopan, or prolonged-release naloxone when combined with prolonged-release oxycodone.

  We searched for RCTs and systematic reviews of RCTs of methylnatrexone, naloxone alone (and in combination with oxycodone), or alvimopam compared with placebo or with each other in people with opioid-induced constipation.

- We included RCTs of the listed interventions prescribed by any route. In the case of naloxone, we included any type (e.g., pegylated), and the combination product prolonged-release naloxone plus oxycodone.

  So far, the new peripherally acting opioid antagonists have only been compared with placebo.

  The RCTs found that alvimopan, methylnaltrexone, and naloxone may be more effective than placebo at improving bowel function in people with opioid-induced constipation.

  There was considerable variation in terms of the characteristics of participants, indications for opioid therapy (e.g., cancer versus non-cancer pain), and type of setting (primary, secondary, and tertiary care).

  Further RCTs comparing these preparations with each other and with conventional laxative therapies are needed.

Clinical context

GENERAL BACKGROUND

Constipation is a common, debilitating, and sometimes dose-limiting side effect from opioids when prescribed for pain control. Opioids cause constipation because they act on peripheral opioid receptors in the gastrointestinal (GI) tract, as well as in the nervous system where their desired analgesic benefits arise. These gastrointestinal opioid receptors are involved in the normal regulation of bowel motility and fluid absorption by the endogenous opioid system. These functions are disturbed when pharmacological doses of therapeutic opioids are presented to the bowel lumen. It, therefore, makes good sense to try to block the action of opioids on these peripheral GI receptors.

FOCUS OF THE REVIEW

This overview focuses on the use of opioid antagonists for managing constipation in people prescribed opioids. Traditionally, laxatives have been used to try and manage constipation when it occurs as a side effect of opioid therapy. These act by relieving the symptoms and effects of opioid-induced constipation (i.e., palliation) by stimulating bowel movement or softening the stools. They do not address the cause of opioid-induced constipation, and the evidence base for their efficacy is poor (see previous version of this topic). The relatively new use of opioid antagonists, on the other hand, represents a targeted approach to stopping the cause of opioid-induced constipation at the bowel opioid receptor level.

COMMENTS ON EVIDENCE

So far, the new peripherally-acting opioid antagonists have only been compared with placebo. There was considerable variation in terms of the characteristics of participants, indications for opioid therapy (e.g., cancer versus non-cancer pain), and type of setting (primary, secondary, and tertiary care). Further RCTs comparing these preparations with each other and with conventional laxative therapies are needed.

SEARCH AND APPRAISAL SUMMARY

The updated literature search for this overview was carried out from the date of the last search, July 2009, to May 2014. A back search from 1966 was performed for the new options added to the scope at this update. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 162 studies. After deduplication and removal of conference abstracts, 84 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 47 studies and the further review of 37 full publications. Of the 37 full articles evaluated, two systematic reviews and one RCT were included at this update.

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. The broader concept of opioid-induced bowel dysfunction (OBD) encompasses a wide range of associated symptoms, including constipation, abdominal distension, colicky pain, gastric fullness, nausea, vomiting, anorexia, confusion, and overflow diarrhoea. [1] It should be noted that these symptoms may also be associated with constipation from other causes, including other drugs. This overview focuses only on constipation in people prescribed opioids. Although most of the data on opioid-induced constipation comes from studies on cancer patients, 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. In the past, opioids were used in cancer for pain (and increasingly for breathlessness) relatively late in the disease process (advanced and terminal cancer), and were prescribed especially by palliative care services. The WHO definition of palliative care is 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". [2] Although this definition of palliative care does not specify incurable or terminal illness, conventionally palliative care applies to people approaching the end of life; that is, people with a prognosis of less than 1 year. There is recognition that, for many people being treated for cancer, good symptom control needs to 'upstream' to those with earlier stages of cancer. Furthermore, cancer survivors are living longer after treatment but may continue to need opioids for a longer period. The management of earlier-stage cancer patients and long-term survivors is now regarded as part of 'supportive care'. The UK National Institute for Health and Care Excellence (NICE) definition of supportive care is 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". [3] 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. The NICE definition of supportive care was written in relation to people with cancer but is applicable to all people with chronic or terminal illness; for example, those with heart failure, neurological disease, or lung disease. There are other *BMJ Clinical Evidence* overviews on Constipation in adults and Constipation in children.

