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Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care (Review)

Candy B, Jones L, Vickerstaff V, Larkin PJ, Stone P

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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 14
OBJECTIVES 15
METHODS 15
RESULTS 19
Figure 1. 20
Figure 2. 22
Figure 3. 23
DISCUSSION 31
AUTHORS' CONCLUSIONS 32
ACKNOWLEDGEMENTS 34
REFERENCES 35
CHARACTERISTICS OF STUDIES 39
DATA AND ANALYSES 57
Analysis 1.1. Comparison 1: Naldemedine versus placebo, Outcome 1: Sponaneous rescue-free bowel movements: Medium term 58
Analysis 1.2. Comparison 1: Naldemedine versus placebo, Outcome 2: Symptoms of opioid withdrawal: Medium term, naldemedine 0.1 mg 58
Analysis 1.3. Comparison 1: Naldemedine versus placebo, Outcome 3: Symptoms of opioid withdrawal: Medium term, naldemedine 0.2 mg 58
Analysis 1.4. Comparison 1: Naldemedine versus placebo, Outcome 4: Symptoms of opioid withdrawal: Medium term, naldemedine 0.4 mg 58
Analysis 1.5. Comparison 1: Naldemedine versus placebo, Outcome 5: Serious adverse events 59
Analysis 1.6. Comparison 1: Naldemedine versus placebo, Outcome 6: Adverse events 59
Analysis 1.7. Comparison 1: Naldemedine versus placebo, Outcome 7: Proportion experiencing diarrhoea 59
Analysis 1.8. Comparison 1: Naldemedine versus placebo, Outcome 8: Proportion who dropped out due to adverse events 60
Analysis 2.1. Comparison 2: Naldemedine dose, Outcome 1: Spontaneous rescue-free bowel movements: Medium term, naldemedine 0.1 mg versus 0.4mg 61
Analysis 2.2. Comparison 2: Naldemedine dose, Outcome 2: Spontaneous rescue-free bowel movements: Medium term, naldemedine 0.1 mg versus 0.2mg naldemedine 61
Analysis 2.3. Comparison 2: Naldemedine dose, Outcome 3: Spontaneous rescue-free bowel movements: Medium term, naldemedine 0.2 mg versus naldemedine 0.4 mg 62
Analysis 2.4. Comparison 2: Naldemedine dose, Outcome 4: Symptoms of opioid withdrawal: Medium term, naldemedine 0.1 mg versus naldemedine 0.4 mg 62
Analysis 2.5. Comparison 2: Naldemedine dose, Outcome 5: Symptoms of opioid withdrawal: Medium term, naldemedine 0.1 mg versus naldemedine 0.2 mg 62
Analysis 2.6. Comparison 2: Naldemedine dose, Outcome 6: Symptoms of opioid withdrawal: Medium term, naldemedine 0.2 mg versus naldemedine 0.4 mg 62
Analysis 2.7. Comparison 2: Naldemedine dose, Outcome 7: Adverse events: naldemedine 0.1 mg versus naldemedine 0.4 mg . 63
Analysis 2.8. Comparison 2: Naldemedine dose, Outcome 8: Adverse events: naldemedine 0.1 mg versus naldemedine 0.2 mg . 63
Analysis 2.9. Comparison 2: Naldemedine dose, Outcome 9: Adverse events: naldemedine 0.2 mg versus naldemedine 0.4 mg . 63
Analysis 2.10. Comparison 2: Naldemedine dose, Outcome 10: Serious adverse events 64
Analysis 2.11. Comparison 2: Naldemedine dose, Outcome 11: Diarrhoea: naldemedine 0.1 mg versus naldemedine 0.4 mg ... 64
Analysis 2.12. Comparison 2: Naldemedine dose, Outcome 12: Diarrhoea: naldemedine 0.1 mg versus naldemedine 0.2 mg ... 64
Analysis 2.13. Comparison 2: Naldemedine dose, Outcome 13: Diarrhoea: naldemedine 0.2 mg versus naldemedine 0.4 mg ... 65
Analysis 2.14. Comparison 2: Naldemedine dose, Outcome 14: Proportion who dropped out due to adverse events: naldemedine 0.1 mg versus naldemedine 0.4 mg 65
Analysis 2.15. Comparison 2: Naldemedine dose, Outcome 15: Proportion who dropped out due to adverse events: naldemedine 0.1 mg versus naldemedine 0.2 mg 65
Analysis 2.16. Comparison 2: Naldemedine dose, Outcome 16: Proportion who dropped out due to adverse events: naldemedine 0.2 mg versus naldemedine 0.4 mg 66

Analysis 3.1. Comparison 3: Naloxone/oxycodone prolonged-release tablets versus oxycodone prolonged-release: adverse event, Outcome 1: Symptoms of opioid withdrawal: medium term 66
Analysis 3.2. Comparison 3: Naloxone/oxycodone prolonged-release tablets versus oxycodone prolonged-release: adverse event, Outcome 2: Serious adverse events 67
Analysis 3.3. Comparison 3: Naloxone/oxycodone prolonged-release tablets versus oxycodone prolonged-release: adverse event, Outcome 3: Adverse events 67
Analysis 3.4. Comparison 3: Naloxone/oxycodone prolonged-release tablets versus oxycodone prolonged-release: adverse event, Outcome 4: Nausea 67
Analysis 3.5. Comparison 3: Naloxone/oxycodone prolonged-release tablets versus oxycodone prolonged-release: adverse event, Outcome 5: Proportion who dropped out due to adverse events 68
Analysis 3.6. Comparison 3: Naloxone/oxycodone prolonged-release tablets versus oxycodone prolonged-release: adverse event, Outcome 6: Use of laxative rescue medication 68
Analysis 3.7. Comparison 3: Naloxone/oxycodone prolonged-release tablets versus oxycodone prolonged-release: adverse event, Outcome 7: Quality of life 68
Analysis 4.1. Comparison 4: Methylnaltrexone versus placebo, Outcome 1: Spontaneous rescue-free bowel movements: short term 70
Analysis 4.2. Comparison 4: Methylnaltrexone versus placebo, Outcome 2: Spontaneous rescue-free bowel movements: medium term 70
Analysis 4.3. Comparison 4: Methylnaltrexone versus placebo, Outcome 3: Patient reported improvement in bowel status: medium term 70
Analysis 4.4. Comparison 4: Methylnaltrexone versus placebo, Outcome 4: Opioid withdrawal symptoms: short term 71
Analysis 4.5. Comparison 4: Methylnaltrexone versus placebo, Outcome 5: Opioid withdrawal symptoms: mean change short term, lower dose (0.15 mg/kg) methylnaltrexone 71
Analysis 4.6. Comparison 4: Methylnaltrexone versus placebo, Outcome 6: Opioid withdrawal symptoms: mean change short term, higher dose (0.30 mg/kg) methylnaltrexone 71
Analysis 4.7. Comparison 4: Methylnaltrexone versus placebo, Outcome 7: Opioid withdrawal symptoms: medium term 71
Analysis 4.8. Comparison 4: Methylnaltrexone versus placebo, Outcome 8: Opioid withdrawal symptoms: mean change medium term, lower dose (0.15 mg/kg) methylnaltrexone 72
Analysis 4.9. Comparison 4: Methylnaltrexone versus placebo, Outcome 9: Opioid withdrawal symptoms: mean change medium term, lower dose (0.3 mg/kg) methylnaltrexone 72
Analysis 4.10. Comparison 4: Methylnaltrexone versus placebo, Outcome 10: Pain intensity: short term 72
Analysis 4.11. Comparison 4: Methylnaltrexone versus placebo, Outcome 11: Pain intensity: Medium term 72
Analysis 4.12. Comparison 4: Methylnaltrexone versus placebo, Outcome 12: Serious adverse event 73
Analysis 4.13. Comparison 4: Methylnaltrexone versus placebo, Outcome 13: Adverse events 73
Analysis 4.14. Comparison 4: Methylnaltrexone versus placebo, Outcome 14: Abdominal pain 73
Analysis 4.15. Comparison 4: Methylnaltrexone versus placebo, Outcome 15: Flatulence 74
Analysis 4.16. Comparison 4: Methylnaltrexone versus placebo, Outcome 16: Vomiting 74
Analysis 4.17. Comparison 4: Methylnaltrexone versus placebo, Outcome 17: Nausea 74
Analysis 4.18. Comparison 4: Methylnaltrexone versus placebo, Outcome 18: Dropouts due to adverse event 75
Analysis 4.19. Comparison 4: Methylnaltrexone versus placebo, Outcome 19: Use of resuce medication 75
Analysis 5.1. Comparison 5: Methylnaltrexone dose, Outcome 1: Spontaneous rescue-free bowel movements: short term 76
Analysis 5.2. Comparison 5: Methylnaltrexone dose, Outcome 2: Spontaneous rescue-free bowel movements: medium term 76
Analysis 5.3. Comparison 5: Methylnaltrexone dose, Outcome 3: Patient reported improvement in bowel status: short term 76
Analysis 5.4. Comparison 5: Methylnaltrexone dose, Outcome 4: Opioid withdrawal symptoms: short term 76
Analysis 5.5. Comparison 5: Methylnaltrexone dose, Outcome 5: Opioid withdrawal symptoms: medium term 77
Analysis 5.6. Comparison 5: Methylnaltrexone dose, Outcome 6: Adverse event 77
APPENDICES 77
FEEDBACK 84
WHAT'S NEW 87
HISTORY 87
CONTRIBUTIONS OF AUTHORS 88
DECLARATIONS OF INTEREST 88
SOURCES OF SUPPORT 88
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 89

INDEX TERMS 89

[Intervention Review]

Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care

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ABSTRACT

Background

Opioid-induced bowel dysfunction (OIBD) is characterised by constipation, incomplete evacuation, bloating, and gastric reflux. It is one of the major adverse events (AEs) of treatment for pain in cancer and palliative care, resulting in increased morbidity and reduced quality of life.

This review is a partial update of a 2008 review, and critiques as previous update (2018) trials only for people with cancer and people receiving palliative care.

Objectives

To assess for OIBD in people with cancer and people receiving palliative care the effectiveness and safety of mu-opioid antagonists (MOAs) versus different doses of MOAs, alternative pharmacological/non-pharmacological interventions, placebo, or no treatment.

Search methods

We searched CENTRAL, MEDLINE, Embase, CINAHL, and Web of Science (December 2021), clinical trial registries and regulatory websites. We sought contact with MOA manufacturers for further data.

Selection criteria

Randomised controlled trials (RCTs) assessing the effectiveness and safety of MOAs for OIBD in people with cancer and people at a palliative stage irrespective of the type of terminal disease.

Data collection and analysis

Two review authors assessed risk of bias and extracted data. The appropriateness of combining data from the trials depended upon sufficient homogeneity across trials. Our primary outcomes were laxation response, effect on analgesia, and AEs. We assessed the certainty of evidence using GRADE and created summary of findings tables.

Main results

We included 10 studies (two new trials) randomising in-total 1343 adults with cancer irrespective of stage, or at palliative care stage of any disease. The MOAs were oral naldemedine and naloxone (alone or in combination with oxycodone), and subcutaneous methylnaltrexone. The trials compared MOAs with placebo, MOAs at different doses, or in combination with other drugs. Two trials of naldemedine and three of naloxone with oxycodone were in people with cancer irrespective of disease stage. The trial on naloxone alone was in people with advanced cancer. Four trials on methylnaltrexone were in palliative care where most participants had advanced cancer. All trials were vulnerable to biases; most commonly, blinding of the outcome assessor was not reported.

Oral naldemedine versus placebo

Risk (i.e. chance) of spontaneous laxations in the medium term (over two weeks) for naldemedine was over threefold greater risk ratio (RR) 2.00, 95% confidence interval (CI) 1.59 to 2.52, 2 trials, 418 participants, I^2 = 0%. Number needed to treat for an additional beneficial outcome (NNTB) 3, 95% CI 3 to 4; moderate-certainty evidence). Earlier risk of spontaneous laxations and patient assessment of bowel change was not reported. Very low-certainty evidence showed naldemedine had little to no effect on opioid withdrawal symptoms. There was little to no difference in the risk of serious (non-fatal) AEs (RR 3.34, 95% CI 0.85 to 13.15: low-certainty evidence). Over double the risk of AEs (non-serious) reported with naldemedine (moderate-certainty evidence).

Low-dose oral naldemedine versus higher dose

Risk of spontaneous laxations was lower for the lower dose (medium term, 0.1 mg versus 0.4 mg: RR 0.69, 95% CI 0.53 to 0.89, 1 trial, 111 participants (low-certainty evidence)). Earlier risk of spontaneous laxations and patient assessment of bowel change not reported. Low-certainty evidence showed little to no difference on opioid withdrawal symptoms (0.1 mg versus 0.4 mg mean difference (MD) -0.30, 95% CI -0.85 to 0.25), and occurrences of serious AEs (0.1 mg versus 0.4 mg RR 0.25, 95% CI 0.03 to 2.17). Low-certainty evidence showed little to no difference on non-serious AEs.

Oral naloxone versus placebo

Risk of spontaneous laxations and AEs not reported. Little to no difference in pain intensity (very low-certainty evidence). Full data not given. The trial reported that no serious AEs occurred.

Oral naloxone + oxycodone versus oxycodone

Risk of spontaneous laxations within 24 hours and in the medium term not reported. Low-certainty evidence showed naloxone with oxycodone reduced the risk of opioid withdrawal symptoms. There was little to no difference in the risk of serious (non-fatal) AEs (RR 0.68, 95% CI 0.44 to 1.06), 3 trials, 362 participants, I^2 = 55%: very low-certainty evidence). There was little to no difference in risk of AEs (low-certainty evidence).

Subcutaneous methylnaltrexone versus placebo

Risk of spontaneous laxations within 24 hours with methylnaltrexone was fourfold greater than placebo (RR 2.97, 95% CI 2.13 to 4.13. 2 trials, 287 participants, I^2 = 31%. NNTB 3, 95% CI 2 to 3; low-certainty evidence). Risk of spontaneous laxations in the medium term was over tenfold greater with methylnaltrexone (RR 8.15, 95% CI 4.76 to 13.95, 2 trials, 305 participants, I^2 = 47%. NNTB 2, 95% CI 2 to 2; moderate-certainty evidence). Low-certainty evidence showed methylnaltrexone reduced the risk of opioid withdrawal symptoms, and did not increase risk of a serious AE (RR 0.59, 95% CI 0.38 to 0.93. I^2 = 0%; 2 trials, 364 participants). The risk of AEs was higher for methylnaltrexone (low-certainty evidence).

Lower-dose subcutaneous methylnaltrexone versus higher dose

There was little to no difference in risk of spontaneous laxations in the medium-term (1 mg versus 5 mg or greater: RR 2.91, 95% CI 0.82 to 10.39; 1 trial, 26 participants very low-certainty evidence), or in patient assessment of improvement in bowel status (RR 0.98, 95% CI 0.71 to 1.35, 1 trial, 102 participants; low-certainty evidence). Medium-term assessment of spontaneous laxations and serious AEs not reported. There was little to no difference in symptoms of opioid withdrawal (MD -0.25, 95% CI -0.84 to 0.34, 1 trial, 102 participants) or occurrence of AEs (low-certainty evidence).

Authors' conclusions

This update's findings for naldemedine and naloxone with oxycodone have been strengthened with two new trials, but conclusions have not changed. Moderate-certainty evidence for oral naldemedine on risk of spontaneous laxations and non-serious AEs suggests in people with cancer that naldemedine may improve bowel function over two weeks and increase the risk of AEs. There was low-certainty evidence on serious AEs. Moderate-certainty evidence for methylnaltrexone on spontaneous laxations over two weeks suggests subcutaneous methylnaltrexone may improve bowel function in people receiving palliative care, but certainty of evidence for AEs was low. More trials are needed, more evaluation of AEs, outcomes patients rate as important, and in children.

PLAIN LANGUAGE SUMMARY

Mu-opioid antagonists for bowel dysfunction due to opioids in people with cancer and people receiving palliative care

Background

Opioids (morphine-like drugs) are used to treat severe pain, but they may cause bowel dysfunction including constipation, incomplete evacuation of the bowels, bloating, and increased reflux (flowing back) of stomach contents into the oesophagus (food pipe). This is because receptors for opioids are found in the gut. Opioid-induced bowel dysfunction may be so severe that people choose to limit pain relief to improve bowel function. Opioid-induced bowel dysfunction is common in people with cancer and those receiving palliative care (when a cure is no longer possible). Laxatives are often the first-choice treatment for opioid-induced bowel dysfunction. They may not always work. Mu-opioid antagonists are specific medicines for opioid-induced bowel dysfunction that have been developed to help reduce the effect of opioids (in the gut. A possible side effect of this treatment however, is reduced pain relief.

Trial characteristics

The aim of this updated review was to determine what we know about the effectiveness and safety of mu-opioid antagonists (MOABs) for the management of opioid-induced bowel dysfunction in people with cancer or receiving palliative care. We only included randomised controlled trials as they provide the most reliable evidence. Randomised controlled trials are a type of study where people are randomly assorted into groups to test interventions, treatments, or drugs. It means that an individual has the same chance of having each intervention, treatment or drug.

We found trials that evaluated the mu-opioid antagonists naldemedine, methylnaltrexone, and naloxone. The trial comparison groups could be a placebo (a substance with no known active effect), usual care, the mu-opioid antagonist at different dose, or in combination with other drugs or another treatment such as a different mu-opioid antagonist.

Key results

Our search to 20th December 2021 found 10 trials involving 1343 adults. The mu-opioid antagonists evaluated in people with cancer were oral naldemedine and naloxone taken in combination with an opioid treatment (for pain). The other mu-opioid antaGonist evaluated in the trials was methylnaltrexone. It was given by injection and evaluated in palliative care where most participants had advanced cancer.

Naldemedine or methylnaltrexone were compared with placebo. Naloxone was compared with a placebo or opioid treatment only.

The overall confidence as in certainty we have in the evidence is very low to moderate (very uncertain to somewhat certain). There were problems with the design of studies, including under-reporting of trial methods.

Bowel movements

Within two weeks of treatment of naldemedine or methylnaltrexone bowel movement probably increases (moderate/somewhat certain evidence); trials did not measure the effects of naloxone within two weeks. There was low (uncertain evidence) confidence that patients found naloxone taken with an opioid treatment and methylnaltrexone improved their symptoms of constipation. Trials of naldemedine did not measure patients assessment of improvement in symptoms of constipation.

Pain relief

There was low confidence in the evidence that there was no impact from naloxone in combination with an opioid or from methylnaltrexone on the treatment relief from pain. There was low (uncertain) confidence in the evidence naldemedine did not change treatment relief from pain.

Risk of serious side effects (e.g. hospitalisation, life-threatening, or fatal) and other side effects

There was low (uncertain) confidence that naldemedine or methylnaltrexone did not cause an increase in the risk of serious side effects. There was low confidence in the evidence that naloxone in combination with an opioid did not increase the risk of serious side effects (adverse reaction).

Naldemedine probably did not increase the risk of other non-serious side effects (moderate certainty/somewhat certain evidence). There was low confidence in the evidence that naloxone taken with opioid treatment did not cause an increase in the risk of a side effect. For methylnaltrexone there was low confidence in the evidence that it did not increase the risk of a side effect.

Conclusion

There was moderate-certainty evidence that naldemedine taken orally improved bowel function within two weeks in adults with cancer and opioid-induced bowel dysfunction but increased the risk of side effects, and that methylnaltrexone taken as an injection improved bowel function over two weeks in people receiving palliative care. The results of this review need to be interpreted with caution as they were not obtained from evidence that was of high-certainty. Outcome evaluations were limited, in particular not all TRIALS measured patient assessment of improvement in bowel movements. There were no studies in children.

SUMMARY OF FINDINGS

Summary of findings 1. Naldemedine compared to placebo for opioid-induced bowel dysfunction in people with cancer irrespective of whether they were receiving palliative care

Naldemedine compared to placebo for opioid-induced bowel dysfunction for people with cancer

Patient or population: people with cancer irrespective of whether receiving palliative care and with opioid-induced bowel dysfunction

Settings: not stated

Intervention: naldemedine

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Naldemedine				
Laxation response: risk of spontaneous rescue-free bowel movements[a] in the short term[b]	—	—	—	—	—	Not reported
Laxation response: risk of spontaneous rescue-free bowel movements[a] in the medium term[c]	355 per 1000	**718 per 1000**	**RR 2.00** (1.59 to 2.52) **NNTB** 3 (3 to 4)	418 (2 studies)	⊕⊕⊕⊝ **Moderate**[d]	
Laxation response: patient assessment of change in bowel status at the end of trial	—	—	—	—	—	Not reported
Symptoms of opioid withdrawal[e] in the medium term[c]	Mean change in opioid withdrawal was 0.0	Mean change in opioid withdrawal was 0.1 **lower** 0.1 mg; 0.3 **higher** 0.2 mg, 0.2 **higher** 0.4 mg	Naldemedine 0.1 mg: **MD -0.10** (-0.56 to 0.36); naldemedine 0.2 mg: **MD 0.30** (-0.21 to 0.81); naldemedine 0.4 mg: **MD 0.20** (-0.36 to 0.76)[d]	112 in comparison with naldemedine 0.1 mg and 0.4 mg, 114 in comparison with 0.2mg (1 study)	⊕⊝⊝⊝ **Very low**[f,g]	

Serious adverse events[h]	13 per 1000	**41 per 1000**	**RR 3.34** (0.85 to 13.15)	418 (2 studies)	⊕⊕⊝⊝ **Low**[d,i]
Adverse events	355 per 1000	**613 per 1000**	**RR 1.49** (1.19 to 1.87)	418 (2 studies)	⊕⊕⊕⊝ **Moderate**[d]

*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).

RR: risk ratio; **NNTB:** number needed to treat for an additional beneficial outcome; **MD**: mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Defined in both trials as having 3 or more laxations (not induced by rescue medication) a week/who had an increase of one of more laxations (not induced by rescue medication) a week from baseline
[b] Within first 24 hours
[c] Over two weeks
[d] Downgraded by one level for serious study limitations because of high risk of attrition bias in one study
e Measured by the Clinical Opioid Withdrawal Scale. Lower scores indicate symptoms of lower severity. Score of 5-12 mild, 13-24 moderate, 25-36 moderately severe, more than 36 severe withdrawal. Maximum score 48.
[f] Downgraded by two levels for very serious study limitations because all of the data were derived from only one study with a high risk of attrition bias
[g] Downgraded by one level for serious imprecision as data were derived from fewer than 400 participants
[h] Serious non-fatal events were reported, definition of what fits this criteria was not provided
[i] Downgraded by one level for serious imprecision due to wide confidence intervals

Summary of findings 2. Low dose naldemedine compared to higher doses for opioid-induced bowel dysfunction in people with cancer irrespective of whether they were receiving palliative care

Low dose naldemedine compared to higher-dose for opioid-induced bowel dysfunction for people with cancer

Patient or population: people with cancer irrespective of whether they are receiving palliative care and with opioid-induced bowel dysfunction

Setting: not stated

Intervention: Naldemedine 0.1 mg daily

Comparison: Naldemedine 0.4 mg daily

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Higher dose 0.4 mg daily	Lower dose 0.1 mg daily				
Laxation response: risk of spontaneous rescue-free bowel movements in the short term[a]	—	—	—	—	—	Not reported
Laxation response: risk of spontaneous rescue-free bowel movements in the medium term[b,c]	821 per 1000	**564 per 1000**	**RR 0.69** (0.53 to 0.89)	111 (1 study)	⊕⊕⊝⊝ **Low**[d,e]	
Laxation response: patient assessment of change bowel status at end of trial	—	—	—	—	—	Not reported
Symptoms of opioid withdrawal[f] **in the medium term**[b]	Mean change in opioid withdrawal 0.2	Mean change in opioid withdrawal **-0.3 lower**	**MD** **-0.30** [-0.85, 0.25]	112 (1 study)	⊕⊕⊝⊝ **Low**[d,e]	
Serious adverse events[g]	0.7 per 1000	**0.2 per 1000**	**RR 0.25** (0.03, 2.17)	112 (1 study)	⊕⊕⊝⊝ **Low**[d,e]	
Adverse events	786 per 1000	**660 per 1000**	**RR 0.84** (0.67,1.06)	112 (1 study)	⊕⊕⊝⊝ **Low**[d,e]	

*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; **RR:** risk ratio; ; **MD**: mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Within first 24 hours following intervention and comparison treatment
[b] Defined in study as having 3 or more laxations (not induced by rescue medication) a week/who had an increase of one of more laxations (not induced by reduce medication) a week from baseline
[c] Measured over two weeks
[d] Downgraded by one level for serious study limitations due to unclear risk of bias (reporting bias)
[e] Downgraded by one level for serious imprecision (fewer than 400 participants for continuous data or fewer than 300 events for dichotomous data).
[f] Measured by the Clinical Opioid Withdrawal Scale. Lower scores indicate symptoms of lower severity. Score of 5-12 mild, 13-24 moderate, 25-36 moderately severe, more than 36 severe withdrawal. Maximum score 48.
[g] Serious non-fatal events were analysed, no further definition by study authors

Summary of findings 3. Naloxone compared with placebo for opioid-induced bowel dysfunction in people with cancer and receiving palliative care

Naloxone compared with placebo for people with cancer and receiving palliative care with opioid-induced bowel dysfunction

Patient or population: people with cancer and receiving palliative care with opioid-induced bowel dysfunction

Settings: community

Intervention: naloxone

Comparison: placebo

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Naloxone				
Laxation response: risk of spontaneous rescue-free bowel movements in the short term[a]	—	—	—	—	—	Not reported
Laxation response: risk of spontaneous rescue-free bowel movements in the medium term[b]	—	—	—	—	—	Not reported
Laxation response: patient assessment of change in bowel status at the end of trial	—	—	—	—	—	Not reported

Symptoms of opioid withdrawal in the medium term	—	—	—	17 (1 study)	—	Full data not provided
Serious adverse events	—	—	—	17 (1 study)	⊕⊝⊝⊝ **Very low**[c,d]	No serious adverse events were reported
Adverse events	—	—	—	—	—	Not reported

*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).

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Within first 24 hours
[b] Between 1 and 14 days
[c] Downgraded by one level for serious study limitations: unclear risk of bias (reporting bias)
[d] Downgraded by two levels for very serious imprecision as sparse data (17 participants)

Summary of findings 4. Naloxone + oxycodone prolonged release tablets compared with oxycodone prolonged-released tablets for opioid-induced bowel dysfunction in people with cancer irrespective of whether they were receiving palliative care

Naloxone + oxycodone prolonged release tablets compared with oxycodone prolonged-released tablets for people with cancer and opioid-induced bowel dysfunction

Patient or population: people with cancer irrespective of whether they were receiving palliative care opioid-induced bowel dysfunction

Settings: community

Intervention: naloxone + oxycodone prolonged-release tablets (OXN PR)

Comparison: oxycodone prolonged-released tablets (OXY PR)

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				

	Oxycodone (OXY PR)	Oxycodone + naloxone (OXN PR)				
Laxation response: risk of spontaneous rescue-free bowel movements in the short term[a]	—	—	—	—	—	Not reported
Laxation response: risk of spontaneous rescue-free bowel movements in the medium term[b]	—	—	—	—	—	Not reported
Laxation response: Patient assessment of change in bowel status[c] **at the end of trial**	data not provided	data not provided	Study 1: Mean change -11.14 (-19.03, -3.24) Study 2: Little to no change p value = 0.264	212 (2 studies)	⊕⊕⊝⊝ **Low**[d,e]	Full data not provided in either study
Symptoms of opioid withdrawal[f] **in the medium term**[b]	Mean 7.27	Mean 0.63 **lower**	**MD -0.63** (-2.44, 1.18)	133 (1 study)	⊕⊕⊝⊝ **Low**[d,e]	—
Serious adverse events[g]	208 per 1000	**141 per 1000**	**RR 0.68** (0.44 to 1.06)	362 (3 studies)	⊕⊝⊝⊝ **Very low**[d,e,h]	—
Adverse events	584 per 1000	**592 per 1000**	**RR 1.01** (0.87 to 1.18)	362 (3 studies)	⊕⊕⊝⊝ **Low**[d,e]	—

*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; **RR:** risk ratio; ; **MD**: mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Within first 24 hours
[b] Between 1 and 14 days
[c] Measured in one study using 3-item Bowel Function Index, where lower scores indicate better bowel function, and scores above 28.8 indicate constipation. Scores range from 0 to 100. In the other study change in bowel habits was measured using a 3-point Likert Scale (worsened, no change, improved)
[d] Downgraded by one level because of serious study limitations (unclear risk of reporting bias)
[e] Downgraded by one level because of serious imprecision (data from fewer than 400 participants)
[f] Measured using the 16-item Modified Subjective Opiate Withdrawal Scale. Lower scores indicate symptoms of lower severity. Range 0 to 64. Further scoring details not reported
[g] Not defined by trial authors
[h] Downgraded by one level because of serious unexplained inconsistency (substantial heterogeneity $I^2 = 55\%$)

Summary of findings 5. Methylnaltrexone compared to placebo for opioid-induced bowel dysfunction in people receiving palliative care irrespective of whether they had cancer

Methylnaltrexone compared to placebo for opioid-induced bowel dysfunction in people receiving palliative care irrespective of whether they had cancer

Patient or population: people receiving palliative care irrespective of whether they had cancer with opioid-induced bowel dysfunction

Setting: hospital and community

Intervention: methylnaltrexone

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with methylnaltrexone				
Laxation response: risk of spontaneous rescue-free bowel movements[a] in the short term[b]	236 per 1000	701 per 1000 (625 to 770)	**RR 2.97** (2.13 to 4.13) **NNTB 3** (2 to 3)	287 (2 studies)	⊕⊕⊝⊝ **Low**[c,d]	
Laxation response: risk of spontaneous rescue-free bowel movements[a] in the medium term[e]	85 per 1000	671 per 1000 (590 to 745)	**RR 8.15** (4.76 to 13.95) **NNTB 2** (2 to 2)	305 (2 studies)	⊕⊕⊕⊝ **Moderate**[c,f]	
Laxation response: patient assessment of change in bowel status[g] at the end of trial	252 per 1000	567 per 1000 (488 to 644)	**RR 2.32** (1.64 to 3.27)*	287 (2 studies)	⊕⊕⊝⊝ **Low**[c,d]	Proportion reporting improvement
Symptoms of opioid withdrawal[h] in the medium term	Mean 8.1	Mean 0.2 **lower**	**MD -0.20** (-0.80 to 0.40)	133 (1 study)	⊕⊕⊝⊝ **Low**[c,d]	

Serious adverse events[i]	238 per 1000	142 per 1000 (88 to 219)	**RR 0.59** (0.38 to 0.93)	364 (2 studies)	⊕⊕⊝⊝ **Low**[c,d]	
Adverse events	700 per 1000	797 per 1000 (745 to 869)	**RR 1.17** (CI 1.05 to 1.30)	518 (3 studies)	⊕⊕⊝⊝ **Low**[c,j]	Heterogeneity was substantial (74%). We did not undertake a sensitivity analyses as none of our predefined criteria for undertaking one were matched.

