Laxatives or methylnaltrexone for the management of constipation in palliative care patients (Review)

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[Intervention Review]

Laxatives or methylnaltrexone for the management of constipation in palliative care patients

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ABSTRACT

Background

Constipation is common in palliative care; it can generate considerable suffering due to the unpleasant physical symptoms. In the first Cochrane Review on effectiveness of laxatives for the management of constipation in palliative care patients, published in 2006, no conclusions could be drawn because of the limited number of evaluations. This article describes the first update of this review.

Objectives

To determine the effectiveness of laxatives or methylnaltrexone for the management of constipation in palliative care patients.

Search methods

We searched databases including MEDLINE and CENTRAL (*The Cochrane Library*) in 2005 and in the update to August 2010.

Selection criteria

Randomised controlled trials (RCTs) evaluating laxatives for constipation in palliative care patients. In the update we also included RCTs on subcutaneous methylnaltrexone; an opioid-receptor antagonist that is now licensed for the treatment of opioid-induced constipation in palliative care when response to usual laxative therapy is insufficient.

Data collection and analysis

Two authors assessed trial quality and extracted data. The appropriateness of combining data from the studies depended upon clinical and outcome measure homogeneity.

Main results

We included seven studies involving 616 participants; all under-reported methodological features. In four studies the laxatives lactulose, senna, co-danthramer, misrakasneham, and magnesium hydroxide with liquid paraffin were evaluated. In three methylnaltrexone.

In studies comparing the different laxatives evidence was inconclusive. Evidence on subcutaneous methylnaltrexone was clearer; in combined analysis (287 participants) methylnaltrexone, in comparison with a placebo, significantly induced laxation at 4 hours (odds ratio 6.95; 95% confidence interval 3.83 to 12.61). In combined analyses there was no difference in the proportion experiencing side effects, although participants on methylnaltrexone suffered more flatulence and dizziness. No evidence of opioid withdrawal was found. In one study severe adverse events, commonly abdominal pain, were reported that were possibly related to methylnaltrexone. A serious adverse event considered to be related to the methylnaltrexone also occurred; this involved a participant having severe diarrhoea, subsequent dehydration and cardiovascular collapse.

Authors' conclusions

The 2010 update found evidence on laxatives for management of constipation remains limited due to insufficient RCTs. However, the conclusions of this update have changed since the original review publication in that it now includes evidence on methylnaltrexone. Here it found that subcutaneous methylnaltrexone is effective in inducing laxation in palliative care patients with opioid-induced constipation and where conventional laxatives have failed. However, the safety of this product is not fully evaluated. Large, rigorous, independent trials are needed.

PLAIN LANGUAGE SUMMARY

Laxatives or methylnaltrexone for the management of constipation in palliative care patients

Palliative care patients commonly experience constipation. This is as a result of the use of medications (in particular opioids) for pain control, as well as disease, dietary and mobility factors. This review aimed to determine the effectiveness of laxatives for the management of constipation in palliative care patients. Two review authors assessed study quality and extracted data. Seven studies involving 616 people were included. The drugs evaluated were lactulose, senna, danthron combined with poloxamer, misrakasneham and magnesium hydroxide combined with liquid paraffin. Methylnaltrexone, a drug only recently licensed, was also evaluated for this updated review. There is some evidence that methylnaltrexone is effective (in comparison with a placebo) at inducing laxation (bowel relaxation) in patients taking opioids who have not had a good response to conventional laxatives. The evidence in the other studies was more limited due to lack of overlap in laxatives evaluated. Further rigorous, independent trials with longer follow up are needed to evaluate the effectiveness of laxatives, including methylnaltrexone.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Methylnaltrexone compared to placebo for the management of constipation in palliative care patients

Patient or population: patients with the management of opioid-induced constipation in palliative care patients
Settings:
Intervention: Methylnaltrexone
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk placebo	Corresponding risk Methylnaltrexone				
Rescue free laxation within 4 hours	146 per 1000	543 per 1000 (396 to 683)	OR 6.95 (3.83 to 12.61)	287 (2 studies)	⊕⊕⊕○ moderate[1,2]	
Rescue free laxation within 24 hours	195 per 1000	568 per 1000 (430 to 695)	OR 5.42 (3.12 to 9.41)	287 (2 studies)	⊕⊕⊕○ moderate[1,2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1] Four limitations unclear: allocation concealment, incomplete outcome data addressed, free of selective reporting, free of other bias; all other limitations not present.
[2] Only two studies available, both with positive results, so publication bias cannot be ruled out.

BACKGROUND

Description of the condition

This is a substantive update of a previously published Cochrane review first published in issue 4, 2006 (Miles 2006).

There are many definitions of constipation. In part this reflects differences in what is normal; for instance in healthy people the range of bowel evacuation is wide: from three times a day to three times a week (Thompson 1999). In general, however, definitions of constipation include a reference to infrequent, difficult or incomplete bowel evacuation that may lead to pain and discomfort; with stools that can range from small, hard 'rocks', to a large bulky mass (McMillan 1989; Norton 1996; Ross 1998; Winney 1998).

Constipation is a common problem in palliative care, where the overall estimated incidence ranges from 18% to 50% of patients (Laugsand 2009; Sykes 2006). The estimates for those receiving opioid treatments are much higher: from 72% (Droney 2008) to 87% of patients (Sykes 1998).

Constipation can generate considerable suffering, including abdominal pain and distension, anorexia, nausea, general malaise and in faecal impaction overflow of diarrhoea. It can also cause headaches, halitosis, restlessness and confusion. There are also significant psychological and social consequences which can contribute to a reduction in an individual's quality of life. The suffering can be so severe that some patients with opioid-induced constipation choose to decrease or even discontinue opioids, thereby preferring to experience inadequate pain control rather than the symptoms of constipation (Thomas 2008).

The causes of constipation can be classified as follows.

- Lifestyle-related, such as having a low-fibre diet, a poor fluid intake, or both. Physical inactivity can bring about a reduction in abdominal muscle activity and stimulation producing a 'sluggish bowel' (Winney 1998). A lack of privacy or environmental factors, or both, such as having to use a bedpan or a commode can inhibit bowel function and predispose to constipation in already debilitated patients.
- Disease-related, such as in patients with an anal fissure, colitis, diverticular disease, haemorrhoids, hernia and rectocoele. The majority of patients accessing palliative care services have a cancer diagnosis and, in the common cancers, particularly bowel and ovarian cancer, gastrointestinal symptoms are a frequent complication (Droney 2008; Dunlop 1989).
- Drug-induced, there are a wide range of drugs that have constipation as a side effect. Palliative care is dominated by a need to achieve pain control; many of the drugs used to achieve this, such as opioids, cause constipation.

Description of the intervention

Prevention and management of constipation relates to cause. Palliative care patients are at risk of developing constipation as a result of changes in their lifestyle. These are attributable to disease progression and are unlikely to be readily resolved. However, given that constipation for the majority of palliative care patients has the potential of being drug-induced, management to promote satisfactory bowel movements commonly involves some form of pharmaceutical administration. Laxatives work by softening faecal matter, through direct stimulation of peristalsis, or both. They are generally classified according to their mode of action: bulk-forming laxatives, osmotic laxatives, stimulant laxatives and faecal softeners and lubricants. The most widely used laxatives are the stimulant preparations: those containing senna, bisacodyl, sodium picosulfate, and wheat bran and lactulose. Bulk-forming laxatives are not ordinarily recommended in palliative care, as patients may not maintain a necessary adequate fluid intake to avoid intestinal obstruction or faecal impaction.

Why it is important to do this review

Studies have evaluated the relative effects of laxatives in the management of constipation in a palliative care setting including the laxatives senna (Agra 1998), docusate (Hurdon 2000), co-danthramer (Sykes 1991a) and polyethylene glycol (Culbert 1998).

Recently, in the United States, the Europe Union and Canada, methylnaltrexone (commercially traded as Relistor), a peripheral opioid receptor antagonist, has been given marketing approval in its subcutaneous form for the treatment of constipation in patients with advanced medical illness who are being treated with opioids for pain and where response to conventional laxatives has not been sufficient. Peripheral opioid receptor antagonists spare the central analgesic properties of opioids but block the peripheral gastro-intestinal opioid receptors responsible for opioid-induced constipation. While these compounds are not classed as laxatives they share the same aim of treating constipation (Thomas 2008).

Recent published clinical practice recommendations, from a pan-European working group, on the management of constipation in palliative care (Larkin 2008), based their work on research evidence including the earlier version of this review (Miles 2006). They recommended the use of a softener and stimulant laxative but advised that the choice of laxatives should be made on an individual basis. These guidelines noted as a new development the use of methylnaltrexone but at the time of writing only one trial of methynaltrexone in a palliative care setting had been published. Therefore an update of this review is timely.

OBJECTIVES

- The primary objective of this systematic review was to determine the effectiveness of laxatives and also, in the 2010

update, methylnaltrexone for the management of constipation in palliative care patients.

- The second objective was to determine the differential efficacy of laxatives used to manage constipation in palliative care.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of the efficacy of laxatives. In the 2010 update, RCTs of the effectiveness of the opioid antagonist methylnaltrexone were also included.
There were no language restrictions. Both published and unpublished studies were eligible for inclusion.

Types of participants

- Studies eligible concerned adult participants receiving palliative care who were given, either as a prophylactic or because they were constipated, a laxative or methylnaltrexone. These studies could be undertaken in any care setting (in-patient, outpatient, day-care, community).
- We excluded studies which included healthy volunteers, participants with constipation as a result of drug misuse and those participants with constipation arising from bowel obstruction.

Types of interventions

All laxatives administered in the management of constipation in palliative care for cancer and other long-term progressive medical conditions were eligible for inclusion. Laxatives included, for example, senna and lactulose. We also included in the 2010 update the opioid antagonist methylnaltrexone. We did not include other opioid antagonists, such as alvimopan, as they are not approved for use in palliative care patients.

Types of outcome measures

Studies were eligible if the outcome measures were reported in terms of relief of constipation. These could include:

- change in frequency of defecation;
- ease of defecation;
- relief of systemic and abdominal symptoms related to constipation, such as an improved appetite, reduction in abdominal pain and distension and lessening of confusion;
- change in quality of life; and
- use of rescue laxatives, such as a rectal suppository or an enema.

We also collected information on adverse effects, including:

- nausea/vomiting;
- pain;
- flatus;
- diarrhoea; and
- faecal incontinence.

Search methods for identification of studies

The aim of the search strategy was to be as comprehensive as possible. We considered and expanded the search strategies of three previously published systematic reviews on laxative use and constipation (Hurdon 2000; Petticrew 1997; Tramonte 1997).

Electronic searches

We used both English and American spellings and names. Searches were restricted to human participants. The subject search used a combination of controlled vocabulary and free-text terms based on a search strategy for searching MEDLINE. Please see Appendix 1 and Appendix 2 for the MEDLINE and CENTRAL search strategies used. We searched electronic databases to identify all relevant studies, irrespective of language. Studies pre-dating 1966 were not sought.

1. The Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, issue 8).
2. MEDLINE search from 1966 to January 2005 - (update to August 2010).
3. EMBASE search from 1980 to January 2005 - (update to August 2010).
4. CANCERLIT from 1980 to March 2001.
5. Science Citation Index from 1981 to March 2005
6. Web of Science March 2005 to August 2010.
7. CINAHL from 1982 to March 2005 (update to August 2010).
8. Databases which provide information on grey literature: SIGLE from 1980 to 2005 (containing British Reports, Translations and Theses), NTIS, DHSS-DATA and Dissertation Abstracts from 1961 to 2005, and Index to Thesis to October 2010.
9. Conference proceedings from both international and national conferences were hand searched and databases on conference proceedings were accessed - Boston Spa Conferences (containing Index of Conference Proceedings) and Inside Conferences 1996 to 2001, Index to Scientific and Technical Proceedings from 1982 to 2005. Also hand searched were conference proceedings for the European Association of Palliative Care 2007 to 2010.

10. National Health Service National Research Register (containing Medical Research Council Directory) (inception to 2007).

Searching other resources

Reference searching

We searched reference lists and undertook a forward citation check of all included studies. We also searched reference lists from relevant review articles. We also sought contact with representatives of pharmaceutical companies for further trial evaluations.

Data collection and analysis

We screened citations identified in our searches for eligibility. If it was not possible to accept or reject a study with certainty, we obtained the full text of the study for further evaluation. Two review authors independently assessed studies in accordance with the above inclusion criteria. Any differences in opinion were resolved by discussion.

Data extraction

We designed a data extraction form specifically for the review. If possible we obtained the following information for each of the eligible studies:

- study methods (trial design, duration, allocation method, blinding, setting, study inclusion criteria);
- participants (number, age, sex, drop-outs/withdrawals);
- laxative(s) (type, dose(s), route of delivery, control used);
- outcome data including laxation response; and
- tolerance and adverse effects including pain and, if taking an opioid, symptoms of withdrawal.

Quality assessment

Two review authors assessed the quality of included RCTs according to the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). Where differences of opinion existed they were resolved by consensus with the other review authors. We assessed four main sources of systematic bias for each included study:
a) selection bias (randomisation sequence and concealment of allocation, and bias at recruitment);
b) performance bias;
c) detection bias;
d) attrition bias (the completeness of follow up, with less than 10% loss to follow up defined as adequate).
We assessed criteria as adequate, inadequate or unclear, according to criteria set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008).

Based on the quality criteria, we planned that studies would be broadly subdivided into the following three categories:
a) all quality criteria met: low risk of bias;
b) one or more of the quality criteria only partly met: moderate risk of bias; and
c) one or more criteria not met: high risk of bias.

Data analysis

Reporting results: measures of treatment effect from individual trials

We reported study results organised by type of intervention treatments evaluated.
We measured treatment effects using dichotomous data, an ordinal rating scale or qualitative evidence.

Dichotomous data

Where dichotomous data were reported, we generated odds ratios (ORs) and their 95% confidence intervals (CIs). We also calculated the risk difference (RD), which is the absolute difference in the proportions in each treatment group.

Continuous data

We assessed effects measures for ordinal data as continuous data. We generated the weighted mean difference (WMD) for continuous and ordinal data where the data were provided as a mean and standard deviation (SD).
If baseline data were reported pre-intervention and post-intervention, we reported means or proportions for both intervention and control groups and calculated the change from baseline. For cross-over trials we only generated, as appropriate, an OR or mean difference for pre-cross-over results.
If limitations in the study data prevented an OR, risk difference or if continuous data a mean difference from being reported, we reported the results with caution due to lack of transparency of the evidence.

Qualitative evidence

We extracted any qualitative data reported in the included studies in consultation with the Cochrane Qualitative Methods Group. Such qualitative data may aim to capture the patient's views on the value of the intervention.

Missing data

Where data were not reported, but could be (e.g. mean presented without its confidence interval) we attempted to contact study authors. For studies using continuous outcomes in which SDs were not reported, and no information was available from the authors, we calculated the SDs via the standard error of the mean (SEM).

Given the nature of this field, there was a significant amount of missing data as a result of trial attrition due to the death of the patient.

Drop-outs

Our primary analysis was based on results from intention-to-treat (ITT) populations, rather than per protocol or other subgroups, and drop-outs were included in analysis. If there were missing data, then we detailed the method of handling them and performed sensitivity analysis to assess how sensitive our results were to the assumptions made in individual studies regarding missing data.

Meta-analysis

Where study data were of sufficient quality and sufficiently similar (in diagnostic criteria, intervention, outcome measure, length of follow up and type of analysis) we combined data in a meta-analysis to provide a pooled effect estimate. We used a fixed-effect model in the first instance. If there was no statistical heterogeneity, we used a random-effects model to check the robustness of the fixed-effect model. If statistical heterogeneity was observed, we used the random-effects model *a priori*.

Heterogeneity

Where meta-analysis was possible, we assessed statistical heterogeneity between the studies using the Chi^2 test and the I^2 statistic (we considered a Chi^2 P value of less than 0.05 or an I^2 value equal to or more than 50% to indicate substantial heterogeneity). If heterogeneity was identified, we planned to undertake subgroup analysis to investigate its possible sources.