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] A British cohort study (274 people with cancer attending a tertiary referral cancer hospital) found that 72% of patients taking oral morphine for pain had mild to severe 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 constipation affected significantly more people taking modified-release oral morphine than taking transdermal fentanyl (45% with modified-release oral morphine *v* 27% with transdermal fentanyl; P <0.001). [7] One further 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 (37% with modified-release oral morphine *v* 16% with transdermal fentanyl; P <0.001). [8] Another systematic review (search date 2007, 4 RCTs, 425 people with moderate-severe cancer pain) comparing oral morphine with transdermal opioids (fentanyl or 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 and myenteric plexus of the gastrointestinal tract. [10] This decreases gastrointestinal motility by decreasing coordinated propulsive peristalsis (at the same time increasing circular contractions), decreases secretions (pancreatic and biliary), and increases intestinal fluid absorption. [10] The opioid-induced increase in circular muscle contractions causes colicky pain. There is also a centrally-mediated effect of opioids on the GI tract so that even spinally administered opioids cause decreased gastric emptying and prolonged oral-caecal transit time. 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. [7] [8] [11] This may be because they are given by a transdermal route, which avoids the gastrointestinal tract. It may also be due to 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, as well as positional problems (e.g., with bedpan use). [12] Lack of privacy for defecation may also play a part for people in hospital. [12] Drugs that can cause or exacerbate constipation include anticholinergics. 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 sensitive measure of physical functioning using 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; **adverse effects**, including abdominal pain and discomfort, reversal of opioid analgesia, and opioid withdrawal symptoms.

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date May 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to May 2014, Embase 1980 to May 2014, The Cochrane Database of Systematic Reviews 2014, issue 4 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment

(HTA) database. We also searched for retractions of studies included in the review. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, including open-label trials, and containing more than 20 individuals (10 in each arm), of whom more than 30% were followed up. There was no minimum length of follow-up. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributor. In consultation with the expert contributor, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the review. In addition, information that did not meet our predefined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' sections. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributor may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following previously reported questions: What are the effects of oral laxatives for constipation in people prescribed opioids? What are the effects of rectally applied medications for constipation in people prescribed opioids? **Data and quality** To aid readability of the numerical data in our overviews, 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). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 13). 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 opioid antagonists for constipation in people prescribed opioids?**

OPTION **ALVIMOPAN** **New**

- For GRADE evaluation of interventions for Constipation: opioid antagonists in people prescribed opioids, see table, p 13 .
- Alvimopan may be more effective than placebo at improving bowel function in people with opioid-induced constipation.
- However, trials have all been based in secondary and tertiary care, and in people with chronic non-malignant pain, and we found no longer-term studies beyond 12 weeks.
- Alvimopan may also be associated with an increase in headache and diarrhoea compared with placebo.

Benefits and harms

Alvimopan versus placebo or no treatment:

We found one systematic review (search date 2012). [15] The review included adults (at least 90% of people over 16 years) with a history of constipation associated with the onset of opioid analgesic use (based on clinical symptoms, a physician's opinion, or specified diagnostic criteria). Included studies had to report a dichotomous outcome measuring response to therapy, any trial duration was accepted, and the review performed an ITT analysis with drop-outs assumed to be treatment failures. If trial reporting did not allow this, it performed an analysis on all people with

evaluable data. Studies including participants with organic constipation or chronic idiopathic constipation were excluded, and authors of included RCTs were contacted to provide additional information. The review included four RCTs (1693 people) comparing oral alvimopan with placebo. All were multi-site RCTs (22–153 sites) based in secondary and tertiary care, and included people with chronic non-malignant pain. Two RCTs included people who were not laxative-refractory, and the laxative status was not reported in two RCTs. Trial duration ranged from 3 to 12 weeks, and all were on a stable opioid dose for 1 week (1 RCT) or 1 month or more (3 RCTs), which could be 10 mg or more of morphine or equivalent (1 RCT) or 30 mg or more of morphine equivalent (3 RCTs). Criteria used to define response to therapy varied between trials. Only one of the four RCTs was reported to be at low risk of bias. [15]