*__The risk in the intervention group__ (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; **MD:** mean difference; **RR:** risk ratio; **NNTB:** number needed to treat for an additional beneficial outcome

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Measured by self-report or clinician report
[b] Within first 24 hours following intervention and comparison treatment
[c]Downgraded once for serious study limitations because of unclear risk of reporting bias
[d]Downgraded once for serious imprecision (data fewer than 400 participants)
[e]Between 1 and 14 days
[f]As the effect size was large we did not downgrade for imprecision
[g]Measured in both studies using the Global Clinical Impression of Change, a scale ranging from 1 to 7, with higher scores indicating better bowel function
[h]Measured using the modified Himmelsbach Opioid Withdrawal Scale. Lower scores indicate symptoms of lower severity. Total scores range from 7 to 28.
[i] Not defined by trial authors
[j]Downgraded once for serious inconsistency because of substantial heterogeneity across trials
*In one trial with 2 comparisons with the same control arm, we combined the intervention groups to form a single pairwise comparison

Summary of findings 6. Methylnaltrexone lower dose compared to higher dose for opioid-induced bowel dysfunction in people receiving palliative care irrespective of whether they had cancer

Methylnaltrexone 1 mg compared to methylnaltrexone 5 mg or greater for opioid-induced bowel dysfunction in people receiving palliative care irrespective of whether they had cancer

Patient or population: people receiving palliative care irrespective of whether they had cancer with opioid-induced bowel dysfunction

Setting: hospital and community

Intervention 1: lower-dose methylnaltrexone (study 1: 3 doses, 1 week, 1 mg; study 2: 1 dose, 0.15 mg/kg)

Intervention 2: higher-dose methylnaltrexone (study 1: 3 doses, 1 week, 5-20 mg; study 2: 1 dose, 0.30 mg/kg)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Higher dose (5 mg)?	Lower dose (1 mg)?				
Laxation response: risk of spontaneous rescue-free bowel movements*[a]* in the short term*[b]*	Study 1: 609 per 1000 Study 2: 639 per 1000	Study 1: **499 per 1000** (250 to 100) Study 2: **681 per 1000** (515 to 904)	Study 1: **RR 0.21** (0.03 to 1.41) Study 2: **RR 1.06** (0.77 to 1.46)	135 (2 studies) Study 1: n = 33 Study 2: n = 102	⊕⊕⊝⊝ **Low**[c,d]	Study data not combined as methylnaltrexone dosing differed substantially per study.
Laxation response: risk of spontaneous rescue-free bowel movements[a], in the medium term*[e]*	647 per 1000	222**per 1000**	**RR 2.91** (0.82 to 10.39)	26 (1 study)	⊕⊝⊝⊝ **Very low**[c,f]	
Laxation response: patient assessment of change in bowel status[g] at the end of trial	58 per 100	60 per 1000	**RR 0.98** (0.71 to 1.35)	102 (1 study)	⊕⊕⊝⊝ **Low**[c,d]	
Symptoms of opioid withdrawal in the medium term	0.25	mean 0.25 **lower**	MD -0.25 (-0.84 to 0.34)	102 (1 study)	⊕⊕⊝⊝ **Low**[c,d]	Data not combined as methylnaltrexone dosing differed.
Serious adverse events	—	—	—	—	—	In one trial, 15 serious adverse events occurred during the ran-

						domised trial phase but it does not report what arm the events occurred in.
Adverse events	Study 1: 1000 per 1000 Study 2: 800 per 1000	Study 1: **1000 per 1000** (1000 to 1000) Study 2: **723 per 1000** (580 to 902)	Study 1: **RR 1.00** (1.00 to 1.00) Study 2: **RR 0.90** (0.73 to 1.13)	135 (2 studies) Study 1: n = 33 Study 2: n = 102	⊕⊕⊝⊝ **Low** [c,d]	Study data not combined as methylnaltrexone dosing differed substantially per study

*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; **MD:** mean difference; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Measured by clinician or self-report
[b] Within first 24 hours following intervention and comparison treatment
[c] Downgraded by one level for serious study limitations: unclear risk of bias (reporting bias)
[d] Downgraded by one level for serious imprecision as fewer than 400 participants.
[e] Between 1 and 14 days
[f] Downgraded by two levels for very serious imprecision as sparse data 26 participants and wide confidence intervals

BACKGROUND

This is an update of the review first published in 2008 (McNicol 2008), and last updated in 2018 (Candy 2018). It is a partial update of the review published in 2008 entitled Mu-opioid antagonists for opioid-induced bowl dysfunction (McNicol 2008). Since publication in 2008, there has been an increase in the number of trials on mu-opioid antagonists (a drug designed to neutralise the effect of opioids on bowel function), and this current review and its last update critiques evidence only for people with cancer and people receiving palliative care.

Description of the condition

Opioids, such as morphine sulphate, oxycodone, and fentanyl, are potent analgesics (medicines to relieve pain). They are recommended in clinical guidelines by the World Health Organization (WHO) including for the management of moderate-to-severe pain from cancer and other populations such as people needing palliative care (WHO 2016). They are widely used, although globally there is wide variation suggesting an under-utilisation of opioids for pain management in some locations (Manjiani 2014).

However, opioids are associated with adverse events. The most common and disabling of these is bowel dysfunction, which can be severe enough for a person to limit their opioid use (Cook 2008). Opioids, regardless of the method of administration (oral, parenteral, transdermal), interfere with gastrointestinal propulsive motility (Leppert 2010). Opioids increase absorption of fluids from the intestine and decrease epithelial secretion. They delay gastric emptying and decrease peristalsis in the gut.

Opioid-induced bowel dysfunction (OIBD) has been described as quote: "A change when initiating opioid therapy from baseline bowel habits that is characterised by any of the following: reduced bowel movement frequency (conventionally less than 3 per week), development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency" (Kumar 2012). It may even lead to stool impaction (Camilleri 2014). In addition to constipation, OIBD describes a constellation of symptoms including bloating, abdominal distention, gastric reflux, abdominal cramping, dry mouth, epigastric fullness, nausea, and vomiting (Leppert 2015; Pappagallo 2001). It can cause psychological distress and agitation in terminally ill people. OIBD increases health service use, sometimes necessitates hospitalisation, and it can dramatically reduce an already compromised quality of life. It may lead to people under-treating their pain (Pizzi 2012); however, since the dose that produces constipation may only be 25% of that required for adequate analgesia, dose reduction is not an appropriate option for management of OIBD (Ketwaroo 2013).

In people with cancer, hospice populations and people with advanced disease, the estimated incidence of OIBD is high, from 60% to 90% (Glare 2006; Panchal 2007; Sykes 1998). Although these estimates are relatively old, there is no evidence to suggest that this is no longer the case. Moreover, surveys have found that large proportion of people skip, decrease or discontinue opioid use because of bowel dysfunction, thereby preferring pain in preference to constipation (Gupta 2015; Cook 2008; LoCasale 2016).

Description of the intervention

The recommended and commonly prescribed preventive and management treatment of OIBD in palliative care and advanced disease is the use of a laxative stimulant and a stool softener, in addition to general measures such as increased food, fibre-rich diet, fluid intake, physical activity, and privacy during defecation (NICE 2016; Larkin 2018; Sera 2018). These measures are not always effective; in people taking opioids, it is estimated that over 80% of people remain constipated despite regular use of laxatives (Coyne 2014; Diego 2011). This inadequate response can be defined as having at least one opioid-induced constipation symptom (incomplete bowel movement, hard stools, straining or false alarms) of moderate severity, while taking at least one type of laxative over four days within the past two weeks.

Mu-opioid antagonists (MOAs), such as methylnaltrexone, naloxone, and naloxegol, are designed specifically to target the pathophysiology of OIBD by 'neutralising' the constipating effect of the opioid. Methylnaltrexone is licensed for the treatment of opioid-induced constipation in palliative care in more than 50 countries (Bader 2013). In clinical guidelines, where methylnaltrexone or other MOAs are considered, it is described to act as an augmentation to laxatives or as an alternative when laxatives fail (European Association of Palliative Care, Caraceni 2012; European Society of Medical Oncology (ESMO), Larkin 2018), and should be used only under advice from a specialist palliative care clinician (Scottish Palliative Care Guidelines 2014). The National Institute for Health and Care Excellence (NICE) recommends naldemedine (NICE 2020) and naloxegol (NICE 2015) for treating OIBD in adults who have had laxative treatment. This is based on both evidence on effect and cost. NICE does not recommend methylnaltrexone because no evidence submission was received from the manufacturer of the technology (NICE 2017).

How the intervention might work

Opioids mediate their gastrointestinal and analgesic effects through the same subclasses of opioid receptors in the human body: mu, kappa, and delta. How each receptor type is involved in OIBD is not fully understood (Neefjes 2014). The peripheral opioid effect on mu-opioid receptors in the gut wall may play a main role in OIBD (Leppert 2010). Co-ordination of motility is disrupted by activation of the mu-opioid receptors that inhibit excitatory and inhibitory neural pathways within the enteric nervous system.

One approach for dissociation of the analgesic effect of opioids is to separate the opioid's central activity from its peripheral activity (Wang 2013). This may be achieved with a peripherally acting opioid receptor antagonist with limited ability to cross the blood-brain barrier and which therefore does not interfere with analgesia (Brown 1985). Alternatively, this can be achieved by use of a preparation that undergoes extensive 'first-pass' metabolism by the liver and so does not enter the systemic circulation.

There are several MOAs in use. Naloxone is commercially available; it is centrally acting but has a narrow therapeutic effect with certain doses reversing desirable analgesia (Camilleri 2011). It undergoes extensive first-pass metabolism and in the correct dosage it does not reverse the analgesic effect of opioids. It is administered orally. The development of a prolonged-release preparation of naloxone to allow as much cover of the small and large intestine as possible when used with oxycodone has led to further studies of the compound (Camilleri 2011). There are several other preparations that do not cross the blood-brain barrier and these include alvimopan, methylnaltrexone, naloxegol, and naldemedine. Alvimopan has a high affinity for peripheral opioid receptors. It is only recommended for short-term use, such as post-surgery, because of the possibility of myocardial events (Merck 2015). It is contraindicated in people with advanced disease (Leppert 2015). Methylnaltrexone is less lipid soluble than naloxone and, therefore, less likely to cross the blood-brain barrier. It is only currently available in subcutaneous formulation. Naloxegol, which is administered orally, has a polyethylene glycol moiety that limits its capacity to cross the blood-brain barrier (Pritchard 2015). Naldemedine is administered orally, and it is a derivative of naloxone, it has a large polar surface that reduces its ability to access the central nervous system (FDA 2017).

Why it is important to do this review

There are reviews of MOAs for OIBD across different populations (e.g. Nee 2018; Ford 2013). However, it is important to evaluate their effectiveness and safety specifically in cancer and in palliative care populations (Bader 2012; Clark 2014). This is because of the differences inherent in these groups that may impact, in a likely negative way, on the effect of MOAs. The impact may differ because of the multi-factorial pathophysiology of constipation in people with cancer and advanced diseases (Leppert 2010). This may include structural abnormalities such as bowel obstruction; pelvic tumours; radiation fibrosis; or metabolic disturbances such as dehydration, hypercalcaemia, and hypokalaemia. It may involve neurological disorders. There may also be general issues increasing the risk and complicating the management of OIBD such as advanced age, depression, drug sedation, chemotherapy, multiple therapies, and a lack of privacy provided as an inpatient for bowel evacuation. As the person's disease progresses, they may have increasing frailty, lower activity, reduced appetite, and eventually multiple organ failure, all of which may impact on bowel function (Bader 2012). Moreover, because of these factors, people with cancer and particularly people at a palliative care stage may have a higher risk than other, less ill populations of experiencing adverse events from MOAs. This review is an update and since its most recent publication we are aware of new trials.

OBJECTIVES

To assess for opioid-induced bowel dysfunction (OIBD) in people with cancer and people receiving palliative care the effectiveness and safety of mu-opioid antagonists (MOAs) versus different doses of MOAs, alternative pharmacological/non-pharmacological interventions, placebo, or no treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised trials are the best design to minimise bias when evaluating the effectiveness of an intervention. We included double-blind, randomised controlled trials (RCTs) evaluating the effectiveness of MOAs, compared to a different MOA or at different doses, an alternative pharmacological or non-pharmacological intervention, a placebo, or no treatment, for OIBD. We did not include open-label extension phases (where both the researchers and participants know whether they are in the intervention trial arm or the comparison arm) of trials or post-hoc analyses of trials because they are at an increased risk of bias. No language restrictions were applied. If there was no full journal publication of the trial, we included a published abstract of the trial's final results if it was of sufficient detail to be able to assess risk of bias. For additional data of any included trials we also sought to identify regulatory (e.g. European Medicines Agency, and the Pharmaceuticals and Medical Devices Agency in Japan) assessments of the manufacturer's trial data from Clinical Study Reports.

Types of participants

Eligible trials concerned participants of any age or either sex who were:

- people with cancer or people at a palliative stage irrespective of disease, or both;
- all or the majority (over 95%) were on a stable opioid regimen and had OIBD that had not resolved from taking laxatives.

We included trials of populations of participants where not all fitted our eligibility criteria so long as at least 50% of the sample were people with cancer or people receiving palliative care or at an advanced stage of their disease or where they provided subgroup analysis in either of these participant groups.

We did not include trials if the MOAs for bowel dysfunction were for associated postoperative ileus (arrest of intestinal peristalsis). This is because this is not caused primarily by opioids (Marderstein 2008). We excluded trials of healthy volunteers, participants with constipation because of drug misuse, and participants with constipation arising from bowel obstruction were excluded.

Types of interventions

We included trials of interventions evaluating a MOA that were either peripherally or systemically acting, and administered at any dose and by any route. These included, for example, methylnaltrexone and naloxone. We included interventions of a MOA if they were evaluated alone or in combination with another drug, for example naloxone in combination with oxycodone.

Our comparator interventions of interest were a different MOA, MOA at different doses, an alternative pharmacological or non-pharmacological intervention, a placebo, or no treatment.

Types of outcome measures

We set four types of primary outcomes of interest and nine secondary outcomes.

Primary outcomes

Primary outcomes of interest

Laxation response:

within 24 hours (short term), 2 weeks (medium-term) and by patient overall assessment of bowel change at the end of the trial:

- self/clinician report of number of spontaneous rescue-free bowel movements (within 24 hours and two weeks, by any scale or measure);
- patient report change in bowel status measured using for instance the three-item Bowel Function Index (BFI), where

scores above 28.8 indicate constipation, or rating via the Patient Global Impression of Change using for bowel status a single rating system of better, no change or worse (within the duration of the trial).

Effect on analgesia: within 24 hours and two weeks, by any scale or measure:

- symptoms of opioid withdrawal such as sweating, tremor, restlessness and anxiety. This could be measured using for instance the Clinical Opioid Withdrawal Scale (COWS), where a total score of greater than five is considered elevated and clinically significant;
- change in analgesic requirements such as a 10% increase in requirements;
- intensity of pain however measured.

Serious adverse events as defined by trial authors.

- number and type of adverse event.

The short-term time point of interest is the first measurement within 24 hours post intervention treatment. This will be taken as within 24 hours of first treatment unless stated otherwise. For medium term this is the first measurement taken between day one and two weeks of intervention treatment. For serious adverse events and adverse events the time point of interest was the duration of the trial.

Secondary outcomes

Number of participants who dropped out due to adverse events.

Other measures of laxation response: by any scale or measure:

- complete evacuation within 24 hours and 2 weeks;
- not straining within 24 hours and 2 weeks;
- overall symptoms of constipation in the longer term (beyond two weeks).

Relief of other constipation-associated symptoms: by any scale or measure:

- abdominal cramping;
- acid reflux;
- bloating;
- decreased appetite;
- difficulty breathing because of pressure in the abdomen;
- discomfort/pain in the abdomen;
- hard stools;
- inability to pass stool when feeling the urge;
- nausea and vomiting;
- passing gas.

Use of rescue medication for laxation.

Quality of life within 24 hours and two weeks: by a validated scale such as the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30).

Participant satisfaction with bowel movements.

Participant preference on bowel treatment.

Unless stated otherwise, our time points of interest were for outcomes over the duration of the trial.

For any primary or secondary outcome, if a trial used several measurements, we selected in order of priority the:

- overall total score or global measure;
- one deemed by the authors as the primary measure;
- measure the sample size calculation was based on;
- measure with the median effect. If there was an even number of outcomes, then we selected the more conservative median effect.

Search methods for identification of studies

Electronic searches

For this update, we searched five databases.

- CENTRAL (Cochrane Library) Issue 12 of 12 2021 (searched from August 2017 to December 2021).
- MEDLINE and MEDLINE in process (Ovid) August 2017 to 17 December 2021.
- Embase (Ovid) August 2017 to 17 December 2021.
- CINAHL (EBSCO) August 2017 to December 2021.
- Web of Science (SCI-Expanded and CPCI-S) August 2017 to 18 December 2021.

The search strategies are listed in Appendix 1.

Searching other resources

We searched two clinical trials registries to October 2020 that were not available via CENTRAL:

- ISRCTN: https://www.isrctn.com/;
- EU Clinical Trials Register (EU-CTR): https://www.clinicaltrialsregister.eu/.

We searched Clinicaltrials.gov and ICTRP via CENTRAL.

We searched for any included trials for drug reports from three regulatory agency websites to October 2020:

- US Food and Drug Administration (FDA);
- European Medicines Agency (EMA);
- Japanese Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau (JPMA).

We searched two pharmaceutical company trials registers:

- AstraZeneca Clinical Trials (www.astrazenecaclinicaltrials.com);
- GlaxoSmithKline Clinical Trial Register (www.gsk-clinicalstudyregister.com);

We checked references lists of included trials and any identified systematic reviews. We also undertook a forward citation search of all included trials. We checked conference proceedings of the National Cancer Research Institute (NCRI) Cancer Conference and the European Association of Palliative Care (EAPC) to October 2020. We contacted authors of any identified relevant conference abstracts to ask for full details of their trials.

We wrote to pharmaceutical companies that are known manufacturers of MOAs to obtain any trial data not available in peer-review publications; these were AstraZeneca, Mundipharma GmbH, Progenics, Shionogi, and Valeant. For this purpose, we adapted a letter developed by authors of a previous Cochrane Review; see Appendix 2 for a copy of this letter.

Data collection and analysis

Selection of studies

Two review authors (BC, LJ) independently screened the citations identified in the database searches. Where it was unclear or likely that the studies fulfilled our inclusion criteria, we retrieved the full-text articles. If disagreements on eligibility had occurred, we would have resolved them by discussion, or if persistent, by a third review author (PS). If necessary for further clarification such as if it was unclear whether the trial identified was completed and whether their findings were available, we sought contact with the study author or sponsor.

Data extraction and management

One review author (BC) extracted data using a standard piloted form and two other review authors checked it for agreement (LJ, VV) before entry into Review Manager [RevMan Web 2020]. In the event of disagreement, it was planned a third review author (PS) would adjudicate. We collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We collected characteristics of the included studies in sufficient detail to populate a table of 'Characteristics of included studies' in the full review.

We extracted the following information.

- Study design (including methods, location, funding sources, study author declarations of interest)
- Setting
- Participants
- Intervention(s), Comparator(s), Outcomes (including measures and time points)
- Numerical data for outcomes of interest

Assessment of risk of bias in included studies

Two review authors (BC, VV) independently assessed risk of bias for each trial using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions (*Higgins 2011), resolving any disagreements by discussion. We completed a risk of bias table for each included trial. We assessed the following.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process: random number table; computer random number generator); and unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process, which were therefore at high risk of bias (odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions before assignment determines whether the intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We assessed the methods as: low risk of bias (telephone or central randomisation; consecutively-numbered, sealed, opaque envelopes); and unclear risk of bias if the method was not clearly stated. We excluded trials that did not conceal allocation, which were therefore at high risk of bias (which may be described as open list or open label).
- Blinding of participants and personnel (checking for possible performance bias). The methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, such as identical tablets matched in appearance or smell, or a double-dummy technique); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved, or it is described as open-label, but it is not clear what is unmasked).
- Blinding of outcome assessment (checking for possible detection bias). The methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study has a clear statement that outcome assessors were unaware of treatment allocation, and ideally describes how this was achieved); unclear risk of bias (study states that outcome assessors were blind to treatment allocation but lacks a clear statement on how it was achieved or it is described as open-label, but it is not clear what is unmasked).
- Incomplete outcome data (attrition bias). We assessed whether there was attrition bias due to the amount, nature, or handling of incomplete outcome data. We judged the trial as having low risk of attrition bias if there were no missing outcome data or the reasons for missing data were unlikely to be related to true outcome, or missing data and reasons for it were similar across trial arms, or the missing data had been imputed using appropriate methods. We judged the trial as high risk if the reason for missing outcome data were likely to be related to the outcome, with either imbalance across trial arms in numbers of reasons for missing data and if an inappropriate application of simple imputation was potentially used. We judged the trial as unclear risk if there was insufficient reporting of attrition to permit judgement of low or high risk.
- Selective outcome reporting (checking if there was a selection of a subset of the original variables recorded on the basis of the results). We assessed selective outcome reporting, if a protocol was available, by comparing outcomes in the protocol and published report. If they were the same we assessed it as low risk in this domain; if they differed, we considered it as high risk. If a protocol was not available, then we compared the outcomes listed in the methods section of an article with the outcomes for which results were reported. If they differed, we considered the trial as high risk. If a protocol was not available and even though the outcomes listed in the methods section and the results section were the same, we considered the trial as having an unclear risk of bias in this domain. Since not all trials have a protocol available, we expected to find a number of trials in this review to be at unclear risk.

Measures of treatment effect

We analysed the data using RevMan 5.4 (RevMan 2020). For dichotomous outcomes, we report risk ratios (RRs) and 95% confidence intervals (CIs). For primary outcomes, we calculated numbers needed to treat (NNT) using the 'treat-as-one-trial' method. To indicate direction of effect, we present where appropriate results as either number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH). For continuous outcomes, we report mean differences (MDs) and 95% CIs. If authors reported both change from baseline and post treatment scores, we preferentially reported change from baseline scores. For cross-over trials, we only generated, as appropriate, a risk ratio (RR) or mean difference (MD) for pre-cross-over results. We undertook a meta-analysis if studies were sufficiently similar in design, population, interventions and outcomes. For trials that used different methods to measure the same continuous outcome, we used standardised mean differences (SMDs) and 95% CsI.

Unit of analysis issues

In our handling of each trial analytic, we considered issues that may have impacted on findings. For these we took guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020). These were:

- groups of participants randomised together with the same intervention (e.g. cluster-randomised trials);
- participants receiving more than one intervention (e.g. cross-over trials);
- multiple observations for the same outcomes (such as repeated measures).

Dealing with missing data

Given the nature of this field, we anticipated there would be a significant amount of missing data as a result of trial attrition due to the death of the participant.

We planned to contact trial authors if we had found data to be missing. For trials using continuous outcomes in which SDs were not reported, and no information was available from the authors, we calculated the SDs using the standard error of the mean (SEM).

Assessment of heterogeneity

We assessed statistical heterogeneity using the I^2 statistic. The I^2 statistic is a reliable and robust test to quantify heterogeneity, since it does not depend on the number of trials or on the between-trial variance. I^2 measures the extent of inconsistency among trials' results, and can be interpreted as the proportion of total variation in trial estimates that is due to heterogeneity rather than sampling error. We considered an I^2 value of greater than 50% to indicate substantial heterogeneity and values between 75% to 100% to indicate considerable heterogeneity (Higgins 2020). Where possible, we planned to undertake sub-analyses or sensitivity analyses in an attempt to explain heterogeneity.

Assessment of reporting biases

To reduce the risk of reporting bias, we undertook comprehensive database and registry searches, including searches of clinical trial registers and drug regulatory agency websites. We also searched websites of, and wrote to, pharmaceutical companies that are known manufacturers of MOAs to identify any further trial data.

We planned to assess reporting biases by assessing funnel plots if there were sufficient studies for such an analysis.

Data synthesis

Where trial data were 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 planned to use a fixed-effect model. For any substantial statistical heterogeneity identified we sought to investigate the extent of heterogeneity.

Subgroup analysis and investigation of heterogeneity

Where heterogeneity was identified in a meta-analysis, we planned as appropriate subgroup and sensitivity analysis to investigate its possible sources. Subgroup analysis explores whether the overall effect varied with different trial populations, and with the nature and content of the interventions. We planned the following subgroup analysis by excluding studies where not all participants had (1) cancer and/or (2) were receiving palliative care or being at an advanced stage of their disease.

Sensitivity analysis

If sufficient trials were available, we planned to perform, in a meta-analysis, sensitivity analyses to explore the influence of:

- trial quality by excluding trials that had a high risk of bias in any domain;
- outcomes measured validated tools by excluding trials that did not use validated tools.

Summary of findings and assessment of the certainty of the evidence

Two review authors (BC, VV) independently rated the certainty of the body of evidence for the primary outcomes. We used the GRADE system to rank the certainty of the evidence using the guidelines provided in Chapter 14 of the *CochraneHandbook for Systematic Reviews of Interventions* (Higgins 2020), GRADEpro Handbook (Schunemann 2013) and GRADE method papers (Guyatt 2011; Guyatt 2013a).

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning grade of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

The GRADE system considers study design as a marker of quality. Randomised controlled trials are considered to be high quality of evidence and can be downgraded for important limitations.

Factors that may decrease the certainty level of a body of evidence are as follows.

- Serious or very serious study limitations (risk of bias)
- Important or serious inconsistency of results
- Some or major indirectness of evidence
- Serious or very serious imprecision

We included six summary of findings tables to present the main findings for mu-opioid antagonists compared to placebo or at a different dose in a transparent and simple tabular format. In particular, we included key information concerning the certainty of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes laxation response in the short and medium terms, patient assessment of bowel change and effect on pain, specifically opioid withdrawal symptoms in the medium-term, adverse and serious adverse events.