Subgroup analysis

We planned to explore clinical heterogeneity and investigate the effect modification of specific participant characteristics that have been identified in general palliative care populations as effect modifiers by performing the following subgroup analyses:

1. By excluding studies of a higher risk of bias.

Sensitivity analysis

We planned to perform sensitivity analyses in order to explore the influence of the following factors:

1. excluding unpublished studies (if there are any);
2. taking account of study quality (low, moderate or high risk of bias);
3. excluding studies by filtering the scales used for measuring effect (validated versus other).

Publication bias

We planned to explore publication bias by using funnel plots.

Presentation of results

We grouped the effects of interventions by type of intervention.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

We identified 186 unique citations in the original search. On initial citation review, we excluded 165. The remaining 21 studies required further examination; of these three met the eligibility criteria. These were Agra 1998, Ramesh 1998 and Sykes 1991a. The 18 excluded studies that had warranted further consideration were mostly excluded as they were evaluating the effect of laxatives in a non-palliative care population. A fourth relevant, but unpublished, study was identified (Sykes 1991b). In the 2010 update 180 unique citations were identified in the main search (of MEDLINE, EMBASE and Cochrane databases). We identified at screening five citations that required further examination; of these four met the eligibility criteria. These were Portenoy 2008, Slatkin 2009 and Thomas 2008. The fourth, Chamberlain 2009, was a paper providing additional analysis on the Thomas 2008 study (see Thomas 2008 for Chamberlain 2009 reference). So seven studies were included in this review in total and 20 were excluded; details of the excluded studies can be seen in the 'Characteristics of excluded studies' table.

Included studies

The seven RCTs (Agra 1998; Portenoy 2008; Ramesh 1998; Slatkin 2009; Sykes 1991a; Sykes 1991b; Thomas 2008) in total analysed 616 participants. Two studies were of cross-over design; the others were parallel design, of which three were multi-centre. The studies were undertaken in North American, British, Spanish and Indian populations. All participants were at an advanced stage of disease and were cared for within a palliative care setting. In one study some participants were recruited from nursing homes. Most participants had a cancer diagnosis. Where described the most common primary cancer site was the lungs. Participants with other diagnoses included advanced cardiovascular disease, AIDS and dementia. The average age of participants ranged from 61 to 72 years.

The drugs assessed were subcutaneous methylnaltrexone (Portenoy 2008; Slatkin 2009; Thomas 2008) and the laxatives, all taken orally, were senna (Agra 1998; Ramesh 1998; Sykes 1991a); lactulose (Agra 1998; Sykes 1991a); danthron combined with

poloxamer (Sykes 1991a); and magnesium hydroxide combined with liquid paraffin (Sykes 1991b). One study also evaluated the effect of misrakasneham (Ramesh 1998), a drug used in traditional Indian medicine as a purgative, containing castor oil, ghee, milk and 21 kinds of herbs. Study comparisons were mostly between different active therapies, including a study of different doses of the active intervention. Two studies on methylnaltrexone compared effect with a placebo. All the newly identified studies in the 2010 update evaluated methylnaltrexone, and they contribute just over half the study participants included in this review (320/616).

Four studies reported that participants had opioid-induced constipation, and in one other an inclusion criterion was that the participants had no bowel movements for two days with reported ongoing constipation (defined as more than two days of no bowel movements and a score of three or more on a five-point scale assessing constipation-related distress). In two studies, the drugs were given as a prophylactic irrespective of whether the participants were constipated at baseline (Agra 1998; Sykes 1991b). In the studies on methylnaltrexone nearly all participants (88% to 99%) were constipated at entry despite taking one or more conventional laxatives. Participants in the methylnaltrexone dose ranging study were required to remain on conventional laxatives throughout the trial (Portenoy 2008). Participants in the studies on methylnaltrexone versus placebo were allowed to remain on laxatives throughout the trials; they do not state the proportion per trial that did (Slatkin 2009; Thomas 2008).

All studies measured laxation response and adverse effects. Commonly, laxation response was captured by self-report and was assessed at several time points over one or two weeks. Timing of the follow up was not clear in two studies (Ramesh 1998; Sykes 1991a). None of the studies report significant baseline differences between the trial arms.

Risk of bias in included studies

All RCTs under-reported key design features. See Figure 1 and Figure 2.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

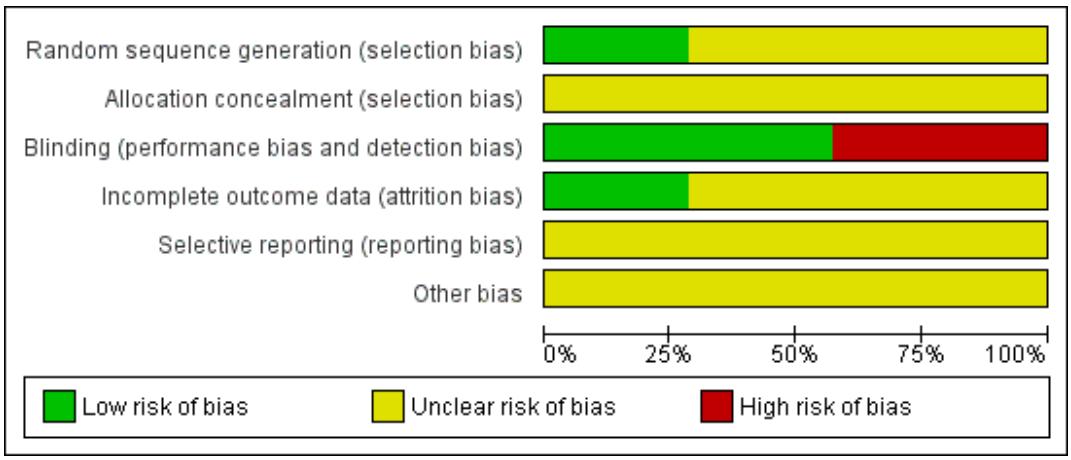
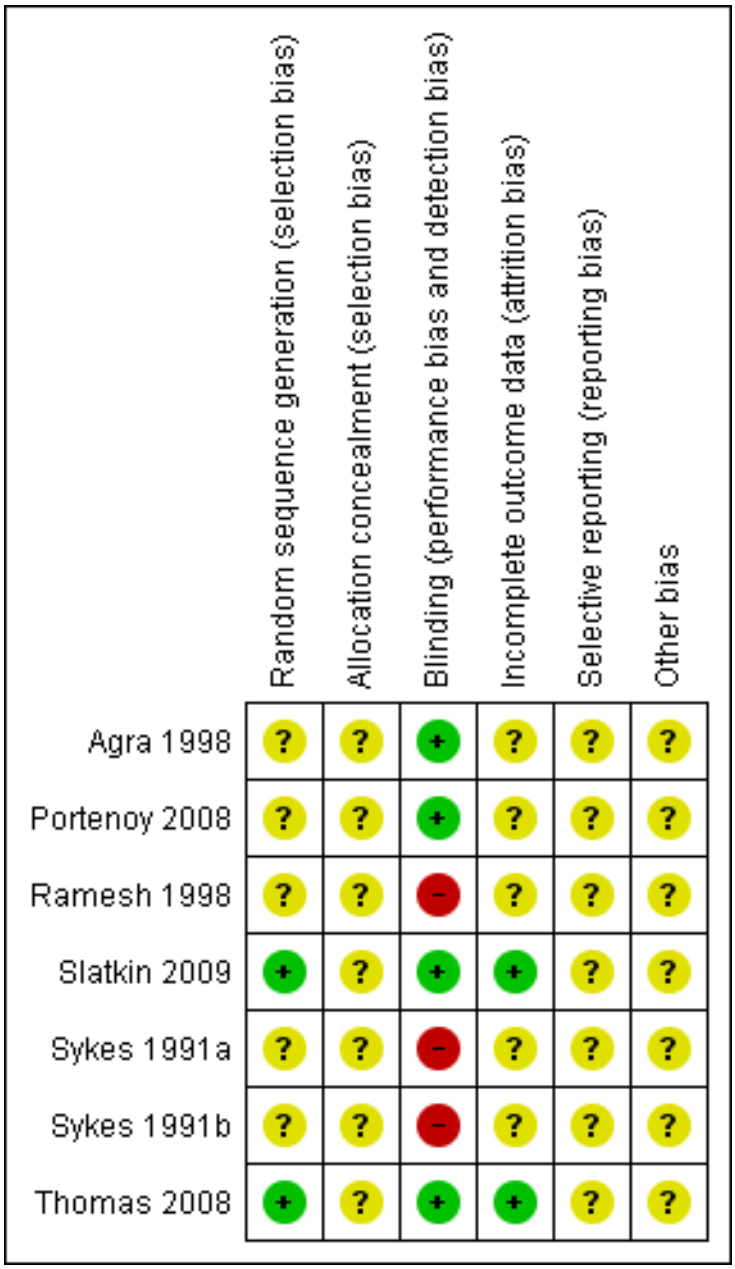


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Four studies did not describe how they generated the random allocation to trial arms (Agra 1998; Portenoy 2008; Sykes 1991a; Sykes 1991b). None of the studies reported methods to conceal random allocation.

Blinding

Blinding was not possible in the laxative trials, owing to differences in the physical characteristics of the drugs (Agra 1998; Ramesh 1998; Sykes 1991a; Sykes 1991b). Complete details on who was blinded in the other trials was only provided by one study (Slatkin 2009).

Incomplete outcome data

Attrition rates were provided by all studies. For five studies there were more than 10% lost to follow up. In the unpublished laxative study only 36% of patients completed the cross-over trial (Sykes 1991b). The paper does not provide reasons why participants did not complete the study. In the other studies many of the participants were lost to follow up because of disease progression rather than because of adverse effects. Non-compliance of 2% to 7% of participants with the laxative regimes was the other main reason for attrition in three studies. Some participants in two of the methylnaltrexone studies withdrew at their request. This ranged from 4% in the placebo-controlled trials to 21% in the dose ranging trial. Neither study provided reasons why the participants choose to withdraw.

None of the studies reported their findings fully.

Effects of interventions

See: **Summary of findings for the main comparison** Methylnaltrexone compared to placebo for the management of constipation in palliative care patients

Co-danthramer versus senna plus lactulose

One cross-over study of 51 participants evaluated the effectiveness of co-danthramer versus senna plus lactulose (Sykes 1991a). Both laxatives were in a liquid format. Neither dosage nor details of the data analyses were reported in full (see Table 1).

Laxation responses

The trialists report that participants receiving 80 mg or more of strong opioid "had a significantly higher stool frequency when taking lactulose plus senna than while receiving co-danthramer, P < 0.01". For participants receiving either a lower dose of opioid or no opioid no statistical difference was reported. For participants' assessments of bowel function they report no statistical difference between trial drugs. Participants in both groups required rescue laxatives (19 whilst on co-danthramer and nine whilst on senna plus lactulose).

Constipation-associated symptoms, pain intensity, opioid withdrawal

Not evaluated.

Acceptability and tolerability

Diarrhoea resulted in suspension of laxative therapy for 24 hours for 15 patients whilst taking lactulose and for five whilst taking co-danthramer. The trialists report that six instances of diarrhoea occurred at opioid doses of at least 80 mg/day whilst taking lactulose and senna; none were associated with co-danthramer. Two participants reported perianal soreness and burning whilst taking co-danthramer. Participant preference was similar between the trial arms (15 for lactulose and senna and 14 for co-danthramer), but they also report that twice as many participants disliked the flavour of co-danthramer compared to senna and lactulose.

Magnesium hydroxide plus liquid paraffin versus senna plus lactulose

One unpublished cross-over trial of 118 participants evaluated the effectiveness of one week of magnesium hydroxide plus liquid paraffin (mean dose per cross-over group 45 ml if taken in first week and 49 ml daily if taken in second week) versus one week of senna plus lactulose (mean dose per cross-over group of 34 ml and 38 ml daily) (Sykes 1991b). Forty-two of the 118 participants completed the trial (see Table 2).

Laxation response

No difference was reported in laxation response between the cross-over groups. The findings did not change by dose of opioid or by the order given in the cross-over of lactulose plus senna with magnesium hydroxide combined with liquid paraffin. They report that the dosage of magnesium hydroxide plus liquid paraffin required to achieve the same frequency of bowel movements was significantly higher than the dosage required with lactulose plus senna. Using data from the pre-cross-over week there was no significant difference in patients' perception of being constipated, or normality of bowel function. Participants in both groups required rescue laxatives, but they report that a significantly greater proportion of participants needed them whilst taking lactulose and

senna compared to magnesium hydroxide plus liquid paraffin. At the end of the trial 54% of participants considered their bowel movements were normal.

Constipation-associated symptoms, pain intensity, opioid withdrawal

Not evaluated.

Acceptability and tolerability

There was no significant difference between treatments in participants reporting diarrhoea. In both groups one participant found the treatment intolerably nauseating. One participant, whilst taking lactulose and senna, suffered gripping abdominal pain. More participants preferred lactulose plus senna over magnesium hydroxide combined with liquid paraffin.

Misrakasneham versus senna

One small study of 36 participants evaluated the effectiveness over two weeks of up to 10 ml of misrakasneham versus senna 24 mg to 72 mg (both in liquid format) (Ramesh 1998) (see Table 3).

Laxation response

There was no statistical difference between the misrakasneham and the senna groups in satisfactory bowel movements (defined as the comfortable feeling that a patient experienced after getting a free, effortless bowel movement at a frequency acceptable to him or her). Participants in the trial were taking various dosages of morphine but results were not analysed in terms of whether different opioid dose influenced laxative results. Six participants required rescue laxatives, of which five were in the senna group.

Constipation-associated symptoms, pain intensity, opioid withdrawal

Not evaluated.

Acceptability and tolerability

Nausea, vomiting and colicky pain were reported by two participants taking misrakasneham. None of the participants withdrew because of inefficiency. Participant preference was split between the groups.

Senna versus lactulose

One study of 75 participants evaluated the effectiveness over four weeks of lactulose 10 mg to 40 mg versus senna 12 mg to 48 mg (both laxatives were in liquid format). Doses were increased according to clinical response; the study authors do not provide details on average doses taken (Agra 1998) (see Table 4).

Laxation response

There was no statistical difference between the senna and the lactulose groups in laxation response, in defecation-free periods and in the mean number of defecation days (senna: mean 8.9 days (SD 6.6 days); lactulose: mean 10.6 days (SD 7.3 days)). Thirty-seven percent of participants completing the study required combined lactulose and senna to relieve constipation. Results were not analysed in terms of whether different opioid dose influenced laxative results.

Constipation-associated symptoms, pain intensity, opioid withdrawal

There was no statistical difference in the general state of health between the trial arms. The prescription of other drugs was similar between the trial arms.

Acceptability and tolerability

An equal number of participants, three per trial group, reported diarrhoea, vomiting and cramps. There was no significant difference in the number of participants who dropped out between the trial arms. Participant preference was not evaluated.

Methylnaltrexone versus placebo

Two studies evaluated subcutaneous methylnaltrexone versus a placebo (Slatkin 2009; Thomas 2008). In one study a single dose (0.15 mg/kg or 0.30 mg/kg) of methylnaltrexone was administered (Slatkin 2009); in the other study methylnaltrexone (0.15 mg/kg) was administered every other day for two weeks (Thomas 2008). See Analysis 1.1; Analysis 1.2 and Table 5.

Laxation response

In combined analysis of the two studies, with a total of 287 participants with opioid-induced constipation despite taking conventional laxatives, there was a significant difference favouring the intervention in rescue-free laxation within four and 24 hours of the first dose of methylnaltrexone. At four hours the OR was 6.95 (95% CI 3.83 to 12.61) (fixed-effect model). The I^2 statistic at 4% suggested minimal heterogeneity between the studies. At 24 hours the OR was 5.42 (95% CI 3.12 to 9.41) (fixed-effect model). The I^2 statistic at 0% suggested no heterogeneity. The proportion of participants that had a laxation response at four hours ranged from 48% to 62% in the methylnaltrexone trial groups and 13% to 15% in the placebo groups. At 24 hours it was 52% to 68% in the active trial arms and 8% to 27% in the placebo groups. A significant difference in laxation response favouring the treatment

group was also found in the multidose study at days three, five, seven, nine, 11 and 13 (Thomas 2008). Also, more participants in the intervention group of this study had three or more rescue-free laxations per week (68% versus 45%) (OR 2.56; 95% CI 1.26 to 5.20).