Frequency of bowel movements

Alvimopan compared with placebo or no treatment Alvimopan (oral) may be more effective than placebo at reducing the proportion who fail to respond to treatment in adults with opioid-induced constipation and chronic non-malignant pain attending secondary and tertiary care (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Failure to respond to treatment					
[15] Systematic review	Adults with chronic non-malignant pain, stable opioid dose, based in secondary and tertiary care 4 RCTs in this analysis	**Failure to respond to treatment (response defined as 1 or more bowel movement [BM] within 8 hours of study drug during each day [1 RCT]; moderate or substantial improvement [1 RCT]; 3 or more spontaneous bowel movements [SBMs] per week with increase of at least 1 SBM from baseline [2 RCTs])** 529/1174 (45%) with alvimopan 310/519 (60%) with placebo	RR 0.71 95% CI 0.65 to 0.78 P <0.00001 NNT 5 95% CI 4 to 11	●○○	alvimopan
[15] Systematic review	Adults with chronic non-malignant pain, stable opioid dose, based in secondary and tertiary care 3 RCTs in this analysis Subgroup analysis by dose (split into lower and higher dose)	**Failure to respond to treatment (response defined as 1 or more BM within 8 hours of study drug during each day [1 RCT]; 3 or more SBMs per week with increase of at least 1 SBM from baseline [2 RCTs])** with lower dose alvimopan with placebo Absolute results not reported	RR 0.80 95% CI 0.69 to 0.93	●○○	alvimopan
[15] Systematic review	Adults with chronic non-malignant pain, stable opioid dose, based in secondary and tertiary care 4 RCTs in this analysis Subgroup analysis by dose (split into lower and higher dose)	**Failure to respond to treatment (response defined as 1 or more BM within 8 hours of study drug during each day [1 RCT]; moderate or substantial improvement [1 RCT]; 3 or more SBMs per week with increase of at least 1 SBM from baseline [2RCTs])** with higher dose alvimopan with placebo Absolute results not reported	RR 0.69 95% CI 0.59 to 0.80	●○○	alvimopan

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] Systematic review	Adults with chronic non-malignant pain, stable opioid dose, based in secondary and tertiary care 4 RCTs in this analysis	**Total number of adverse events** with alvimopan with placebo Absolute results not reported	RR 1.07 95% CI 0.98 to 1.17	⟷	Not significant
[15] Systematic review	Adults with chronic non-malignant pain, stable opioid dose, based in secondary and tertiary care 4 RCTs in this analysis	**Diarrhoea** with alvimopan with placebo Absolute results not reported	RR 1.56 95% CI 1.01 to 2.40 NNH 28 95% CI 16 to 100	●○○	placebo
[15] Systematic review	Adults with chronic non-malignant pain, stable opioid dose, based in secondary and tertiary care 3 RCTs in this analysis	**Headache** with alvimopan with placebo Absolute results not reported	RR 1.52 95% CI 1.02 to 2.27 NNH 33 95% CI 16 to 200	●○○	placebo

Alvimopan versus methylnaltrexone or naloxone:

We found one systematic review (search date 2012), which found no RCTs. [15] We found no subsequent RCTs.

Further information on studies

[15] The review noted that most included trials (and all 4 RCTs with alvimopan) recruited people in secondary and tertiary care, so results may not be generalisable to people with opioid-induced constipation presenting in primary care. Also, all participants had chronic non-malignant pain.

[15] Group analysis on all opioid antagonists: the review also reported a group analysis on all opioid antagonists together (see option on Naloxone, p 8).

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.

Alvimopan can be taken orally. It does not cross the blood-brain barrier, and so is not likely to reverse therapeutic central nervous system effects of opioids. It is licensed in the US but not in the UK.

OPTION METHYLNALTREXONE New

- For GRADE evaluation of interventions for Constipation: opioid antagonists in people prescribed opioids, see table, p 13 .

- Methylnaltrexone may be more effective than placebo at improving bowel function in people with opioid-induced constipation.
- However, trials varied widely with regard to the regimens used and the exact outcomes studied, and we found no longer-term studies beyond 12 weeks.
- Methylnaltrexone may also be associated with an increase in cramps and diarrhoea compared with placebo.

Benefits and harms

Methylnaltrexone versus placebo/no treatment:

We found one systematic review (search date 2012), which included RCTs with a dichotomous outcome measuring response to treatment in people with opioid-induced constipation (see option on Alvimopan, p 4). [15] The review included six RCTs (1610 people) comparing methylnaltrexone with placebo. Trial size ranged from 22 to 803 people. People were recruited in primary and secondary care (2 RCTs), secondary and/or tertiary care (2 RCTs), or the setting was not reported (2 RCTs). Three RCTs included people who were laxative refractory, two RCTs included people who were not laxative refractory, and the remaining RCT did not state laxative status. Two RCTs included people with advanced illness (life expectancy 1 month or more), two RCTs included people with chronic non-malignant pain, and the remaining RCTs were in people with an orthopaedic procedure or were part of a methadone maintenance programme (a small trial of 22 people). Criteria used to define response to treatment varied between RCTs, as did the method of administration (subcutaneous in 4 RCTs, oral in 1 RCT, intravenous in 1 RCT), length of administration (from single dose to as required for 12 weeks), and criteria used to define opioid-induced constipation. The review noted that three RCTs of the six RCTs were at low risk of bias.