RESULTS

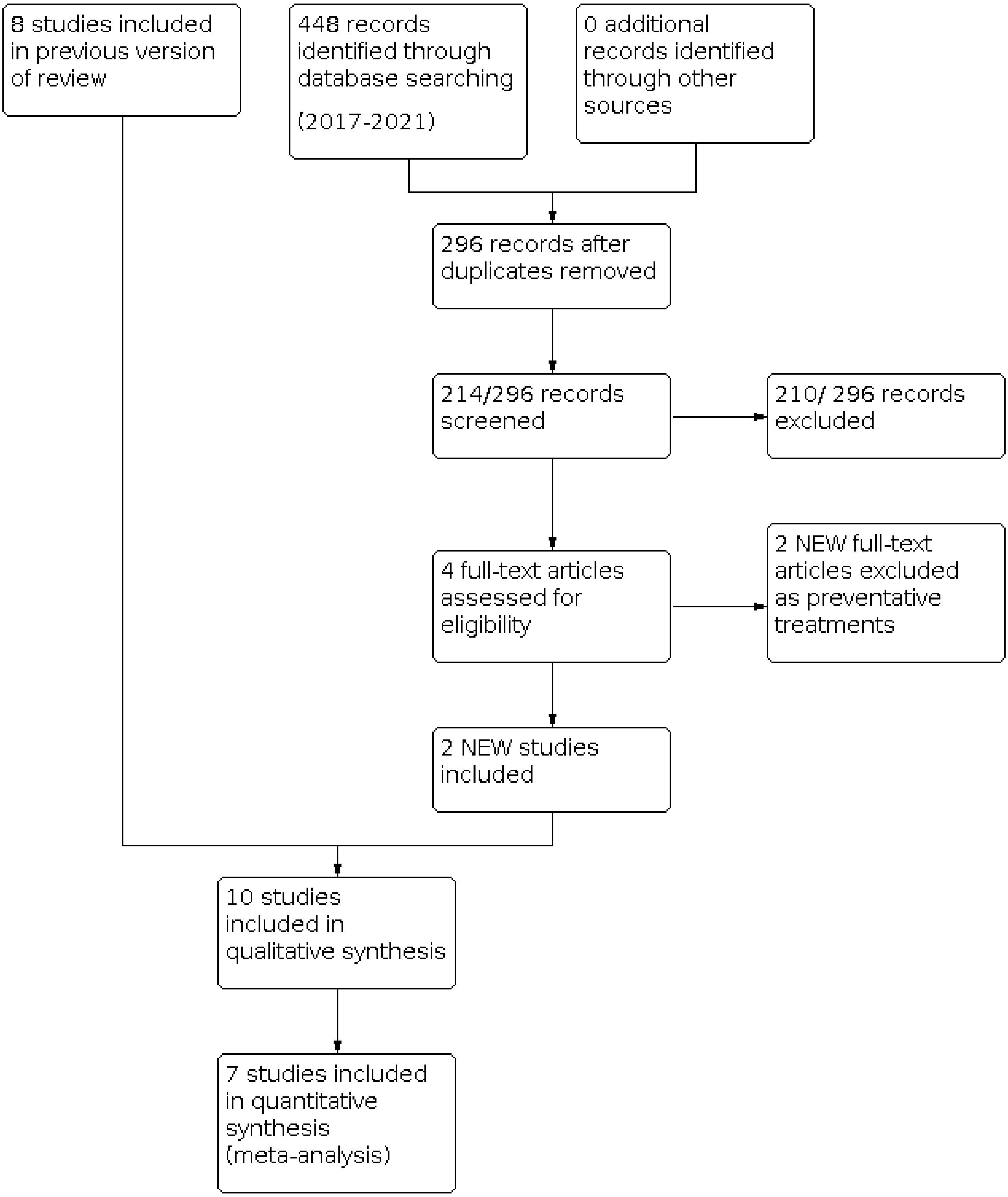
Description of studies

See Characteristics of included studies; Characteristics of excluded studies.

Results of the search

In this update, we identified 296 unique citations. See Figure 1 for the flowchart of the screening process. We identified two new trials (Katakami 2017b; Lee 2017), adding these to those included in the last version resulted in a total of 10 included trials with 1343 participants (Ahmedzai 2012; Bull 2015; Dupoiron 2017; Katakami 2017a; Portenoy 2008; Slatkin 2009; Sykes 1996; Thomas 2008).

Figure 1. Study flow diagram.



For five included trials we identified regulatory assessments undertaken by theEuropean Medicines Agency (EMA), and the US Food and Drug Administration (FDA) , and the Pharmaceuticals and Medical Devices Agency in Japan of the manufacturers' Clinical Study Reports (Ahmedzai 2012; Katakami 2017a; Katakami 2017b; Slatkin 2009; Thomas 2008). Only one of the regulatory assessments provided additional data, this was for use of rescue medication (Thomas 2008). We identified two regulatory reports, but they did not provide any additional data; they are referenced under Ahmedzai 2012 for oxycodone + naloxone, and Slatkin 2009 for methylnaltrexone.

Included studies

All trials were multi-centre parallel randomised controlled trials (RCTs), except one which was a single-centre cross-over RCT (Sykes 1996). Eight trials had sponsorship from a pharmaceutical company (Ahmedzai 2012; Bull 2015; Dupoiron 2017; Katakami 2017a; Katakami 2017b; Lee 2017; Slatkin 2009; Thomas 2008). Two trials involved research sites in multiple countries. In one this included sites in Australia, Czech Republic, France, Germany, Hungary, Israel, the Netherlands, Poland, and the UK (Ahmedzai 2012), and in the other France, Germany, Poland, and the UK (Dupoiron 2017). In the other trials, populations were from North America (Bull 2015; Portenoy 2008; Slatkin 2009; Thomas 2008), Japan (Katakami 2017a; Katakami 2017b), South Korea (Katakami 2017a; Lee 2017), and the UK (Sykes 1996). Four trials had multiple community and hospital care settings including inpatients and outpatients of a hospice or hospital, and long-term care facilities (Bull 2015; Lee 2017; Slatkin 2009; Thomas 2008). Three were based in the community (Ahmedzai 2012; Dupoiron 2017; Sykes 1996). The other three did not report the setting (Katakami 2017a; Katakami 2017b; Portenoy 2008).

In all trials the majority of participants had a primary diagnosis of cancer. Four trials included participants with chronic cancer pain who were not described as being at an advanced disease stage (Ahmedzai 2012; Dupoiron 2017; Katakami 2017a; Katakami 2017b). The six other trials evaluated effects in participants with an advanced disease including cancer, and other conditions such as AIDS or circulatory disease. Where reported, authors described what they meant by advanced disease by using general terms such as terminal, end-stage, or metastatic cancer. Nine of the trials excluded patients in situations that may affect efficacy of trial by compounding constipation such as any disease processes suggestive of abnormalities of the gastrointestinal tract, or the use of chemotherapy. In the other trial this is not stated in the exclusion criteria but the investigators 'confirmed prior to inclusion that the constipation was caused or aggravated by opioid use' (Dupoiron 2017).

All participants were adults. At baseline all participants were on a stable opioid regimen, and had opioid-induced bowel dysfunction (OIBD). Eight trials specified that the indication for opioids was pain (Ahmedzai 2012; Dupoiron 2017; Katakami 2017a; Katakami 2017b; Lee 2017; Portenoy 2008; Slatkin 2009; Thomas 2008). The other two trials did not state the indication (Bull 2015; Sykes 1996). Nine trials reported that all or the majority (90% or greater) of participants were taking regular laxatives. In the 10th trial, patients were not eligible if they had been taking regular laxatives for one or more weeks before screening (Lee 2017).

Three trials had multiple trial arms (Katakami 2017a; Portenoy 2008; Slatkin 2009), the others were two-armed. The mu-opioid antagonists (MOAs) were either compared with a placebo or with the MOA administered either at different doses or in combination with other drugs. In four trials, the MOA was subcutaneous methylnaltrexone (Bull 2015; Portenoy 2008; Slatkin 2009; Thomas 2008). Four other trials tested oral naloxone; in one naloxone only (Sykes 1996), and in three oxycodone (an opioid) in combination with naloxone (Ahmedzai 2012; Dupoiron 2017; Lee 2017). The other two trials evaluated oral naldemedine (Katakami 2017a; Katakami 2017b). We identified no trials that evaluated naloxegol or other MOAs.

Laxation response was measured in eight trials as self, carer or clinician report (Bull 2015; Katakami 2017a; Katakami 2017b; Lee 2017; Portenoy 2008; Slatkin 2009; Sykes 1996; Thomas 2008). Two trials measured response using the Bowel Function Index (BFI) (three items, the lower the score the better bowel function) (Ahmedzai 2012; Dupoiron 2017). Effect on analgesia was measured either using self-rated pain scores or symptoms of opioid withdrawal. To measure symptoms of opioid withdrawal, three trials used the modified Himmelsbach withdrawal scale (seven items; higher scores indicating greater severity) (Portenoy 2008; Slatkin 2009; Thomas 2008), and two the Clinical Opioid Withdrawal Scale (COWS) (11 items, higher scores indicating more symptoms and severity. A score greater than 36 indicates severe withdrawal) (Katakami 2017a; Katakami 2017b). All trials reported the incidence of serious adverse events.

Further details of these trials including MOAs dose and schedule, and study funding source are shown in the Characteristics of included studies tables.

Ongoing studies and studies awaiting classification

We identified four trials whose results are yet to be published, of these two are evaluating methylnaltrexone (Neefjes 2014; Peppin 2013), one naloxegol (NCT03067708), and one oxycodone/naloxone (Wong 2019). We identified six for which we are awaiting classification on their eligibility; this is mainly as we have insufficient details on study population. Further details of these are in the Characteristics of ongoing studies and Characteristics of studies awaiting classification, respectively.

Excluded studies

We excluded eight trials, three because they did not include participants with cancer or at the palliative stage of a disease, three as they were not RCTs, and two as the interventions were preventive. These trials are listed in the Characteristics of excluded studies.

Risk of bias in included studies

All trials were vulnerable to a number of biases, most commonly this included an unclear risk of detection bias. See Figure 2; Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

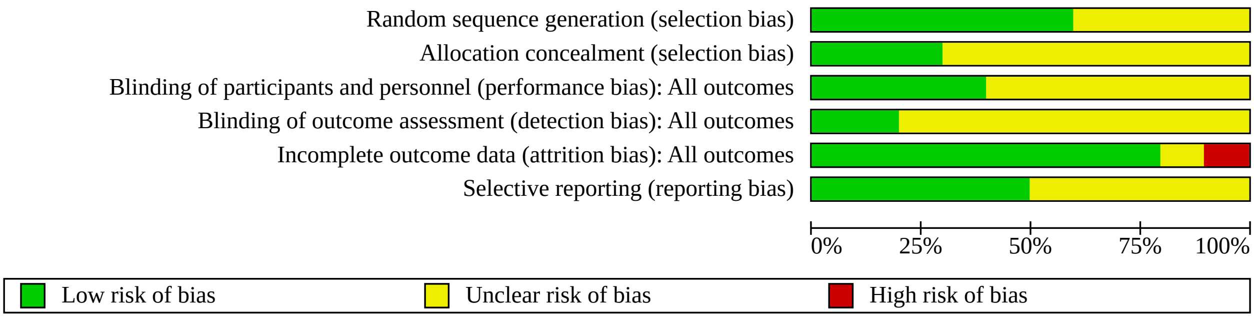
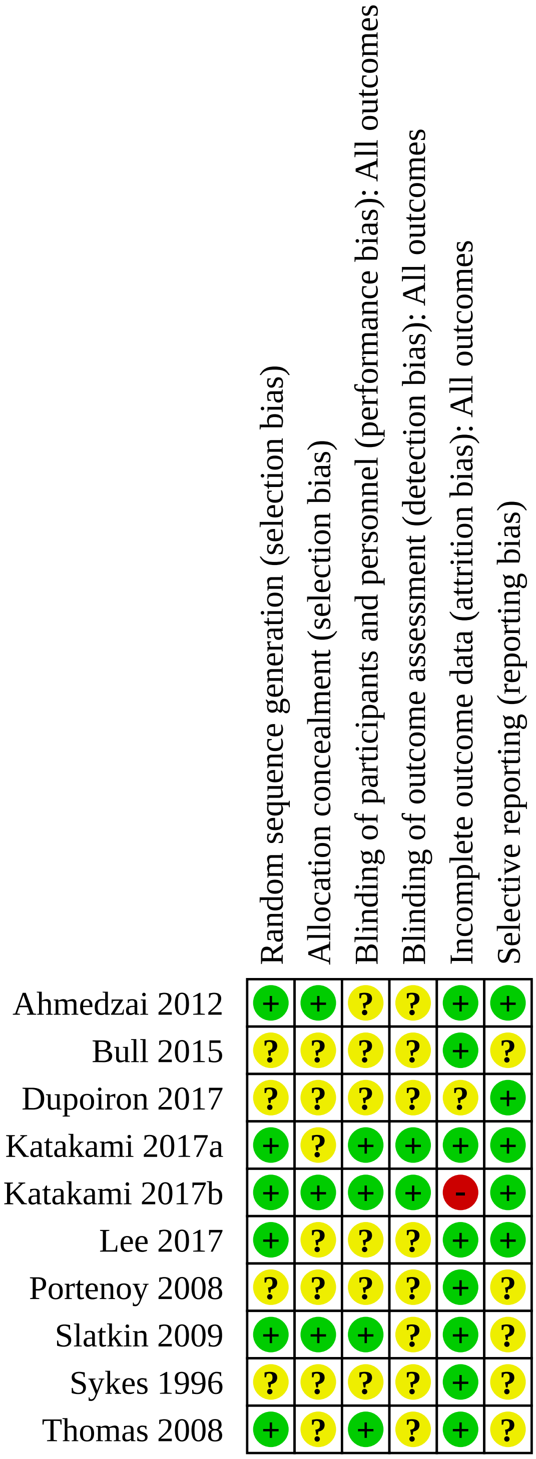


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

The method of randomisation sequence generation was described adequately in six trials (Ahmedzai 2012; Katakami 2017a; Katakami 2017b; Lee 2017; Slatkin 2009; Thomas 2008), and we judged them to be at low risk of bias. In four trials the risk of bias was unclear as they did not provide any details.

Allocation concealment

Three trials adequately described allocation concealment (Ahmedzai 2012; Katakami 2017b; Slatkin 2009). In seven trials the risk of bias was unclear as they did not provide any details.

Blinding

Performance bias

Four trials were at a low risk of performance bias (Katakami 2017a; Katakami 2017b; Slatkin 2009; Thomas 2008). In six trials this was unclear as they did not provide any details.

Detection bias

Two trials were at a low risk of detection bias (Katakami 2017a; Katakami 2017b). In eight trials it was unclear as they did not provide any details.

Incomplete outcome data

The risk of attrition bias was low in eight trials. In one trial it was high risk as attrition was unbalanced between the trial arms with more leaving because of adverse events in the intervention arm (Katakami 2017b). In another trial risk was unclear as it was not stated how many had dropped out of the subgroup of people with cancer (Dupoiron 2017).

Selective reporting

The risk of selective reporting was unclear in five trials as there were no published protocols to check.The other five were low risk of bias as they had a protocol and whose report on outcome measurements was consistent with those in the published results paper (Ahmedzai 2012; Dupoiron 2017; Katakami 2017a; Katakami 2017b; Lee 2017).

Other potential sources of bias

None of serious concern.

Effects of interventions

See: **Summary of findings 1** Naldemedine compared to placebo for opioid-induced bowel dysfunction in people with cancer irrespective of whether they were receiving palliative care; **Summary of findings 2** Low dose naldemedine compared to higher doses for opioid-induced bowel dysfunction in people with cancer irrespective of whether they were receiving palliative care; **Summary of findings 3** Naloxone compared with placebo for opioid-induced bowel dysfunction in people with cancer and receiving palliative care; **Summary of findings 4** Naloxone + oxycodone prolonged release tablets compared with oxycodone prolonged-released tablets for opioid-induced bowel dysfunction in people with cancer irrespective of whether they were receiving palliative care; **Summary of findings 5** Methylnaltrexone compared to placebo for opioid-induced bowel dysfunction in people receiving palliative care irrespective of whether they had cancer; **Summary of findings 6** Methylnaltrexone lower dose compared to higher dose for opioid-induced bowel dysfunction in people receiving palliative care irrespective of whether they had cancer

The trials varied in mu-opioid antagonists (MOA) evaluated and comparison, and how they reported the outcomes. This limited the number of combined analyses.

Naldemedine versus placebo

Two trials (418 participants) of people with cancer irrespective of disease stage evaluated the effectiveness of two weeks of oral treatment with naldemedine compared to placebo (Katakami 2017a; Katakami 2017b). In one trial the oral doses of naldemedine were per arm 0.1 mg, 0.2 mg or 0.4 mg daily for two weeks (Katakami 2017a), and in the other 0.2 mg daily for two weeks (Katakami 2017b).

Primary outcomes

See Summary of findings 1 for this comparison.

Laxation response

Response in the short term was not reported. Two trials (418 participants) reported response in the medium term (Katakami 2017a; Katakami 2017b). The risk (i.e. chance) of spontaneous laxations over two weeks in those taking naldemedine was more than three times the risk for those taking placebo (risk ratio (RR) 2.00, 95% confidence interval (CI) 1.59 to 2.52, 2 trials, 418 participants, I^2 = 0%; number needed to treat for an additional beneficial outcome (NNTB) 3, 95% CI 3 to 4. Analysis 1.1. Katakami 2017a; Katakami 2017b). We judged the certainty of evidence for laxation response within two weeks to be moderate. We downgraded evidence by one level for serious limitations to the study design as one study had a high risk of attrition bias.

Patient assessment of change in bowel status was not reported.

Effect on analgesia

Short term effect on analgesia was not reported. Only one trial (112 participants) reported on opioid withdrawal symptoms in the medium term (Katakami 2017a).

Naldemedine may have little to no effect on opioid withdrawal symptoms compared to placebo in the medium term (over two weeks since first dose) (naldemedine 0.1 mg: mean difference (MD) -0.10, 95% CI -0.56 to 0.36, 1 trial, 112 participants. Analysis 1.2; naldemedine 0.2 mg: MD 0.30, 95% CI -0.21 to 0.81, 1 trial, 114 participants. Analysis 1.3; naldemedine 0.4 mg: MD 0.20, 95% CI -0.36 to 0.76, 1 trial, 112 participants. Analysis 1.4. Katakami 2017a). We judged the certainty of evidence as very low. We downgraded the certainty of evidence by two levels for very serious limitations to the study design as data derived from only one study with a high risk of attrition bias and one level because of serious imprecision as data were derived from fewer than 400 participants.

Change in analgesic requirements and pain intensity were not reported.

Serious adverse events

Two trials (418 participants) reported serious adverse events over course of follow-up (to two weeks in Katakami 2017a; to six weeks in Katakami 2017b).

Naldemedine may have little to no impact on the risk of non-fatal serious adverse events compared to placebo (RR 3.34, 95% CI 0.85 to 13.15, 2 trials, 418 participants, I^2 = 0%. Analysis 1.5. Katakami 2017b; Katakami 2017a). Eleven non-fatal serious adverse events occurred in the naldemedine arms. In one trial four of the seven non-fatal serious adverse events in the naldemedine arm were considered to be related to the study drug, these were two cases of diarrhoea, one case of vomiting and one abnormal hepatic function test (Katakami 2017b). In the other trial there were in the naldemedine arm one case of each of gastro-intestinal haemorrhage, pneumonia, anaemia and asthenia, the investigators do not state whether they considered these events related to the study drug (Katakami 2017a). One death occurred in one trial (Katakami 2017a), and two in the other (Katakami 2017b). All three occurred in the naldemedine trial arms, the deaths were not considered to be related to naldemedine. We judged the certainty of evidence on risk of non-fatal serious adverse events as low. We downgraded the certainty of evidence by two levels, one for serious limitations to the study design (in one study there was a high risk of attrition bias) and one level for serious imprecision (wide confidence intervals).

Number and type of adverse events

Two trials (418 participants) reported number and type of adverse event over course of follow-up (to two weeks in Katakami 2017a; to six weeks in Katakami 2017b).

There was over double the risk of adverse events reported in naldemedine arms compared to placebo arms (RR 1.49, 95% CI 1.19 to 1.87, 2 trials, 418 participants, I^2 = 0%. Analysis 1.6. Katakami 2017b; Katakami 2017a). We judged the certainty of evidence as moderate. We downgraded the certainty of evidence by one level for serious limitations to the study design (in one study there was a high risk of attrition bias).

The most common adverse event in both trials was diarrhoea. There was four times the risk of diarrhoea in naldemedine arms compared to placebo arms (RR 1.85, 95% CI 1.22 to 2.82, 2 trials, 419 participants, I^2 = 17%. Analysis 1.7. Katakami 2017b; Katakami 2017a).

Secondary outcomes

Number who dropped out due to adverse events

Outcome reported in two trials over the course of follow-up (to two weeks in Katakami 2017a; to six weeks in Katakami 2017b).

The risk of drop out of the study due to adverse events was over eight-times greater in the naldemedine arms compared to placebo arms (RR 5.18, 95% CI 1.28 to 20.91, 2 trials, 420 participants, I^2 = 0%. Analysis 1.8. Katakami 2017b; Katakami 2017a).

Other measures of laxation responses

Only one trial (193 participants) reported this outcome (Katakami 2017b).

There were more spontaneous laxations that felt like a complete evacuation in the naldemedine arm compared to placebo arm (MD 2.05, 95% CI 1.29 to 2.81, 1 trial, 193 participants, full data not provided. Katakami 2017b). There were more spontaneous laxations without straining in the naldemedine arm compared to placebo arm (MD 2.67, 95% CI 1.20 to 4.15, 1 trial, 193 participants, full data not provided. Katakami 2017b).

Relief of other constipation-associated symptoms

Only one trial (193 participants) reported this outcome (Katakami 2017b).

There was little to no difference in overall relief of symptoms (e.g. bloating, abdomen discomfort or pain) between the naldemedine arm and placebo arm at two weeks (mean change -0.25 naldemedine, mean change -0.18 placebo, P value = not significant, 1 trial, 193 participants. Full data not provided. Katakami 2017b).

Quality of life

Only one trial (193 participants) reported this outcome (Katakami 2017b).

There was little to no difference in quality of life between the naldemedine arm and placebo arm at two weeks (mean change -0.25 naldemedine, mean change-0.15 placebo, P value = 0.08, 1 trial, 193 participants. Full data not provided. Katakami 2017b).

Satisfaction with bowel movements

Only one trial (193 participants) reported this outcome (Katakami 2017b).

There was less dissatisfaction with bowel movements in the naldemedine arm compared with placebo arm at two weeks (mean change -0.50 naldemedine arm, mean change -0.16 placebo arm, P value = 0.015, 1 trial, 193 participants. Full data not provided. Katakami 2017b).

Use of rescue medication for laxation over course of trial, and participant preference

These outcomes were not reported.

Low dose naldemedine versus higher dose naldemedine

Only one trial (225 participants) evaluated the effectiveness of two weeks of oral treatment with naldemedine at different doses, 0.1 mg, 0.2 mg, or 0.4 mg daily, in people with cancer irrespective of disease stage (Katakami 2017a).

Primary outcomes

See Summary of findings 2 for primary outcomes.

Laxation response

Laxation response was not reported in the short term. The trial (225 participants) reported the outcome in the medium term (Katakami 2017a).

There were fewer spontaneous laxations in the naldemedine 0.1 mg arm compared with higher dose arms of naldemedine 0.2 mg and 0.4 mg over two weeks (0.1 mg versus 0.4 mg: RR 0.69, 95% CI 0.53 to 0.89 1 trial, 111 participants. Analysis 2.1; 0.1 mg versus 0.2 mg: RR 0.73, 95% CI 0.55 to 0.95, 1 trial, 113 participants. Analysis 2.2). There was little to no difference in risk of spontaneous laxations between naldemedine 0.2 mg arm compared to naldemedine 0.4 mg arm (RR 0.94, 95% CI 0.79 to 1.14, 114 participants. Analysis 2.3). We judged the certainty of evidence on laxation response as low. We reduced it by one level because of serious study limitations because of unclear risk of bias (reporting bias) and one level because of serious imprecision (data derived from fewer than 400 participants).

Patient assessment of change in bowel status was not reported.

Effect on analgesia

Effect in short term was not reported. The trial (225 participants) reported opioid withdrawal symptoms in the medium term (Katakami 2017a).

There was little to no difference on opioid withdrawal symptoms between the three naldemedine dose arms (0.1 mg versus 0.2 mg. MD -0.40, 95% CI -0.90 to 0.10, 114 participants. Analysis 2.5; 0.1 mg versus 0.4 mg MD -0.30, 95% CI -0.85 to 0.25, 112 participants. Analysis 2.4; 0.2 mg versus 0.4 mg: MD 0.10, 95% CI -0.49 to 0.69, 114 participants.Analysis 2.6). We judged the certainty of evidence for effect on analgesia (opioid withdrawal) to be low. We downgraded the certainty of evidence by one level for serious limitations to the study design unclear risk of bias (reporting bias) and imprecision (data derived from fewer than 400 participants).

Change in analgesic requirements and pain intensity were not reported.

Serious adverse events

One trial (225 participants) reported this outcome (Katakami 2017a).

There was little to no difference in occurrence of serious adverse events between the dose arms (0.1 mg versus 0.4 mg RR 0.25, 95% CI 0.03 to 2.17, 112 participants (Analysis 2.10). There were five serious adverse events. Four of the events occurred in the highest dose arm (naldemedine 0.4 mg). One participant each experienced pneumonia, anaemia, or asthenia. One participant died due to bile duct cancer. The other participant experienced a gastrointestinal bleed (taking naldemedine 0.1 mg). The investigators considered the death unrelated to the study drug. Judgements on whether the other events were related to the study drug were not reported. We judged the certainty of evidence for serious adverse events to be low. We downgraded the certainty of evidence by two levels, one for serious limitations to the study design and one for serious imprecision. This was because of unclear risk of bias (reporting bias) and a limited number of events.

Number and type of adverse events

The trial (225 participants) reported these outcomes (Katakami 2017a).

There was little to no difference in the occurrence of an adverse event between the three naldemedine dose arms (0.1 mg versus 0.4 mg RR 0.84, 95% CI 0.67 to 1.06, 1 trial, 112 participants. Analysis 2.7; 0.1 mg versus 0.2 mg RR 0.98, 95% CI 0.76 to 1.27, 1 trial, 114 participants Analysis 2.8; 0.2 mg versus 0.4 mg RR 0.86, 95% CI 0.68 to 1.07, 1 trial, 114 participants. Analysis 2.9). We judged the certainty of evidence on risk of an adverse event to be low. We downgraded the certainty of evidence by one level for serious limitations to the study design and one level for serious imprecision. This was because of unclear risk of bias (reporting bias) and data derived from fewer than 400 participants).

The most common adverse event was diarrhoea. There were fewer events of diarrhoea in the naldemedine 0.1 mg arm compared with the naldemedine 0.4 mg arm (RR 0.61, 95% CI 0.40 to 0.95, 1 trial, 112 participants. Analysis 2.11). There was little to no difference in the proportion experiencing diarrhoea between naldemedine 0.1 mg arm and naldemedine 0.2 mg arm (RR 0.73, 95% CI 0.46 to 1.15, 1 trial, 114 participants. Analysis 2.12) and between 0.2 mg naldemedine arm and 0.4 mg naldemedine arm (RR 0.84, 95% CI 0.59 to 1.21, 1 trial, 114 participants. Analysis 2.13).

Secondary outcomes

Number who dropped out due to adverse events

The trial (225 participants) reported this outcome (Katakami 2017a).

There was little to no difference in the proportion of participants who dropped out of the study due to adverse events between naldemedine dose arms (e.g. 0.1 mg versus 0.4 mg MD 0.75, 95% CI 0.18 to 3.20, 1 trial, 112 participants Analysis 2.14; Analysis 2.15; Analysis 2.16).

Other measures of laxation response

The trial (225 participants) reported this outcome (Katakami 2017a).

There was a lower frequency of spontaneous laxations without straining in the naldemedine 0.4 mg arm compared with either of the two arms of naldemedine at lower doses (0.2 mg P value 0.04; 0.1 mg P value = < 0.001, full data not provided). There was little to no difference in the frequency without straining of spontaneous laxations between naldemedine 0.1 mg and 0.2 mg (P value = 0.16, full data not provided). There was a greater feeling of complete evacuation in naldemedine arms 0.4 mg (P value = < 0.001) and 0.2 mg (P value = 0.04) arms compared to naldemedine 0.1 mg arm (full data not provided). There was little to no difference in the feeling of complete evacuation between naldemedine arms taking either 0.4 mg or 0.2 mg (P value = 0.12, full data not provided).

Other secondary outcomes

Relief of other constipation-associated symptoms, use of rescue medication for laxation, satisfaction with bowel movements, quality of life, and participant preference were not reported.

Naloxone versus placebo

Only one cross-over trial (17 participants) evaluated the effectiveness of oral naloxone compared with placebo in people with advanced cancer (Sykes 1996). The participants received two days of either placebo or naloxone followed by another two days on the trial agent that was not received on day one and two. This was without washout, as in there was no treatment phase designed to reduce biased results by separating the two treatment phases of the trial to eliminate 'carry-over' effects from the first trial drug, placebo or naloxone. Naloxone was given four-hourly for a total daily dose of 0.5%, 1%, 2%, 5%, 10%, or 20% of the total daily dose of morphine.

Primary outcomes

See Summary of findings 3.

Laxation response

This outcome was not reported.

Effect on analgesia

The trial (17 participants) reported in the medium term opioid withdrawal symptoms and pain intensity (Sykes 1996). There was little to no difference in pain intensity experienced between when the participants were taking naloxone and placebo. Full data not provided, including pre-cross-over results provided. There was insufficient evidence provided to make a GRADE judgement on certainty of evidence.

Change in analgesic requirements was not reported.

Serious adverse events

The trial (17 participants) reported on this outcome (Sykes 1996). There were no serious adverse events reported. We judged the certainty of evidence on risk for a serious adverse event to be very low. We downgraded the certainty of evidence on risk by one level for serious limitations to the study design and two levels for very serious imprecision. This was because of unclear risk of bias (reporting bias) and data derived from fewer than 400 participants.

Number and type of adverse events

These outcomes were not reported.

Secondary outcomes

Number who dropped out due to adverse events

The trial (17 participants) reported this outcome (Sykes 1996).