In both studies it was reported that the time to laxation significantly favoured the treatment group (single-dose trial median 1.1 hours versus > 24 hours, P = < 0.0001; multiple-dose trial median after the first dose 6.3 hours versus > 48 hours, P = < 0.001. The shorter time to laxation in the methylnaltrexone group persisted for each of the seven doses (P < 0.002 for all comparisons).

In the multi-dose study they report that a similar proportion of participants in the active and the placebo arm had watery bowel movements following administration of the trial drugs (16% versus 17%) (Thomas 2008). Also, among participants with laxation within 24 hours of a dose of the study drug, in both trial arms stool consistency improved.

In the single-dose trial, using the Global Clinical Impression of Change Scale (GCIC), the proportions of participants that reported an improvement in constipation distress at four hours favoured the active trial arm (OR 3.63; 95% CI 1.58 to 8.34) (Slatkin 2009). The multidose trial assessed patients' and clinicians' impression of improvement using the GCIC at days seven and 14 (Thomas 2008). In three of these assessments there was a significant difference favouring the active intervention group, but there was no significant difference between the trial arms at day 14, based on the clinician's assessment.

In the single-dose study the study authors state that the study demonstrated no dose-response relationship (between 0.15 mg and 0.3 mg per kilogram doses) in laxation and no correlation between laxation response and baseline opioid dose (Slatkin 2009). Dose response was not assessed in the other study but at day eight, if participants had had fewer than three rescue-free laxations, the initial volume of the study drug was doubled (to 0.30 mg of methylnaltrexone per kilogram) (Thomas 2008). Twenty of 61 in the active arm required this and of these 24% had a laxation response.

In both studies participants could continue on conventional laxatives. In one study at least 84% of participants in the active group took a conventional laxative during the study. However, it is unclear in both studies how frequently participants also took a conventional laxative.

Constipation-associated symptoms, pain intensity, opioid withdrawal

In the multidose study they assessed pain and symptoms of opioid withdrawal using the Modified Himmelsbach Withdrawal Scale, at three time points (Thomas 2008) . They found no significant difference between the trial arms. In the single-dose administration of methylnaltrexone study there was no overall change from the baseline pain scores or in having symptoms of opioid withdrawal (median changes were 0) (Slatkin 2009).

Acceptability and tolerability

In combined analysis, with a total of 288 participants, the proportion experiencing side effects was not significantly different between those in the active trial arm, taking methylnaltrexone, and those in the placebo arm (OR 1.96; 95% CI 0.60 to 6.44, random-effects model), although the I^2 statistic at 78% suggests a high risk of heterogeneity between the trials. In the single-dose study significantly more in the intervention group had side effects, whereas in the multidose study the proportions between the trial arms were similar.

In combined analysis, with a total of 288 participants, significantly more in the intervention group experienced flatulence (OR 2.66; 95% CI 1.07 to 6.62, fixed-effect model; the I^2 statistic at 0% suggested no heterogeneity between the studies) and dizziness (OR 4.35; 95% CI 1.04 to 18.18, fixed-effect model; the I^2 statistic at 0% suggested no heterogeneity between the studies). There was no significant difference in combined analysis between the trial arms in abdominal pain, restlessness, nausea, pain exacerbated, vomiting or asthenia. In analysis based on one study there was no significant difference between the trial arms in sweating, nausea, malignant-neoplasm progression, body temperature, peripheral oedema, diarrhoea, lethargy, dehydration, rhinorrhoea, upper abdominal pain, fatigue, anxiety, arthralgia, abdominal distension or tenderness tachycardia, hypotension or somnolence.

In the single-dose study the authors report that during the double-blind and subsequent open-label phase 19 participants experienced severe adverse events that were possibly related to methylnaltrexone, with some experiencing more than one event (Slatkin 2009). These were: 15 incidents of abdominal pain, three of increased sweating, two of increased pain and one each of burning at the injection site, vomiting, diarrhoea, asthenia, increased blood pressure, dehydration, muscular cramps, loss of consciousness, tremor, delirium, hallucination, dyspnoea and flushing.

In the same study serious adverse events did not occur during the trial phase but were reported in three participants during the subsequent open-label phase. One participant had flushing and another delirium possibly related to methylnaltrexone (Slatkin 2009). A third had severe diarrhoea and subsequent dehydration and cardiovascular collapse considered to be related to the drug. In the other study they report that severe adverse events occurred in 8% of participants in the methylnaltrexone group and 13% in the placebo group (Thomas 2008). The 11 serious adverse events in those who received methylnaltrexone were: aneurysm ruptured, respiratory arrest, dyspnoea exacerbated, suicidal ideation, aggression, malignant neoplasm progression, concomitant disease progression, myocardial ischaemia, coronary artery disease aggravated and congestive heart failure aggravated. The investigators considered all serious adverse events as either not related or unlikely to be related to the trial drug.

Ninety-seven percent (147/152) of participants in the single-dose study and 66% (89/134) in the multidose study opted to continue into an open-label phase.

Dose ranging trial of methylnaltrexone

One small study of 33 participants compared the effectiveness of 1 mg (n = 10), 5 mg (n = 7), 12.5 mg (n =10) and 20 mg (n =6) of subcutaneous methylnaltrexone (Portenoy 2008) (see Table 6).

Laxation response

Laxation effect within four and 24 hours of intervention dose was measured at days one, three and five. Following the initial treatment dose they found no dose-response relationship across the three highest doses. In further analysis between higher doses, of 5 mg or more, with those receiving a dose of 1 mg the evidence was mixed. There was no difference between trial arms in the proportion having a bowel movement within four hours at day one or within 24 hours at days one and three, however, there was a significant difference, favouring the higher dose, of a bowel movement within four hours at days three and five and at day five within 24 hours. The study reports that the median time to laxation was 1.26 hours for patients dosed at 5 mg or greater and in the 1 mg group it was greater than 48 hours. This difference was statistically significant (P = 0.0003). However, the wide confidence intervals in their analyses indicate that the results were underpowered.

Results were not analysed in terms of whether different opioid doses influenced laxative results.

Constipation-associated symptoms, pain intensity, opioid withdrawal

They report no differences in pain among the dose groups at baseline, on dosing days one, three and five or at the end of the trial. They also report that there was no evidence of methylnaltrexone-induced opioid withdrawal. There was no difference in patient satisfaction scores between the dose groups.

Acceptability and tolerability

All participants experienced at least one treatment-emergent adverse event. There was no significant difference between the lower dose group compared to the other doses in the proportion of participants who had a treatment related adverse event or discontinued because of an adverse event. The types of adverse events were similar between the dose groups. The most common adverse event was abdominal pain. Two participants discontinued the trial because of an adverse event. One was an 84-year old man who withdrew due to syncope (12.5 mg dose). The event was transient and resolved without sequelae; the investigators assessed that it was related to the medication. A 20-year old man was withdrawn after receiving three doses due to abdominal cramping, assessed as probably related to the study medication. Five participants experienced a non-death serious adverse events: lymphadenectomy, febrile neutropenia, depressed level of consciousness, suicide attempt and delirium; all were considered unrelated to study medication. One participant died during the trial; the event was unrelated to the study medication.

DISCUSSION

Summary of main results

This review sought to determine the effectiveness of the administration of laxatives and the opioid antagonist methylnaltrexone for the management of constipation in palliative care patients. We identified seven studies. Studies either compared the effectiveness of two different laxatives, compared methylnaltrexone with a placebo or different doses of methylnaltrexone. In the methylnaltrexone placebo-controlled trials an undisclosed proportion of participants continued to take conventional laxatives. The effectiveness of methylnaltrexone was not compared with a laxative and none of the trials compared a laxative with a placebo; all comparisons were made between different laxatives.

No differences in effectiveness were demonstrated between lactulose and senna, lactulose with senna compared to magnesium hydroxide and liquid paraffin, or between misrakasneham and senna. Between lactulose and senna versus co-danthramer the authors of one study reported that there was a significant difference, favouring the group who took lactulose and senna, in stool frequency. However, they report that there was no significant difference between lactulose and senna compared with co-danthramer in participants' assessment of bowel function. All studies that compared different laxatives reported that a few (one to three) participants suffered side effects. The most commonly reported events were nausea, vomiting, diarrhoea and abdominal pain. In the study comparing lactulose and senna with magnesium hydroxide and liquid paraffin emulsion a participant from each group withdrew because of intolerable nausea and gripping abdominal pain. Participant preferences were only reported in two studies; one showed a preference for lactulose plus senna over magnesium hydroxide combined with liquid paraffin (Sykes 1991b). The other found no difference in preference.

Overall completeness and applicability of evidence

More evidence was provided on the effect of methylnaltrexone where, based on evidence from two studies totaling 287 participants, it was found to be more effective than a placebo at inducing

a laxation response and that this response was rapid. In a small (n = 33) dose ranging trial methylnaltrexone was more effective at inducing laxation at 5 mg or greater compared to a dose of 1 mg. In these methylnaltrexone trials, most of the participants were constipated at baseline despite using conventional laxative therapy. In both placebo-controlled trials participants could continue on conventional laxatives. In one study at least 84% of participants in the active group took a conventional laxative during the trial. However, it is unclear in both studies how frequently participants also took a conventional laxative. In these studies, overall methylnaltrexone was well tolerated and acceptable to participants, although significantly more participants in the methylnaltrexone groups suffered flatulence (22/165 versus 7/123) and dizziness (12/165 versus 2/123). The proportions of participants per study in the active intervention group with abdominal pain differed but in combined analysis this was not significant. Serious adverse events were reported in two methylnaltrexone studies, although as these are a fragile population perhaps these events are not unexpected and for most the investigators considered the event as either not related or unlikely to be related to the trial drug. In the dose ranging study two participants had an event considered as related to the drug. One was an 84-year old man who withdrew from the trial due to syncope (12.5 mg dose); the event was transient and resolved without sequelae. A 20-year old man was also withdrawn after receiving three doses from this trial due to abdominal cramping, which the authors felt was probably related to the study medication. In the single-dose trial three participants had a serious adverse event in the subsequent open phase; this was flushing in one participant and in another delirium. A third had severe diarrhoea and subsequent dehydration and cardiovascular collapse. This chain of events was considered to be related to the drug.

In all included studies a number of participants remained constipated and were given rescue laxatives. None of the studies explored differences in follow-up characteristics, such as disease progression or drug use, between responders and non-responders.

Our review findings are limited. The studies on the effectiveness of laxatives could not be combined in analysis as they compared different treatments. The sample sizes of most studies (five of seven) were likely to be under-powered to find a true effect as they involved less than 100 participants. Studies had some methodological limitations; in five studies there was a high attrition rate and in two this was over 50% (Sykes 1991a; Sykes 1991b).

Agreements and disagreements with other studies or reviews

There have been earlier systematic reviews in overlapping areas, but all were undertaken before the findings from both the methylnaltrexone effectiveness studies identified in this review were published. One previous Cochrane systematic review has evaluated the evidence on the effectiveness of opioid antagonists versus conventional pharmacological or non-pharmacological treatments for opioid-induced bowel dysfunction (McNicol 2008). Two of the four studies they included evaluated the effects of methylnaltrexone; the other two were on alvimopan. Alvimopan is no longer being developed as an agent for improving opioid-induced constipation as it has been linked to a higher risk of cardiovascular events, fractures and skin cancers in this population (FDA 2008). In this Cochrane Review studies involved small samples sizes. They concluded that both drugs showed promise in treating opioid-induced bowel dysfunction but that post-marketing and cost-effectiveness studies are needed in a wider population to assess their utility fully. A similar conclusion of the need for more evidence was reached in a non-Cochrane systematic review on peripherally-acting opioid antagonists in the treatment of opiate-related constipation (Becker 2007).

AUTHORS' CONCLUSIONS

Implications for practice

Whilst this update reviews conclusions remain unchanged from the original review (Miles 2006) in that no new studies on the effectiveness of laxatives were identified, this current version has new conclusions in regards to the additional studies it included on methylnaltrexone.

The review cannot provide any information from the studies identified on what may be the optimal laxative management of constipation in palliative care patients. The review found that laxative use in the management of constipation in this patient group is based on limited research evidence. Specifically, there have been no randomised controlled trials (RCTs) on any laxative that have evaluated laxation response rate, patient tolerability and acceptability. There have been a few RCTs on the comparative advantages of different laxatives. The limited evidence from these studies suggests that the laxatives evaluated, including the commonly used laxatives lactulose and senna, were of similar effectiveness in this patient group. There is some evidence on the effectiveness of methylnaltrexone, indicating that in comparison to placebo and in patients where conventional laxative therapy is sub-optimal, methylnaltrexone improves laxation. However, these evaluations only measured effects in the short term. In the treatment group more participants suffered flatulence and dizziness and there were also reports of some serious adverse events that may be associated with the active drug. In all studies, on conventional laxatives and methylnaltrexone, a proportion of participants in the active intervention group remained constipated and required rescue laxatives. Also, it is unclear in the studies whether there were clinical differences, such as disease progression, in the participants who did not respond to the intervention therapy compared to those that did. In addition, in the methylnaltrexone placebo-controlled studies

it is unclear how frequently participants also took a conventional laxative.

Implications for research

Rigorous and independent RCTs measuring standardised and clinically relevant outcomes in a clearly defined population are needed to establish the effectiveness of laxatives and opioid antagonists in the management of constipation in palliative care patients. High attrition rates in the included studies and the relatively small numbers of eligible participants in any one palliative care unit suggest that any trial of laxative efficacy should be multi-centred. It is recommended that future trials should be designed and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement (Moher 2001).

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REFERENCES

References to studies included in this review

Agra 1998 *{published data only}*
Agra Y, Sacristan A, Gonzalez M, Ferrari M, Portugues A, Calvo MJ. Efficacy of senna versus lactulose in terminal cancer patients treated with opioids. *Journal of Pain and Symptom Management* 1998;**15**:1–7.

Portenoy 2008 *{published data only}*
Portenoy RK, Thomas J, Moehl Boatwright ML, Galasso FL, Stambler N, Von Gunten CF, et al.Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomised, parallel group, dose-ranging study. *Journal of Pain and Symptom Management* 2008;**35**:458–68.

Ramesh 1998 *{published data only}*
Ramesh P, Suresh Kumar K, Rajagopal M, Balachandran P, Warrier P. Managing morphine-induced constipation: a controlled comparison of the ayurvedic formulation and senna. *Journal of Pain and Symptom Management* 1998;**16** (4):240–4.

Slatkin 2009 *{published data only}*
Slatkin N, Thomas J, Lipman AG, Wilson G, Boatwright ML, Wellman C, et al.Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. *Journal of Supportive Oncology* 2009;**7**:39–46.

Sykes 1991a *{published data only}*
Sykes N. A clinical comparison of laxatives in a hospice. *Palliative Medicine* 1991;**5**:307–14.

Sykes 1991b *{published data only}*
Sykes N. A clinical comparison of lactulose and senna with magnesium hydroxide and liquid paraffin emulsion in a palliative care population. Unpublished data 1991.

Thomas 2008 *{published data only}*
Chamberlain BH, Cross K, Winston JL. Methylnaltrexone treatment of opioid induced constipation in patients with advanced illness. *Journal of Pain and Symptom Management* 2009;**38**:683–90.
* Thomas J, Karver S, Cooney GA, Chamberlain BH, Watt CK, Slatkin NE, et al.Methylnaltrexone for opioid-induced constipation in advanced illness. *New England Journal of Medicine* 2008;**358**:2332–44.

References to studies excluded from this review

Abernethy 2003 *{published data only}*
Abernethy AP, Currow DC, Frith P, Fazekas BS, McHugh A, Bui C. Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. *BMJ* 2003;**327**: 523–8.

Crowther 1978 *{published data only}*
Crowther A. Management of constipation in terminally ill patients. *Journal of International Medical Research* 1978;**6** (4):348–50.

Daeninck 1999 *{published data only}*
Daeninck PJ, Bruera E. Reduction in constipation and laxative requirements following. *Journal of Pain and Symptom Management* 1999;**18**:4.