Frequency of bowel movements

Methylnaltrexone compared with placebo or no treatment Methylnaltrexone may be more effective than placebo at reducing the proportion of people who fail to respond to treatment in adults with opioid-induced constipation. However, there was considerable variation among trials in the regimen used (both route of administration and treatment duration) and the criteria used to define treatment success (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Failure to respond to treatment					
[15] Systematic review	Adults with advanced illness, in chronic non-malignant pain, having an orthopaedic procedure, or part of a methadone maintenance programme, based in primary, secondary, and/or tertiary care 6 RCTs in this analysis	**Failure to respond to treatment (response defined as defecation within 1 minute of infusion [1 RCT], 3 or more rescue-free bowel movements [BM] per week [3 RCTs], rescue-free BM within 24 hours of dose [1 RCT] or BM within 4 hours of first dose)** 533/1095 (49%) with methylnaltrexone 332/515 (65%) with placebo	RR 0.67 95% CI 0.54 to 0.84 P = 0.0004 NNT 3 95% CI 2 to 10 Significant heterogeneity in this analysis (I^2 = 72%, P for heterogeneity 0.003; see Further information on studies)	●○○	methylnaltrexone

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] Systematic review	Adults with advanced illness, chronic non-malignant pain, or having an orthopaedic procedure, based in primary, secondary, and tertiary care 4 RCTs in this analysis	**Total number of adverse events** with methylnaltrexone with placebo Absolute results not reported	RR 1.24 95% CI 0.98 to 1.57	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[15] Systematic review	Adults with advanced illness, chronic non-malignant pain, or having an orthopaedic procedure, based in primary, secondary, and tertiary care 4 RCTs in this analysis	**Diarrhoea** with methylnaltrexone with placebo Absolute results not reported	RR 1.94 95% CI 1.13 to 3.30 NNH 30 95% CI 18 to 111	●○○	placebo

Methylnaltrexone versus alvimopan or naloxone:

We found one systematic review (search date 2012), which found no RCTs. [15] We found no subsequent RCTs.

Further information on studies

[15] *Heterogeneity* The review noted that, because of the wide range of doses used, the range of definitions of opioid-induced constipation, and different criteria of response, subgroup analysis by these characteristics was not possible. An analysis that restricted studies to those using 2 or more days of treatment reduced the heterogeneity (4 RCTs, RR failure to respond 0.79, 95% CI 0.70 to 0.88, I^2 = 16%; absolute numbers not reported). [15]

[15] Group analysis on all opioid antagonists: The review also reported a group analysis on all opioid antagonists together (see option on Naloxone, p 8).

Comment:

Clinical guide

Opioids cause constipation because they act on peripheral opioid receptors in the gastrointestinal (GI) tract, as well as in the nervous system where their analgesic benefits arise. It, therefore, makes good sense to try to block the action of opioids on these peripheral GI receptors. 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. At these doses, it does not cause any significant reversal of opioid analgesia or opioid withdrawal. The methyl moiety prevents its absorption from the bowel, so it also prevents constipation without altering pain control. 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. Its main side-effect is temporary diarrhoea or abdominal cramps. Because of lack of data in patients with brain metastases where penetration across the blood-brain barrier may be altered, it should be used with caution in this situation. [16] [17] [18]

OPTION NALOXONE New

- For GRADE evaluation of interventions for Constipation: opioid antagonists in people prescribed opioids, see table, p 13 .
- We searched for RCTs on naloxone prescribed by any route and any type (e.g., pegylated), and included the combination product prolonged-release naloxone plus oxycodone.
- Naloxone may be more effective than placebo at improving bowel function in people with opioid-induced constipation. However, we found no longer-term studies beyond 12 weeks.

Benefits and harms

Naloxone versus placebo/no treatment:

We found two systematic reviews. [15] [19] The first systematic review (search date 2012) included RCTs with a dichotomous outcome measuring response to treatment in people with opioid-induced constipation and pooled data.