Four participants dropped out due to adverse events. Two participants withdrew from the study whilst taking naloxone, one because of general deterioration in health while taking naloxone (although not thought to be a causal relationship), and one participant withdrew because of nausea after two doses of naloxone at the 10% level (5 mg in this case). One participant because of diarrhoea experienced while receiving the placebo. One participant withdrew because of severe diarrhoea caused by the lactulose taken as part of the test on bowel function.

Other outcomes

Other measures of laxation response, relief of other constipation-associated symptoms, use of rescue medication for laxation, quality of life, patient satisfaction with bowel movements, and participant preference were not reported.

Naloxone with oxycodone versus oxycodone

Three trials (368 participants) evaluated the effectiveness of oxycodone with naloxone prolonged-release tablets (OXN PR) compared with oxycodone prolonged-release (OXY PR) tablets in people with cancer (Ahmedzai 2012; Dupoiron 2017; Lee 2017). In one trial, participants had cancer at any stage and the drug dose for OXN PR was up to 120 mg daily over four weeks of treatment (Ahmedzai 2012). In one of the other trials they evaluated five weeks of OXN PR up to 160 mg daily in people with cancer and non-cancer pain. We included the trial's participant subset data on 46 people with cancer (Dupoiron 2017). The third trial evaluated four weeks of OXN PR up to 80 mg daily in participants with moderate to severe cancer pain (Lee 2017).

Primary outcomes

See Summary of findings 4 for primary outcomes.

Laxation response

Risk of spontaneous rescue-free laxations was not reported in the short or medium term.

Two trials (212 participants) reported patient assessment of change in bowel status over the course of the trial (at five weeks Ahmedzai 2012, and at four weeks since start of treatment Lee 2017). In one trial there was more improvement in bowel status in the OXN PR arm compared to OXY PR arm (mean change – 11.14, 95% CI -19.03 to -3.24, 1 trial, 133 participants, full data not provided Ahmedzai 2012). In the other there was little to no change in bowel status between trial arms (P value = 0.264, 1 trial, 79 participants, full data not provided Lee 2017). We judged the certainty of evidence on patient assessment of change in bowel status as low. We downgraded by one level because of serious limitations to the study design (unclear risk of reporting bias), and one level for serious imprecision (data derived from fewer than 400 participants).

Effect on analgesia

Short-term effects were not reported. Only one trial (133 participants) reported opioid withdrawal symptoms in the medium term (Ahmedzai 2012).

There was little to no difference in opioid withdrawal symptoms between OXN PR arm and OXY PR arm at one week following end of treatment (MD -0.63, 95% CI -2.44 to 1.18 , 1 trial, 133 participants. Analysis 3.1). We judged the certainty of evidence on opioid withdrawal symptoms as low. We downgraded by one level because of serious study limitations (unclear risk of bias reporting bias) and one level for serious imprecision (data derived from fewer than 400 participants).

Medium-term effect on change in analgesic requirements and pain intensity were not reported.

Serious adverse events

Three trials (362 participants) reported this outcome (Ahmedzai 2012; Dupoiron 2017; Lee 2017).

There was little to no difference in the proportion of participants experiencing a serious adverse event (SAE) between OXN PR arms and OXY PR arms (RR 0.68, 95% CI 0.44 to 1.06) I^2 = 55%, 3 trials, 362 participants. Analysis 3.2). We were unable to explore the substantial statistical heterogeneity found as none of the trials fitted our criteria for either subgroup or sensitivity analyses. One trial attributed all 12 events to the study drugs; there were eight events in the OXN PR arm and four in the OXY PR arm (Ahmedzai 2012). In the other trials, one attributed none of the events to the study drug (Dupoiron 2017) and the other does not detail whether the events could be attributed to the study drug (Lee 2017). In one trial 18 participants died, nine in each trial arm (Ahmedzai 2012), in one of the other trials one participant died in the OXN PR arm and three in the OXY PR arm (Dupoiron 2017). None of the deaths were attributed to the trial drugs. The other trial did not report any deaths (Lee 2017). We judged the certainty of evidence of serious adverse events to be very low. We downgraded by one level because of serious study limitations (unclear risk of bias reporting bias), one for serious imprecision (data derived from fewer than

400 participants) and one for serious inconsistency (substantial unexplained heterogeneity).

Number and type of adverse events

Three trials (362 participants) reported these outcomes (Ahmedzai 2012; Dupoiron 2017; Lee 2017).

There was little to no difference in the proportion of participants experiencing an adverse event between OXN PR arms and OXY PR arms (RR 1.01; 95% 0.87 to 1.18. I^2 = 0%; 3 trials, 362 participants. Analysis 3.3). We judged the certainty of evidence for number of adverse events to be low. We downgraded by one level because of serious study limitations (unclear risk of bias reporting bias) and one level for serious imprecision (data derived from fewer than 400 participants).

A common adverse event reported in all three trials was nausea. Fewer participants experienced nausea in the OXN PR arms compared with OXY PR arms (RR 0.55, 95% CI 0.33 to 0.94. I^2 = 0%; 3 trials, 362 participants. Analysis 3.4).

Secondary outcomes

Number who dropped out due to adverse events

Two trials (312 participants) reported this outcome (Ahmedzai 2012; Lee 2017).

There was little to no difference in the proportion of participants who dropped out of the study due to adverse events between the OXN PR arm and OXY PR arm (RR 1.25, 95% CI 0.73 to 2.15; 2 trials, 312 participants, I^2 = 58%, Analysis 3.5. Ahmedzai 2012; Lee 2017).

Use of rescue medication for laxation

Two trials (220 participants) reported this outcome (Ahmedzai 2012; Dupoiron 2017). There was little to no difference in the use of rescue medication (oral bisacodyl) between the OXN PR arms and OXY PR arms (SMD -0.27, 95% CI -0.53 to -0.00. 2 trials, 220 participants, I^2 = 0%. Analysis 3.6. Ahmedzai 2012; Dupoiron 2017).

Quality of life

Two trials (200 participants) reported this outcome (Ahmedzai 2012; Lee 2017). There was little to no difference in quality of life at four weeks between the OXN PR arms and OXY PR arms (SMD 0.08, 95% CI -0.20 to 0.35, 2 trials, 200 participants, I^2 = 0%. Analysis 3.7. Ahmedzai 2012; Lee 2017).

Other outcomes

Relief of other constipation-associated symptoms in the short to medium term, other measures of laxation response, participant satisfaction with bowel movements, and participant preference were not reported.

Methylnaltrexone versus placebo

Three trials (518 participants) evaluated the effectiveness of subcutaneous methylnaltrexone compared to placebo in people with advanced disease, of which the majority of participants had cancer (Bull 2015; Slatkin 2009; Thomas 2008). One trial involved two active treatment arms; a single dose of either methylnaltrexone 0.15 mg/kg or 0.30 mg/kg (Slatkin 2009). The other two trials administered methylnaltrexone every other day for two weeks. One trial administered methylnaltrexone 0.15 mg/kg of bodyweight (Thomas 2008), and the other trial, with the aim of improving ease of administration, administered methylnaltrexone 8 mg to participants whose bodyweight was between 38 kg and 62 kg, or methylnaltrexone 12 mg if they weighed more than 62 kg (Bull 2015).

Primary outcomes

See Summary of findings 5 .

Laxation response

Two trials (287 participants) reported short-term outcome (Slatkin 2009; Thomas 2008). The risk of spontaneous rescue-free laxations within 24 hours of the first treatment dose was over three times greater in the methylnaltrexone arm compared to the placebo arm (RR 2.97, 95% CI 2.13 to 4.13. 2 trials, 287 participants, I^2 = 31%. NNTB 3, 95% CI 2 to 3. Analysis 4.1. Slatkin 2009; Thomas 2008). We judged the certainty of evidence for laxation within 24 hours of the first dose to be low. We downgraded by one level for serious study limitations (unclear risk of bias due to reporting bias) and one for serious imprecision (data from fewer than 400 participants).

Two trials (305 participants) reported medium-term outcome. The risk of spontaneous rescue-free laxations was more than seven times greater in the medium term in the methylnaltrexone arms compared to placebo arms (RR 8.15, 95% CI 4.76 to 13.95, 2 trials, 305 participants, I^2 = 47%. NNTB 2, 95% CI 2 to 2 Analysis 4.2. Bull 2015; Thomas 2008). We judged the certainty of evidence for laxation response over two weeks to be moderate. We downgraded by one level for serious study limitations (unclear risk of bias due to reporting bias). As the effect size was large, we did not downgrade for serious imprecision because data were derived from fewer than 400 participants.

Two trials report change in patient assessed bowel status over the course of the trial (287 participants) (Slatkin 2009; Thomas 2008). Improvement in bowel status was three times greater in patients in the methylnaltrexone arms compared to placebo arms (RR 2.32, 95% CI 1.64 to 3.27, 2 trials, 287 participants. Analysis 4.3. Slatkin 2009; Thomas 2008). We judged the certainty of evidence for patient assessment of change in bowel status to be low. We downgraded by one level for serious study limitations (unclear risk of bias due to reporting bias) and one for serious imprecision (data from fewer than 400 participants).

Effect on analgesia

Two trials reported opioid withdrawal symptoms in the short term (287 participants) (Slatkin 2009; Thomas 2008) and two trials (285 participants) in the medium-term (Slatkin 2009; Thomas 2008). Two trials (285 participants) reported on pain intensity in the short term (Slatkin 2009; Thomas 2008).

There was little to no difference in effect on opioid withdrawal symptoms in the short term between methylnaltrexone arms at different doses and placebo arms (at four hours post treatment: methylnaltrexone 0.15 mg/kg MD -0.05, 95% CI -0.56 to 0.46, 1 trial, 99 participants. Analysis 4.5. Slatkin 2009; methylnaltrexone 0.30 mg/kg MD -0.01, 95% CI -0.40 to 0.38, 1 trial, 107 participants. Analysis 4.6. Slatkin 2009; in the other trial at 24 hours MD 0.00, 95% CI -0.46 to 0.46, 1 trial, 133 participants. Analysis 4.4. Thomas 2008).

There was little to no difference in effect on opioid withdrawal symptoms between methylnaltrexone and placebo in the medium term (MD -0.20, 95% CI -0.80 to 0.40, 1 trial, 133 participants. Analysis 4.7. Thomas 2008; methylnaltrexone 0.15 mg/kg MD -0.40, 95% CI -0.90 to 0.10, 1 trial, 99 participants; Analysis 4.8. Slatkin 2009; methylnaltrexone 0.30 mg/kg MD -0.15, 95% CI -0.57 to 0.27, 1 trial 107 participants Analysis 4.9. Slatkin 2009). We judged the certainty of evidence for effect in short to medium term on opioid withdrawal symptoms to be low. We downgraded the certainty of evidence by one level for serious study limitations because of unclear risk of bias (reporting bias) and one for serious imprecision (data derived from fewer than 400 participants).

Those in the methylnaltrexone 0.15 mg/kg arm experienced reduced pain intensity compared to placebo in the short term (at four-hours following the intervention) (MD -0.20, 95% CI -1.02 to 0.62, 1 trial. 133 participants. Analysis 4.10. Thomas 2008). There was little to no difference in pain intensity in the short term in those in the methylnaltrexone 0.3 mg/kg arm compared to placebo (MD -0.25, 95% CI -0.91 to 0.41, 1 trial, 152 participants. Analysis 4.11. Slatkin 2009).

We judged the certainty of evidence for effect on pain intensity to be low. We downgraded the certainty of evidence by two levels, one for serious study limitations (unclear risk of bias due to reporting bias) and one for serious imprecision (data derived from fewer than 400 participants).

Change in analgesic requirements was not reported.

Serious adverse events

Two trials reported this outcome (364 participants) (Bull 2015; Thomas 2008).

There were fewer serious adverse events in those in the methylnaltrexone arm than for those in the placebo arm (RR 0.59, 95% CI 0.38 to 0.93; I^2 = 0%; 2 trials, 364 participants. Analysis 4.12. Bull 2015; Thomas 2008). In both trials, the investigators considered all serious adverse events as either not related or unlikely to be related to the trial drug. In Thomas 2008, the type of serious adverse events in the 11 participants who were receiving methylnaltrexone were: aneurysm ruptured, respiratory arrest, exacerbation of dyspnoea, suicidal ideation, aggression, malignant neoplasm progression, concomitant disease progression, myocardial ischaemia, aggravation of coronary artery disease, and aggravation of congestive heart failure. Bull 2015 did not describe the types of serious adverse events.

Althouh one trial did not report serious adverse events occurring during the randomised phase (Slatkin 2009), during its open-label phase three participants experienced such an event. One participant had flushing, one participant had delirium possibly related to methylnaltrexone, and one participant had severe diarrhoea and subsequent dehydration and cardiovascular collapse considered to be related to methylnaltrexone.

We judged the certainty of evidence for risk of a serious adverse event to be low. We downgraded the evidence by one level for study limitations (unclear risk of bias due to reporting bias) and one for serious imprecision (data derived from fewer than 400 participants).

Number and type of adverse events

Three trials reported this outcome (518 participants) (Bull 2015; Slatkin 2009; Thomas 2008).

More participants in methylnaltrexone arms experienced adverse events than those in the placebo arms (RR 1.17, 95% CI 1.05 to 1.30; I^2 = 74% suggesting substantial heterogeneity between trials, 3 trials, 518 participants. Analysis 4.13). We considered subgroup and sensitivity analyses to explore heterogeneity but none of the trials characteristics fulfilled any of our planned possible sources of heterogeneity. We judged the certainty of evidence for adverse events to be low. It was downgraded by two levels; one for study limitations (unclear risk of reporting bias) and one because of inconsistency due to substantial statistical heterogeneity between the trials.

Adverse events were reported as severe, this was based on data from two trials (Slatkin 2009; Thomas 2008). One reported that during the trial and open-label phase that 19 participants had severe events that were possibly related to methylnaltrexone (Slatkin 2009). In the other trial more participants in the placebo group experienced severe adverse events than in the intervention group (5/63 (8%) with methylnaltrexone versus 9/71 (13%) with placebo). The third trial did not report on severity (Bull 2015).

All three trials reported that participants in both methylnaltrexone and placebo arms experienced abdominal pain, flatulence, nausea, and vomiting (Bull 2015; Slatkin 2009; Thomas 2008). There were more reports of abdominal pain in the methylnaltrexone arm compared to placebo (RR 2.18, 95% CI 1.50 to 3.18, I^2 = 65% suggesting substantial heterogeneity between trials, 3 trials, 667 participants. Analysis 4.14). We did not undertake a sensitivity analyses as none of the trials characteristics fulfilled any of our planned possible sources of heterogeneity. There was little to no difference between the methylnaltrexone and placebo arms in the proportion who experienced flatulence (RR 1.88, 95% CI 0.99 to 3.57, I^2 = 0%, 3 trials, 667 participants. Analysis 4.15) or who experienced vomiting (RR 0.95, 95% CI 0.55 to 1.65, I^2 = 0%, 3 trials, 667 participants. Analysis 4.16). There were more reports of nausea in the methylnaltrexone arm compared to placebo (RR 1.89, 95% CI 1.26 to 2.85, I^2 = 0%, 3 trials, 667 participants. Analysis 4.17).

Secondary outcomes

Number who dropped out due to adverse events

Two trials (364 participants) reported this outcome (Bull 2015; Thomas 2008). There was little to no difference in the proportion of participants who dropped out of the study due to adverse events between the trial arms (RR 1.22, 95% CI 0.54 to 2.76, I^2 = 0%; 2 trials, 363 participants. Analysis 4.18). The other trial reported no dropouts occurred due to adverse events Slatkin 2009.

Use of rescue medication for laxation

Two trials (363 participants) reported this outcome (Bull 2015; Thomas 2008). Fewer in the methylnaltrexone arm needed for rescue medication for laxation compared to placebo (RR 0.67, 95% CI 0.49 to 0.91, I^2 = 0%; 2 trials, 363 participants. Analysis 4.19).

Other secondary outcomes

Other measures of laxation responses and symptoms of constipation, satisfaction with bowel treatments, quality of life and participant preference were not reported.

Low dose methylnaltrexone versus high dose methylnaltrexone

Two trials (518 participants) evaluated different dosing regimens of methylnaltrexone in people with advanced disease (Portenoy 2008; Slatkin 2009). One trial, irrespective of bodyweight, explored fixed doses of methylnaltrexone 1 mg, 5 mg, 12.5 mg, or 20 mg in 33 participants (Portenoy 2008). Because of the limited number of participants in the trials, we provide outcomes for participants taking 1 mg compared to participants taking 5 mg or greater. The drug was administered on alternate days over one week. The other trial compared one dose of different dose-ranging schedules of 0.15 mg/kg for 47 participants with 0.3 mg/kg for 55 participants (Slatkin 2009). We did not combine the data because the dosing schedules differed.

Primary outcomes

See Summary of findings 6 for primary outcomes for methylnaltrexone 1 mg compared to methylnaltrexone 5 mg.

Laxation response

Two trials (135 participants) reported short-term outcome. There was little to no difference in risk of spontaneous rescue-free bowel movements within first 24 hours (at fours hours after first dose) between participants taking a lower dose to those on a higher dose (dose 1 mg compared to 5-20 mg, RR 0.21, 95% CI 0.03 to 1.41, 1 trial, 33 participant.Analysis 5.1.Portenoy 2008; dose 0.15 mg/kg compared to 0.3 mg/kg, RR 1.06, 95% CI 0.77 to 1.46, 1 trial, 102 participants. Analysis 5.1. Slatkin 2009). We judged the certainty of evidence for laxation response within 24 hours as low. We downgraded the certainty of evidence by one level for serious study limitations and one level for serious imprecision. This was because of unclear risk of bias (reporting bias) and fewer than 400 participants.

Only one trial (26 participants) reported outcomes in the medium term (after dosing at day three) (Portenoy 2008). There was little to no difference in risk of spontaneous rescue-free bowel movements between participants receiving 1 mg compared to participants receiving 5 mg or greater within four hours of dose on day three (day three: RR 2.91, 95% CI 0.82, 10.39; 1 trial, 26 participants. Analysis 5.2). We judged the certainty of evidence for laxation response at day three to be very low. We downgraded the certainty of evidence by one level for serious study limitations (unclear risk of reporting bias) and two for very serious imprecision (sparse data, 26 participants). Patient-reported overall improvement in symptoms of constipation was not reported in the medium term.

Patient-reported assessment of change in bowel status was reported in only one trial (Slatkin 2009). There was little to no difference in improvement between dose arms at the end of the double-blind phase (RR 0.98, 95% CI 0.71 to 1.35, 1 trial, 102 participants. Analysis 5.3). We judged the certainty of evidence for patient-reported assessment of change in bowel status to be low. We downgraded the certainty of evidence by one level for serious study limitations and one level for serious imprecision. This was because of unclear risk of bias (reporting bias) and fewer than 400 participants.

Effect on analgesia

Two trials (135 participants) report on effect on analgesia in the short to medium term (Portenoy 2008; Slatkin 2009). There was little to no difference between trial arms in the mean change in symptoms of opioid withdrawal from baseline to four-hour evaluation or medium term (MD -0.04, 95% CI -0.58 to 0.50, 1 trial, 102 participants. Slatkin 2009. Analysis 5.4; MD -0.25, 95% CI -0.84 to 0.34, 1 trial, 102 participants. Slatkin 2009. Analysis 5.5). In the other trial there was also little to no difference in the short term and medium term between trials arms in pain levels or symptoms of opioid withdrawal (data not provided) (33 participants) (Portenoy 2008).

Change in analgesic requirements was not reported.

We judged the certainty of evidence for effect on analgesia to be low. We downgraded the certainty of evidence by one level for serious study limitations and one level for serious imprecision. This was because of unclear risk of bias (reporting bias) and fewer than 400 participants.

Serious adverse events

Two trials (135 participants) reported on serious adverse events (Portenoy 2008; Slatkin 2009). In one trial, 15 participants experienced a serious adverse event (Portenoy 2008). Which trial arm they were in was not reported. The events were lymphadenectomy, febrile neutropenia, depressed level of consciousness, suicide attempt, and delirium. All were considered unrelated to study drug. In the other trial, no serious adverse events occurred during the randomised trial phase, although during the open-label phase three participants experienced such an event of which one had severe diarrhoea and subsequent dehydration and cardiovascular collapse (Slatkin 2009). These were considered to be related to the study drug. We did not judge the certainty of evidence for serious adverse events as data were not complete.

Number and type of adverse events

Two trials reported on adverse events (135 participants) (Portenoy 2008; Slatkin 2009). There was little to no difference in the occurrence of adverse events between the different dose arms in either study. We did not combine the study data as the dosing differed substantially per study (RR 1.00, 95% CI 1.00 to 1.00, 33 participants. Portenoy 2008; RR 0.90, 95% CI 0.73 to 1.13, 102 participants. Slatkin 2009). The most common adverse event in both trials and per trial arm was abdominal pain. We judged the quality of certainty for adverse events to be low. This was because of serious study limitations due to unclear risk of bias (reporting bias) and imprecision (fewer than 400 participants).

Secondary outcomes

Number who dropped out due to adverse events

Two trials reported on this outcome (135 participants) (Portenoy 2008; Slatkin 2009). In one trial, one participant in methylnaltrexone 12.5 mg arm discontinued the trial because of an adverse event (Portenoy 2008). This was an 84-year-old man who withdrew due to syncope. The event was transient and resolved without sequelae; the investigators assessed that it was related to the medication. This trial also reported that in the open-label phase, after receiving three doses, a 20-year-old man was withdrawn from the trial due to abdominal cramping that was considered as probably related to the trial medication. In the other trial, none of the participants discontinued because of an adverse event (Slatkin 2009).

Use of rescue medication for laxation

Only one trial (33 participants) reported this outcome (Portenoy 2008). Those in methylnaltrexone 1 mg arm required a rescue laxative approximately twice as often as those in the higher dose groups of 5 mg, 12.5 mg, and 20 mg (data were not provided).

Satisfaction with bowel movements

Only one trial (33 participants) reported this outcome (Portenoy 2008). There was little to no difference in satisfaction with bowel movements between trials arms. Data were not provided.

Other secondary outcomes

Other measures of laxation response in short to medium term and rescue-free laxation response in the longer term, relief of other constipation-associated symptoms, quality of life, preference were not reported.

DISCUSSION

Summary of main results

This is an update of the review first published in 2008, and last updated in 2018. We sought to determine the effectiveness and safety of mu-opioid antagonists (MOAs) for opioid-induced bowel dysfunction (OIBD) in people with cancer and people receiving palliative care. Where reported (9/10) studies excluded patients in situations that may affect efficacy by compounding constipation such as any disease processes suggestive of abnormalities of the gastrointestinal tract, and chemotherapy. Five of the 10 randomised controlled trials (RCTs) included explored outcomes in cancer populations irrespective of disease stage. Two of these studies compared oral naldemedine with placebo, one of which also compared dosing regimens, and the other three compared oral prolonged-released oxycodone/naloxone with oxycodone alone. Oral naloxone only compared with placebo was evaluated in people with advanced cancer. The other four trials compared subcutaneous methylnaltrexone either with placebo or different regimens of methylnaltrexone in palliative care populations, in which the majority of participants had advanced cancer.

Naldemedine compared with placebo in people with cancer

We found moderate-certainty evidence that in the medium term (over two weeks) naldemedine may increase the risk of spontaneous laxations and the risk of adverse events. There was no clear evidence that it has little to no impact on opioid withdrawal symptoms or risk of serious adverse events. We found this evidence was of very low certainty on opioid withdrawal symptoms, and low for serious adverse events. Patient assessment of bowel status was not reported.

Low-dose naldemedine compared with higher-dose naldemedine in people with cancer

The risk of spontaneous laxations in the medium term and risk of serious adverse events may be higher when naldemedine administered at 4 mg compared to 1 mg, but we found the evidence is of low certainty. There was little to no difference in doses in the impact on opioid withdrawal symptoms or risk of adverse events, but we found the evidence was of low certainty. Patient assessment of bowel status not reported.

Naloxone compared with placebo in people with advanced cancer

There was no reported data on laxation response, patient assessment of bowel status, effect on analgesia, serious adverse events or adverse events.

Naloxone with oxycodone versus oxycodone in people with cancer

Therewere no reported data on risk of spontaneous laxations. We found low-certainty evidence which is inconsistent in whether naloxone with oxycodone compared to oxycodone only improves patients assessment of bowel status. There was little to no difference between naloxone with oxycodone compared to oxycodone on impact on opioid withdrawal symptoms or risk of adverse events, but we found the evidence was of low certainty. We found very low-certainty evidence that naloxone with oxycodone has little to no impact on the risk of serious adverse events.

Methylnaltrexone compared with placebo in people receiving palliative care

We found moderate-certainty evidence that in the medium term methylnaltrexone may increase the risk of spontaneous laxations and low-certainty evidence that it may improve patient assessment of bowel status. There was little to no difference between methylnaltrexone compared with placebo on impact on opioid withdrawal symptoms or that it increases the risk of a serious adverse event, but we found this evidence of low certainty. We found low-certainty evidence that methylnaltrexone increases the risk of adverse events.

Methylnaltrexone 1 mg compared with 5 mg or greater

We found low- to very low-certainty evidence that there was little to no difference in impact between methylnaltrexone at 1 mg compared to 5 mg or greater on laxation response in the short and medium term. There was little to no difference on patient assessment of bowel status, opioid withdrawal symptoms, and adverse events but the evidence was of low certainty. Serious adverse events were underreported.

Overall completeness and applicability of evidence

We sought trial evidence widely beyond published papers. Where available, we obtained regulatory documents; although these provided few new data.

Our review findings were limited. The trials were few and this limited our combined analyses. In some analyses, there was statistical heterogeneity across the trials. In regards to the primary outcomes, this related to adverse effects of methylnaltrexone in comparison to placebo. We did not undertake sensitivity analyses as none of the trial characteristics fulfilled our criteria for possible sources of heterogeneity. The evidence on naldemedine was from two trials from the same research group. The trial on naloxone only measured one of our four primary outcomes of interest.

The body of evidence could be argued as stronger for methylnaltrexone, as more evidence was provided on our primary outcomes of interest. It is important to reflect that this is overall of low-certainty evidence, and in one of the four methylnaltrexone trials the assessment of impact of the drug may have been affected as participants in the placebo arm were on higher doses of opioids than those in the methylnaltrexone arm. Our analysis was more limited on methylnaltrexone dose response as we were unable to combine the studies because of different dosing schedules.

Participant outcomes were under evaluated. Only two trials assessed quality of life (Ahmedzai 2012; Katakami 2017b). Few trials reported on impact of MOAs on the intensity of pain. This may be as it is hard to assess formally as it is subjective, but it is an important to measure. There are also other outcomes that were not measured in any of these trials that earlier research suggests need further exploration. This includes whether MOAs, in particular methylnaltrexone, increase cancer survival (Janku 2015).

We found, as we did in our previous update, no completed trials that fulfilled our inclusion criteria on naloxegol, which in 2014 was approved by the FDA for use in OIBD in people without cancer. However, there are trials of naloxegol that are registered as ongoing, the most recent is from 2017 (NCT03067708). Evaluations on the development of new MOAs for OIBD, their effectiveness, and safety is an active research field. We found 11 trials in populations of people with cancer or people receiving palliative care (or both) that were in progress, awaiting assessment or were completed, but published results were not yet available at the time of publishing this review.

Quality of the evidence

None of the evidence for the primary outcomes was judged as high certainty. The certainty was mostly low or very-low, commonly because of study limitations (because of attrition or reporting bias) alongside serious or very serious imprecision because data involved a limited or very limited number of participants/events. Some evidence, on spontaneous rescue-free laxations and adverse events regarding naldemedine compared with placebo, was judged as moderate. It was down-graded once because of serious risk of attrition bias. The only other outcome whose evidence was judged as moderate was spontaneous rescue-free laxations in the medium term regarding methylnaltrexone compared with placebo; here it was downgraded because of unclear risk of reporting bias. In two instances where we were able to combine data another quality issue occurred; this was regarding inconsistency across trials because of substantial unexplained heterogeneity. This occurred in the comparison of methylnaltrexone with placebo for adverse advents and in comparison, of naloxone + oxycodone compared with oxycodone alone for serious adverse events.

Potential biases in the review process

We sought trial evidence widely, including five citation databases. We sought unpublished trial data from pharmaceutical and regulatory agencies databases. However, there are limited guidelines in how to seek unpublished data and searching regulatory agency websites is not straightforward.

We limited inclusion to trials that specified that their participants had cancer, or were in palliative care, irrespective of disease stage. This is likely to have led to a loss of data, as trials we excluded may have included people with such characteristics, but the trial papers did not provide this level of detail.

We included trials with methodological limitations. In addition, there is a potential problem due to carry-over effects in the cross-over designed trial (Sykes 1996), and our combined analysis was limited by the number of trials available. As different MOA time points of greatest potential differ, in any future updates primary outcome time points may be need to be reconsidered and not standardised as in this update.

Agreements and disagreements with other studies or reviews

This is an update of a Cochrane systematic review examining the evidence for MOAs, as in its last version (Candy 2018) it is looking specifically for OIBD in cancer and palliative care populations. This update identified two new trials, whilst the certainty of the evidence for naldemedine has changed, the overall conclusions have not changed from the last published version.