Foss 2001 *{published data only}*
Foss J. A review of the potential role of methylnaltrexone in opioid bowel dysfunction. *American Journal of Surgery* 2001;**182**(Suppl):19S–26S.

Foss 2009 *{published data only}*
Foss J. How safe and effective is methylnaltrexone for the treatment of opioid-induced constipation in advanced illness?. *Nature Clinical Practice Gastroenterology and Hepatology* 2009;**6**:12–13.

Haazen 1999 *{published data only}*
Haazen L, Noorduin H, Megens A, Meert T. The constipation-inducing potential of morphine and transdermal fentanyl. *European Journal of Pain* 1999;**3** (Suppl A):9–15.

Koninger 2004 *{published data only}*
Koninger JS, Butters M, Redecke JD, Z'graggen K. Transverse coloplasty pouch after total mesorectal excision: functional assessment of evacuation. *Diseases of the Colon and Rectum* 2004;**47**(10):1586–93.

Maywin 2002 *{published data only}*
Maywin L, Wittbrodt E. Low dose oral naloxone reverses opioid-induced constipation and analgesia. *Journal of Pain and Symptom Management* 2002;**23**(1):48–53.

Meissner 2009 *{published data only}*
Meissner W, Leyendecker P, Mueller-Lissner S, Nadstawek J, Hopp M, Ruckes, et al.A randomised controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid induced constipation. *European Journal of Pain* 2009;**13**:56–64.

Moss 2008 *{published data only}*
Moss J. Peripheral opioid receptor antagonists: pain relief without side effects. *Southern African Journal of Anaesthesia and Analgesia* 2008;**14**:96.

Muir 2004 *{published data only}*
Muir JG, Yeow EG, Keogh J, Pizzey C, Bird AR, Sharpe K, et al.Combining wheat bran with resistant starch has more beneficial effects on fecal indexes than does wheat bran alone. *American Journal of Clinical Nutrition* 2004;**79**: 1020–8.

Nadstawek 2008 *{published data only}*
Nadstawek J, Leyendecker P, Hopp M, Ruckes C, Wirz S, Fleischer W, et al.Patient assessment of a novel therapeutic approach for the treatment of severe, chronic pain.. *International Journal of Clinical Practice* 2008;**62**:1159–67.

RCN 2006 *{published data only}*
Addison R, Smith M. *Digital rectal examination and manual removal of faeces*. Vol. **revised 2006**, London: Royal College of Nursing, 2000:1–12.

Saunders 2004 *{published data only}*
Saunders JR, Williams NS, Eccersley AJP. The combination of electrically stimulated gracilis neonatal sphincter and continent colonic conduit: a step forward for total anorectal reconstruction?. *Diseases of the Colon and Rectum* 2004;**47** (3):354–63.

Schoorl 1997 *{published data only}*
Schoorl J, Zylicz Z. Laxative policy for terminal patients ineffective. *Nederlands Tijdscrift voor Geneeskunde* 1997; **141**:823–6.

Spiller 2003 *{published data only}*
Spiller GA, Story JA, Furumoto EJ, Chezem JC, Spiller M. Effect of tartaric acid and dietary fibre from sun-dried raisins on colonic function and on bile acid and volatile fatty acid excretion in healthy adults. *British Journal of Nutrition* 2003;**90**:803–7.

Sykes 1996a *{published data only}*
Sykes NP. An investigation of the ability of oral naloxalones to correct opioid related constipation in patients with advanced cancer. *Palliative Medicine* 1996;**10**:135–44.

Sykes 1998 *{published data only}*
Sykes N. The relationship between opioid use and laxative use in terminally ill cancer patients. *Palliative Medicine* 1998;**12**:375–82.

Walsh 2000 *{published data only}*
Walsh D, Doona M, Molnar M, Lipnickey V. Symptom control in advanced cancer: important drugs and routes of administration. *Seminars in Oncology* 2000;**27**(1):69–83.

Wenk 2000 *{published data only}*
Wenk R, Bertolino M, Ochoa J, Cullen C, Bertucelli N, Bruera E. Laxative effects of fresh baker's yeast (letter). *Journal of Pain and Symptom Management* 2000;**19**(3): 163–4.

Additional references

Becker 2007
Becker G, Galandi D, Blum HE. Peripherally acting opioid antagonists in the treatment of opiate-related constipation: a systematic review. *Journal of Pain & Symptom Management* 2007;**34**:547–65.

Culbert 1998
Culbert P, Gillett H, Ferguson A. Highly effective new oral therapy for faecal impaction. *British Journal of General Practice* 1998;**48**:1599–6000.

Droney 2008
Droney J, Ross J, Gretton S, Welsh K, Sato H, Riley J. Constipation in cancer patients on morphine. *Supportive Care in Cancer* 2008;**16**:453–9.

Dunlop 1989
Dunlop GM. A study of the relative frequency and importance of gastrointestinal symptoms and weakness in patients with far advanced cancer. *Palliative Medicine* 1989; **4**:37–43.

FDA 2008
Gastrointestinal Drugs Advisory Committee Meeting. Silver Spring, MD: US Food and Drug Administration Center for Drug Evaluation and Research. January 23, 2008. http://www.fda.gov/ohrms/dockets/AC/cder08.html#gdac.

Higgins 2008
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Hurdon 2000
Hurdon V, Viola R, Schorder C. How useful is docusate in patients at risk for constipation? A systematic review of the evidence in the chronically ill. *Journal of Pain and Symptom Management* 2000;**19**:130–6.

Larkin 2008
Larkin PJ, Sykes NP, Centeno C, Ellershaw JE, Elsner F, Eugene B, et al.The management of constipation in palliative care: clinical practice recommendations. *Palliative Medicine* 2008;**22**:796–807.

Laugsand 2009
Laugsand EA, Kaasa S, de Conno F, Hanks G, Klepstad P, Research Steering Committee of the EAPC. Intensity and treatment of symptoms in 3,030 palliative care patients: a cross-sectional survey of the EAPC Research Network. *Journal of Opioid Management* 2009;**5**:11–21.

McMillan 1989
McMillan SC, Williams FA. Validity and reliability of the constipation assessment scale. *Cancer Nursing* 1989;**12**(3): 183–8.

McNicol 2008
McNicol ED, Boyce D, Carr DB. Mu-opioid antagonists for opioid-induced bowel dysfunction. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [Art. No.: CD006332. DOI: 10.1002/14651858.CD006332.pub2]

Moher 2001
Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *BMC Medical Research Methodology* 2001;**357**:1191–4.

Norton 1996
Norton C. The causes and nursing management of constipation. *British Journal of Nursing* 1996;**3**:1252–8.

Petticrew 1997
Petticrew M, Watt I, Sheldon T. Systematic review of the effectiveness of laxatives in the elderly. Health Technology Assessment 1997; Vol. 1, issue 13.

Ross 1998
Ross H. Constipation: cause and control in an acute hospital setting. *British Journal of Nursing* 1998;**7**(15): 907–13.

Sykes 2006
Sykes NP. The pathogenesis of constipation. *Journal of Supportive Oncology* 2006;**4**:212–8.

Thomas 2008
Thomas JR, Cooney GA, Slatkin NE. Palliative care and pain: new strategies for managing opioid bowel dysfunction. *Journal of Palliative Medicine* 2008;**11**:S1–S19.

Thompson 1999
Thompson WG, Longsteth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999;**45**: 1143–7.

Tramonte 1997
Tramonte SM, Mulrow CD, Amato MG, O'Keefe ME, Ramirez G. The treatment of chronic constipation in adults: a systematic review. *Journal of General Internal Medicine* 1997;**12**:15–24.

Winney 1998
Winney J. Constipation. *Primary Health Care* 1998;**8**:31–6.

References to other published versions of this review

Miles 2006
Miles C, Fellowes D, Goodman ML, Wilkinson SSM. Laxatives for the management of constipation in palliative care patients. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [Art. No.: CD003448. DOI: 10.1002/14651858.CD003448.pub2]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agra 1998

Methods	RCT, single-centre, parallel-group design
Participants	91 randomised Spanish palliative care unit male and female (n = 33) outpatients. Of these 75 remaining in the study for at least 7 days were analysed. All had a documented cancer with a life expectancy of less than 6 months. The most common cancer was lung tumour (30%) followed by breast (11%) Exclusions included colectomy, steatorrhoea or aphagia, as well as those with a Karnofsky index below 10% and those having taken opioids or laxatives during the 72-hour period to the initiation of the study Baseline characteristics: mean age in senna group 69.8 (SD 12.2) and in lactulose group 66.1 (SD 11.0), pain score in senna group 4.2 (SD 2.8), in lactulose group 4.9 (SD 2.5) . The mean morphine doses were in the senna group (mean 70.9 mg, SD 64.9 mg) and in the lactulose group (mean 78.9 mg, SD 52.5 mg)
Interventions	Oral liquid Drug 1 = starting 2 doses daily of 15 ml (10 g) lactulose Drug 2 = starting 2 doses daily of 0.4 ml (12 mg) senna The daily doses were increased if no bowel movement for 3 days. Maximum doses were 60 ml (40 g) of lactulose and 1.6 ml (48 mg) of senna. Drugs were given as a prophylactic when opioids were started Duration of treatment: 27 days
Outcomes	Main outcome were defecation-free intervals of 72 hours, days with defecation, general health status and treatment cost
Notes	Trial authors recommend use of senna based on cost advantage

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"...randomisation stratified by age and gender"; no other details
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	"The laxatives were supplied by the hospital pharmaceutical service and administered by the Palliative Care Unit in uni-doses of identical volume (the laxative was dissolved in water), in closed opaque flasks to prevent prescribers from identifying them. Yet, as texture and taste could not be homogenized, patients were able to differentiate between

Agra 1998 (*Continued*)

		one and the other drug"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	82% of recruited patients included in analysis 16 lost to follow up (6 in senna group, 10 in lactulose) in first 4 days; one due to diarrhoea and no response to treatment, 4 because of non-compliance, 4 due to death, 5 due to permanent hospitalisation and 2 to relocation By the end of the 27 days, 37 patients were lost; 21 in the senna group and 16 in the lactulose group. Three developed vomiting, 5 refused to continue in the protocol, 17 died and 12 were hospitalised The authors state that those who dropped out were not particularly different from those who completed follow up
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	Sample size calculation made but not met

Portenoy 2008

Methods	RCT, multi-centre, parallel-group design
Participants	33 opioid-treated American male and female (n = 18) patients with advanced disease (defined as terminal or end-stage, such as advanced metastatic cancer and AIDS but with a life expectancy of at least 4 weeks and stable vital signs) for which they were receiving palliative care and were receiving chronic opioid therapy for pain Patients were eligible if they were receiving any opioid drug on a daily basis at a dose that had been stable for at least 2 weeks and was expected to remain stable for an additional 4 weeks or more, and despite no or conventional laxative therapy they had no bowel movements for 2 days and reported ongoing constipation, defined as more than 2 days with no bowel movement and a score of 3 or more on a 5-point scale assessing constipation related distress Patients were excluded if they had a fever or otherwise unstable vital sign, a liver function test 3 times the upper limit of normal, a serum creatinine level 2 times the upper limit or a platelet count < 50,000/mm^3, a new regime or dose change of concurrent gastrointestinal-motility altering medications during 3 weeks prior to study enrolment, a history of gastrointestinal obstruction or other condition that could compromise drug action, a diagnosis of active peritoneal cancer, a history of peritoneal catheter placement for chemotherapy or dialysis, were known hypersensitive to methylnaltrexone naltrexone or naloxone or if any investigational drug or experimental product had been administered within the previous 30 days Mean age 61 years (SD 19.0) (range 20 to 87). Most were Caucasian (79%). Primary diagnosis at baseline were 28/33 cancer, 3 sickle cell disease and 2 AIDS. Most patients

Portenoy 2008 (*Continued*)

	were receiving a laxative at baseline (88%). The mean opioid (morphine equivalent) dose at baseline, mg/day was 289.9 (SD 308.0), median 180 mg/day, range 9 mg/day to 1, 207 mg/day. Mean number of bowel movements per week was 1.9
Interventions	Drug 1 = subcutaneous methylnaltrexone 1 mg Drug 2 = subcutaneous methylnaltrexone 5 mg Drug 3 = subcutaneous methylnaltrexone 12.5 mg The initial dose range of 1 mg, 5 mg or 12.5 mg was extended by adding a 20 mg group during the study while still maintaining the double-blind Duration of treatment 1 week; dosages were received on day 1, 3 and 5 Patients who were on laxative therapy at baseline (29/33) were required to remain taking the laxatives throughout the trial
Outcomes	Laxative response (bowel movement) within 4 hours of dosing. Other endpoints included laxation within 4 hours of subsequent doses, during the 24-hour period after each dose, time to laxation, the use of rescue laxatives. Also subjective outcomes of constipation-associated symptoms, pain intensity, symptoms potentially due to opioid withdrawal or side effects and patient satisfaction
Notes	Funded by Progenics pharmaceuticals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind - participant blinded, no other details on who is blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	22/33 completed study 7 discontinued "at patient request", 1 discontinued because of intolerable adverse event Unclear if used intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	Sample size calculation made and met

Ramesh 1998

Methods	RCT, single-centre, parallel-group design
Participants	36 Indian palliative care unit male and female patients (n = 25) with advanced cancer aged 15 years and older who were started on oral morphine for the first time and had opioid-induced constipation. Exclusion criteria were infants and children, patients with intestinal obstruction, patients already on laxatives, patients who were constipated even before the intake of morphine, patients already undergoing Ayurvedic therapy as some medicines may have a laxative action The most common cancers patients recruited had were of the lung, tongue, breast, oesophagus or cervix. The majority of the participants were aged between 51 to 70 years
Interventions	Oral tablet Drug 1 = misrakasneham (starting at 2.5 ml) Drug 2 = senna (starting at 24 mg) in 3 steps of doses if previous level failed Maximum doses were 72 mg senna and 10 ml Ayurvedic preparation Duration of treatment 2 weeks Given as a prophylactic when opioids started
Outcomes	Effect on opioid-induced constipation: bowel movement
Notes	Trial authors recommend use of misrakasneham based on favourable toxicity profile and cost advantage. This preparation may be difficult to obtain for use in the UK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly allocated to the 2 study groups (25 each) by drawing lots (sampling with replacement)
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	High risk	The difference between the physical forms of the 2 drugs necessitated an open trial rather than a double-blind study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	80% (n = 20) of misrakasneham and 64% (n = 16) of senna patients completed the trial. One from the misrakasneham group and 4 from the senna group dropped out of the trial because of irregular laxative administration. None dropped out because of inefficacy Unclear if used intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	-

Ramesh 1998 (*Continued*)

Other bias	Unclear risk	-

Slatkin 2009

Methods	RCT, multi-centre, parallel-group design forward
Participants	154 hospice and other palliative care settings, male and female (n = 70) American patients with advanced illness (life expectancy 1 to 6 months) and opioid-induced constipation. On a stable opioid regimen for the control of pain/discomfort for 3 of more days before randomisation, had a stable scheduled laxative regimen for 3 or more days prior to treatment, no clinically significant laxation within 48 hours prior to the first study drug dose, had stable vital signs, aged above 18 years and not pregnant and using an effective method of birth control Not included were patients with previous treatment of methylnaltrexone, prior treatment with naltrexone or naloxone, participation in any other studies involving investigational products within 30 days before screening, any disease process suggestive of gastrointestinal obstruction, any potential non-opioid cause of bowel dysfunction that in the opinion of the investigator may have been primarily responsible for constipation, history of current peritoneal catheter for intraperitoneal, chemotherapy or dialysis, clinically significant active diverticular disease, evidence of faecal impaction by physical examination or x-ray, surgically acute abdomen, faecal ostomy, pregnancy or nursing At baseline: mean age of included patients was 65.3 years (SD 14.96). Primary diagnosis cancer (125/154), cardiovascular disease (8), HIV/AIDS (1), and other (20). Apart from 8 participants all had some level of constipation distress. 95% were using a laxative. Oral morphine equivalents, median mg/day 186.5, range 8 mg/day to 12,2560 mg/day
Interventions	Drug 1 = single subcutaneous injection methylnaltrexone (0.15 mg/kg) Drug 2 = single subcutaneous injection methylnaltrexone (0.3 mg/kg) Drug 3 = placebo One dose followed by 28-day open phase. Baseline laxative regimens taken at time of study entry could be continued throughout the study. Rescue laxatives, defined as laxatives administered on a PRN basis were allowed but not within 4 hours before or after administration of the double-blind dose
Outcomes	The primary outcome was the proportion of patients with laxation within 4 hours after administration of the double-blind dose. Patients needing rescue laxative or disimpaction within 4 hours of dosing were considered non-responders Secondary outcomes included the proportion of patients with rescue-free laxation within 24 hours post-dosing, improvement in global clinical impression of change (GCIC) scale (defined as a rating of slightly better, somewhat better or much better), improvement in constipation distress (defined as a change by at least one category toward none), and improvement in stool consistency. Additional secondary outcomes included changes in baseline pain, symptoms/signs of central opioid withdrawal and adverse events
Notes	This study was sponsored by Progenics Pharmaceuticals, Inc. Sample size calculation made and met Baseline characteristics: states “baseline characteristics were well balanced among the treatment groups”. This included laxatives use, age, gender, race, weight, primary diag-