[15] The second systematic review (search date 2013) did not pool data and included both RCT and non-RCT data. [19] It included three large RCTs included in the pooled analysis in the first review, and one further RCT not included in the first review. [20] We have, therefore, reported the pooled analysis, [15] and reported the further RCT direct from its original report. [20] The first review included four RCTs (798 people), one of which was small (332 people; 265 people; 202 people; 9 people). The three largest RCTs were based in primary and secondary care (1 RCT), secondary care alone (1 RCT), and secondary and tertiary care (1 RCT), and all three RCTs included participants with chronic non-malignant pain who were not laxative refractory. Participants in all four RCTs were on a stable dose of opioids, and duration of treatment ranged from 3 to 12 weeks. Two trials used oral normal-release naloxone, while two RCTs used a fixed-dose prolonged-release oral oxycodone/naloxone (2:1 fixed ratio) preparation (see Further information on studies). The review reported that two of the four RCTs were at low risk of bias. The additional double-blind RCT (185 people) compared prolonged-release oxycodone/naloxone with prolonged-release oxycodone alone in people with moderate to severe chronic cancer pain for 4 weeks. [20] Participants were aged 18 years or older and required opioid treatment (see Further information on studies). It reported changes in Bowel Function Index scores (3-item questionnaire measuring ease of defecation, feeling of incomplete bowel evacuation, and personal judgement of constipation, with total score expressed on a 0–100 scale). Additional outcome measures included EORTC QLQ-C30 constipation scale, use of laxatives, pain relief using the Brief Pain Inventory (BPI), and opioid withdrawal.

Frequency of bowel movements

Naloxone compared with placebo or no treatment Naloxone (oral) may be more effective than placebo at reducing the proportion of people who fail to respond to treatment in adults with opioid-induced constipation (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Failure to respond to treatment					
[15] Systematic review	Adults with chronic non-malignant pain based in primary, secondary, and tertiary care 4 RCTs in this analysis	**Failure to respond to treatment (response defined as 3 or more complete spontaneous bowel movements [BM] per week after 4 weeks [2 RCTs], no need for laxatives [1 RCT], and satisfaction with relief of constipation [1 RCT])** 199/450 (44%) with naloxone 244/348 (70%) with placebo 2 RCTs used oral normal-release naloxone and 2 RCTs used fixed-dose prolonged-release oral oxycodone/naloxone (2:1 fixed ratio) preparations	RR 0.64 95% CI 0.56 to 0.72 P <0.00001 NNT 4 95% CI 3 to 5	●○○	naloxone
[20] RCT	185 adults with moderate to severe cancer pain	**Change from baseline in Bowel Function Index (BFI) score (0–100) , 4 weeks** with PR oxycodone/naloxone plus PR oxycodone placebo with PR oxycodone plus PR oxycodone/naloxone placebo Absolute results reported graphically 157 people in this analysis	Difference 11.14 95% CI 3.24 to 19.03 P <0.01 The RCT reported that changes in BFI scores of 12 or more represent clinically meaningful changes, while those <7.5 are unlikely to be clinically meaningful	○○○	PR oxycodone/naloxone

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] Systematic review	Adults with chronic non-malignant pain based in primary, secondary, and tertiary care 2 RCTs in this analysis	**Total number of adverse effects** with naloxone with placebo Absolute results not reported	RR 1.13 95% CI 0.97 to 1.32	⟷	Not significant
[20] RCT	185 adults with moderate to severe cancer pain	**Proportion of people with adverse effects (any)** 79/92 (86%) with PR oxycodone/naloxone plus PR oxycodone placebo 71/92 (77%) with PR oxycodone plus PR oxycodone/naloxone placebo	Significance not reported		
[20] RCT	185 adults with moderate to severe cancer pain	**Total number of adverse effects related to study medication as assessed by the study investigator** 77 with PR oxycodone/naloxone plus PR oxycodone placebo 62 with PR oxycodone plus PR oxycodone/naloxone placebo	Significance not reported		

Naloxone versus alvimopan or methylnaltrexone:

We found two systematic reviews (search date 2012; [15] and 2013 [19]), which found no RCTs. We found no subsequent RCTs.

Further information on studies

[15] One included RCT was small (9 people) and will not be discussed further here. Of the remaining three included RCTs, the first RCT (202 people) included people on a stable oxycodone dose and compared oral naloxone with placebo for 4 weeks. The other two RCTs (265 people; 322 people) used an oral oxycodone/naloxone prolonged-release preparation in a 2:1 fixed dose ratio for 12 weeks. Although the three RCTs used different criteria for success (first RCT: no need for laxatives; second and third RCTs: 3 or more complete spontaneous bowel movements [CSBMs] per week after 4 weeks), all three RCTs found a similar magnitude of effect (failure to respond to treatment: first RCT, RR 0.61, 95% CI 0.47 to 0.79; second RCT, RR 0.66, 95% CI 0.54 to 0.81; third RCT, RR 0.63, 95% CI 0.51 to 0.78).