There are reviews that have evaluated the effect of MOAs for OIBD across different populations, although no recent Cochrane Review. One review identified 14 trials, in addition to four of the trials included in this review, they;included trials on methadone-induced constipation and trials involving participants receiving an opioid for chronic non-malignant pain (Ford 2013). In their meta-analysis of 14 trials of 4101 participants the authors found the MOAs methylnaltrexone, naloxone, and alvimopan were superior to placebo for the treatment of opioid-induced constipation. However, the numbers of adverse events were significantly more common. In a more recent review in which the authors included trials of any treatments approved for opioid-induced constipation; these included both MOAs and the laxatives lubiprostone and prucalopride (Nee 2018). The authors identified 26 trials and came to similar conclusions on MOAs. In recognition of the heterogeneity they observed across the trials, to identify possible moderating factors they undertook sensitivity analysis and a meta-regression. They found that treatments were more likely to be effective in study populations taking higher doses of opioids at baseline or refractory to laxatives. In this review our data is more limited preventing a repeat of their sensitivity analysis.

AUTHORS' CONCLUSIONS

Implications for practice

For people with cancer and people receiving palliative care with opioid-induced bowel dysfunction

In people with cancer who have opioid-induced bowel dysfunction (OIBD), despite laxative use, we found moderate certainty in the evidence that the mu-opioid antagonist (MOA), naldemedine, taken orally may improve bowel function within two weeks of the start of administration. We found very low certainty in the evidence whether naldemedine has little to no increase in risk of increasing symptoms of opioid withdrawal. We found low-certainty evidence that naldemedine has little to no increase in chances of a serious adverse event. We found moderate-certainty evidence that naldemedine increases the chances of experiencing a non-serious adverse event. The most common non-serious adverse event is diarrhoea. Patient assessment of improvement in bowel status was not reported.

Trials on the effect of naloxone alone or in combination with oxycodone in treating OIBD in people with cancer did not measure bowel function within two weeks of the start of administration. For naloxone in combination with oxycodone we found low-certainty evidence that it has no impact on symptoms of opioid withdrawal and adverse events, and very low-certainty evidence that it has no effect on risk of serious adverse events (SAEs).

We found moderate-certainty evidence in palliative care that when conventional laxatives have failed that the MOA, methylnaltrexone, administered subcutaneously, can be successful within two weeks in improving bowel function. We found low-certainty evidence that methylnaltrexone improves peoples assessment of their bowel status, improves within 24 hours bowel function, and that it has little to no effect on symptoms of opioid withdrawal. There is low-certainty evidence that it does not increase the chances of SAEs and that it has little to no effect on adverse events.

We found no studies on children, and no head-to-head trials of MOAs (two MOAs compared with each other).

For clinicians

In this update, our overall conclusions have not changed. For people with cancer, there is moderate-certainty evidence that oral naldemedine may be effective within two weeks of administration in inducing laxation where conventional laxatives have failed. Patient assessment of change in bowel status was not reported in the included trials. There is low-certainty evidence that naldemedine has little to no impact on symptoms of opioid withdrawal. There were in one of the two trials that assessed naldemedine five serious adverse events in participants in the naldemedine arm, and no serious adverse events in participants taking placebo. It is not clear if any of the events were related to naldemedine. We judged this as low-certainty evidence on whether this drug increases the risk of serious adverse events. There was low-certainty evidence that naldemedine did increases the chances of experiencing another (non-serious) adverse event; commonly this was diarrhoea.

In palliative care where conventional laxatives have failed, there is low-certainty evidence that methylnaltrexone is effective in the short term (within 24 hours). Over two weeks, there is moderate-certainty evidence that methylnaltrexone is effective in inducing laxation for a proportion of people in palliative care with OIBD There is low-certainty evidence that methylnaltrexone improves peoples assessment of their bowel status. There is low-certainty evidence that methylnaltrexone has little to no impact on symptoms of opioid withdrawal. Methylnaltrexone may be associated with an increase in certain adverse events, such as abdominal pain and flatulence but this evidence is of low certainty. There is low-certainty evidence to suggest that this medication has little to no increase in the risk of serious adverse events.

Trials on naloxone alone or in combination with oxycodone in treating OIBD in people with cancer did not measure laxation response within two weeks of drug administration. For naloxone in combination with oxycodone there is low-certainty evidence to support the suggestion that it has little to no impact on analgesia or in the risk of adverse events. There is very low-certainty evidence that naloxone in combination with oxycodone has little to no impact on the risk of SAEs.

These treatments were tested in studies that excluded patients in situations that may affect efficacy by compounding constipation such as any disease processes suggestive of abnormalities of the gastrointestinal tract, and chemotherapy. All these treatments are unlikely to be effective in all people and not all outcomes have been fully evaluated, for example, treatment satisfaction and preference. We found no studies on children. There have been no head-to-head trials, so it is difficult to compare their impact on OIBD.

For policy makers

In adults in palliative care, when conventional laxatives have failed, subcutaneous methylnaltrexone at two weeks, and in people with cancer oral naldemedine at two weeks may be successful in improving bowel function. In adults with cancer and those receiving palliative care, laxatives are first-line drug therapy. When conventional laxatives have failed, subcutaneous methylnaltrexone is a second-line therapy if an immediate response is required. Oral naldemedine is a second-line therapy if an immediate laxation is not essential.

For funders of the intervention

There is sufficient evidence in palliative care for adults that when conventional laxatives have failed subcutaneous methylnaltrexone may improve bowel function within two weeks and low-certainty evidence it may improve function within 24 hours. There is sufficient evidence that in adults with cancer oral naldemedine may improve bowel function within two weeks of start of administration. Evidence on naldemedine impact on bowel function is not reported. We would encourage funders to consider, when conventional laxatives have failed, subcutaneous methylnaltrexone as a second-line therapy if an immediate response is required. Oral naldemedine is a second-line therapy if an immediate laxation is not essential.

Implications for research

We found four trials that were ongoing, and six awaiting further detail on whether they fulfilled our eligibility criteria. This includes evaluation of naloxegol. Therefore, some of the suggestions listed in this section may need to be modified once the results of these trials are published. Two ongoing trials, which were excluded based on our current inclusion criteria of treatment for people with OIBD, are evaluating whether naldemedine alone or as an adjunct may prevent OIBD starting (jRCTs031200397; Ozaki 2020). This suggests any future update of this review may want to also consider use of MOAs as a preventative treatment in these patient groups.

General

Rigorous randomised controlled trials (RCTs) measuring standardised and clinically- and participant-relevant outcomes are needed to establish the effectiveness and safety of MOAs. Head-to-head comparisons should be considered. Trials should be reported according to the CONSORT statement and its extensions such as for cross-over trials (Schulz 2010).

Design

Attrition rates in the included trials and the relatively small numbers of eligible participants in any one palliative care treatment unit suggest that trials should involve participants recruited from multiple centres.

Measurement (endpoints)

There is a need to include multiple measures in addition to laxation response, these include analgesia effect, pain intensity, tolerability, quality of life, participant preference, and costs.

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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]

Candy 2018

Candy B, Jones L, Vickerstaff V, Larkin PJ, Stones P. Mu-opioid antagonists for opioid induced bowel dysfunction in people with cancer and people receiving palliative care. *Cochrane Database of Systematic Reviews* 2018, Issue 6. Art. No: CD006332. [DOI: 10.1002/14651858.CD006332.pub3]

McNicol 2007

McNicol ED, Boyce D, Carr DB, Schumann R. Mu-opioid antagonists for opioid-induced bowel dysfunction. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No: CD006332. [DOI: 10.1002/14651858.CD006332]

McNicol 2008

McNicol ED, Boyce D, Schumann R, 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]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ahmedzai 2012

Study characteristics	
Methods	Randomised, parallel, controlled, multi-centre trial. International with sites in Australia, Czech Republic, France, Germany, Hungary, Israel, the Netherlands, Poland, and the UK
Participants	**Aim:** to investigate whether oxycodone with naloxone prolonged release (OXN PR) can improve constipation and maintain analgesia compared with oxycodone prolonged release only (OXY) PR tablets, in people with cancer. **Inclusion criteria:** people with chronic moderate/severe cancer pain and requiring 24-hour opioid therapy. **Exclusion criteria:** clinically unstable disease or significant cardiovascular, renal, hepatic, or psychiatric disease; clinically significant gastrointestinal disease or significant structural abnormalities of the gastrointestinal tract; cyclic chemotherapy within 2 weeks before screening visit or planned during the core trial (shown in the past to influence bowel function); radiotherapy that would influence bowel function or pain during the double-blind phase. **Participants:** 184 participants were randomised to the study of which 94 were men and 90 women. In the intervention arm mean age 61 years (SD not reported). In comparison arm mean age 64 years (SD not reported). The most common primary cancer sites were breast (19%), lung (13%), and prostate (10%). 26% had bone metastases. At the start of the trial, 183/184 (99.5%) participants had constipation-induced or worsened by their opioid medication. A similar number were also taking laxatives. **Setting:** community

Ahmedzai 2012 *(Continued)*

Interventions	**Intervention:** OXN PR starting at and up titrated to 120 mg/day, n = 92 **Comparison:** OXY PR starting at and up titrated to 120 mg/day, n = 92 **Duration:** daily for 4 weeks
Outcomes	**Primary outcomes:** symptoms of constipation as measured by Bowel Function Index (BFI), efficacy for management of chronic cancer pain as measured by the Brief Pain Inventory-Short Form (BPI-SF) **Secondary outcomes:** use of rescue medication, quality of life (European Quality of life EuroQual-5D (QOL-EQ-5D) instrument and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ)), Patient Assessment of Constipation Symptoms, opioid withdrawal using the modified Subjective Opiate Withdrawal Scale, and safety **Outcomes measured:** at 4 weeks (at end of treatment)
Notes	**Author conflict of interests:** author Ahmedzai has received research funding, honoraria, consultancies and participated in advisory boards for Mundipharma the pharmaceutical company the produced the intervention drug. Nauck has received honoraria, consultancies and participated in advisory boards for Mundipharma. Hopp, Leyendecker and Bosse are employees of Munipharma. The other author declares no conflicts. **Funding:** Mundipharma GmbH produce the intervention drug. **Trial registration:** NCT00513656/OXN2001

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned to treatments (1:1 allocation ratio) using a pseudo-random number generator in a computer program."
Allocation concealment (selection bias)	Low risk	Quote: "randomisation schedule prepared by the Clinical Supplies Department of the Sponsor or an associated company."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	133/184 completed the trial. Less than a third in each group dropped out. Similar proportion dropped out in each group
Selective reporting (reporting bias)	Low risk	Trial registry entry lists the same outcomes as trial paper

Bull 2015

Study characteristics

Methods	Randomised, controlled, parallel, multi-centred trial in the USA

Bull 2015 *(Continued)*

Participants	**Aim:** to determine the efficacy and safety of fixed-dose subcutaneous methylnaltrexone in people with advanced illness and opioid-induced constipation in a variety of healthcare situations (inpatient, outpatient, home, hospice, and long-term care facilities). **Inclusion criteria:** participants aged > 18 years with advanced illness (defined as a terminal illness such as incurable cancer or other end-stage disease) and a life expectancy of ≥ 1 month and opioid-induced constipation (< 3 bowel movements in the last week and no bowel movement in 24 hours or 48 hours) and who were receiving stable doses of laxatives and opioids. **Exclusion criteria:** people with a disease process suggestive of gastrointestinal obstruction or clinically significant active diverticular disease, fecal impaction, peritonitis, bowel surgery 10 days before dosing, or fecal ostomy, or with a bodyweight < 38 kg. **Participants:** 230 participants were randomised to the study of which 118 were men and 112 women. Mean age in intervention arm 65.3 years (SD 12.9) and in placebo arm 65.7 years (SD 13.0). 216/230 of white race. Primary diagnosis cancer in 66% of participants (152/230). The majority (58/78) of the other participants had pulmonary, cardiovascular, or neurological disease. **Settings:** hospital and community
Interventions	**Intervention:** subcutaneous methylnaltrexone 8 mg (bodyweight of 38 kg to < 62 kg) or 12 mg (bodyweight > 62 kg) n =116 **Comparison:** placebo n = 114 **Duration:** both were administered every other day over 2 weeks
Outcomes	**Primary outcome:** percentage of participants with rescue-free bowel movement (RFBM) within 4 hours after at the most 2 of the doses in the first week of treatment and safety (including adverse events, clinical laboratory tests, vital signs and concomitant medication **Secondary outcomes:** % with the first RFBM within 4 hours after the first dose, number of BMs within 24 hours after dosing per week **Outcomes measured:** over 2 weeks of the intervention treatment
Notes	**Author conflict of interests:** author Bull is on the speaker's bureau and advisory board of Salix, the pharmaceutical company that produces the drug. As has Author Wellman, who has also received research funding from Salix and Progenics Pharmaceuticals who also manufacture methylnaltrexone. Israel is an employee and shareholder in Progenics. Barrettt and Forbes are employees of Salix. **Funding:** technical editorial and medical writing assistance from Salix Pharmaceuticals Limited. This company produce the intervention drug. **Trial registration:** NCT00672477

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned." No other details
Allocation concealment (selection bias)	Unclear risk	Quote: "randomly assigned." No other details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details provided

Bull 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	27/116 in the intervention group and 20/114 in placebo were lost to follow-up. Reason for loss were similar in both trial arms.
Selective reporting (reporting bias)	Unclear risk	Not clear. In trial registry entry they report 'other' measurements but don't describe what they are

Dupoiron 2017

Study characteristics	
Methods	Randomised, controlled, parallel trial unclear what country participants were from
Participants	**Aim:** to evaluate the tolerability and efficacy of OXN PR doses up to oxycodone/naloxone 160 mg/80 mg compared with OXY PR formulation. **Inclusion criteria:** adults with cancer and non-cancer pain requiring opioids on a stable dose of OXY PR for ≥ 4 consecutive days prior to randomisation and have a pain score of ≤ 4 with ≤ 2 doses of OXY PR analgesic rescue medication per day for either the last 3 consecutive days or 4 of the last 7 days. Constipation caused or aggravated by opioids was confirmed by the participant and the investigator and evidenced by a medical need of regular laxatives to have ≥ 3 bowel evacuations per week or by having < 3 bowel evacuations when not taking a laxative. **Exclusion criteria:** included hypersensitivity to oxycodone, naloxone; active alcohol or drug abuse or history of opioid abuse (or both); unreported illicit drug use (including cannabis); any condition in which opioids were contraindicated or if they had diarrhoea. **Participants:** 243 participants were randomised to the study, of which a subsample, 46, were people with cancer pain. Mean age in whole sample 57.9 years (SD 11.03) in OXN PR arm and 57.5 years (SD 12.33) in OXY PR arm. Subsample demographics on people with cancer not provided. **Setting:** community
Interventions	**Intervention:** starting dose during the double-blind phase dependent on the effective, stable analgesic dose established in the run-in period, titration up to maximum daily dose of OXN PR 160 mg was permitted after 1 week **Comparison:** OXY PR equivalent dosage to participants in the intervention arm **Duration:** up to 5 weeks
Outcomes	**Primary outcomes:** change in mean bowel function scores using the BFI, pain scores using the Pain Intensity Scale (PIS). **Secondary outcomes:** analgesic and laxative rescue medication, complete SBMs, and quality of life (EuroQol EQ-5D-3L) **Outcomes measured:** 1, 2, 4, and 5 weeks since baseline
Notes	**Author conflict of interests:** Author Loewenstein has contributed to seminars and workshops for Mundipharma, the pharmaceutical company that produces the intervention drug. Authors Kremers, Bosse and Hopp are employees of Munipharma. The other authors have not declared any association with the company.

Dupoiron 2017 *(Continued)*

	Funding: Mundipharma GmbH who produce the intervention drug. **Trial registration:** NCT01438567 Study comprised of 3 phases: prerandomisation phase consisting of a screening period and a run-in period, a double-blind phase, and an extension phase. In the run-in phase, OXY PR was titrated to analgesic effect to determine the starting dose to be used after randomisation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned." No other details
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States the trial is double-blinded but does say who is blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	16/120 men and 18/123 women in whole sample dropped out per arm. Number who dropped in the subset of 46 people with cancer not reported
Selective reporting (reporting bias)	Low risk	Trial registry lists the same outcomes as trial paper

Katakami 2017a

Study characteristics

Methods	Randomised, controlled, parallel, multi-centred trial in Korea and Japan
Participants	**Aim:** to evaluate the dose, efficacy, and safety of naldemedine for the treatment of opioid-induced constipation in people with cancer in Japan and Korea. **Inclusion criteria:** adults aged ≥ 18 years with cancer pain, stable regimen of opioid for > 2 weeks, complicated with opioid-induced constipation despite regular laxative use. **Exclusion criteria:** new cancer therapy or any therapy with obvious effects on GI functions within 14 days before enrolment, radiotherapy or surgery within 28 days before enrolment, constipation potentially attributable to causes other than opioid analgesics (such as mechanical intestinal obstruction), or presence of other known clinically significant GI, bowel, or pelvic disorders. **Participants:** 227 participants were randomised to the study, 134 were men and 93 women. Mean age by trial arm: naldemedine 0.1 mg: 65.8 years (SD 11.5), naldemedine 0.2 mg: 63.4 years (SD 10.4), naldemedine 0.4 mg: 64.2 years (SD 10.7); placebo: 64.2 (SD 9.6). Most participants had lung cancer, other cancers included breast and colorectal. All as graded by the ECOG Performance Status were ambulatory. Care setting not stated. **Setting:** Not stated

Katakami 2017a *(Continued)*

Interventions	**Intervention 1:** naldemedine 0.1 mg daily, n = 56 **Intervention 2:** naldemedine 0.2 mg daily, n = 58 **Intervention 3:** naldemedine 0.4 mg daily, n = 56 **Comparison:** placebo, n = 57 **Duration:** all administered daily for 2 weeks
Outcomes	**Primary outcome:** change from baseline in the frequency of spontaneous bowel movements (SBM) per week measured by self-report. **Secondary outcomes:** SBM responder rate, change from baseline in frequency of complete SBM, change from baseline in frequency of SBM without straining, adverse events, and opiate withdrawal **Outcomes measured:** over 2 weeks since baseline
Notes	**Author conflict of interests:** Auther Katakami has received research funding from Shionogi and Co Ltd, the pharmaceutical company that produced the intervention drug. Authors Yokota and Suzuki are employees and have stock or other ownership in Shionogi. Narabayashi and Boku have a consulting or advisory role in Shionogi, Boku has also received an honorarium from the company. **Funding:** Shionogi and Co Ltd who produce the intervention drug. **Trial registration:** JapicCTI-111510

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Achieved quote: "using the dynamic allocation procedure of the registration centre, where the maximum intergroup difference in the participant number at each study site did not exceed two."
Allocation concealment (selection bias)	Unclear risk	Probably occurred as allocation provided remotely but not stated specifically
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and all team members blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All team members blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants, 1/57 in placebo group and 1/56 in naldemedine 0.1 mg were lost to follow-up.
Selective reporting (reporting bias)	Low risk	Trial registry entry lists the same outcomes as trial paper

Katakami 2017b

Study characteristics

Katakami 2017b *(Continued)*

Methods	Randomised, controlled, parallel, multi-centred trial in Japan
Participants	**Aim:** to evaluate the efficacy and safety of naldemedine for the treatment of opioid induced constipation in patients with cancer. **Inclusion criteria:** Eastern Cooperative Oncology Group performance status ≤ 2, any cancer type that did not directly affect GI function, and a cancer condition expected to remain stable for the extent of the study. Patients were on a stable daily dose of opioids for ≥ 2 weeks before screening and had OIC. The diagnostic criteria for OIC were five or fewer spontaneous bowel movements (SBMs; a bowel movement not induced by rescue laxatives) and experience with straining, incomplete evacuation, and/or hard stools in 25% or more of all BMs during the 2 weeks before random assignment. To ensure that target patients had some functional BMs and were not at an increased risk of bowel perforations, patients who did not have a BM for ≥ 7 consecutive days were excluded. **Exclusion criteria:** Patients also were excluded if they had never taken laxatives to treat OIC, if they received chemotherapy that could affect GI function, started a new chemotherapy ≤ 14 days before screening, had a scheduled change in chemotherapy during the study, or had other conditions that may affect bowel transit. **Participants:** 195 participants were randomised to the study 119 were men and 74 women. Mean age by trial arm naldemedine: 63.8 years (SD 9.4), placebo: 63.6 years (SD 11.8). Most commonly participants had lung cancer, other cancers included breast and large intestine. ECOG Performance Status were ambulatory. Care setting not stated. **Setting:** not stated
Interventions	**Intervention 1:** naldemedine 0.2 mg **Intervention 2:** placebo **Duration:** Daily for 2-weeks
Outcomes	**Primary outcomes:** proportion of spontaneous bowel movements (SBM) responders within 2-week treatment period. Defined as a patients with three or more SBMs/week who had an increase of one or more SBM/week from baseline. Mesured by patient self-report. **Secondary outcomes:** frequency of SBMs/week, SBMs with a feeling of complete evacuation (CSBMs)/week, and SBMs without straining/week. Safety assessments in both studies included summary measures of treatment-emergent AEs (TEAEs). Opioid withdrawal was assessed with the clinician-administered Clinical Opioid Withdrawal Scale (COWS) scoring method. **Measured at:** over two weeks since baseline
Notes	**Author conflict of interests:** author Katakami has received research funding from Shionogi and Co Ltd, the pharmaceutical company that produced the intervention drug. Shinozaki has received an honoraria from Shionogi. Yokota, Arai and Tada are employees and hold stock or other ownership in Shionogi. Narabayahi has a consulting or advisory role for Shionogi. Boku has received honoraria from Shiongi. **Funding:** Three members of the author team received funding from Shionogi**.** This company produce the intervention drug. **Trial registration:** JAPIC-CTI-132340

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote:"Random assignment was performed with an interactive web response system and a stochastic minimization method to ensure that the difference

Katakami 2017b *(Continued)*

		between patients in each treatment group was two or fewer at any given study site"
Allocation concealment (selection bias)	Low risk	Quote:"The person responsible for random assignment and treatment allocation stored the randomisation codes in a sealed envelope, which were revealed only after all data from case report forms were locked"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"All investigators and patients were blinded to the treatment allocation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"All investigators and patients were blinded to the treatment allocation"
Incomplete outcome data (attrition bias) All outcomes	High risk	Rate of attrition not balanced across trials arms (14/97 versus 8/96), with more dropping out with adverse event in the intervention than in the placebo arm (10/97 versus 1/96)
Selective reporting (reporting bias)	Low risk	Trial registry lists the same outcomes as trial paper

Lee 2017

Study characteristics	
Methods	Randomised, controlled, multi-centre, parallel-group open-label trial in Korea
Participants	**Aim:** to compare controlled-release oxycodone/naloxone (OXN-CR) and controlled release oxycodone (OX-CR) in terms of analgesic efficacy, occurrence rate of constipation**,** and safety. **Inclusion criteria:** 20 years or older, moderate to severe cancer-related pain that required continuous treatment with a strong opioid analgesic and opioid-naive or previously received only weak opioids, or not treated with naloxone or strong opioids within 4 weeks before screening. **Exclusion criteria:** treatment with OXN-CR or OX-CR within 4 weeks or chemotherapy or radiotherapy within 2 weeks before screening visit, predominantly non-cancer related pain treatment with stable doses of laxatives for one week or more, major surgery within a month or planned surgery or clinically significant gastrointestinal non cancer disease or significant structural abnormalities of the gastrointestinal track or impairment of major organs. Participants: 117 participants were randomised to the study of which 82 were men and 35 women. 28 participants were 70 years or older, the others were aged below 70. Most commonly participants had colorectal cancer, other cancers included gastric and lung. All bar two participant's cancer had metastasis. Care setting not stated. **Community:** Setting.
Interventions	**Intervention 1:** oral OXN-CR starting dose of 20 mg/10 mg and to a maximum of 80 mg/40 mg. **Intervention 2:** oral OX-CR 20 mg and up titrated to a maximum of 80 mg. Up-titration permitted at the discretion of the investigator for the following reasons: use of analgesic rescue medication at least twice daily; increased NRS pain score compared with that on the previous visit; or inadequate pain control at the existing dose. **Duration:** daily over four weeks.

Lee 2017 *(Continued)*

Outcomes	**Primary outcomes:** change in pain score measured by 11-point numerical rating score from baseline to week 4. **Secondary outcomes:** dose, duration of use, administration of rescue medication, change in bowel habits measured by 3-point Likert Scale (worsened, no change, improved) and quality of life measured by European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30). **Outcomes measured:** weeks 1 and 4 since baseline
Notes	**Author conflict of interests:** author Eum is an employee of Mundipharma the pharmaceutical company that produced the intervention drug. All other authors declare no conflict of interests. **Funding:** Mundipharma Korea Ltd who produce the intervention drug. **Trial registration:** NCT01313780

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation lists
Allocation concealment (selection bias)	Unclear risk	The trial is described as open-label but does not state what is unmasked
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial is described as open-label but does not state what is unmasked
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial is described as open-label but does not state what is unmasked
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar level of attrition across arms, not stated that attrition was based on impact of interventions
Selective reporting (reporting bias)	Low risk	Trial registry entry lists the same outcomes as trial paper

Portenoy 2008

Study characteristics

Methods	Randomised, controlled, multi-centre, parallel-group trial in the USA
Participants	**Aim:** to assess the efficacy and safety of subcutaneous methylnaltrexone in a population of people with advanced illness and opioid-induced constipation, and to clarify whether there was a dose-response relationship for the purpose of dose selection in further clinical evaluations. **Inclusion criteria:** advanced disease (defined as terminal or end-stage, such as advanced metastatic cancer and AIDS but with a life expectancy of ≥ 4 weeks and stable vital signs) for which they were receiving palliative care and were receiving any opioid drug on a daily basis at a dose that had been stable for ≥ 2 weeks and were expected to remain stable for an additional ≥ 4 weeks, and despite no or

Portenoy 2008 *(Continued)*

	conventional laxative therapy they had no BMs for 2 days and reported ongoing constipation, defined as > 2 days with no BM and a score of ≥ 3 on a 5-point scale assessing constipation-related distress. **Exclusion criteria:** fever or otherwise unstable vital signs; liver function test 3 times the upper limit of normal, serum creatinine level 2 times the upper limit, or a platelet count < 50,000/mm^3; new regimen or dose change of concurrent gastrointestinal motility-altering medications during 3 weeks prior to trial enrolment; history of gastrointestinal obstruction or other condition that could compromise drug action; diagnosis of active peritoneal cancer; history of peritoneal catheter placement for chemotherapy or dialysis; known hypersensitivity to methylnaltrexone, naltrexone, or naloxone; or if any investigational drug or experimental product had been administered within the previous 30 days. **Participants:** 33 participants were randomised to the study, of which 15 were men and 18 women. Mean age 61 years (SD 19.0) (range 20-87 years). 79% were white people. Primary diagnoses at baseline were 28/33 cancer, 3 sickle cell disease, and 2 AIDS. 88% of participants were receiving a laxative at baseline. The mean opioid (morphine equivalent) dose at baseline was 289.9 mg/day (SD 308.0), median 180 mg/day, range 9-1207 mg/day. Mean number of BMs per week was 1.9. Care setting not stated. **Setting:** not stated.
Interventions	**Intervention 1:** subcutaneous methylnaltrexone 1 mg, n = 10 **Intervention 2:** subcutaneous methylnaltrexone 5 mg, n = 7 **Intervention 3:** subcutaneous methylnaltrexone 12.5 mg, n = 10 The initial dose range of 1 mg, 5 mg, or 12.5 mg was extended by adding a 20 mg group (n = 6) during the trial while still maintaining the double-blind. **Duration:** 3 doses over 1 week
Outcomes	**Primary outcomes:** laxative response within 4 hour of the initial dose measured by clinician/self-report. **Secondary outcomes:** laxation within 4 hours of subsequent doses, during the 24-hour period after each dose, time to laxation, use of rescue laxatives, subjective outcomes of constipation-associated symptoms, pain intensity, symptoms potentially due to opioid withdrawal or adverse events, and participant satisfaction. **Outcomes measured:** up to 24 hours per dose, and 30 days after last dose.
Notes	**Author conflict of interests:** there was no conflict of interest statement. **Funding:** Progenics Pharmaceuticals who produce the intervention drug. **Trial registration:** none provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After providing consent, patients were initially randomised in a ratio of 1:1:1 to receive 1 mg, 5 mg, or 12.5 mg of methylnaltrexone."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details on who was blinded

Portenoy 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details on who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	22/33 completed trial. 7 discontinued "at patient request", three from the 12.5 mg arm and one each from the 1 mg and 5 mg arm and two from 20 mg arm. One in the 20mg arm discontinued because of "intolerable" adverse event
Selective reporting (reporting bias)	Unclear risk	Trial was not registered prior and no protocol available