Slatkin 2009 (*Continued*)

	nosis, functional status, use of morphine, pain and constipation distress

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...randomly assigned in blocks of three to the three treatment groups in a 1:1:1 ratio. Computer generated randomisation scheme performed by a statistician external to the sponsor"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"...syringe contents were blinded to patients and staff administering injections"
Incomplete outcome data (attrition bias) All outcomes	Low risk	154/157 eligible entered study 152/154 completed trial (1 died and 1 was non-compliant) Analysis on an intention-to treat-basis
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Sykes 1991a

Methods	RCT, single-centre, cross-over group design
Participants	51 British hospice patients with cancer who had not under gone bowel diversion, were not clinically obstructed and who required a laxative. Patients were receiving either more or less than 80 mg of strong opioid a day
Interventions	Drug 1 = senna and lactulose (in equal quantities) liquid Drug 2 = equivalent volume of co-danthramer Starting doses of laxatives were set by the protocol in relation to opioid dosage and subsequently modulated according to clinical response. Does not provide further detail on doses Duration of treatment: 1 week twice daily Cross-over: switched to the alternative for a further week
Outcomes	Stool form and frequency, failure (absence of a single stool passed spontaneously during a treatment week), use of rescue laxatives, patient's assessment of bowel function, patient preference and adverse events
Notes	-

Sykes 1991a (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	High risk	"Not possible because of physical characteristics of drugs"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	58/117 completed the cross-over (of the 58, 6 patients were excluded from analysis because of breaches in the protocol and another as "data unclear") None dropped out because of inefficacy Not reported if intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Sykes 1991b

Methods	RCT, single-centre, cross-over group design
Participants	118 British hospice inpatients with cancer who had had no bowel diversion, showed no evidence of intestinal obstruction, required a laxative and had a life expectancy of at least 2 weeks
Interventions	Drug 1 = magnesium hydroxide plus liquid paraffin. Doses were modified according to response. Mean dose was 45 ml daily (week 1) and 49 ml daily (week 2) Drug 2 = senna plus lactulose. Doses were modified according to response. Mean dose was 38 ml daily (week 1) and 34 ml daily (week 2) Duration of each treatment per patient was 1 week and then switched to the alternative for a further week
Outcomes	Stool frequency, rates of failure, diarrhoea, use of rescue laxatives and patient's assessments of bowel function
Notes	Unpublished data

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Sykes 1991b (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	High risk	"...blinding not possible because of physical characteristics of the drugs"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	42/118 patients completed cross-over trial. None dropped out because of inefficacy One withdrew because of abdominal pain associated with the use of lactulose plus senna Not reported if intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Thomas 2008

Methods	RCT, multi-centre, parallel-group design
Participants	133 male and female adult American patients from 27 nursing homes, hospice sites or other palliative care centres in the USA and Canada (78 with cancer, 15 cardiovascular disease, 14 COPD, 8 dementia and 19 with other diseases) who had a terminal illness with a life expectancy > 1 month, were receiving stable doses of opioids for analgesia and had opioid-induced constipation (defined as no more than 3 laxations in the previous week or no laxation in the previous 48 hours) despite having taken laxatives for 3 or more days Median age in methylnaltrexone group 70 years (range 34 to 93) in the placebo group 72 (range 39 to 98). Opioid dose: methylnaltrexone group mean 417 mg/day, median 150 mg/day, range 9 mg/day to 4160 mg/day, placebo group mean 339 mg/day, median 100 mg/day, range 10 mg/day to 10,160 mg/day. 98% in the methylnaltrexone and 99% in placebo group were using laxatives
Interventions	Drug 1 = subcutaneous methylnaltrexone at a dose of 0.15 mg per kilogram of body weight Drug 2 = placebo Dose every other day, duration of treatment 2 weeks Patients could continue their baseline laxative regimen throughout the study and take rescue laxatives as needed, though not within 4 hours before or after receiving a dose of the study drug
Outcomes	Primary outcome: rescue-free defecation within 4 hours after first dose and laxation within 4 hours after 2 or more of the first 4 doses. Consistency (from watery to hard) and difficulty of laxation. Adverse effects were assessed using the National Cancer Institute's

Thomas 2008 (*Continued*)

	Common Toxicity Criteria (rated on a scale from 'none' to 'very much'). Patients were also assessed on the Modified Himmelsbach Withdrawal Scale for opioid withdrawal (on 7 symptoms including yawning, lacrimation, rhinorrhoea, perspiration, tremor, piloerection and restlessness)
Notes	Power calculation met 133/134 eligible recruited, 106/134 completed study. 52/62 in the active arm and 54/71 in the placebo arm Source of funding: Progenics Pharmaceuticals Baseline characteristics: states "no major differences in baseline demographic or clinical characteristics or performance status ratings". At baseline, the median oral morphine-equivalent dose was 150 mg per day in the methylnaltrexone group and 100 mg in the placebo group. In both groups, the median number of laxative drug classes used was 2

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule, blocked according to study centre
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; does not state who is masked
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% on day 1 and 86% on day 7. Intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

BM = bowel movement
COPD = chronic obstructive pulmonary disease
s.d. = significant difference(s)
n.s.d. = no significant difference(s)

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abernethy 2003	Not assessing the effects of laxatives in palliative care
Crowther 1978	Not a controlled trial
Daeninck 1999	Not assessing the effects of laxatives in palliative care
Foss 2001	Not assessing the effects of laxatives in palliative care
Foss 2009	Commentary on findings of an included RCT
Haazen 1999	Not assessing the effects of laxatives in palliative care
Koninger 2004	Not assessing the effects of laxatives in palliative care
Maywin 2002	Not assessing the effects of laxatives in palliative care
Meissner 2009	Not assessing the effects of laxatives in palliative care
Moss 2008	Commentary on included RCT
Muir 2004	Not assessing the effects of laxatives in palliative care
Nadstawek 2008	Not assessing the effects of laxatives in palliative care
RCN 2006	Not assessing the effects of laxatives in palliative care
Saunders 2004	Not assessing the effects of laxatives in palliative care
Schoorl 1997	Mixed laxatives used. Not possible to distinguish effect of individual regimes
Spiller 2003	Not assessing the effects of laxatives in palliative care
Sykes 1996a	Not assessing the effects of laxatives in palliative care
Sykes 1998	Not an effectiveness trial
Walsh 2000	Not assessing the effects of laxatives in palliative care
Wenk 2000	Not a RCT

RCT = randomised controlled trial

DATA AND ANALYSES

Comparison 1. Methylnaltrexone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion who had rescue-free laxation within 4 hours	2	287	Odds Ratio (M-H, Fixed, 95% CI)	6.95 [3.83, 12.61]
2 Laxation within 24 hours	2	287	Odds Ratio (M-H, Fixed, 95% CI)	5.42 [3.12, 9.41]
3 Tolerability: proportion experiencing side effects	2	288	Odds Ratio (M-H, Random, 95% CI)	1.96 [0.60, 6.44]
4 Abdominal pain	2	288	Odds Ratio (M-H, Random, 95% CI)	3.98 [0.44, 35.65]
5 Flatulence	2	288	Odds Ratio (M-H, Fixed, 95% CI)	2.66 [1.07, 6.62]
6 Restlessness	2	288	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.26, 1.73]
7 Pain exacerbated	2	261	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.18, 1.48]
8 Dizziness	2	288	Odds Ratio (M-H, Fixed, 95% CI)	4.35 [1.04, 18.18]
9 Vomiting	2	288	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.28, 1.69]
10 Asthenia	2	255	Odds Ratio (M-H, Fixed, 95% CI)	2.84 [0.76, 10.56]
11 Rescue-free laxation with 24 hours	2	287	Odds Ratio (M-H, Fixed, 95% CI)	5.42 [3.12, 9.41]

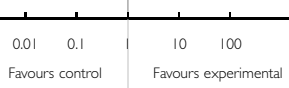
Analysis 1.1. Comparison 1 Methylnaltrexone versus placebo, Outcome 1 Proportion who had rescue-free laxation within 4 hours.

Review: Laxatives or methylnaltrexone for the management of constipation in palliative care patients

Comparison: 1 Methylnaltrexone versus placebo

Outcome: 1 Proportion who had rescue-free laxation within 4 hours

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Slatkin 2009	61/102	7/52		41.3 %	9.56 [3.93, 23.27]
Thomas 2008	30/62	11/71		58.7 %	5.11 [2.27, 11.53]
Total (95% CI)	**164**	**123**		**100.0 %**	**6.95 [3.83, 12.61]**
Total events: 91 (Experimental), 18 (Control)					
Heterogeneity: Chi^2 = 1.04, df = 1 (P = 0.31); I^2 =4%					
Test for overall effect: Z = 6.39 (P < 0.00001)					
Test for subgroup differences: Not applicable					

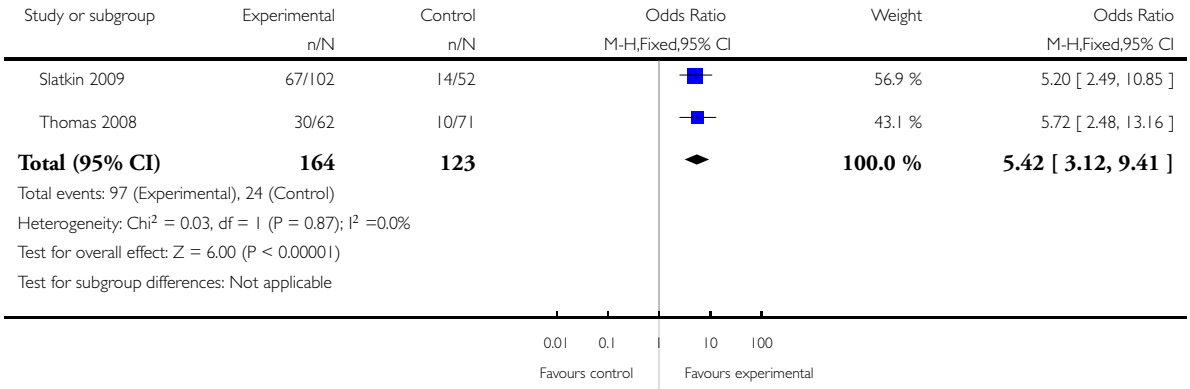


Analysis 1.2. Comparison 1 Methylnaltrexone versus placebo, Outcome 2 Laxation within 24 hours.

Review: Laxatives or methylnaltrexone for the management of constipation in palliative care patients

Comparison: 1 Methylnaltrexone versus placebo

Outcome: 2 Laxation within 24 hours

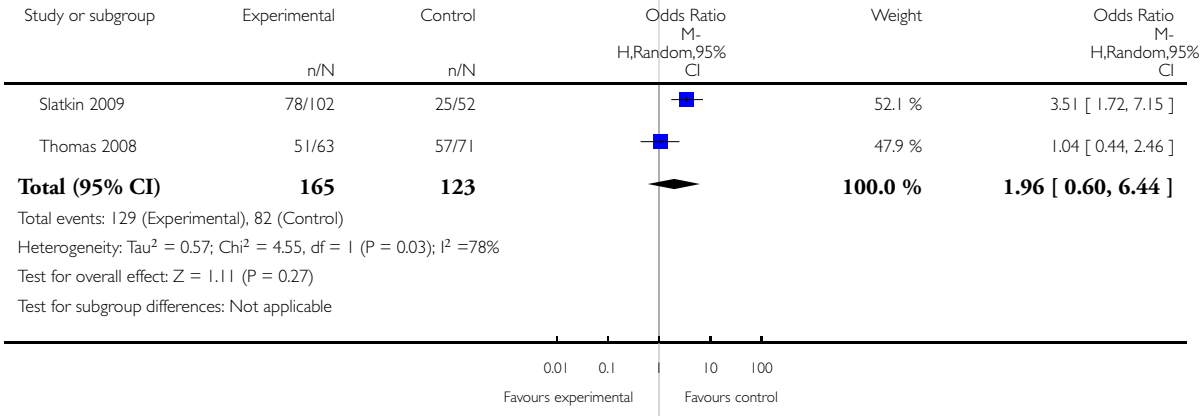


Analysis 1.3. Comparison 1 Methylnaltrexone versus placebo, Outcome 3 Tolerability: proportion experiencing side effects.

Review: Laxatives or methylnaltrexone for the management of constipation in palliative care patients

Comparison: 1 Methylnaltrexone versus placebo

Outcome: 3 Tolerability: proportion experiencing side effects

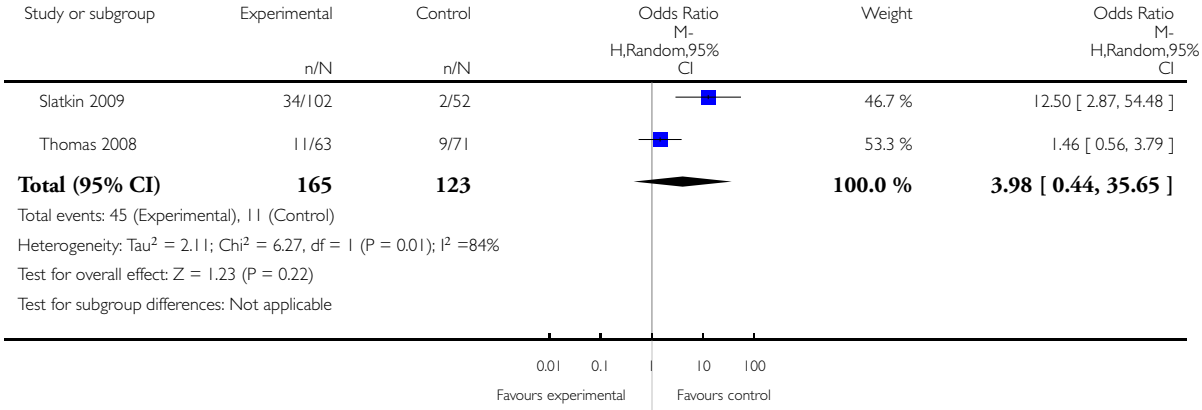


Analysis 1.4. Comparison 1 Methylnaltrexone versus placebo, Outcome 4 Abdominal pain.

Review: Laxatives or methylnaltrexone for the management of constipation in palliative care patients

Comparison: 1 Methylnaltrexone versus placebo

Outcome: 4 Abdominal pain



Analysis 1.5. Comparison 1 Methylnaltrexone versus placebo, Outcome 5 Flatulence.

Review: Laxatives or methylnaltrexone for the management of constipation in palliative care patients

Comparison: 1 Methylnaltrexone versus placebo

Outcome: 5 Flatulence

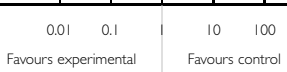
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Slatkin 2009	14/102	2/52		35.8 %	3.98 [0.87, 18.22]
Thomas 2008	8/63	5/71		64.2 %	1.92 [0.59, 6.21]
Total (95% CI)	**165**	**123**		**100.0 %**	**2.66 [1.07, 6.62]**

Total events: 22 (Experimental), 7 (Control)

Heterogeneity: $Chi^2 = 0.56$, df = 1 (P = 0.45); $I^2 = 0.0\%$

Test for overall effect: Z = 2.10 (P = 0.036)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 Methylnaltrexone versus placebo, Outcome 6 Restlessness.