[15] *Group analysis on all opioid antagonists* Although we have reported on the effects of individual agents separately, the review also pooled data on all opioid receptor antagonists together (including 4 RCTs on alvimopan, 4 RCTs on methylnaltrexone, and 3 RCTs on naloxone) and found no significant difference between groups in reversal of analgesia (11 RCTs, 3074 people, RR 0.76, 95% CI 0.37 to 1.55). The review did not report an analysis by individual agent.

[20] The RCT described the method of randomisation and was double-blinded. In total, 133/184 (72%) of participants completed the study. Twenty-eight people who had dropped out early in the study were excluded from the analysis. Three of the six authors were employees of the pharmaceutical company that had funded the trial. The RCT found no significant difference between groups in total laxative (oral bisacodyl) usage (P = 0.17). It found no evidence of reversal of analgesia or of opioid withdrawal with the combination of prolonged-release oxycodone/naloxone.

Comment:

Clinical guide

Opioids cause constipation because they act on peripheral opioid receptors in the gastrointestinal (GI) tract, as well as in the nervous system where their analgesic benefits arise. It, therefore, makes good sense to try to block the action of opioids on these peripheral GI receptors. Taken orally, normal-release naloxone can block GI opioid receptors, but it is partly absorbed into the systemic circulation and as a result it can penetrate the central nervous system, potentially reversing the therapeutic action of opioids and causing opioid withdrawal. 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; however, the therapeutic window is narrow, so that it is easy to lose pain control or to cause opioid withdrawal. [21] [22] [23] 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. The slow delivery of the prolonged-release naloxone component results in more than 95% of it being metabolised in the liver, so that its systemic circulation and penetration into the CNS is limited and, at the manufacturer's recommended dosing, does not cause reversal of the oxycodone component. [20] Although this specific combination restricts the choice of opioid being used for pain to oxycodone, the evidence so far is that it may prevent the development of troublesome opioid-induced constipation without reversal of analgesia or causing opioid withdrawal. [24]

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.

Brief Pain Inventory The Brief Pain Inventory is a questionnaire used to assess the severity and the impact of pain on daily functions. It asks about the severity of pain, impact of pain on daily function, location of pain, pain medications, and amount of pain relief in the past 24 hours or the past week.

EORTC QLQ-C30 The European Organisation for Research and Treatment Quality of Life Questionnaire consists of five functioning scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea/vomiting, and pain), six single time scales (dyspnoea, sleep disturbances, appetite loss, constipation, diarrhoea, and financial impact), and the global quality-of-life scale.

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.

SUBSTANTIVE CHANGES

Alvimopan Restructured to form new option. One systematic review added. [15] Categorised as 'likely to be beneficial'.

Methylnaltrexone Restructured to form new option. One systematic review added. [15] Categorised as 'beneficial'.

Naloxone Restructured to form new option. Two systematic reviews [15] [19] and one RCT added. [20] Categorised as 'beneficial'.

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Disclaimer

GRADE **Evaluation of interventions for Constipation: opioid antagonists in people prescribed opioids.**

Important outcomes				Frequency of bowel movements					
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of opioid antagonists for constipation in people prescribed opioids?									
4 (1693) [15]	Frequency of bowel movements	Alvimopan versus placebo or no treatment	4	–1	0	–1	0	Low	Quality point deducted for weak methods (1 of 4 RCTs at low risk of bias, diverse response criteria in analysis); directness point deducted for unclear generalisability (all based in secondary/tertiary care, all in chronic non-malignant pain)
6 (1610) [15]	Frequency of bowel movements	Methylnaltrexone versus placebo/no treatment	4	–1	–1	0	0	Low	Quality point deducted for weak methods (3 of 6 RCTs at low risk of bias, diverse response criteria in analysis); consistency point deducted for significant heterogeneity
5 (955) [15] [19] [20]	Frequency of bowel movements	Naloxone versus placebo/no treatment	4	–2	0	0	0	Low	Quality points deducted for weak methods (2 of 4 RCTs at low risk of bias, diverse response criteria in analysis, no ITT analysis in 1 RCT) and incomplete reporting of results

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.