Slatkin 2009

Study characteristics	
Methods	Randomised, controlled, parallel-group, multi-centre controlled trial
Participants	**Aim:** to assess the safety and efficacy of a single subcutaneous injection of methylnaltrexone (0.15 mg/kg or 0.3 mg/kg) versus placebo. **Inclusion criteria:** aged > 18 years, advanced illness (such as incurable cancer or end-stage AIDS and life expectancy 1-6 months) and opioid-induced constipation. On a stable opioid regimen for the control of pain/discomfort for ≥ 3 days before randomisation, had a stable scheduled laxative regimen for ≥ 3 days prior to treatment, no clinically significant laxation within 48 hours prior to the first trial drug dose, had stable vital signs, and not pregnant and using an effective method of birth control. Baseline laxative regimens taken at time of trial entry could be continued throughout the trial. Rescue laxatives, defined as laxatives administered on an as needed basis were allowed but not within 4 hours before or after administration of the double-blind dose. **Exclusion criteria:** previous treatment with methylnaltrexone, naltrexone, or naloxone; recent participation in any other studies involving investigational products; any disease process suggestive of gastrointestinal obstruction; any potential non-opioid cause of bowel dysfunction; history of current peritoneal catheter for intraperitoneal administration, chemotherapy administration, or dialysis; clinically active diverticular disease; evidence of faecal impaction; surgically acute abdomen; faecal ostomy; pregnancy; or breastfeeding **Participants:** 154 participants were randomised to the study of which 84 were men and 70 women at 17 hospice and other palliative care settings in America. Mean age 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 8-12,2560 mg/day. **Setting:** community and hospital.
Interventions	**Intervention 1:** single subcutaneous injection methylnaltrexone 0.15 mg/kg, n = 47 **Intervention 2:** single subcutaneous injection methylnaltrexone 0.3 mg/kg, n = 55 **Comparison:** placebo, n = 52 **Duration:** 1-week double-blind phase, followed by 28-day open phase
Outcomes	**Primary outcome:** proportion of participants with rescue-free laxation within 4 hours after administration of the double-blind dose, measured by self report. Measured self report/clinician report. Participants needing rescue laxative or disimpaction within 4 hours of dosing were considered non-responders. **Secondary outcomes:** proportion of participants with rescue-free laxation within 24 hours post dosing; improvement in Global Clinical Impression of Change (GCIC) scale (defined as a rating of slightly

Slatkin 2009 *(Continued)*

	better, somewhat better, or much better); improvement in constipation distress (defined as a change by at least 1 category towards none); improvement in stool consistency; changes in baseline pain, symptoms/signs of central opioid withdrawal, and adverse events. **Outcomes measured:** to 6 days following first dose.
Notes	**Author conflict of interests:** two of the authors, Israel and Stambler, are employees and stakeholders of Progenics pharmaceuticals. The other authors, Lipman, Portenoy, Slatkin, and Thomas, have received honorarium for attending advisory meetings by Progenics/Wyeth Pharmaceuticals (both involved in development of methylnaltrexone). **Funding:** Progenics Pharmaceuticals who produce the intervention drug. **Trial registration:** 301/NCT00401362

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...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)	Low risk	Quote: "computer-generated randomisation scheme performed by a statistician external to the sponsor."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"syringe contents were blinded to patients and staff administering injections"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	152/154 completed trial (1 died and 1 was non-compliant both in trial arm of higher dose of methylnaltrexone) Analysis on an intention-to-treat basis
Selective reporting (reporting bias)	Unclear risk	Not clear trial registry entry only describes the primary outcome that is reported in the trial paper

Sykes 1996

Study characteristics

Methods	Randomised, controlled, single-centre, cross-over trial
Participants	**Aim:** to assess in a dose-ranging trial the use of oral naloxone in opioid-related constipation in participants with advanced cancer **Inclusion criteria:** participants with advanced cancer (definition not provided) receiving either morphine or diamorphine analgesia orally. All required laxatives prior to trial and their use was continued during the trial except for lactulose **Exclusion criteria:** fecal stomas or history of constipation prior to using opioid analgesia

Sykes 1996 *(Continued)*

	Participants: 27 participants were randomised to the study. of which 13 were men and 14 women. Mean age 64 years, median 65 years, range 44-88 years. 9 participants had breast cancer; 5 bronchus; 3 prostate; 2 oesophagus, and 1 each of rectum, kidney, bladder, stomach, colon, fallopian tube, malignant melanoma, and fibrosarcoma); 3 participants had liver metastases, 2 had hepatomegaly; no participant had constipation prior to using opioid analgesia. **Setting:** patients in a UK hospice.
Interventions	Morphine or diamorphine oral (maintenance dose) **Intervention:** naloxone oral every 4 hours for total daily dose of 0.5%, 1%, 2%, 5%, 10%, or 20% of total daily dose of morphine. The participants received "one level" (a lower level) of naloxone. Then after 2 participants at 0.5% to 5% had received the drug without slowing bowel transit time the dose was increased. In higher doses, the increase was following no slowing effect in 4 participants, n = 17 **Comparison:** placebo: chloroform water, n = 17 **Duration:** 2 days each treatment arm (parallel washout)
Outcomes	**Outcomes:** small bowel transit time by lactulose/hydrogen breath test; pain by 4-point scale (0 = no pain, 3 = severe pain), serious adverse events
Notes	**Author conflict of interests:** there was no conflict of interest statement. **Funding:** Charities, Cancer Relief Macmillan Fund, and the Wolfson Foundation. Naloxone was donated by MacFarlan Smith (pharmaceutical company). **Trial registration:** none

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated randomised but no further details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details provided on who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided on who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data analysis of 12 participants were reported. Of the 5 not included, 1 declined. 4 were withdrawn, 2 because of diarrhoea (1 occurred while on placebo, 1 caused by the lactulose taken as part of the small bowel transit time test), 1 was withdrawn because of general deterioration, and 1 because of nausea which the trialists felt was not related to the intervention).
Selective reporting (reporting bias)	Unclear risk	Trial was not registered prior and no protocol available

Thomas 2008

Study characteristics	
Methods	Randomised, controlled, multi-centre, parallel trial
Participants	**Aim:** to assess the safety and efficacy of subcutaneous methylnaltrexone for treating opioid-induced constipation in participants with advanced illness. **Inclusion criteria:** participants 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 ≤ 3 laxations in the previous week or no laxation in the previous 48 hours) despite having taken laxatives for ≥ 3 days. Participants could continue their baseline laxative regimen throughout the trial and take rescue laxatives as needed, though not within 4 hours before or after receiving a dose of the trial drug. **Exclusion criteria:** participants whose constipation was not primarily caused by opioids, mechanical gastrointestinal obstruction, an indwelling peritoneal catheter, clinically active diverticular disease, fecal impaction, acute surgical abdomen, and fecal ostomy. **Participants:** 133 participants were randomised to the study. 58 men and 76 women from North America. They were from 27 nursing homes, hospice sites, or other palliative care centres in the USA and Canada (78 with cancer, 15 cardiovascular disease, 14 chronic obstructive pulmonary disease, 8 dementia, and 19 with other diseases). Median age in methylnaltrexone group 70 years (range 34-93 years) and in the placebo group 72 years (range 39-98 years). Opioid dose: methylnaltrexone group: mean 417 mg/day, median 150 mg/day, range 9-4160 mg/day; placebo group: mean 339 mg/day, median 100 mg/day, range 10-10,160 mg/day. 98% in the methylnaltrexone and 99% in placebo group were using laxatives. **Setting:** community.
Interventions	**Intervention:** subcutaneous methylnaltrexone 0.15 mg/kg bodyweight, n = 62 **Comparison:** placebo, n = 71 Dose every other day **Duration of treatment:** 2 weeks
Outcomes	**Primary outcome:** laxation within 4 hours after first dose measured by self-report. **Secondary outcomes:** laxation within 4 hours after ≥ 2 of the first 4 doses. Consistency (from watery to hard) and difficulty of laxation. Adverse events were assessed using the National Cancer Institute's Common Toxicity Criteria (rated on a scale from 'none' to 'very much'). Participants were also assessed on the Modified Himmelsbach Opiate Withdrawal Scale (on 7 symptoms including yawning, lacrimation, rhinorrhoea, perspiration, tremor, piloerection, and restlessness) **Outcomes measured:** over 2 weeks since baseline
Notes	**Author conflict of interests:** project supported by Progenics Pharmaceuticals who manufacture the intervention drug, methylnaltrexone. Two of the authors of the paper are employees of Progenics. **Funding:** Progenics Pharmaceuticals who produce the intervention drug supported the trial and two of the authors (Kramer and Isreal) are employees and have an equity interest in the company. The four other authors, Thomas, Karvey, Cooney and Slatkin have received consulting fees and sit on advisory boards of Wyeth Pharmaceuticals who are also developing the intervention drug. **Trial registration:** 302/NCT00402038

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Thomas 2008 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule, blocked according to trial centre
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "syringe contents were blinded to patients and staff administering injections"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	106/133 completed trial
Selective reporting (reporting bias)	Unclear risk	Not clear as trial registry entry only states primary outcome that was reported in the paper

BM: bowel movement; ECOG: Eastern Cooperative Oncology Group; CGIC: Clinical Global Impression of Change; n: number of participants; OXN PR: oxycodone/naloxone prolonged release; OXY PR: oxycodone prolonged release; RFBM: rescue-free bowel movements; SBM: spontaneous bowel movement; SD: standard deviation.

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

Study	Reason for exclusion
Dupoiron 2017b	Not an RCT
jRCTs031200397	Preventative treatment
Meissner 2009	Study of people with chronic pain not palliative care or cancer
Mori 2017	Not an RCT
Nadstawek 2008	Study of people with chronic pain not palliative care or cancer
Ozaki 2020	Preventative treatment
Poelaert 2015	Not an RCT
Vondrackova 2008	Study of people with chronic (low back) pain not palliative care or cancer

RCT: randomised controlled trial.

Characteristics of studies awaiting classification *[ordered by study ID]*

Dimitroulis 2014

Methods	RCT

Dimitroulis 2014 *(Continued)*

Participants	People with non-small cell lung cancer receiving opioids for chronic pain
Interventions	Intervention: methylnaltrexone Comparison: placebo
Outcomes	Spontanous bowel movements
Notes	

EUCTR000657-39

Methods	RCT
Participants	People with opioid-induced constipation. Does not state if any have cancer
Interventions	Intervention: naloxone Comparison: placebo
Outcomes	Spontanous bowel movements
Notes	From EU trial register. Results are written but provides no contact details

NCT01438567

Methods	RCT
Participants	People with and without cancer pain
Interventions	Intervention: oxycodone/naloxone Comparison: oxycodone alone
Outcomes	Pain and bowel function
Notes	

NCT02321397

Methods	RCT
Participants	People with and without cancer with pain
Interventions	Intervention 1: oxycodone/naloxone higher-dose Intervention 2: oxycodone/naloxone lower-dose
Outcomes	Pain and bowel function
Notes	

NCT02574819

Methods	RCT
Participants	People with advanced illness
Interventions	Intervention: methylnaltrexone Comparison: placebo
Outcomes	Laxation
Notes	Sponsors: Jiangsu Chia-tai Tianqing Pharmaceutical Co, Ltd

Webster 2013

Methods	RCT
Participants	Participants with opioid-induced constipation. Participants had non-malignant or cancer-related pain. No breakdown provided of number with cancer and no subanalysis of effect in group with cancer
Interventions	Intervention: naloxegol Compariosn: placebo
Outcomes	Spontaneous bowel movements
Notes	No response from authors to clarify population details and further details for analysis

RCT: randomised controlled trial.

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

NCT03067708

Study name	Naloxegol in treating patients with stage IIIB-IV non-small cell Lung cancer
Methods	RCT
Participants	People with stage IIIB-IV non-small cell lung cancer
Interventions	Naloxegol
Outcomes	Feasibility and safety
Starting date	2017
Contact information	Gupta P, Minneapolis VA Health Care System
Notes	estimated end date August 2027

Neefjes 2014

Study name	Clinical evaluation of the efficacy of methylnaltrexone in resolving constipation-induced by different opioid subtypes combined with laboratory analysis of immunomodulatory and anti-angiogenic effects of methylnaltrexone
Methods	Multi-centre RCT
Participants	People receiving palliative care with opioid-induced constipation
Interventions	Intervention: methylnaltrexone Comparison: unclear
Outcomes	Differences in the efficacy of methylnaltrexone prescribed to resolve opioid-induced constipation between 3 commonly used opioid subtypes: morphine sulphate, oxycodone, and fentanyl
Starting date	Not stated, protocol published in 2014. Trial ongoing as reported December 2015
Contact information	ECW Neefjes, Department of Medical Oncology, VU University Medical Center, Cancer Center Amsterdam, the Netherlands, e.neefjes2@vumc.nl
Notes	ID NCT01955213. No information on whether completed or published, 2/2/21

Peppin 2013

Study name	Effect of subcutaneous methylnaltrexone on patient-reported outcomes in advanced illness patients with opioidiInduced constipation
Methods	RCT
Participants	People with advanced illness
Interventions	Intervention: methylnaltrexone Comparison: placebo
Outcomes	Participant-reported outcomes of constipation distress, bowel movement difficulty, and Global Clinical Impression of Change
Starting date	Not stated, conference abstract with findings published in 2013
Contact information	J Peppin. Progenics Pharmaceuticals Inc, Tarrytown, NY sponsored trial
Notes	Did not include results section so unclear if trial is the same as any identified in a full published paper.

Wong 2019

Study name	A multi-centre, randomised, phase IV study to compare the efficacy of oxycodone/naloxone verses oxycodone prolonged release tablets in patients with advanced cancer
Methods	RCT
Participants	Advanced cancer

Wong 2019 *(Continued)*

Interventions	oxycodone/naloxone compared to oxycodone only
Outcomes	analgesic efficacy, relieve of constipation
Starting date	2019
Contact information	Aaron.Wong@petermac.org
Notes	

RCT: randomised controlled trial.

DATA AND ANALYSES

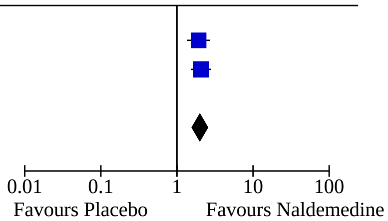
Comparison 1. Naldemedine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Sponaneous rescue-free bowel movements: Medium term	2	418	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [1.59, 2.52]
1.2 Symptoms of opioid withdrawal: Medium term, naldemedine 0.1 mg	1	112	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.56, 0.36]
1.3 Symptoms of opioid withdrawal: Medium term, naldemedine 0.2 mg	1	114	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.21, 0.81]
1.4 Symptoms of opioid withdrawal: Medium term, naldemedine 0.4 mg	1	112	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.36, 0.76]
1.5 Serious adverse events	2	418	Risk Ratio (M-H, Fixed, 95% CI)	3.34 [0.85, 13.15]
1.6 Adverse events	2	418	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.19, 1.87]
1.7 Proportion experiencing diarrhoea	2	419	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.22, 2.82]
1.8 Proportion who dropped out due to adverse events	2	420	Risk Ratio (M-H, Fixed, 95% CI)	5.18 [1.28, 20.91]

Analysis 1.1. Comparison 1: Naldemedine versus placebo, Outcome 1: Sponaneous rescue-free bowel movements: Medium term

Study or Subgroup	Naldemedine Events	Naldemedine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Katakami 2017a	122	169	21	56	48.7%	1.93 [1.36 , 2.73]
Katakami 2017b	69	97	33	96	51.3%	2.07 [1.53 , 2.80]
Total (95% CI)		**266**		**152**	**100.0%**	**2.00 [1.59 , 2.52]**
Total events:	191		54			

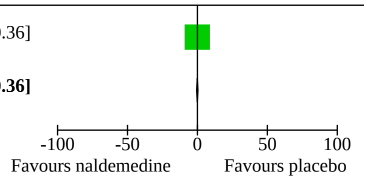
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 5.88 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Naldemedine versus placebo, Outcome 2: Symptoms of opioid withdrawal: Medium term, naldemedine 0.1 mg

Study or Subgroup	Naldemedine 0.1 mg Mean	Naldemedine 0.1 mg SD	Naldemedine 0.1 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Katakami 2017a	-0.1	1.2	56	0	1.3	56	100.0%	-0.10 [-0.56 , 0.36]
Total (95% CI)			**56**			**56**	**100.0%**	**-0.10 [-0.56 , 0.36]**

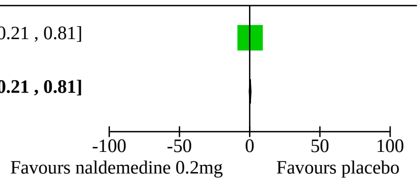
Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.67)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Naldemedine versus placebo, Outcome 3: Symptoms of opioid withdrawal: Medium term, naldemedine 0.2 mg

Study or Subgroup	Naldemedine 0.2 mg Mean	Naldemedine 0.2 mg SD	Naldemedine 0.2 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Katakami 2017a	0.3	1.5	58	0	1.3	56	100.0%	0.30 [-0.21 , 0.81]
Total (95% CI)			**58**			**56**	**100.0%**	**0.30 [-0.21 , 0.81]**

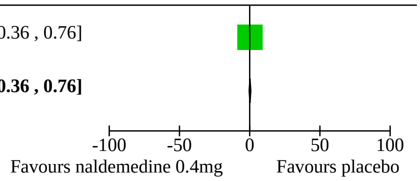
Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.25)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Naldemedine versus placebo, Outcome 4: Symptoms of opioid withdrawal: Medium term, naldemedine 0.4 mg

Study or Subgroup	Naldemedine 0.4 mg Mean	Naldemedine 0.4 mg SD	Naldemedine 0.4 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Katakami 2017a	0.2	1.7	56	0	1.3	56	100.0%	0.20 [-0.36 , 0.76]
Total (95% CI)			**56**			**56**	**100.0%**	**0.20 [-0.36 , 0.76]**

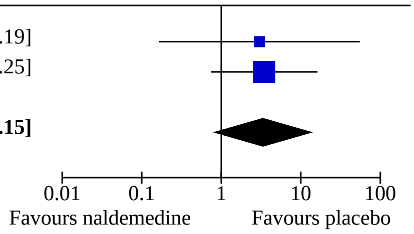
Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Naldemedine versus placebo, Outcome 5: Serious adverse events

Study or Subgroup	Naldemedine Events	Naldemedine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Katakami 2017a	4	169	0	56	27.1%	3.02 [0.16 , 55.19]
Katakami 2017b	7	97	2	96	72.9%	3.46 [0.74 , 16.25]
Total (95% CI)		**266**		**152**	**100.0%**	**3.34 [0.85 , 13.15]**
Total events:	11		2			

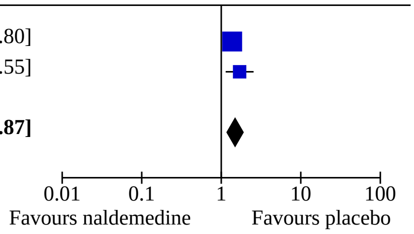
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.73 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Naldemedine versus placebo, Outcome 6: Adverse events

Study or Subgroup	Naldemedine Events	Naldemedine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Katakami 2017a	120	169	29	56	63.4%	1.37 [1.05 , 1.80]
Katakami 2017b	43	97	25	96	36.6%	1.70 [1.14 , 2.55]
Total (95% CI)		**266**		**152**	**100.0%**	**1.49 [1.19 , 1.87]**
Total events:	163		54			

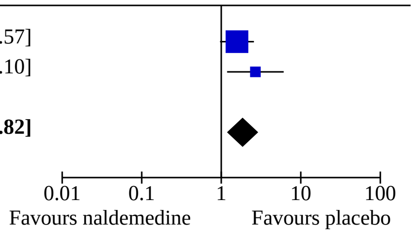
Heterogeneity: Chi² = 0.78, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 3.44 (P = 0.0006)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Naldemedine versus placebo, Outcome 7: Proportion experiencing diarrhoea

Study or Subgroup	Naldemedine Events	Naldemedine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Katakami 2017a	67	170	14	56	75.0%	1.58 [0.97 , 2.57]
Katakami 2017b	19	97	7	96	25.0%	2.69 [1.18 , 6.10]
Total (95% CI)		**267**		**152**	**100.0%**	**1.85 [1.22 , 2.82]**
Total events:	86		21			

Heterogeneity: Chi² = 1.21, df = 1 (P = 0.27); I² = 17%
Test for overall effect: Z = 2.89 (P = 0.004)
Test for subgroup differences: Not applicable

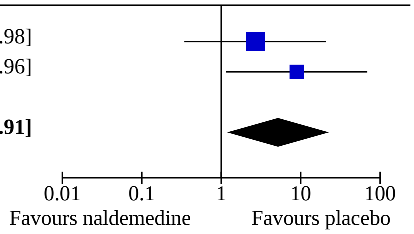


Analysis 1.8. Comparison 1: Naldemedine versus placebo, Outcome 8: Proportion who dropped out due to adverse events

Study or Subgroup	Naldemedine Events	Naldemedine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Katakami 2017a	8	170	1	57	59.8%	2.68 [0.34 , 20.98]
Katakami 2017b	9	97	1	96	40.2%	8.91 [1.15 , 68.96]
Total (95% CI)		**267**		**153**	**100.0%**	**5.18 [1.28 , 20.91]**
Total events:	17		2			

Heterogeneity: Chi² = 0.66, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 2.31 (P = 0.02)
Test for subgroup differences: Not applicable

Risk Ratio
M-H, Fixed, 95% CI



Comparison 2. Naldemedine dose

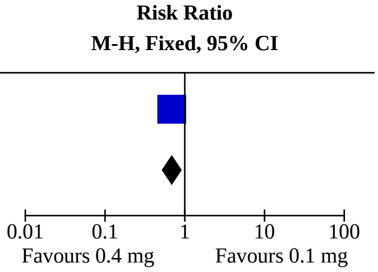
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Spontaneous rescue-free bowel movements: Medium term, naldemedine 0.1 mg versus 0.4mg	1	111	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.53, 0.89]
2.2 Spontaneous rescue-free bowel movements: Medium term, naldemedine 0.1 mg versus 0.2mg naldemedine	1	113	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.55, 0.95]
2.3 Spontaneous rescue-free bowel movements: Medium term, naldemedine 0.2 mg versus naldemedine 0.4 mg	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.79, 1.14]
2.4 Symptoms of opioid withdrawal: Medium term, naldemedine 0.1 mg versus naldemedine 0.4 mg	1	112	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.85, 0.25]
2.5 Symptoms of opioid withdrawal: Medium term, naldemedine 0.1 mg versus naldemedine 0.2 mg	1	114	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.90, 0.10]
2.6 Symptoms of opioid withdrawal: Medium term, naldemedine 0.2 mg versus naldemedine 0.4 mg	1	114	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.49, 0.69]
2.7 Adverse events: naldemedine 0.1 mg versus naldemedine 0.4 mg	1	112	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.67, 1.06]
2.8 Adverse events: naldemedine 0.1 mg versus naldemedine 0.2 mg	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.76, 1.27]
2.9 Adverse events: naldemedine 0.2 mg versus naldemedine 0.4 mg	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.68, 1.07]
2.10 Serious adverse events	1	112	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.11 Diarrhoea: naldemedine 0.1 mg versus naldemedine 0.4 mg	1	112	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.40, 0.95]
2.12 Diarrhoea: naldemedine 0.1 mg versus naldemedine 0.2 mg	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.46, 1.15]
2.13 Diarrhoea: naldemedine 0.2 mg versus naldemedine 0.4 mg	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.59, 1.21]
2.14 Proportion who dropped out due to adverse events: naldemedine 0.1 mg versus naldemedine 0.4 mg	1	112	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.18, 3.20]
2.15 Proportion who dropped out due to adverse events: naldemedine 0.1 mg versus naldemedine 0.2 mg	1	114	Risk Ratio (M-H, Fixed, 95% CI)	3.11 [0.33, 28.99]
2.16 Proportion who dropped out due to adverse events: naldemedine 0.2 mg versus naldemedine 0.4 mg	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.03, 2.09]

Analysis 2.1. Comparison 2: Naldemedine dose, Outcome 1: Spontaneous rescue-free bowel movements: Medium term, naldemedine 0.1 mg versus 0.4mg

Study or Subgroup	0.1 mg Events	0.1 mg Total	0.4 mg Events	0.4 mg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Katakami 2017a	31	55	46	56	100.0%	0.69 [0.53 , 0.89]
Total (95% CI)		**55**		**56**	**100.0%**	**0.69 [0.53 , 0.89]**
Total events:	31		46			

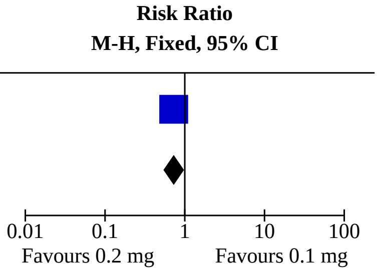
Heterogeneity: Not applicable
Test for overall effect: Z = 2.81 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Naldemedine dose, Outcome 2: Spontaneous rescue-free bowel movements: Medium term, naldemedine 0.1 mg versus 0.2mg naldemedine

Study or Subgroup	0.1 mg Events	0.1 mg Total	0.2 mg Events	0.2 mg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Katakami 2017a	31	55	45	58	100.0%	0.73 [0.55 , 0.95]
Total (95% CI)		**55**		**58**	**100.0%**	**0.73 [0.55 , 0.95]**
Total events:	31		45			

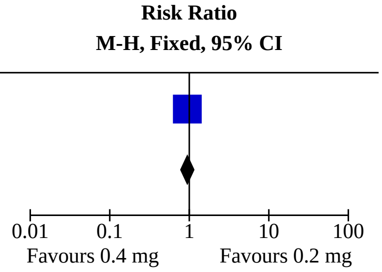
Heterogeneity: Not applicable
Test for overall effect: Z = 2.31 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Naldemedine dose, Outcome 3: Spontaneous rescue-free bowel movements: Medium term, naldemedine 0.2 mg versus naldemedine 0.4 mg

	0.2 mg		0.4 mg			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Katakami 2017a	45	58	46	56	100.0%	0.94 [0.79 , 1.14]
Total (95% CI)		**58**		**56**	**100.0%**	**0.94 [0.79 , 1.14]**
Total events:	45		46			

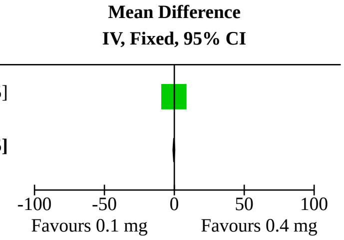
Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Naldemedine dose, Outcome 4: Symptoms of opioid withdrawal: Medium term, naldemedine 0.1 mg versus naldemedine 0.4 mg

		0.1 mg			0.4 mg			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Katakami 2017a	-0.1	1.2	56	0.2	1.7	56	100.0%	-0.30 [-0.85 , 0.25]
Total (95% CI)			**56**			**56**	**100.0%**	**-0.30 [-0.85 , 0.25]**

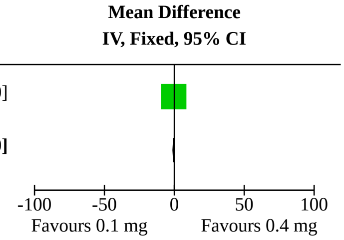
Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Naldemedine dose, Outcome 5: Symptoms of opioid withdrawal: Medium term, naldemedine 0.1 mg versus naldemedine 0.2 mg

		0.1 mg			0.2 mg			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Katakami 2017a	-0.1	1.2	56	0.3	1.5	58	100.0%	-0.40 [-0.90 , 0.10]
Total (95% CI)			**56**			**58**	**100.0%**	**-0.40 [-0.90 , 0.10]**

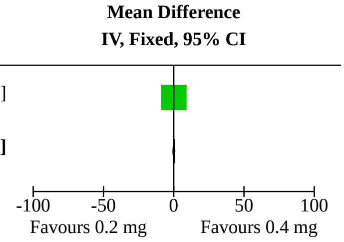
Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Naldemedine dose, Outcome 6: Symptoms of opioid withdrawal: Medium term, naldemedine 0.2 mg versus naldemedine 0.4 mg

		0.2 mg			0.4 mg			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Katakami 2017a	0.3	1.5	58	0.2	1.7	56	100.0%	0.10 [-0.49 , 0.69]
Total (95% CI)			**58**			**56**	**100.0%**	**0.10 [-0.49 , 0.69]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable

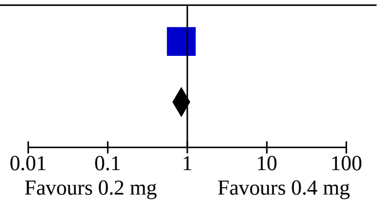


Analysis 2.7. Comparison 2: Naldemedine dose, Outcome 7: Adverse events: naldemedine 0.1 mg versus naldemedine 0.4 mg

	0.1 mg		0.4 mg			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Katakami 2017a	37	56	44	56	100.0%	0.84 [0.67 , 1.06]
Total (95% CI)		**56**		**56**	**100.0%**	**0.84 [0.67 , 1.06]**
Total events:	37		44			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.46 (P = 0.14)
Test for subgroup differences: Not applicable

Risk Ratio
M-H, Fixed, 95% CI

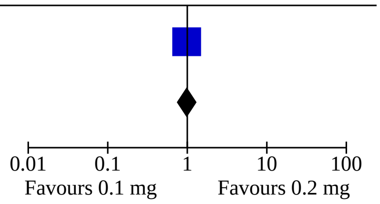


Analysis 2.8. Comparison 2: Naldemedine dose, Outcome 8: Adverse events: naldemedine 0.1 mg versus naldemedine 0.2 mg