Review: Laxatives or methylnaltrexone for the management of constipation in palliative care patients

Comparison: 1 Methylnaltrexone versus placebo

Outcome: 6 Restlessness

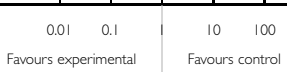
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Slatkin 2009	8/102	4/52		47.2 %	1.02 [0.29, 3.56]
Thomas 2008	2/63	6/71		52.8 %	0.36 [0.07, 1.83]
Total (95% CI)	**165**	**123**		**100.0 %**	**0.67 [0.26, 1.73]**

Total events: 10 (Experimental), 10 (Control)

Heterogeneity: $Chi^2 = 1.01$, df = 1 (P = 0.31); $I^2 = 1\%$

Test for overall effect: Z = 0.83 (P = 0.41)

Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 Methylnaltrexone versus placebo, Outcome 7 Pain exacerbated.

Review: Laxatives or methylnaltrexone for the management of constipation in palliative care patients

Comparison: 1 Methylnaltrexone versus placebo

Outcome: 7 Pain exacerbated

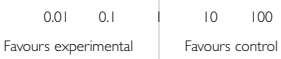
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Slatkin 2009	8/102	2/25		31.7 %	0.98 [0.19, 4.92]
Thomas 2008	2/63	7/71		68.3 %	0.30 [0.06, 1.50]
Total (95% CI)	**165**	**96**		**100.0 %**	**0.52 [0.18, 1.48]**

Total events: 10 (Experimental), 9 (Control)

Heterogeneity: Chi^2 = 1.04, df = 1 (P = 0.31); I^2 =4%

Test for overall effect: Z = 1.23 (P = 0.22)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 Methylnaltrexone versus placebo, Outcome 8 Dizziness.

Review: Laxatives or methylnaltrexone for the management of constipation in palliative care patients

Comparison: 1 Methylnaltrexone versus placebo

Outcome: 8 Dizziness

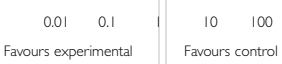
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Slatkin 2009	7/102	0/52		26.1 %	8.25 [0.46, 147.26]
Thomas 2008	5/63	2/71		73.9 %	2.97 [0.56, 15.90]
Total (95% CI)	**165**	**123**		**100.0 %**	**4.35 [1.04, 18.18]**

Total events: 12 (Experimental), 2 (Control)

Heterogeneity: Chi^2 = 0.39, df = 1 (P = 0.53); I^2 =0.0%

Test for overall effect: Z = 2.02 (P = 0.044)

Test for subgroup differences: Not applicable

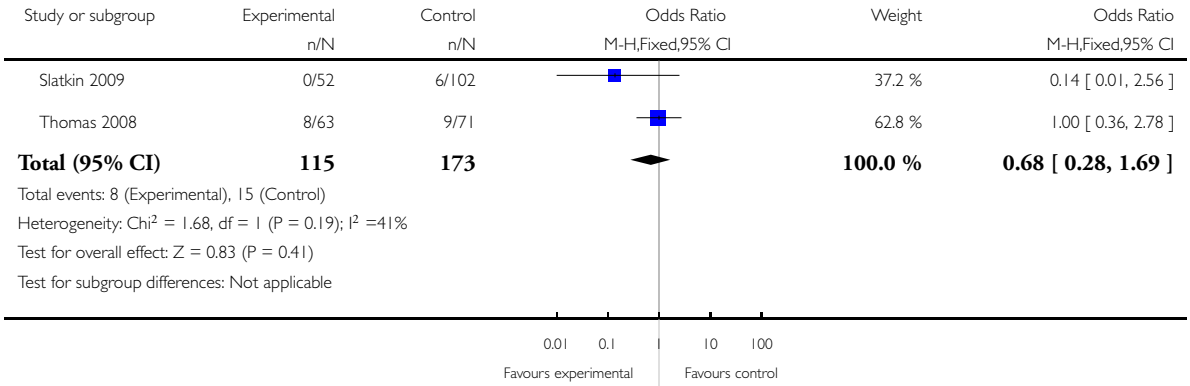


Analysis 1.9. Comparison 1 Methylnaltrexone versus placebo, Outcome 9 Vomiting.

Review: Laxatives or methylnaltrexone for the management of constipation in palliative care patients

Comparison: 1 Methylnaltrexone versus placebo

Outcome: 9 Vomiting

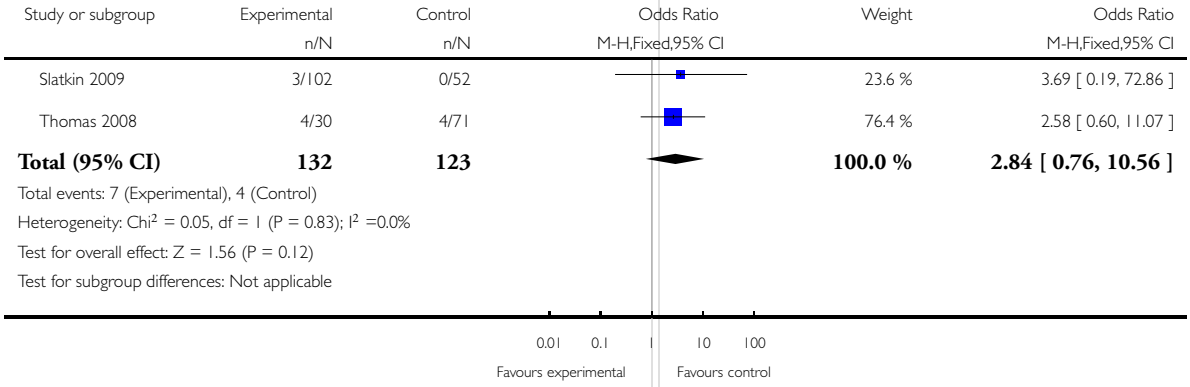


Analysis 1.10. Comparison 1 Methylnaltrexone versus placebo, Outcome 10 Asthenia.

Review: Laxatives or methylnaltrexone for the management of constipation in palliative care patients

Comparison: 1 Methylnaltrexone versus placebo

Outcome: 10 Asthenia

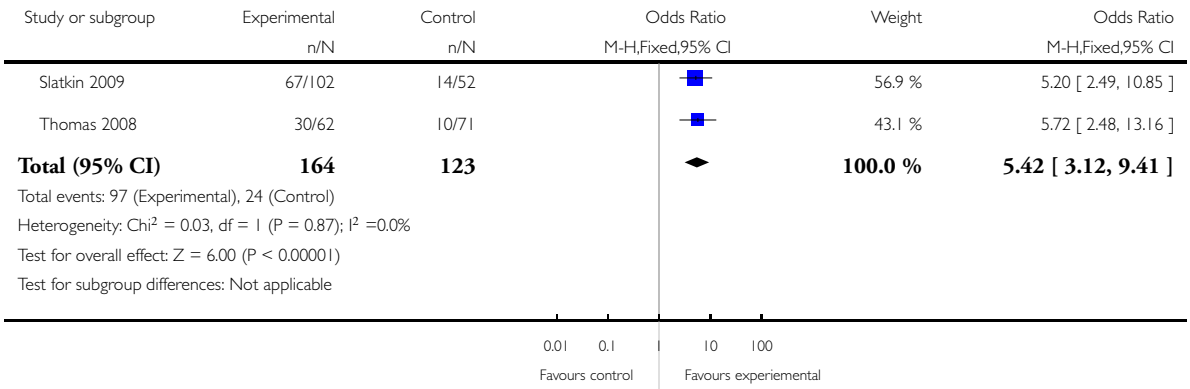


Analysis 1.11. Comparison 1 Methylnaltrexone versus placebo, Outcome 11 Rescue-free laxation with 24 hours.

Review: Laxatives or methylnaltrexone for the management of constipation in palliative care patients

Comparison: 1 Methylnaltrexone versus placebo

Outcome: 11 Rescue-free laxation with 24 hours



ADDITIONAL TABLES

Table 1. Co-danthramer versus lactulose with senna

Outcome or subgroup	Participants	Effect estimate*
Bowel movements in patients receiving strong opioid analgesia (taking 80 mg or more)	17	"Lactulose plus senna was associated with significantly higher frequency (regardless of which laxative taken first) (P value = < 0.01)"
Bowel movements in patients receiving opioid analgesia (less than 80 mg) or no opioid analgesia	21	"No statistical difference between the trial arms"
No bowel movement in treatment week	Unclear	While patients were receiving co-danthramer this occurred 11 times versus once in other trial arm (P value = 0.01)
Suspension of laxative therapy for 24 hours	Unclear	Occurred more frequently on lactulose with senna (15 cases) than co-danthramer (5) (P value = 0.05)
Rescue laxatives	Unclear	14 patients received a rescue laxative only while taking co-danthramer but not with lactulose and senna. Four patients received rescue laxatives while taking lactulose and senna but not with co-danthramer. Five received rescue laxatives both while taking both trial treatments

Table 1. Co-danthramer versus lactulose with senna (*Continued*)

Patient assessment of bowel function	Unclear	The reported mean change in patient assessment of their bowel function was not significant between drugs at the first week prior to cross-over or in the week following cross-over
Patient preference	58	"While favourable comments about agents effectiveness and flavour were evenly shared, twice as many patients disliked the flavour of co-danthramer as that of lactulose with senna"
Diarrhoea	Unclear	"...diarrhoea resulted in the suspension of laxative therapy got 24 hours occurred more frequently with lactulose and senna compared to co-danthramer (15 versus 5)"
Adverse effects	Unclear	Two patients reported per-anal soreness and burning on co-danthramer

*If data available and appropriate effect estimate is presented as an odds ratio (OR) or a mean difference (MD). If not available or appropriate then effect is reported as stated in the trial.

Table 2. Magnesium hydroxide plus liquid paraffin versus senna plus lactulose

Magnesium hydroxide plus liquid	**Participants**	**Effect outcome***
Laxation response	35	"For all patients and for the subgroups who either were or were not receiving strong opioids there was no statistical difference in stool frequency between the two trial treatment groups". At the end of the trial 19/35 (54%) of patients had bowel function they accepted as normal
Treatment failure	29	Two patients passed no spontaneous stool with either treatment
Loose stools	unclear	There was no significant difference between treatments in the proportion of patients reporting loose stools
Rescue laxatives	unclear	"...rectal measures were used on ten occasions during treatment with senna plus lactulose and 23 occasions while magnesium hydroxide plus liquid paraffin was being used"
Patient assessment of constipation	35	OR 1.10; 95% CI 0.28 to 4.26**
Patient assessment of diarrhoea	35	OR 0.67; 95% CI 0.10 to 4.58**
Patient assessment of normality of bowel function	35	OR 1.11; 95% CI 0.29 to 4.21**
Patient preference	32	8/32 (magnesium hydroxide plus liquid paraffin) versus 19/32 (senna and lactulose group)

Table 2. Magnesium hydroxide plus liquid paraffin versus senna plus lactulose (*Continued*)

Adverse events	unclear	In both groups 1 patient found the treatment intolerably nauseating. One person suffered gripping abdominal pain with lactulose and senna

*If data available and appropriate effect estimate is presented as an odds ratio (OR) or a mean difference (MD). If not available or appropriate then effect is reported as stated in the trial. **Effect outcome used data prior to cross-over.

Table 3. Misrakasneham versus senna

Outcome or subgroup	Participants	Effect estimate*
Satisfactory bowel movements with no side effects	28	OR 7.67; 95% CI 0.37 to 158.01

* If data available and appropriate effect estimate is presented as an odds ratio (OR) or a mean difference (MD). If not available or appropriate then effect is reported as stated in the trial.

Table 4. Senna versus lactulose

Outcome or subgroup	Participants	Effect estimate*
Mean number of defecation days	75	MD -0.10; 95% CI -0.60 to 0.40
Defecation-free days	75	MD 0.00; 95% CI -0.48 to 0.48
General state of health	75	MD -0.10; 95% CI -0.31 to 0.11

*If data available and appropriate effect estimate is presented as an odds ratio (OR) or a mean difference (MD). If not available or appropriate then effect is reported as stated in the trial.

Table 5. Methylnaltrexone versus placebo: outcomes assessed in one trial

Outcome or subgroup	Participants	Effect estimate
Rescue-free laxation within 4 hours after 2 or more doses	93	OR 11.20; 95% CI 3.55 to 35.29
Rescue-free laxation within 4 hours at day 3	122	OR 8.25; 95% CI 3.07 to 22.16
Rescue-free laxation within 4 hours at day 5	121	OR 5.99; 95% CI 2.43 to 14.78
Rescue-free laxation within 4 hours at day 7	115	OR 8.25; 95% CI 2.61 to 26.06

Table 5. Methylnaltrexone versus placebo: outcomes assessed in one trial (*Continued*)

Rescue-free laxation within 4 hours at day 9	114	OR 4.36; 95% CI 1.74 to 10.90
Rescue-free laxation within 4 hours at day 11	103	OR 5.58; 95% CI 1.89 to 16.48
Rescue-free laxation within 4 hours at day 13	98	OR 7.29; 95% CI 2.25 to 23.69
Improvement in constipation distress at 4 hours	99	OR 3.63; 95% CI 1.58 to 8.34
Improvement in constipation distress at day 1	133	OR 2.41; 95% CI 1.17 to 4.96
Improvement in constipation distress at day 7	133	OR 0.42; 95% CI 0.21 to 0.85
Improvement in constipation distress at day 14	133	OR 1.54; 95% CI 0.78 to 3.07
Among responders laxation response rate within 30 minutes of first dose	42	OR 5.46; 95% CI 1.01 to 29.54
Among responders laxation response rate within 60 minutes of first dose	41	OR 3.30; 95% CI 0.78 to 13.88
Patients who did not respond to the first dose but responded to second dose	84	OR 5.37; 95% CI 1.62 to 17.75
Three or more laxation per week	133	OR 2.56; 95% CI 1.26 to 5.20
Global Clinical Impression: clinician rating better day 7	106	OR 4.19; 95% CI 1.86 to 9.48
Global Clinical Impression: patient rating better day 7	106	OR 5.12; 95% CI 2.22 to 11.81
Global Clinical Impression: clinician rating better day 14	106	OR 2.12; 95% CI 0.97 to 4.62
Global Clinical Impression: patient rating better day 14	106	OR 2.63; 95% CI 1.20 to 5.74
Worst pain in last 24 hours at day 1	133	MD -0.70; 95% CI -1.53 to 0.13
Worst pain in last 24 hours at day 7	133	MD 0.00; 95% CI -0.85 to 0.85

Table 5. Methylnaltrexone versus placebo: outcomes assessed in one trial (*Continued*)

Worst pain in last 24 hours at day 14	133	MD 0.20; 95% CI -0.68 to 1.08
Current level of pain at day 1	133	MD -0.20; 95% CI -1.02 to 0.62
Current level of pain at day 7	133	MD -0.10; 95% CI -0.95 to 0.75
Current level of pain at day 14	133	MD 0.70; 95% CI -0.13 to 1.53
Mean change in current pain scores	133	MD -0.72; 95% CI -2.08 to 0.64
Symptoms of opioid withdrawal at day 1	133	MD 0.10; 95% CI -0.46 to 0.66
Symptoms of opioid withdrawal at day 7	133	MD -0.20; 95% CI -0.80 to 0.40
Symptoms of opioid withdrawal at day 14	133	OR 5.42; 95% CI 3.12 to 9.41
Score on Modified Himmelsbach Withdrawal Scale Day 1	133	MD 0.00; 95% CU -0.47 to 0.47
Score on Modified Himmelsbach Withdrawal Scale Day 7	133	MD 0.20; 95% CI -0.40 to 0.80
Score on Modified Himmelsbach Withdrawal Scale Day 14	133	MD 0.10; 95% CI -0.63 to 0.83
Mean change at 4 hours of symptoms of opioid withdrawal	36	MD -0.05; 95% CI -0.92 to 0.82
Mean change at 48 hours of symptoms of opioid withdrawal	46	MD -0.40; 95% CI -1.08 to 0.28
Patients with >- 1 serious adverse event	134	OR 2.56; 95% CI 1.26 to 5.20
Malignant neoplasm progression	134	OR 0.86; 95% CI 0.30 to 2.47
Sweating increased	154	OR 1.02; 95% CI 0.29 to 3.56
Nausea	154	OR 5.54; 95% CI 0.69 to 44.55
Rhinorrhoea	154	OR 3.19; 95% CI 0.37 to 27.20
Upper abdominal pain	154	OR 2.63; 95% CI 0.30 to 23.11
Fatigue	154	OR 2.08; 95% CI 0.23 to 19.11
Anxiety	154	OR 5.92; 95% CI 0.32 to 109.21