	0.1 mg		0.2 mg			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Katakami 2017a	37	56	39	58	100.0%	0.98 [0.76 , 1.27]
Total (95% CI)		**56**		**58**	**100.0%**	**0.98 [0.76 , 1.27]**
Total events:	37		39			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.89)
Test for subgroup differences: Not applicable

Risk Ratio
M-H, Fixed, 95% CI

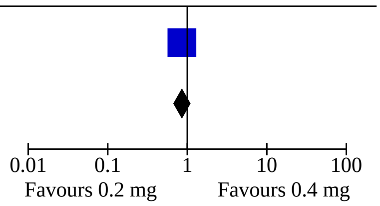


Analysis 2.9. Comparison 2: Naldemedine dose, Outcome 9: Adverse events: naldemedine 0.2 mg versus naldemedine 0.4 mg

	0.2 mg		0.4 mg			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Katakami 2017a	39	58	44	56	100.0%	0.86 [0.68 , 1.07]
Total (95% CI)		**58**		**56**	**100.0%**	**0.86 [0.68 , 1.07]**
Total events:	39		44			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.35 (P = 0.18)
Test for subgroup differences: Not applicable

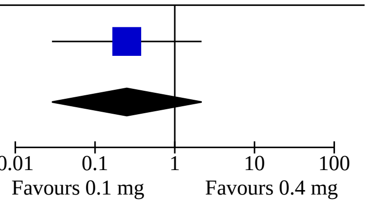
Risk Ratio
M-H, Fixed, 95% CI



Analysis 2.10. Comparison 2: Naldemedine dose, Outcome 10: Serious adverse events

Study or Subgroup	0.1 mg Events	0.1 mg Total	0.4 mg Events	0.4 mg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Katakami 2017a	1	56	4	56	100.0%	0.25 [0.03 , 2.17]
Total (95% CI)		**56**		**56**	**100.0%**	**0.25 [0.03 , 2.17]**
Total events:	1		4			

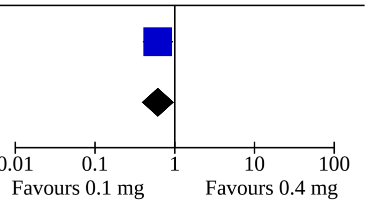
Heterogeneity: Not applicable
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Not applicable



Analysis 2.11. Comparison 2: Naldemedine dose, Outcome 11: Diarrhoea: naldemedine 0.1 mg versus naldemedine 0.4 mg

Study or Subgroup	0.1 mg Events	0.1 mg Total	0.4 mg Events	0.4 mg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Katakami 2017a	19	56	31	56	100.0%	0.61 [0.40 , 0.95]
Total (95% CI)		**56**		**56**	**100.0%**	**0.61 [0.40 , 0.95]**
Total events:	19		31			

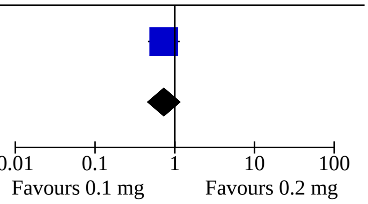
Heterogeneity: Not applicable
Test for overall effect: Z = 2.21 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 2.12. Comparison 2: Naldemedine dose, Outcome 12: Diarrhoea: naldemedine 0.1 mg versus naldemedine 0.2 mg

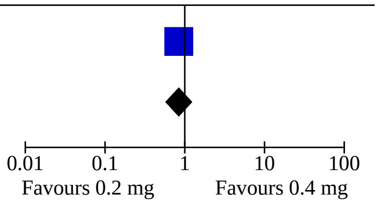
Study or Subgroup	0.1 mg Events	0.1 mg Total	0.2 mg Events	0.2 mg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Katakami 2017a	19	56	27	58	100.0%	0.73 [0.46 , 1.15]
Total (95% CI)		**56**		**58**	**100.0%**	**0.73 [0.46 , 1.15]**
Total events:	19		27			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.35 (P = 0.18)
Test for subgroup differences: Not applicable



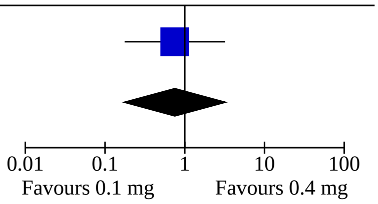
Analysis 2.13. Comparison 2: Naldemedine dose, Outcome 13: Diarrhoea: naldemedine 0.2 mg versus naldemedine 0.4 mg

Study or Subgroup	0.2 mg Events	0.2 mg Total	0.4 mg Events	0.4 mg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Katakami 2017a	27	58	31	56	100.0%	0.84 [0.59 , 1.21]
Total (95% CI)		**58**		**56**	**100.0%**	**0.84 [0.59 , 1.21]**
Total events:	27		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.94 (P = 0.35)						
Test for subgroup differences: Not applicable						



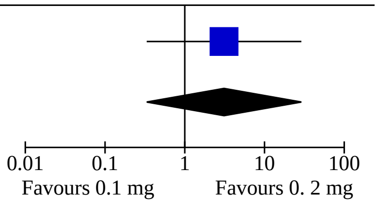
Analysis 2.14. Comparison 2: Naldemedine dose, Outcome 14: Proportion who dropped out due to adverse events: naldemedine 0.1 mg versus naldemedine 0.4 mg

Study or Subgroup	0.1 mg Events	0.1 mg Total	0.4 mg Events	0.4 mg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Katakami 2017a	3	56	4	56	100.0%	0.75 [0.18 , 3.20]
Total (95% CI)		**56**		**56**	**100.0%**	**0.75 [0.18 , 3.20]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Not applicable						



Analysis 2.15. Comparison 2: Naldemedine dose, Outcome 15: Proportion who dropped out due to adverse events: naldemedine 0.1 mg versus naldemedine 0.2 mg

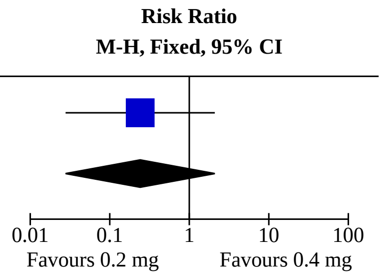
Study or Subgroup	0.1 mg Events	0.1 mg Total	0.2 mg Events	0.2 mg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Katakami 2017a	3	56	1	58	100.0%	3.11 [0.33 , 28.99]
Total (95% CI)		**56**		**58**	**100.0%**	**3.11 [0.33 , 28.99]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Not applicable						



Analysis 2.16. Comparison 2: Naldemedine dose, Outcome 16: Proportion who dropped out due to adverse events: naldemedine 0.2 mg versus naldemedine 0.4 mg

	0.2 mg		0.4 mg			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Katakami 2017a	1	58	4	56	100.0%	0.24 [0.03 , 2.09]
Total (95% CI)		**58**		**56**	**100.0%**	**0.24 [0.03 , 2.09]**
Total events:	1		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: Not applicable



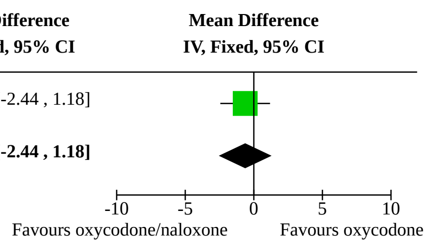
Comparison 3. Naloxone/oxycodone prolonged-release tablets versus oxycodone prolonged-release: adverse event

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Symptoms of opioid withdrawal: medium term	1	133	Mean Difference (IV, Fixed, 95% CI)	-0.63 [-2.44, 1.18]
3.2 Serious adverse events	3	362	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.44, 1.06]
3.3 Adverse events	3	362	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.87, 1.18]
3.4 Nausea	3	362	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.33, 0.94]
3.5 Proportion who dropped out due to adverse events	2	312	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.73, 2.15]
3.6 Use of laxative rescue medication	2	220	Std. Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.53, -0.00]
3.7 Quality of life	2	200	Std. Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.20, 0.35]

Analysis 3.1. Comparison 3: Naloxone/oxycodone prolonged-release tablets versus oxycodone prolonged-release: adverse event, Outcome 1: Symptoms of opioid withdrawal: medium term

	Oxycodone/naloxone			Oxycodone				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Ahmedzai 2012	6.64	5.97	66	7.27	4.59	67	100.0%	-0.63 [-2.44 , 1.18]
Total (95% CI)			**66**			**67**	**100.0%**	**-0.63 [-2.44 , 1.18]**

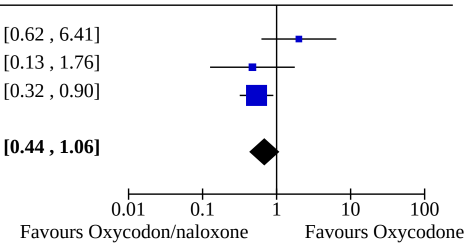
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Naloxone/oxycodone prolonged-release tablets versus oxycodone prolonged-release: adverse event, Outcome 2: Serious adverse events

Study or Subgroup	Oxycodone/naloxone Events	Oxycodone/naloxone Total	Oxycodone Events	Oxycodone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahmedzai 2012	8	92	4	92	10.6%	2.00 [0.62 , 6.41]
Dupoiron 2017	3	28	5	22	14.9%	0.47 [0.13 , 1.76]
Lee 2017	15	64	28	64	74.5%	0.54 [0.32 , 0.90]
Total (95% CI)		**184**		**178**	**100.0%**	**0.68 [0.44 , 1.06]**
Total events:	26		37			

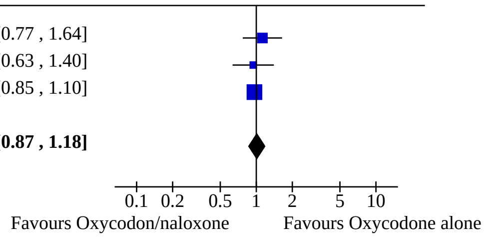
Heterogeneity: Chi² = 4.40, df = 2 (P = 0.11); I² = 55%
Test for overall effect: Z = 1.72 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Naloxone/oxycodone prolonged-release tablets versus oxycodone prolonged-release: adverse event, Outcome 3: Adverse events

Study or Subgroup	Oxycodone/naloxone Events	Oxycodone/naloxone Total	Oxycodone Events	Oxycodone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahmedzai 2012	36	92	32	92	30.2%	1.13 [0.77 , 1.64]
Dupoiron 2017	18	28	15	22	15.9%	0.94 [0.63 , 1.40]
Lee 2017	55	64	57	64	53.9%	0.96 [0.85 , 1.10]
Total (95% CI)		**184**		**178**	**100.0%**	**1.01 [0.87 , 1.18]**
Total events:	109		104			

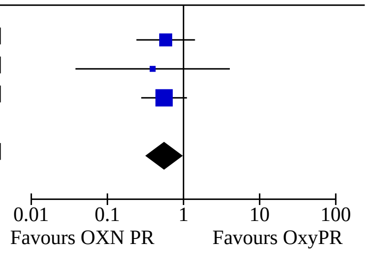
Heterogeneity: Chi² = 0.89, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Naloxone/oxycodone prolonged-release tablets versus oxycodone prolonged-release: adverse event, Outcome 4: Nausea

Study or Subgroup	Oxycodone/naloxone Events	Oxycodone/naloxone Total	Oxycodone Events	Oxycodone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahmedzai 2012	7	92	12	92	37.2%	0.58 [0.24 , 1.42]
Dupoiron 2017	1	28	2	22	6.9%	0.39 [0.04 , 4.06]
Lee 2017	10	64	18	64	55.8%	0.56 [0.28 , 1.11]
Total (95% CI)		**184**		**178**	**100.0%**	**0.55 [0.33 , 0.94]**
Total events:	18		32			

Heterogeneity: Chi² = 0.10, df = 2 (P = 0.95); I² = 0%
Test for overall effect: Z = 2.18 (P = 0.03)
Test for subgroup differences: Not applicable

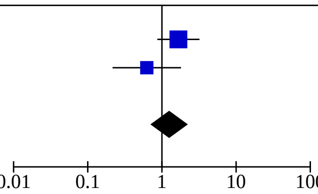


Analysis 3.5. Comparison 3: Naloxone/oxycodone prolonged-release tablets versus oxycodone prolonged-release: adverse event, Outcome 5: Proportion who dropped out due to adverse events

Study or Subgroup	Oxycodone/naloxone Events	Oxycodone/naloxone Total	Oxycodone Events	Oxycodone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahmedzai 2012	20	92	12	92	60.0%	1.67 [0.87 , 3.21]
Lee 2017	5	64	8	64	40.0%	0.63 [0.22 , 1.81]
Total (95% CI)		**156**		**156**	**100.0%**	**1.25 [0.73 , 2.15]**
Total events:	25		20			

Heterogeneity: Chi² = 2.38, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 0.80 (P = 0.42)
Test for subgroup differences: Not applicable

Risk Ratio M-H, Fixed, 95% CI

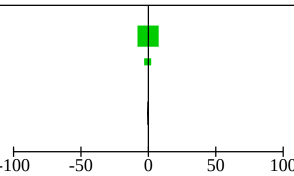


Analysis 3.6. Comparison 3: Naloxone/oxycodone prolonged-release tablets versus oxycodone prolonged-release: adverse event, Outcome 6: Use of laxative rescue medication

Study or Subgroup	Oxycodone/naloxone Mean	Oxycodone/naloxone SD	Oxycodone/naloxone Total	Oxycodone Mean	Oxycodone SD	Oxycodone Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ahmedzai 2012	26.1	27.6	92	32.69	31.26	92	84.4%	-0.22 [-0.51 , 0.07]
Dupoiron 2017	0.6	1.1	21	1.5	2.3	15	15.6%	-0.52 [-1.19 , 0.16]
Total (95% CI)			**113**			**107**	**100.0%**	**-0.27 [-0.53 , -0.00]**

Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 1.98 (P = 0.05)
Test for subgroup differences: Not applicable

Std. Mean Difference IV, Fixed, 95% CI

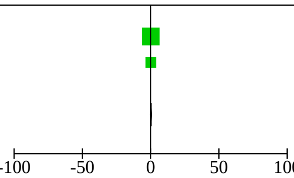


Analysis 3.7. Comparison 3: Naloxone/oxycodone prolonged-release tablets versus oxycodone prolonged-release: adverse event, Outcome 7: Quality of life

Study or Subgroup	Oxycodone/naloxone Mean	Oxycodone/naloxone SD	Oxycodone/naloxone Total	Oxycodone Mean	Oxycodone SD	Oxycodone Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ahmedzai 2012	0.5	0.33	66	0.49	0.38	67	66.7%	0.03 [-0.31 , 0.37]
Lee 2017	3.88	1.38	36	3.65	1.21	31	33.3%	0.17 [-0.31 , 0.66]
Total (95% CI)			**102**			**98**	**100.0%**	**0.08 [-0.20 , 0.35]**

Heterogeneity: Chi² = 0.24, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable

Std. Mean Difference IV, Fixed, 95% CI



Comparison 4. Methylnaltrexone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Spontaneous rescue-free bowel movements: short term	2	287	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [2.13, 4.13]
4.2 Spontaneous rescue-free bowel movements: medium term	2	305	Risk Ratio (M-H, Fixed, 95% CI)	8.15 [4.76, 13.95]
4.3 Patient reported improvement in bowel status: medium term	2	287	Risk Ratio (M-H, Fixed, 95% CI)	2.32 [1.64, 3.27]

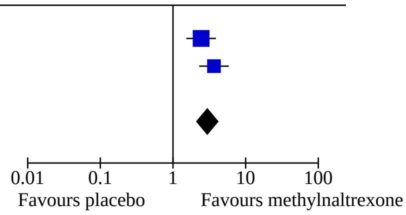
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4 Opioid withdrawal symptoms: short term	1	133	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.46, 0.46]
4.5 Opioid withdrawal symptoms: mean change short term, lower dose (0.15 mg/kg) methylnaltrexone	1	99	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.56, 0.46]
4.6 Opioid withdrawal symptoms: mean change short term, higher dose (0.30 mg/kg) methylnaltrexone	1	107	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.40, 0.38]
4.7 Opioid withdrawal symptoms: medium term	1	133	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.80, 0.40]
4.8 Opioid withdrawal symptoms: mean change medium term, lower dose (0.15 mg/kg) methylnaltrexone	1	99	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.90, 0.10]
4.9 Opioid withdrawal symptoms: mean change medium term, lower dose (0.3 mg/kg) methylnaltrexone	1	107	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.57, 0.27]
4.10 Pain intensity: short term	1	133	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.02, 0.62]
4.11 Pain intensity: Medium term	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.12 Serious adverse event	2	364	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.38, 0.93]
4.13 Adverse events	3	518	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.05, 1.30]
4.14 Abdominal pain	3	667	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [1.50, 3.18]
4.15 Flatulence	3	667	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [0.99, 3.57]
4.16 Vomiting	3	667	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.55, 1.65]
4.17 Nausea	3	667	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [1.26, 2.85]
4.18 Dropouts due to adverse event	2	363	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.54, 2.76]
4.19 Use of resuce medication	2	363	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.49, 0.91]

Analysis 4.1. Comparison 4: Methylnaltrexone versus placebo, Outcome 1: Spontaneous rescue-free bowel movements: short term

	Methylnaltrexone		Placebo			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Slatkin 2009	67	102	14	52	57.0%	2.44 [1.53 , 3.90]
Thomas 2008	48	62	15	71	43.0%	3.66 [2.29 , 5.86]
Total (95% CI)		**164**		**123**	**100.0%**	**2.97 [2.13 , 4.13]**
Total events:	115		29			

Heterogeneity: Chi² = 1.45, df = 1 (P = 0.23); I² = 31%
Test for overall effect: Z = 6.45 (P < 0.00001)
Test for subgroup differences: Not applicable

Risk Ratio
M-H, Fixed, 95% CI

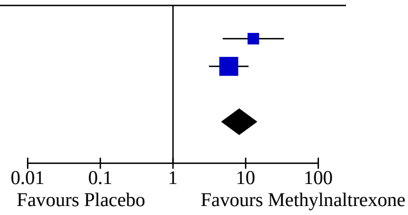


Analysis 4.2. Comparison 4: Methylnaltrexone versus placebo, Outcome 2: Spontaneous rescue-free bowel movements: medium term

	Methylnaltrexone		Placebo			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Bull 2015	56	90	4	82	33.3%	12.76 [4.84 , 33.62]
Thomas 2008	46	62	9	71	66.7%	5.85 [3.12 , 10.97]
Total (95% CI)		**152**		**153**	**100.0%**	**8.15 [4.76 , 13.95]**
Total events:	102		13			

Heterogeneity: Chi² = 1.89, df = 1 (P = 0.17); I² = 47%
Test for overall effect: Z = 7.65 (P < 0.00001)
Test for subgroup differences: Not applicable

Risk Ratio
M-H, Fixed, 95% CI

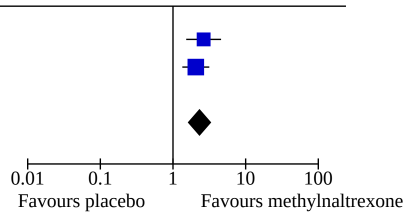


Analysis 4.3. Comparison 4: Methylnaltrexone versus placebo, Outcome 3: Patient reported improvement in bowel status: medium term

	Methylnaltrexone		Placebo			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Slatkin 2009	57	102	11	52	43.9%	2.64 [1.52 , 4.59]
Thomas 2008	36	62	20	71	56.1%	2.06 [1.34 , 3.16]
Total (95% CI)		**164**		**123**	**100.0%**	**2.32 [1.64 , 3.27]**
Total events:	93		31			

Heterogeneity: Chi² = 0.50, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 4.79 (P < 0.00001)
Test for subgroup differences: Not applicable

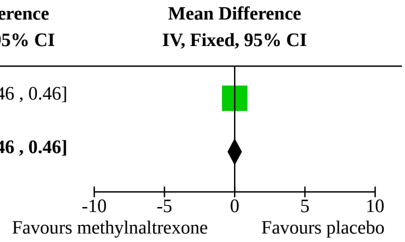
Risk Ratio
M-H, Fixed, 95% CI



Analysis 4.4. Comparison 4: Methylnaltrexone versus placebo, Outcome 4: Opioid withdrawal symptoms: short term

Study or Subgroup	Methylnaltrexone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Thomas 2008	7.8	1.2	62	7.8	1.5	71	100.0%	0.00 [-0.46 , 0.46]
Total (95% CI)			**62**			**71**	**100.0%**	**0.00 [-0.46 , 0.46]**

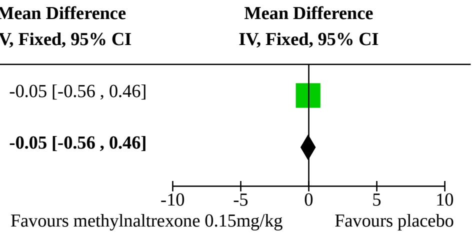
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 4.5. Comparison 4: Methylnaltrexone versus placebo, Outcome 5: Opioid withdrawal symptoms: mean change short term, lower dose (0.15 mg/kg) methylnaltrexone

Study or Subgroup	Methylnaltrexone 0.15 mg/ Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Slatkin 2009	-0.21	1.55	47	-0.16	0.9	52	100.0%	-0.05 [-0.56 , 0.46]
Total (95% CI)			**47**			**52**	**100.0%**	**-0.05 [-0.56 , 0.46]**

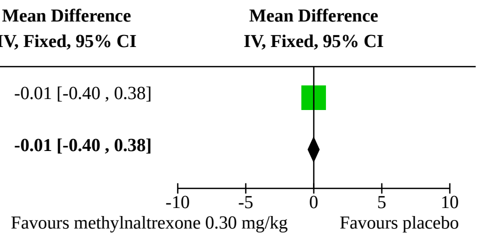
Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)
Test for subgroup differences: Not applicable



Analysis 4.6. Comparison 4: Methylnaltrexone versus placebo, Outcome 6: Opioid withdrawal symptoms: mean change short term, higher dose (0.30 mg/kg) methylnaltrexone

Study or Subgroup	Methylnaltrexone 0.30 mg/ Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Slatkin 2009	-0.17	1.16	55	-0.16	0.9	52	100.0%	-0.01 [-0.40 , 0.38]
Total (95% CI)			**55**			**52**	**100.0%**	**-0.01 [-0.40 , 0.38]**

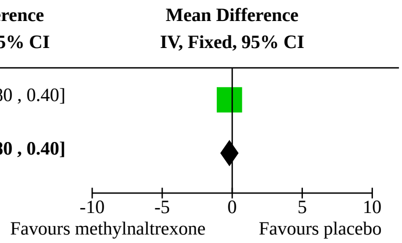
Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable



Analysis 4.7. Comparison 4: Methylnaltrexone versus placebo, Outcome 7: Opioid withdrawal symptoms: medium term

Study or Subgroup	Methylnaltrexone Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Thomas 2008	7.9	1.7	62	8.1	1.8	71	100.0%	-0.20 [-0.80 , 0.40]
Total (95% CI)			**62**			**71**	**100.0%**	**-0.20 [-0.80 , 0.40]**

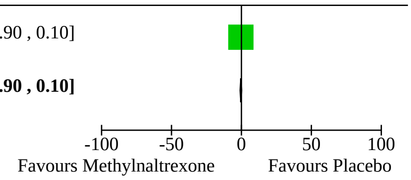
Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



Analysis 4.8. Comparison 4: Methylnaltrexone versus placebo, Outcome 8: Opioid withdrawal symptoms: mean change medium term, lower dose (0.15 mg/kg) methylnaltrexone

	Methylnaltrexone			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Slatkin 2009	-0.5	1.6	47	-0.1	0.76	52	100.0%	-0.40 [-0.90 , 0.10]
Total (95% CI)			**47**			**52**	**100.0%**	**-0.40 [-0.90 , 0.10]**

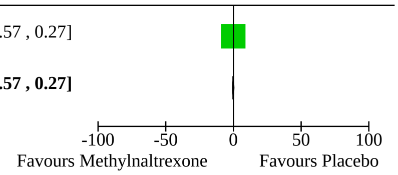
Heterogeneity: Not applicable
Test for overall effect: Z = 1.56 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 4.9. Comparison 4: Methylnaltrexone versus placebo, Outcome 9: Opioid withdrawal symptoms: mean change medium term, lower dose (0.3 mg/kg) methylnaltrexone

	Methylnaltrexone 0.3 mg/kg			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Slatkin 2009	-0.25	1.38	55	-0.1	0.76	52	100.0%	-0.15 [-0.57 , 0.27]
Total (95% CI)			**55**			**52**	**100.0%**	**-0.15 [-0.57 , 0.27]**

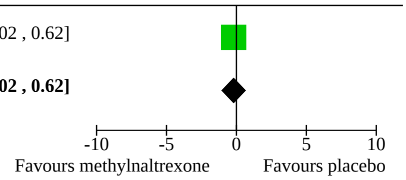
Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 4.10. Comparison 4: Methylnaltrexone versus placebo, Outcome 10: Pain intensity: short term

	Methylnaltrexone			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Thomas 2008	3.4	2.3	62	3.6	2.5	71	100.0%	-0.20 [-1.02 , 0.62]
Total (95% CI)			**62**			**71**	**100.0%**	**-0.20 [-1.02 , 0.62]**

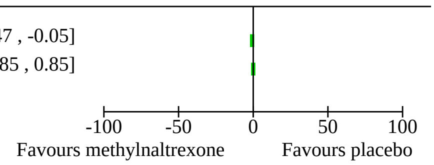
Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



Analysis 4.11. Comparison 4: Methylnaltrexone versus placebo, Outcome 11: Pain intensity: Medium term

	Methylnaltrexone			Placebo			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Slatkin 2009	-0.74	1.98	47	0.02	1.56	52	-0.76 [-1.47 , -0.05]
Thomas 2008	5.2	2.4	62	5.2	2.6	71	0.00 [-0.85 , 0.85]

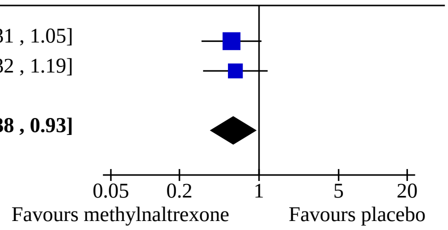
Test for subgroup differences: Not applicable



Analysis 4.12. Comparison 4: Methylnaltrexone versus placebo, Outcome 12: Serious adverse event

	Methylnaltrexone		Placebo			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Bull 2015	14	116	24	114	56.3%	0.57 [0.31 , 1.05]
Thomas 2008	11	63	20	71	43.7%	0.62 [0.32 , 1.19]
Total (95% CI)		**179**		**185**	**100.0%**	**0.59 [0.38 , 0.93]**
Total events:	25		44			

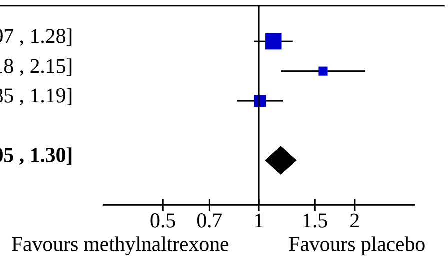
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 2.30 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 4.13. Comparison 4: Methylnaltrexone versus placebo, Outcome 13: Adverse events

	Methylnaltrexone		Placebo			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Bull 2015	95	116	84	114	49.4%	1.11 [0.97 , 1.28]
Slatkin 2009	78	102	25	52	19.3%	1.59 [1.18 , 2.15]
Thomas 2008	51	63	57	71	31.3%	1.01 [0.85 , 1.19]
Total (95% CI)		**281**		**237**	**100.0%**	**1.17 [1.05 , 1.30]**
Total events:	224		166			

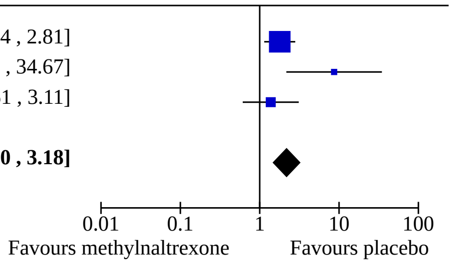
Heterogeneity: Chi² = 7.62, df = 2 (P = 0.02); I² = 74%
Test for overall effect: Z = 2.91 (P = 0.004)
Test for subgroup differences: Not applicable



Analysis 4.14. Comparison 4: Methylnaltrexone versus placebo, Outcome 14: Abdominal pain

	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Bull 2015	79	265	19	114	70.5%	1.79 [1.14 , 2.81]
Slatkin 2009	34	102	2	52	7.0%	8.67 [2.17 , 34.67]
Thomas 2008	11	63	9	71	22.5%	1.38 [0.61 , 3.11]
Total (95% CI)		**430**		**237**	**100.0%**	**2.18 [1.50 , 3.18]**
Total events:	124		30			

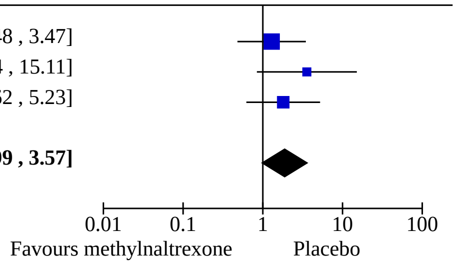
Heterogeneity: Chi² = 5.77, df = 2 (P = 0.06); I² = 65%
Test for overall effect: Z = 4.06 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 4.15. Comparison 4: Methylnaltrexone versus placebo, Outcome 15: Flatulence

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bull 2015	15	265	5	114	48.7%	1.29 [0.48 , 3.47]
Slatkin 2009	14	102	2	52	18.5%	3.57 [0.84 , 15.11]
Thomas 2008	8	63	5	71	32.8%	1.80 [0.62 , 5.23]
Total (95% CI)		**430**		**237**	**100.0%**	**1.88 [0.99 , 3.57]**
Total events:	37		12			

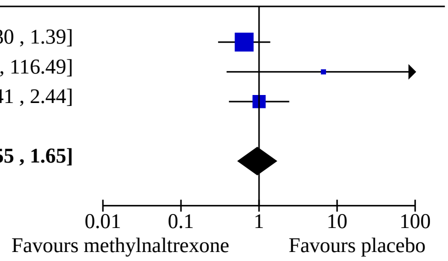
Heterogeneity: Chi² = 1.32, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 1.93 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 4.16. Comparison 4: Methylnaltrexone versus placebo, Outcome 16: Vomiting

Study or Subgroup	Methylnaltrexone Events	Methylnaltrexone Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bull 2015	15	265	10	114	60.5%	0.65 [0.30 , 1.39]
Slatkin 2009	6	102	0	52	2.9%	6.69 [0.38 , 116.49]
Thomas 2008	8	63	9	71	36.6%	1.00 [0.41 , 2.44]
Total (95% CI)		**430**		**237**	**100.0%**	**0.95 [0.55 , 1.65]**
Total events:	29		19			

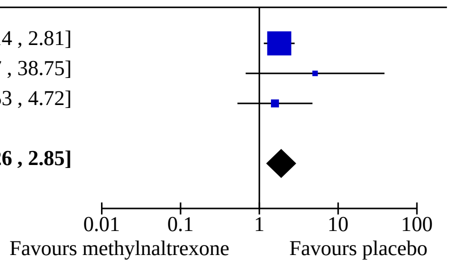
Heterogeneity: Chi² = 2.77, df = 2 (P = 0.25); I² = 28%
Test for overall effect: Z = 0.19 (P = 0.85)
Test for subgroup differences: Not applicable



Analysis 4.17. Comparison 4: Methylnaltrexone versus placebo, Outcome 17: Nausea

Study or Subgroup	Methylnaltrxone Events	Methylnaltrxone Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bull 2015	79	265	19	114	81.5%	1.79 [1.14 , 2.81]
Slatkin 2009	10	102	1	52	4.1%	5.10 [0.67 , 38.75]
Thomas 2008	7	63	5	71	14.4%	1.58 [0.53 , 4.72]
Total (95% CI)		**430**		**237**	**100.0%**	**1.89 [1.26 , 2.85]**
Total events:	96		25			

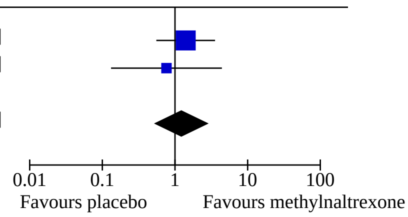
Heterogeneity: Chi² = 1.08, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 3.07 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 4.18. Comparison 4: Methylnaltrexone versus placebo, Outcome 18: Dropouts due to adverse event

Study or Subgroup	Methylnaltrexone Events	Methylnaltrexone Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bull 2015	10	116	7	114	71.6%	1.40 [0.55 , 3.56]
Thomas 2008	2	62	3	71	28.4%	0.76 [0.13 , 4.42]
Total (95% CI)		**178**		**185**	**100.0%**	**1.22 [0.54 , 2.76]**
Total events:	12		10			

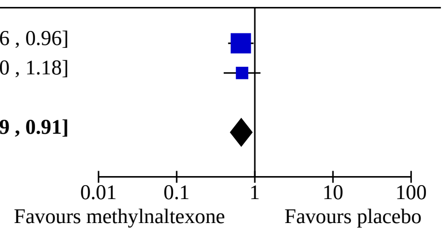
Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



Analysis 4.19. Comparison 4: Methylnaltrexone versus placebo, Outcome 19: Use of resuce medication

Study or Subgroup	Methylnaltrexone Events	Methylnaltrexone Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bull 2015	31	116	46	114	66.6%	0.66 [0.46 , 0.96]
Thomas 2008	15	62	25	71	33.4%	0.69 [0.40 , 1.18]
Total (95% CI)		**178**		**185**	**100.0%**	**0.67 [0.49 , 0.91]**
Total events:	46		71			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 2.54 (P = 0.01)
Test for subgroup differences: Not applicable



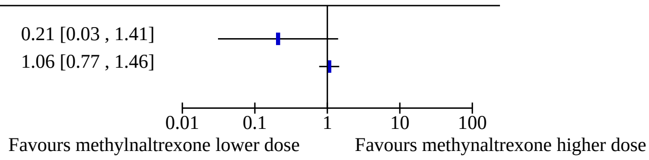
Comparison 5. Methylnaltrexone dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Spontaneous rescue-free bowel movements: short term	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.2 Spontaneous rescue-free bowel movements: medium term	1	26	Risk Ratio (M-H, Fixed, 95% CI)	2.91 [0.82, 10.39]
5.3 Patient reported improvement in bowel status: short term	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.71, 1.35]
5.4 Opioid withdrawal symptoms: short term	1	102	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.58, 0.50]
5.5 Opioid withdrawal symptoms: medium term	1	102	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.84, 0.34]
5.6 Adverse event	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 5.1. Comparison 5: Methylnaltrexone dose, Outcome 1: Spontaneous rescue-free bowel movements: short term

Study or Subgroup	Lowest dose Events	Lowest dose Total	Higher dose Events	Higher dose Total	Risk Ratio M-H, Fixed, 95% CI
Portenoy 2008	1	10	11	23	0.21 [0.03 , 1.41]
Slatkin 2009	29	47	32	55	1.06 [0.77 , 1.46]

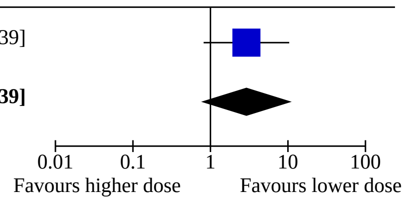
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5: Methylnaltrexone dose, Outcome 2: Spontaneous rescue-free bowel movements: medium term

Study or Subgroup	Higher dose Events	Higher dose Total	Lower dose Events	Lower dose Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Portenoy 2008	11	17	2	9	100.0%	2.91 [0.82 , 10.39]
Total (95% CI)		**17**		**9**	**100.0%**	**2.91 [0.82 , 10.39]**
Total events:	11		2			

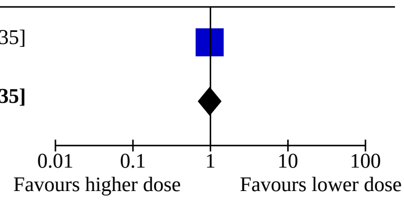
Heterogeneity: Not applicable
Test for overall effect: Z = 1.65 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5: Methylnaltrexone dose, Outcome 3: Patient reported improvement in bowel status: short term

Study or Subgroup	Higher dose Events	Higher dose Total	Lower dose Events	Lower dose Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Slatkin 2009	32	55	28	47	100.0%	0.98 [0.71 , 1.35]
Total (95% CI)		**55**		**47**	**100.0%**	**0.98 [0.71 , 1.35]**
Total events:	32		28			

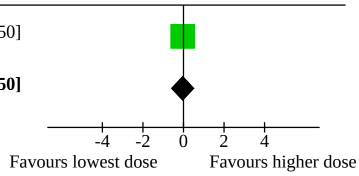
Heterogeneity: Not applicable
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable



Analysis 5.4. Comparison 5: Methylnaltrexone dose, Outcome 4: Opioid withdrawal symptoms: short term

Study or Subgroup	Lowest dose Mean	Lowest dose SD	Lowest dose Total	Higher dose Mean	Higher dose SD	Higher dose Total	Weight	Mean Difference IV, Fixed, 95% CI
Slatkin 2009	-0.21	1.55	47	-0.17	1.16	55	100.0%	-0.04 [-0.58 , 0.50]
Total (95% CI)			**47**			**55**	**100.0%**	**-0.04 [-0.58 , 0.50]**

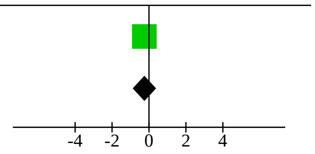
Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable



Analysis 5.5. Comparison 5: Methylnaltrexone dose, Outcome 5: Opioid withdrawal symptoms: medium term

	Lowest dose			Higher dose				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Slatkin 2009	-0.5	1.6	47	-0.25	1.38	55	100.0%	-0.25 [-0.84 , 0.34]
Total (95% CI)			**47**			**55**	**100.0%**	**-0.25 [-0.84 , 0.34]**

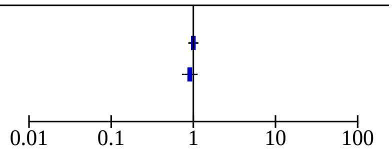
Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable



Analysis 5.6. Comparison 5: Methylnaltrexone dose, Outcome 6: Adverse event

	Lowest dose		Higher dose		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI
Portenoy 2008	10	10	23	23	1.00 [0.87 , 1.15]
Slatkin 2009	34	47	44	55	0.90 [0.73 , 1.13]

Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategies for searches run in 2021

157 -Mu-opioid antagonists for opioid-induced bowel dysfunction December 2021

Database searched	Date of last search	June 2020	Dec 2021	TOTAL
CENTRAL (The Cochrane Library) Issue 12 of 12, 2021 (searched Aug 2017 to Dec 2021)	20/12/21	139	35	174
MEDLINE & MEDLINE in Process (OVID) Aug 2017 to Dec 17 2021	20/12/21	48	28	76
Embase (OVID) Aug 2017 to 2021 Dec 17	20/12/21	35	27	62
CINAHL (EBSCO) Aug 2017 to Dec 2021	20/12/21	10	21	31
Web of Science ISI (SCI-EXPANDED & CPCI-S) Aug 2017 to 18/12/21	20/12/21	69	36	105
Total		**301**	**147**	**448**

(Continued)

After de-duplication	**214**	**82**	**296**

CENTRAL

#1 MESH DESCRIPTOR Constipation

#2 (constipat* or laxation or (bowel near2 dysfunction*)):TI,AB,KY

#3 MESH DESCRIPTOR Ileus EXPLODE ALL TREES

#4 MESH DESCRIPTOR Gastrointestinal Motility EXPLODE ALL TREES

#5 MESH DESCRIPTOR Gastrointestinal Tract EXPLODE ALL TREES

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 MESH DESCRIPTOR Narcotic Antagonists EXPLODE ALL TREES

#8 Naltrexone or Naloxone or Methylnaltrexone or nalmefene or Alvimopan or ADL 8-2698 or LY246736 or pentazocine or nalbuphine or buprenorphine or dezocine or butorphanol or loperamide or PAMORA or ALKS37 or RDC-1036 or movantik or naloxegol or naldemedine or NKTR-118 or TD-1211 or axelopran or CB-5945 or bevenopran or ADL5945 or Tegaserod or N-methylnaltrexone or SP-333 or MOA-728 or alvimopan or Targinact:TI,AB,KY

#9 MESH DESCRIPTOR Receptors, Opioid EXPLODE ALL TREES

#10 ((neoplasm* or cancer* or carcinoma* or neoplasia* or adenocarcinoma* or tumor or malignan* or tumour*)):TI,AB,KY

#11 MESH DESCRIPTOR neoplasms EXPLODE ALL TREES

#12 ((palliat* or terminal* or endstage or hospice* or (end near3 life) or (care near3 dying) or ((advanced or late or last or end or final) near3 (stage* or phase*)))):TI,AB,KY

#13 MESH DESCRIPTOR Palliative Care

#14 MESH DESCRIPTOR Terminal Care EXPLODE ALL TREES

#15 #12 OR #13 OR #14

#16 #10 OR #11

#17 #7 OR #8 OR #9

#18 #15 OR #16

#19 #6 AND #17 AND #18

MEDLINE

1. Constipation/

2. (constipat* or laxation or (bowel adj2 dysfunction*)).tw.

3. exp Ileus/

4. exp Gastrointestinal Motility/

5. exp Gastrointestinal Tract/

6. 1 or 2 or 3 or 4 or 5

7. exp Narcotic Antagonists/

8. (Naltrexone or Naloxone or Methylnaltrexone or nalmefene or Alvimopan or ADL 8-2698 or LY246736 or pentazocine or nalbuphine or buprenorphine or dezocine or butorphanol or loperamide or PAMORA or ALKS37 or RDC-1036 or movantik or naloxegol or naldemedine

or NKTR-118 or TD-1211 or axelopran or CB-5945 or bevenopran or ADL5945 or Tegaserod or N-methylnaltrexone or SP-333 or MOA-728 or alvimopan or Targinact).tw.

9. exp Receptors, Opioid/

10. 7 or 8 or 9

11. (neoplasm* or cancer* or carcinoma* or neoplasia* or adenocarcinoma* or tumor or malignan* or tumour*).tw.

12. exp Neoplasms/

13. 11 or 12

14. (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*))).tw.

15. Palliative Care/

16. exp Terminal Care/

17. 14 or 15 or 16

18. 13 or 17

19. randomized controlled trial.pt.

20. controlled clinical trial.pt.

21. randomized.ab.

22. placebo.ab.

23. drug therapy.fs.

24. randomly.ab.

25. trial.ab.

26. 19 or 20 or 21 or 22 or 23 or 24 or 25

27. exp animals/ not humans.sh.

28. 26 not 27

29 6 and 10 and 18 and 28

30 (201708* or 201709* or 201710* or 201711* or 201712* or 2018* or 2019* or 2020*).ed.

31 29 and 30

Embase

1 Constipation/

2 (constipat* or laxation or (bowel adj2 dysfunction*)).tw.

3 exp Ileus/

4 exp Gastrointestinal Motility/

5 exp Gastrointestinal Tract/

6 1 or 2 or 3 or 4 or 5

7 exp Narcotic Antagonist/

8 (Naltrexone or Naloxone or Methylnaltrexone or nalmefene or Alvimopan or ADL 8-2698 or LY246736 or pentazocine or nalbuphine or buprenorphine or dezocine or butorphanol or loperamide or PAMORA or ALKS37 or RDC-1036 or movantik or naloxegol or naldemedine

or NKTR-118 or TD-1211 or axelopran or CB-5945 or bevenopran or ADL5945 or Tegaserod or N-methylnaltrexone or SP-333 or MOA-728 or alvimopan or Targinact).tw.

9 exp Opiate receptor/

10 7 or 8 or 9

11 exp neoplasm/

12 (neoplasm* or cancer* or carcinoma* or neoplasia* or adenocarcinoma* or tumor or malignan* or tumour*).tw.

13 11 or 12

14 (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*))).tw.

15 exp palliative therapy/

16 terminal care/ or hospice care/

17 14 or 15 or 16

18 13 or 17

19 random$.tw.

20 factorial$.tw.

21 crossover$.tw.

22 cross over$.tw.

23 cross-over$.tw.

24 placebo$.tw.

25 (doubl$ adj blind$).tw.

26 (singl$ adj blind$).tw.

27 assign$.tw.

28 allocat$.tw.

29 volunteer$.tw.

30 Crossover Procedure/

31 double-blind procedure.tw.

32 Randomized Controlled Trial/

33 Single Blind Procedure/

34 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33

35 (animal/ or nonhuman/) not human/

36 34 not 35

37 6 and 10 and 18 and 36

38 (201708* or 201709* or 201710* or 201711* or 201712* or 2018* or 2019* or 2020*).dd. 39 37 and 38

CINAHL

(+ SIGN RCT filter - https://www.sign.ac.uk/what-we-do/methodology/search-filters/))

S17 S5 AND S8 AND S16

S16 S11 OR S15

S15 S12 OR S13 OR S14

S14 (MH "Terminal Care+")

S13 (MH "Palliative Care")

S12 (palliat* or terminal* or endstage or hospice* or (end N3 life) or (care N3 dying) or ((advanced or late or last or end or final) N3 (stage* or phase*))) Expanders - Apply equivalent subjects

S11 S9 or S10

S10 (neoplasm* or cancer* or carcinoma* or neoplasia* or adenocarcinoma* or tumor or malignan* or tumour*)

S9 (MH "Neoplasms+")

S8 S6 OR S7

S7 Naltrexone or Naloxone or Methylnaltrexone or nalmefene or Alvimopan or ADL 8-2698 or LY246736 or pentazocine or nalbuphine or buprenorphine or dezocine or butorphanol or loperamide or PAMORA or ALKS37 or RDC-1036 or movantik or naloxegol or naldemedine or NKTR-118 or TD-1211 or axelopran or CB-5945 or bevenopran or ADL5945 or Tegaserod or N-methylnaltrexone or SP-333 or MOA-728 or alvimopan or Targinact

S6 (MH "Narcotic Antagonists+")

S5 S1 OR S2 OR S3 OR S4

S4 (MH "Gastrointestinal Motility+")

S3 (MH "Intestinal Obstruction+")

S2 (constipat* or laxation or (bowel N2 dysfunction*))

S1 (MH "Constipation")

Web of Science

16 #15 and #10

15 #11 or #12 or #13 or #14

14 TS=trial* OR TI=trial*

13 TI=clin* OR TS=clin*

12 TI=randomi* OR TS=randomi*

11 TS=Randomized clinical trial* OR TI=Randomized clinical trial*

10 #5 and #6 and #9

9 #7 or #8

8 TOPIC:((palliat* or terminal* or endstage or hospice* or (end near/3 life) or (care near/3 dying) or ((advanced or late or last or end or final) near/3 (stage* or phase*))))

7 TOPIC: ((neoplasm* or cancer* or carcinoma* or neoplasia* or adenocarcinoma* or tumor or malignan* or tumour*))

6 TOPIC: Naltrexone or Naloxone or Methylnaltrexone or nalmefene or Alvimopan or ADL 8-2698 or LY246736 or pentazocine or nalbuphine or buprenorphine or dezocine or butorphanol or loperamide or PAMORA or ALKS37 or RDC-1036 or movantik or naloxegol or naldemedine or NKTR-118 or TD-1211 or axelopran or CB-5945 or bevenopran or ADL5945 or Tegaserod or N-methylnaltrexone or SP-333 or MOA-728 or alvimopan or Targinact

5 #4 or #3 or #2 or #1

4 TOPIC: ("Gastrointestinal Tract")

3 TOPIC:("Gastrointestinal Motility")

2 TOPIC: (Ileus)

1 TOPIC: ((constipat* or laxation or (bowel near/2 dysfunction*)))

Appendix 2. Letter to pharmaceutical companies

Example, as was sent to AstraZeneca, of letter sent to pharmaceutical companies

Research and Communications

Manager (or equivalent)

AstraZeneca (Global HQ)

Floors 7-9,

2 Kingdom Street,

Paddington Central,

London, W2 6BD, UK

Email: b.candy@ucl.ac.uk

Phone: +44 020767997

March 31st 2016

Dear Sir or Madam

Mu-opioid antagonists for opioid-induced bowel dysfunction in cancer and palliative care patients - a Cochrane systematic review

We address you in order to request your assistance. We are conducting a systematic review on the effect of mu-opioid antagonists for opioid-induced bowel dysfunction in cancer and palliative care patients. We are working with the Cochrane Pain, Palliative and Supportive Care Review Group (www.papas.cochrane.org).

Our systematic review intends to include all relevant literature empirically describing both the positive and possibly negative effects of mu-opioid antagonists. We believe that conducting this review is in the common interest of patients, doctors and pharmaceutical manufacturers. Furthermore, it is an important ethical issue. The results from this review will, in the future, guide authorities, clinicians and researchers when it comes to considering the use of a mu-opioid antagonist in the treatment of opioid-induced bowel dysfunction for cancer and palliative care patients.

Our Cochrane review will be comprehensive. The currently included studies come from our search for literature through international scientific databases. However, the published literature only provides us with limited and possibly selective knowledge, since it is unlikely that all studies and data are available through these databases. By contacting authors of significant publications, experts in the field and pharmaceutical companies, we hope to be informed of additional studies, published as well as unpublished. This approach has been used in other Cochrane systematic reviews investigating medical preparations for common illnesses such as Attention Deficit Hyperactivity Disorder (http://www.bmj.com/content/351/bmj.h5203).

We hope you will assist us with providing studies and data that are relevant for our review. We are aware from searches of electronic citation databases including PubMed and clinicaltrials.gov of one trial for which AstraZeneca are the responsible party/study sponsors (NCT01384292). As previously noted, we are interested in data regarding both positive and negative effects of mu-opioid antagonists for opioid-induced bowel dysfunction in cancer and palliative care patients, from randomised clinical trials, regardless of the year the data were recorded or published.

We will state which companies we have been in contact with, and acknowledge those who have assisted us with provision of data. We would be happy to meet a representative from your company if you would like to speak in person. If you have any questions, please contact us.

Enclosed below in this letter is a list of the currently included studies in our review.

We look forward to your response.

Yours faithfully

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(copy sent via info@astrazeneca.com)

List of the currently included studies in our review

Ahmedzai SH, Nauck F, Bar-Sela G, Bosse B, Leyendecker P, Hopp M. A randomized, double-blind, active- controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/ severe, chronic cancer pain. Palliative Medicine 2012; 26: 50-60.

Bull J, Wellman CV, Israel RJ, Barrett AC, Paterson C, Forbes WP. Fixed-Dose Subcutaneous Methylnaltrexone in Patients with Advanced Illness and Opioid-Induced Constipation: Results of a Randomized, Placebo-Controlled Study and Open-Label Extension. Journal of Palliative Medicine 2015;18:593-600.

Chamberlain BH, Cross K, Winston JL, Thomas J, Wang W, Su C, Israel RJ. Methylnaltrexone Treatment of Opioid-Induced Constipation in Patients with Advanced Illness. Journal of Pain and Symptom Management 2009;38: 683-90.

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.

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 NP. An investigation of the ability of oral naloxone to correct opioid-related constipation in patients with advanced cancer. Palliative Medicine 1996;10:135-44.

Thomas J, Karver S, Cooney GA, et al. A randomized, placebo-controlled trial of subcutaneous methylnaltrexone for the treatment of opioid- induced constipation in patients with advanced illness. New England Journal of Medicine 2008;358: 2332-4.

FEEDBACK

Feedback on methylnaltrexone in palliative care, March 2011,

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 people receiving palliative care. Some of the comments specifically relate 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 methylnaltrexone group (150 mg [9-4160 mg]), 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 anaemia, 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 0.15 mg per kilogram of body weight) or an equal volume of placebo administered subcutaneously on alternate days for two 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 arbitrary 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 methylnaltrexone 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 and 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 two 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.
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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. New England Journal of Medicine 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 methylnaltrexone 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 long-term 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 methylnaltrexone 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 methylnaltrexone 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

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

WHAT'S NEW

Date	Event	Description
20 December 2021	New search has been performed	This review has been updated to include results of a new search on 20 December 2021
17 February 2021	New citation required but conclusions have not changed	Two new studies identified, bringing the total included to 10. In total, 1343 male and female adults with cancer irrespective of stage or at a palliative care stage of any disease were randomised across the studies. Overall conclusions have not changed.

HISTORY

Protocol first published: Issue 1, 2007
Review first published: Issue 2, 2008

Date	Event	Description
11 May 2011	New citation required and conclusions have changed	The inclusion criteria have changed. We now include patient populations of cancer and palliative care, and assess the intervention mu-opioid antagonists for opioid-induced bowel dysfunction. The methods have changed to reflect current Cochrane guidelines and changes to the inclusion criteria. There are new conclusions on the mu-opioid antagonist naldemedine. Conclusions on other mu-opioid antagonists have not changed. A Summary of Findings Table has been added.
24 September 2010	Amended	Contact details updated.

Date	Event	Description
30 October 2008	Amended	Further RM5 changes
11 April 2008	Amended	Converted to new review format.
8 February 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

In the 2018 review update

Independent assessment of eligibility of trials in new searches: BC and LJ.

Data extraction: BC and checked by LJ and VV.

Statistical support: VV.

Updating of all review sections was drafted by BC and checked and critiqued by other members of the review update team (LJ, PJL, PS, and VV). This is apart from the 'Summary of findings' tables, which were drafted by VV and checked and critiqued by BC.

In the 2022 update

Developed and ran the search strategy: BC/LJ/VV/PS/PL with PaPaS Information Specialist’s support
Obtained copies of studies: BC
Selected which studies to include: BC/LJ
Extracted data from studies: BC/VV
Entered data into RevMan: BC/VV
Carried out the analysis: BC/VV
Interpreted the analysis: BC/LJ/VV/PS/PL
Drafted the review: BC/LJ/VV/PS/PL

DECLARATIONS OF INTEREST

BC: none known.

LJ: none known.

VV: none known.

PJL: none known. PJL is a Professor of Palliative Care Nursing University Hospital of Lausanne, Switzerland.

PS: none known. PS is a consultant in Palliative Medicine at University College London Hospital and Parkside Private Hospital (London).

SOURCES OF SUPPORT

Internal sources

- Marie Curie Care, UK

  Supported the salaries of BC, VV, PS through a departmental programme grant (MCCCFPO-16-U).

External sources

- National Institute for Health Research (NIHR), UK

  Cochrane Infrastructure funding to the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2022 Update

In the methods section, we give more detail on types of studies we include. We give more detail on outcomes and time points of interest. We set out ad hoc rules on selection of outcomes. These include types of outcomes and outcome time points of interest, and what outcome to select when multiple measures were reported. Selection decisions were pragmatic based on clinical relevance, and robustness of measures such as selecting global score of a scale as opposed to subscales. We added to the primary outcomes a user-important outcome, this was patient assessment of change in bowel status. We no longer include as a risk of bias domain sample size as this is no longer recommended by Cochrane PaPas group. We updated our use of GRADE in judging imprecision, we now downgrade evidence once if the data is from fewer than 400 participants for continuous data and fewer than 300 events for dichotomous data. These changes have resulted in some changes in the results section, including our certainty of evidence.

2018 Update

We included the population of interest in the title.

We merged two reviews (Candy 2011; McNicol 2008). The update review differed in inclusion criteria from the two reviews it is updating (Candy 2011; McNicol 2008). This is in population of interest, which in the update is restricted to cancer and palliative care. In one of the earlier reviews there was no restriction on population (McNicol 2008). Since publication, there are more trials on Mu-opioid antagonists (MOAs) for opioid-induced bowel dysfunction (OIBD), particularly in postoperative populations. This current review update was restricted in population to allow us to complete the review in a timely manner. A review on MOAs for OIBD in other populations is planned, to be undertaken by another team that has relevant clinical expertise. This review update also differs in interventions. The other review it is update, is a review on the effectiveness of laxatives and the MOA, methylnaltrexone, in palliative care populations (Candy 2011). This current review update included all MOAs to reflect new drug developments. We did not include trials on laxatives in palliative care as the findings of these are reported elsewhere (Candy 2015).

We updated the background section to reflect new research findings.

We updated the methods section to reflect current Cochrane guidelines, in particular in risk of bias and quality assessment. The outcomes of interest differed from previous versions. In part this can be accounted for because the population differed. In the current version, we also extended our search methods to clinical trial registers and online regulatory documents. A previous version of the review (McNicol 2008) used Jadad score to assess trial quality (Jadad 1996). The current review differed as it assessed the risk of bias of trial findings as set out in the current version of the *Cochrane Handbook for Systematic Reviews on interventions* (Higgins 2011). It also assesses the certainty of the evidence using the GRADE system (Guyatt 2013a) and provided summary of findings tables.

Some of the aspects on reporting in the other earlier version (McNicol 2008) were not relevant in the current update because of updated Cochrane guidelines and inclusion criteria differences. These reasons accounted for differences in the sections on analysis, specifically on unit of analysis issues, missing data, and subgroup analysis. Unlike earlier versions, this review update did not detail how we would assess publication bias, as we were unable to do this analysis because of the limited number of trials.

In this update, in addition to trials presented in full journal publication we sought to include any online clinical trial results summaries of otherwise unpublished clinical trial or trial data relating to the published trial.

There are difference from the original protocol in regards to comparison groups; we now consider trials that compare different doses of MOAs. The addition is because of the clinical usefulness of knowing the effect of a drug at a lower dose.

INDEX TERMS

Medical Subject Headings (MeSH)

Constipation [chemically induced] [drug therapy]; Defecation [drug effects]; Gastrointestinal Agents [therapeutic use]; Intestinal Diseases [chemically induced] [*drug therapy]; Nalbuphine [therapeutic use]; Naloxone [adverse effects] [therapeutic use]; Naltrexone [adverse effects] [analogs & derivatives] [therapeutic use]; Narcotic Antagonists [adverse effects] [*therapeutic use]; Neoplasms [*complications]; Opioid-Related Disorders [*drug therapy]; Oxycodone [adverse effects] [therapeutic use]; Palliative Care; Piperidines [therapeutic use]; Quaternary Ammonium Compounds [therapeutic use]; Randomized Controlled Trials as Topic; Receptors, Opioid, mu [antagonists & inhibitors]

MeSH check words

Female; Humans; Male