Table 5. Methylnaltrexone versus placebo: outcomes assessed in one trial (*Continued*)

Arthralgia	154	OR 1.55; 95% CI 0.16 to 15.23
Somnolence	154	OR 4.80; 95% CI 0.25 to 90.82
Increase in body temperature	134	OR 2.97; 95% CI 0.56 to 15.90
Peripheral oedema	134	OR 2.97; 95% CI 0.56 to 15.90
Diarrhoea	134	OR 1.54; 95% CI 0.33 to 7.15
Lethargy	134	OR 1.14; 95% CI 0.27 to 4.74
Dehydration	134	OR 0.55; 95% CI 0.10 to 3.11
Abdominal distension	134	OR 0.17; 95% CI 0.02 to 1.49
Abdominal tenderness	134	OR 0.27; 95% CI 0.03 to 2.48
Tachycardia	134	OR 0.27; 95% CI 0.03 to 2.48
Hypotension	134	OR 0.12; 95% CI 0.01 to 2.24
Fall	134	OR 0.15; 95% CI 0.02 to 1.23
Contact laxatives	133	OR 0.39; 95% CI 0.13 to 1.22
Stool softeners used during study	133	OR 0.99; 95% CI 0.50 to 1.97
Magnesium compounds as laxatives used during study	133	OR 0.46; 95% CI 0.22 to 0.95
Osmotic agents as laxatives used during study	133	OR 0.73; 95% CI 0.36 to 1.49
Enemas used during study	133	OR 0.59; 95% CI 0.28 to 1.25
Reported use of any laxatives among those who had a bowel movement within 4 hours after greater than or equal to 4 trial doses during the 2-week study		33 in methylnaltrexone versus 1 in placebo

* If data available and appropriate effect estimate is presented as an odds ratio (OR) or a mean difference (MD). If not available or appropriate then effect is reported as stated in the trial.

Table 6. Methylnaltrexone dose ranging

Methylnaltrexone 5 mg or greater versus 1 mg	Participants	Effect estimate*
Bowel movement within 4 hours day 1	33	OR 8.25; 95% CI 0.89 to 76.12
Bowel movement within 4 hours day 3	26	OR 6.42; 95% CI 1.00 to 41.21
Bowel movement within 4 hours day 5	23	OR 31.36; 95% CI 1.50 to 654.16
Bowel movement within 24 hours day 1	33	OR 1.56; 95% CI 0.35 to 6.94
Bowel movement within 24 hours day 3	26	OR 4.80; 95% CI 0.85 to 27.20
Bowel movement within 24 hours day 5	23	OR 13.20; 95% CI 1.24 to 140.68
Median time to laxation		1.26 hours for patients dosed at 5mg or greater, in the 1 mg group it was greater than 48 hours; this was statistically significant, P value = 0.0003
Pain		There was no difference in pain among the dose groups at baseline or at any of the follow ups
Opioid withdrawal		There was no evidence of methylnaltrexone-induced opioid withdrawal during the trial
Tolerability: proportion experiencing an adverse event	33	All patients experienced at least 1 adverse event
Patient satisfaction		There were no trends in patient satisfaction scores
Acceptability: proportion discontinued treatment due to an adverse event	33	OR 2.44; 95% CI 0.14 to 43.47

*If data available and appropriate effect estimate is presented as an odds ratio (OR) or a mean difference (MD). If not available or appropriate then effect is reported as stated in the trial.

APPENDICES

Appendix 1. MEDLINE search strategy

Original search in 2005

#1 CONSTIPATION (single term MeSH)
#2 DEFECATION (single term MeSH)
#3 FECAL INCONTINENCE (single term MeSH)
#4 FECES (single term MeSH)
#5 DIARRHEA (single term MeSH)
#6 IRRITABLE BOWEL SYNDROME (single term MeSH)
#7 (constipat* or (hard near stool*) or (bowel near symptom*) or (impact* near stool*) or (impact* near faeces) or (impact* near faeces) or (fecal* near incontin*) or (faecal* adj incontin*) or (fecal* near impact*) or (faecal* near impact*) or (loose near stool*) or diarrh* or faeces or faeces))
#8 (defecat* or (bowel* near function*) or (bowel* near habit*) or (bowel* near symptom*) or (evacuat* near faeces) or (evacuat* near faeces) or (evacuat* near bowel*) or (bowel* near symptom*) or (bowel near movement*) or (intestin* near motility) or (colon near transit*) or (void* near bowel*) or (strain* near bowel*) or (irritable adj bowel adj syndrome))
#9 FECAL IMPACTION (single term MeSH)
#10 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)
#11 CATHARTICS (EXPLODE MeSH)
#12 cathartic*
#13 laxative* or purgative*
#14 (methylcellulose or celevac* or cologel* or lactulose* or duphalac* or osmolax* or (magnesium adj hydroxide) or (milk adj magnesia*) or actonorm* or aludrox* or carbellon* or maalox* or mucaine* or mucogel*))
#15 (bisacodyl* or dantron* or danthron* or codanthramer* or co-danthrusate* or normax* or capsuvac* or (docusate adj sodium*) or (dioctyl adj sodium adj sulphosuccinate) or (fletcher* adj enemette*) or norgalax* or (norgalax* adj micro-enema*) or (sodium adj picosulfate) or dulco-lax* or (dulco-lax adj perles*) or laxoberal* or dioctyl* or docusol* or grangula* or phenolphthalein* or senna* or manevac* or senokot* or senako* or glycerol or glycerin or (glycerin adj suppositor*) or (glycerol adj suppositor*) suppositor* or (osmotic adj laxative))
#16 ((syrup adj figs) or (syrup near figs) or califig* or calsalettes* or ex-lax* or (exlax adj senna*) or fam-lax-senna* or (juno adj junipah adj salts*) or (jackson* adj herbal adj laxative) or (nylax adj senna*) or (potter* adj cleansing adj herb*) or rhuaka* or cascara))
#17 (ispagula or ispaghula or fybogel* or isogel* or ispagel* or konsyl* or regulan* or (sodium adj alginate) or sterculia* or normacol* or pancreatin or creon* or nutrizym* or pancrease* or pancrex*))
#18 (lactulose or lactitol or (magnesium adj compound*) or (magnesium adj hydroxide) or (magnesium adj sulphate) or (epsom adj salts) or (magnesium adj salt*) or (magnesium adj citrate) or (sodium adj acid adj phosphate) or (sodium adj salts) or (sodium adj citrate) or (micolette adj micro-enema*) or (micralax adj micro-enema*) or (relaxit adj micro-enema) or macrogols or idrolax* or movicol* or lactuga* or regulose* or duphalac*))
#19 ((faecal adj softener*) or (fecal adj softener*) or (liquid adj paraffin) or (arachis adj oil) or (fletcher* adj arachis adj oil adj retention adj enema*) or (phosphate adj enema*) or (fleet* adj fletcher* adj phosphate adj enema*))
#20 (bran or trifyba or (dietary adj fibre) or (dietary adj fiber) or enema* or glycerin or (polyethylene adj glycol*) or sorbitol or anthraquinone* or (bowel adj cleaning adj solution*) or citramag* or picolax* or (klean adj prep*) or sanochemia or norgine* or bulk forming or (bulk adj forming) or castranol or cellulose or glucitol or glycerol or roughage or (fruit adj juice*) or prune* or rhubarb))
#21 (#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
#22 PALLIATIVE CARE (single term MeSH)
#23 TERMINAL CARE (single term MeSH)
#24 TERMINALLY ILL (single term MeSH)
#25 HOSPICE CARE (single term MeSH)
#26 (palliat* or terminal* or advanced cancer* or hospice* or (end near life) or (care near dying) or oncolog* or (cancer adj care) or (cancer adj patient*) or (terminal adj care) or cancer*))
#27 (#22 or #23 or #24 or #25 or #26)
#28 (#10 and #21 and #27).

Update search in 2010

[mp = title, original title, abstract, name of substance word, subject heading word]
1 Palliative Care/
2 Terminal Care/
3 Terminally Ill/
4 Hospice Care/
5 (palliat* or terminal* or endstage or hospice* or (end adj3 life) or (care adj3 dying) or ((advanced or late or last or end or final) adj3 (stage* or phase*))).mp.
6 1 or 2 or 3 or 4 or 5
7 exp Cathartics/ or exp Laxatives/
8 (cathartic* or bowel evacuant or laxative* or purgative*).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
9 (methylcellulose or celevac* or cologel* or lactulose* or duphalac* or osmolax* or (magnesium adj hydroxide) or (milk adj2 magnesia*) or actonorm* or aludrox* or carbellon* or maalox* or mucaine* or mucogel*).mp.
10 (bisacodyl* or dantron* or danthron* or codanthramer* or co-danthrusate* or normax* or capsuvac* or (docusate adj2 sodium*) or (dioctyl adj2 sodium adj2 sulphosuccinate) or (fletcher* adj2 enemette*) or norgalax* or (sodium adj2 picosulfate) or dulco-lax* or perles* or laxoberal* or dioctyl* or docusol* or grangula* or phenolphthalein* or senna* or manevac* or senokot* or senako* or glycerol or glycerin or suppositor*).mp.
11 ((syrup adj3 fig*) or califig* or calsalettes* or ex-lax* or exlax or fam-lax-senna* or (juno adj2 junipah adj2 salts*) or (jackson* adj2 herb*) or (nylax adj2 senna*) or (potter* adj2 cleansing adj2 herb*) or rhuaka* or cascara).mp.
12 (ispagula or ispaghula or fybogel* or isogel* or ispagel* or konsyl* or regulan* or (sodium adj2 alginate) or sterculia* or normacol* or pancreatin* or creon* or nutrizym* or pancrease* or pancrex*).mp.
13 (lactulose or lactitol or (magnesium adj2 (salt* or compound* or hydroxide or sulphate* or citrate*)) or (epsom adj2 salt*) or (sodium adj2 acid adj2 phosphate) or (sodium adj2 (salts or citrate)) or (micolette adj2 micro-enema*) or (micralax adj2 micro-enema*) or (relaxit adj2 micro-enema*) or macrogols or idrolax* or movicol* or lactuga* or regulose* or duphalac*).mp.
14 (((faecal or fecal) adj2 softener*) or (liquid adj2 paraffin) or ((arachis adj2 oil) and fletcher*) or (phosphate adj2 enema*) or (fleet* adj2 fletcher* adj2 phosphate adj2 enema*)).mp.
15 (bran or trifyba or (dietary adj2 (fibre or fiber)) or enema* or glycerin or (polyethylene adj2 glycol*) or sorbitol or anthraquinone* or (bowel adj2 cleaning adj2 solution*) or citramag* or picolax* or (klean adj2 prep*) or sanochemia or norgine* or "bulk forming" or (bulk adj2 forming) or castranol or cellulose or glucitol or glycerol or roughage or (fruit adj2 juice*) or prune* or rhubarb).mp.
16 (Fibrelief or codanthrusate or norgalax or senna or sodium picosulfate or dulcolax or bowl cleansing or frangula or aloes or colocynth or jalap or osmotic or laxido or magnesium hydroxide or magnesium sulphate or carbalax or fleet enema or citrafleet or moviprep or fleet phospho-soda or methylnaltrexone or relistor or macrogol or peanut oil or danlax or codalax or poloxamer or manevac).mp.
17 7 or 13 or 8 or 16 or 11 or 10 or 14 or 9 or 12 or 15
18 Constipation/
19 Defecation/
20 Fecal Incontinence/
21 Feces/
22 Diarrhea/
23 Irritable Bowel Syndrome/
24 Fecal Impaction/
25 (constipat* or (hard adj3 stool*) or (bowel adj3 symptom*) or (impact* adj3 stool*) or (impact* adj3 feces) or (impact* adj3 faeces) or (fecal* adj3 incontin*) or (faecal* adj3 incontin*) or (fecal* adj3 impact*) or (faecal* adj3 impact*) or (loose adj3 stool*) or diarrh* or faeces or feces).mp.
26 (defecat* or (bowel* adj3 function*) or (bowel* adj3 habit*) or (bowel* adj3 symptom*) or (evacuat* adj3 feces) or (evacuat* adj3 faeces) or (evacuat* adj3 bowel*) or (bowel* adj3 symptom*) or (bowel adj3 movement*) or (intestin* adj3 motility) or (colon adj3 transit*) or (void* adj3 bowel*) or (strain* adj3 bowel*) or (irritable adj bowel adj syndrome)).mp.
27 23 or 20 or 24 or 26 or 19 or 25 or 18 or 21 or 22
28 27 and 6 and 17
29 randomized controlled trial.pt.
30 controlled clinical trial.pt.
31 randomized.ab.

32 placebo.ab.
33 drug therapy.fs.
34 randomly.ab.
35 trial.ab.
36 groups.ab.
37 or/29-36
38 (animals not (humans and animals)).sh.
39 37 not 38
40 39 and 28

Appendix 2. CENTRAL search August 2010

#1	MeSH descriptor Constipation, this term only	614
#2	MeSH descriptor Defecation, this term only	384
#3	MeSH descriptor Fecal Incontinence, this term only	293
#4	MeSH descriptor Feces, this term only	1690
#5	MeSH descriptor Diarrhea, this term only	1680
#6	MeSH descriptor Irritable Bowel Syndrome, this term only	224
#7	MeSH descriptor Fecal Impaction, this term only	10
#8	(constipat* or (hard near stool*) or (bowel near symptom*) or (impact* near stool*) or (impact* near feces) or (impact* near faeces) or (fecal* near incontin*) or (faecal* next incontin*) or (fecal* near impact*) or (faecal* near impact*) or (loose near stool*) or diarrh* or faeces or feces)	11963
#9	(defecat* or defaecat* or (bowel* near function*) or (bowel* near habit*) or (bowel* near symptom*) or (evacuat* near feces) or (evacuat* near faeces) or (evacuat* near bowel*) or (bowel* near symptom*) or (bowel near movement) or (intestin* next motility) or (colon* near transit*) or (void* near bowel*) or (strain* near bowel*) or (irritable next bowel next syndrome))	2725
#10	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)	13352
#11	MeSH descriptor Cathartics explode all trees	878
#12	MeSH descriptor Laxatives explode all trees	16
#13	(cathartic* or laxative* or purgative* or "bowel evacuant")	799

(*Continued*)

#14	(methylcellulose or celevac* or cologel* or lactulose* or duphalac* or osmolax* or (magnesium next hydroxide) or (milk next magnesia*) or actonorm* or alludrox* or carbellon* or maalox* or mucaine* or mucogel*)	1254
#15	(bisacodyl* or dantron* or danthron* or co-danthramer* or co-danthrusate* or normax* or capsuvac* or (docusate next sodium*) or (dioctyl next sodium next sulphosuccinate) or (fletcher* next enemette*) or norgalax* or (norgalax* next micro-enema*) or (sodium next picosulphate) or duco-lax* or (duco-lax next perles*) or laxoberal* or dioctyl* or docusol* or granqula* or phenolphthalein* or senna* or manevac* or senokot* or senoko* or glycerol or glycerin or (glycerin next suppositor*) or (glycerol next suppositor*) or suppositor* or (osmotic next laxative*))	2525
#16	(syrup near figs) or califig* or calsalettes* or ex-lax* or (exlax next senna) or fam-lax-senna* or (juno next junipah next salts*) or (jackson* next herbal next laxative) or (nylax next senna*) or (potter* next cleansing next herb*) or rhuaka* or cascara	13
#17	(ispagula or ispaghula or fybogel* or isogel* or ispagel* or konsyl* or regulan* or (sodium next alginate) or sterculia* or normacol* or pancreatin or creon* or nutrizym* or pancrease* or pancrex*)	316
#18	(lactulose* or lactitol or (magnesium next compound*) or (magnesium next hydroxide) or (magnesium next sulphate) or (epsom next salts) or (magnesium next salt*) or (magnesium next citrate) or (sodium next acid next phosphate) or (sodium next salts) or (sodium next citrate) or (micolette next micro-enema*) or (micralax next micro-enema*) or (relaxit next micro-enema) or macrogols or idrolax* or movicol* or lactuga* or regulose* or duphalac*)	2258
#19	(faecal next softener*) or (fecal next softener*) or (liquid next paraffin) or (arachis next oil) or (fletcher* next arachis next oil next retention next enema*) or (phosphate next enema*) or (fleet next fletcher* next phosphate next enema*)	89
#20	(bran or trifyba or (dietary next fibre) or (dietary next fiber) or enema* or glycerin or (polyethylene next glycol*) or sorbitol or anthraquinone* or (bowel next cleaning next solution*) or citramag* or picolax* or (klean next prep*) or sanochemia or norgine* or (bulk next forming) or castranol or cellulose or glucitol or glycerol or roughage or (fruit next juice*) or prune* or rhubarb)	5983

(*Continued*)

#21	Fibrelief or codanthrusate or norgalax or senna or sodium picosulfate or dulcolax or bowl cleansing or frangula or aloes or colocynth or jalap or osmotic or laxido or magnesium hydroxide or magnesium sulphate or carbalax or fleet enema or citrafleet or moviprep or fleet phospho-soda or methylnaltrexone or relistor or macrogol or peanut oil or danlax or codalax or poloxamer or manevac or Targinact or naloxone	3839
#22	(#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21)	12386
#23	MeSH descriptor Palliative Care, this term only	1175
#24	MeSH descriptor Terminal Care, this term only	211
#25	MeSH descriptor Terminally Ill, this term only	57
#26	MeSH descriptor Hospice Care, this term only	82
#27	(palliat* or carboxy-terminal* or terminal* or oncolog* or cancer* or (advanced next cancer*) or hospice* or (end near life) or (care near dying))	67932
#28	(#23 OR #24 OR #25 OR #26 OR #27)	67932
#29	(#10 AND #22 AND #28)	211
#30	(#29), from 1800 to 2004	137
#31	(#29 AND NOT #30)	74

FEEDBACK

Feedback

Summary

After reviewing the Cochrane review (1), our group feels it is important to highlight a few issues around the use of methylnaltrexone for the management of constipation in palliative care patients. Some of the comments are made specified to the original trials by Thomas et al. and Slatkin et al. (2, 3)

1) Factors that could affect overall beneficial treatment effect due to differences at baseline between treatment groups

Although it was noted that the two groups were well balanced at baseline in Thomas 2008, a few parameters were not balanced. For example:

- The median dose of opioid was greater, though not statistically significant, in the placebo group (100 mg [10 to 10,160 mg]) compared to methlynaltrexone group (150mg [9-4160mg]), that would give an advantage to the methylnaltrexone arm because it could of lead to more treatment resistant constipation in the placebo group.

- Another baseline difference was the primary diagnosis. 20% of patients in the placebo group had "other" as their primary diagnosis compared to 8% in the methylnaltrexone arm. "Other" included diagnosis such as "failure to thrive, amyotrophic lateral sclerosis, end-stage multiple sclerosis, malabsorption syndrome, pernicious anemia, rheumatoid arthritis, Buerger's disease, cerebral vascular accident, idiopathic pulmonary fibrosis, peripheral vascular disease, diabetes mellitus, hypoxic brain injury, multiple systems failure, chronic pain or multiple fractures, and end-stage Parkinson's disease." Most of these "other" diagnosis may further reduce patients' mobility and oral intake leading to treatment resistant constipation. A 12% increase in such diagnosis in the placebo group favours treatment advantage in the methylnaltrexone arm.

Implication - It is possible that these issues can affect the overall treatment effect; however, it would be difficult to assess whether it was overestimated or underestimated.

2) Questionable dosing regimen

In the study by Thomas 2008, the study investigator decided to study regular dosing of methylnaltrexone (at a dose of 0.15mg per kilogram of body weight) or an equal volume of placebo administered subcutaneously on alternate days for 2 weeks even after patient had a regular bowel movement. "Would this **questionable dosing regimen** be followed in regular clinical practice? Would these patients be subjected to unnecessary adverse effects? Of note, both FDA and Health Canada have recently issued warning on rare cases of gastrointestinal perforation with the use of methylnaltrexone. (4, 5)

Implication - Once effective, is there a need to continue regular dosing?

3) Questionable place of therapy

It seems as though the placebo group in Thomas 2008 was at a disadvantage from the start. Patients were constipated on their laxative regimens prior to randomization and were randomized to receive those same regimens plus placebo. A better clinical question would be to compare the effect of methylnaltrexone against other bowel agents. For example: in certain jurisdictions, a step-wise approach to bowel care is utilized with enema or digital disimpaction being the final step. This might have been a better comparator intervention.

Implication - Methylnaltrexone place in therapy is unknown

4) Questionable primary outcome

- Both studies (Thomas 2008 and Slatkin 2009) used the primary endpoint as laxation within 4 hours after first dose of methylnaltrexone. In patients who had "fewer than three laxations during the preceding week." would laxation within 12 hours be a reasonable outcome parameter? The 4 hour cutoff point is arbritary and it seems like the focus of both trials were looking at the speed of laxation instead of whether or not patients had bowel movements. This primary outcome is problematic because it would not include bowel movements that occurred after 4 hours. However, this data might be captured in the "rescue free laxation within 24 hours". Data for this outcome is only reported as percentages for laxations within 24 hours instead of numerical values. The FDA analysis reported details for number of laxations within 24 hours of the first dose but not for subsequent doses) (6)
- It is important to note that there were no statistically significant differences between methylnaltrexone and placebo in the use of rescue therapies, enemas or disimpaction despite the statistical significance (for laxation within 4 hours) of methylnaltrexone. The incidence of weekly bowel movements was also similar in the methylnaltexone and placebo group during the second week of Thomas et al's study. A better way of looking at this would be to count all bowel movements then break it down by time and then compared whether it is rescue free laxation or not.
- Based on the pharmacokinetic parameter differences it is almost certain that methylnaltrexone would be superior to other laxatives within the 4 hour window. However, the clinical relevance question mentioned above still remains therefore we feel better outcome may have been to assess what is normal bowel frequency in these patients and see how many of them returned to normal bowel frequency.
- Camilleri et al conducted a phase 3, placebo-controlled trial that looked at the efficacy, safety, and effect on quality of life of prucalopride in patients with severe chronic constipation. In this study, their primary efficacy end points were proportion of patients having three or more spontaneous, complete bowel movements per week, averaged over 12 weeks. Future studies can consider adopting these primary endpoints instead of laxation within 4 hours. (7)

Implication - Clinical relevancy of primary outcome is questionable.

5) Missing data and **questionable data collection**

It appears data for 6 people are missing from Figure 2 Panel B compared to the number of patients randomized in the study by Thomas 2008. In figure 1, 104 patients (52 in methylnaltrexone group an 54 in placebo group) completed the study; however, only 98 patients (47 in methylnaltrexone group and 51 in placebo group) can be accounted for in Figure 2 Panel B's Day 13 results. We are not sure what happened to these 6 patients.

Also from Figure 2 Panel B, the numbers of patients responding on days between doses are missing. The data for patients who had bowel movement between doses, is not shown.

Implication - Difficult to assess methylnaltrexone true effect without knowledge of the missing data and data collection process.

6) Interpretation of drugs beneficial effect problematic

Both studies (Thomas 2008 and Slatkin 2009) allowed patients to continue their baseline laxative regimen throughout the study and take rescue laxatives as needed, though not within 4 hours before or after receiving a dose of the study drug. Here is a scenario - If a patient was given senna 5 hours prior to the study drug and patient had a bowel movement 1 hour after methylnaltrexone, it would be difficult to assess whether it is due to senna or methylnaltrexone. More importantly, both studies did not report the number of patients who received rescue laxatives.

Implication - Difficult to assess whether patients who had bowel movements were due to methylnaltrexone or baseline laxative regimen.

7) Impact on quality of life - not assessed

Quality of life was not assessed in either study - This is especially important given the patient population that would be on methylnaltrexone. It would be interesting to see whether methylnaltrexone has an impact on patients' quality of life. Another way of looking is that methylnaltrexone rapidly induced laxation compared to other laxatives but does this speed translate to an improved quality of life.

Implication - Quality of life data is unknown.

8) Inclusion criteria - clinical practice implication

Study population included many patients who did not report severe constipation at baseline and whose background regimens were not optimized. About one-third of patients in the trials were receiving only one class of laxative at baseline. In addition, the median number of laxative drugs classes used was only 2.

Implication - Methylnaltrexone place in therapy is unknown.

9) Length of study

One study (Slatkin 2009) was a single dose trial while the other study (Thomas 2008) was only 2 weeks in duration. It would be interesting to see a trial with longer follow up period in order to assess long-term effects of methylnaltrexone.

Implication - Long term efficacy and safety data are unknown.

References:

1. Candy B, Jones L, Goodman ML, Drake R, Tookman A. Laxatives or methylnaltrexone for the management of constipation in palliative care patients. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD003448. DOI: 10.1002/14651858.CD003448.pub3.
2. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med 2008;358:2332-2343. [18509120]
3. Slatkin N, Thomas J, Lipman AG, Wilson G, Boatwright ML, Wellman C, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. Journal of Supportive Oncology 2009;7:39-46.
4. Safety Information. (2010). Relistor (methylnaltrexone bromide) subcutaneous injections. Retrieved from http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm221639.htm
5. Drug and Health Products. (2010). Health Canada Endorsed Important Safety Information on RELISTOR® (methylnaltrexone bromide). Retrieved from http://www.hc-sc.gc.ca/dhp-mps/alt˙formats/pdf/medeff/advisories-avis/prof/2010/relistor˙hpc-cps-eng.pdf
6. Drug Approval Package. (2008). Relistor (Methylnaltrexone Bromide) Subcutaneous Injection Medical Review. Retrieved from http://www.accessdata.fda.gov/drugsatfda˙docs/nda/2008/021964s000TOC.cfm
7. Camilleri M, Kerstens R, Vandeplassche L. A Placebo-Controlled Trial of Prucalopride for Severe Chronic Constipation. N Engl J Med 2008; 358:2344-54.

Reply

1) Factors that could affect overall beneficial treatment effect due to differences at baseline between treatment groups

Implication - It is possible that these issues can affect the overall treatment effect; however, it would be difficult to assess whether it was overestimated or underestimated.

Our response: Yes it is difficult to assess the effect of these differences, but as the trial authors state these were not statistically significant. We conclude in review that further larger, independent trials are needed.

2) Questionable dosing regimen

Implication - Once effective, is there a need to continue regular dosing?

Our response: Dosing regimes in clinical studies and those used in the clinical setting may differ. We did not highlight this in the review, but we will in future updates. We state in our conclusions that the drug has not been fully evaluated on safety.

3) Questionable place of therapy

Implication - Methylnaltrexone place in therapy is unknown.

Our response: Yes none of the studies compared methylaltrexone with an alternative pharmacological regimen. Therefore, the efficacy or safety of these compounds relative to other interventions is unknown. This we noted in the discussion section.

4) Questionable primary outcome

Implication - Clinical relevancy of primary outcome is questionable.

Our response: We agree that the longterm effect of methylnaltrexone has not been established and this is one of our review recommendations.

There is no gold standard in assessing the effects of laxatives. It is acknowledged that other authors use alternative endpoints.

5) Missing data and **questionable data collection**

Implication - Difficult to assess methylnaltrexone true effect without knowledge of the missing data and data collection process.

Our response: Yes the trialist do not provide information on why there is missing data on 6 patients at day 13. However, we did not use this data in our meta-analysis.

6) Interpretation of drugs beneficial effect problematic

Implication - Difficult to assess whether patients who had bowel movements were due to methylnaltrexone or baseline laxative regimen.

Our response: We agree that it is difficult to assess whether patients had bowel movements due to methylnaltrexone or baseline laxative regimen. However methynaltrexone is used as an adjuvant when response to laxatives has been insufficient. It is not used as an alternative to regular laxatives.

We call for further trials, and we highlight through the review use of rescue laxatives in trial participants. We note that neither study reports the number of patients who received rescue laxatives.

7) Impact on quality of life - not assessed

Implication - Quality of life data is unknown.

Our response: We agree it is unknown the impact on quality of life. We did not highlight this in our review, but if further trials do not evaluate quality of life we will discuss this in future updates of this review.

8) Inclusion criteria - clinical practice implication

Implication - Methylnaltrexone place in therapy is unknown.

Our response: The review evaluated whether trials demonstrated an effect of methynaltrexone as an adjunctive laxative in patients with opioid induced constipation. We think that the trials demonstrate an effect.

Each medical unit has it's own individual preferences on optimal laxative prescribing. As a consequence the choice of drug and dosing schedule is dependant on individual preferences. Further research needs to be done to explore the drugs place in therapy.

9) Length of study

Implication - Long term efficacy and safety data are unknown.

Our response: Yes we call for this too.

Contributors

Bridget Candy (author), Kate Seers (Feedback Editor), Aaron Tejani and Damen Man (Feedback comments).

WHAT'S NEW

Last assessed as up-to-date: 5 December 2010.

Date	Event	Description
6 July 2011	Amended	Amendment to contributors of Feedback submitted for Issue 6, 2011
11 May 2011	Feedback has been incorporated	Feedback was received and the author has responded. Please see the Feedback section in the review for details

HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 4, 2006

Date	Event	Description
6 December 2010	New citation required and conclusions have changed	The background and methods were updated, three new studies were added to the review (Portenoy 2008; Slatkin 2009; Thomas 2008), and the conclusions were revised to include Methylnaltrexone. The review was updated by a new set of authors
20 August 2010	New search has been performed	Search updated to August 2010.
30 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

MG, SW and DF developed the original protocol. CM, MG and DF refined and ran the searches, reviewed papers, extracted data and wrote the report. SW reviewed papers and contributed to the report. BC will be responsible for any future update of this review.

In the 2010 review update BC and LJ independently assessed eligibility of studies in new searches. Data extraction undertaken by BC and checked by LJ. Statistical support provided by RD. Updating of all review sections undertaken by BC and checked by other members of the review update team (LJ, RD, AT and MG).

DECLARATIONS OF INTEREST

Janssen-Cilag has funded a Marie Curie Cancer Care study of the management of constipation in palliative care. Part of the remit of this study included a systematic review of the use of laxatives in the management of constipation for patients receiving palliative care. Janssen-Cilag do not manufacture or promote laxatives.

SOURCES OF SUPPORT

Internal sources

- Marie Curie Cancer Care, UK.

External sources

- Janssen-Cilag Ltd UK in original review (but not for the 2010 review update), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences by section between the original review and the 2010 update:

- Background: reordered, references updated and now includes some discussion on opioid antagonists.
- Inclusion criteria: no longer excludes opioid antagonists.
- Methods: now includes details on analysis and current methods of risk of bias assessment.
- Results: includes analysis of three new studies and more detail on previous studies.
- Discussion: conclusions changed in light of findings from new studies.

INDEX TERMS

Medical Subject Headings (MeSH)

*Palliative Care; Analgesics, Opioid [adverse effects]; Anthraquinones [therapeutic use]; Cathartics [adverse effects; *therapeutic use]; Constipation [chemically induced; *drug therapy]; Lactulose [therapeutic use]; Magnesium Hydroxide [therapeutic use]; Naltrexone [adverse effects; *analogs & derivatives; therapeutic use]; Paraffin [therapeutic use]; Quaternary Ammonium Compounds [adverse effects; therapeutic use]; Randomized Controlled Trials as Topic; Senna Extract [therapeutic use]

MeSH check words

Humans