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TITLE PAGE

Title: Efficacy of Pharmacological Therapies for the Treatment of Opioid-induced Constipation: Systematic Review and Network Meta-analysis.

Short running head: Treatment of Opioid-induced Constipation: Network Meta-analysis.

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Abbreviations:

b.i.d	twice-daily
BM	bowel movement
CI	confidence interval
GI	gastrointestinal
MeSH	medical subject heading
o.d.	once-daily
NNT	number needed to treat
OIC	opioid-induced constipation

PR	prolonged release
QALY	quality-adjusted life year
RCT	randomised controlled trial
RR	relative risk
SUCRA	surface under the cumulative ranking curve
t.i.d	three times daily

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ABSTRACT

Objective: Opioids are increasingly prescribed in the West, and have deleterious gastrointestinal consequences. Pharmacological therapies to treat opioid-induced constipation (OIC) are available, but their relative efficacy is unclear. We performed a systematic review and network meta-analysis to address this deficit in current knowledge.

Design: We searched MEDLINE, EMBASE, EMBASE Classic, and the Cochrane central register of controlled trials through to December 2017 to identify randomised controlled trials (RCTs) of pharmacological therapies in the treatment of adults with OIC. Trials had to report a dichotomous assessment of overall response to therapy, and data were pooled using a random effects model. Efficacy and safety of pharmacological therapies was reported as a pooled relative risk (RR) with 95% confidence intervals (CIs) to summarise the effect of each comparison tested, and ranked treatments according to their P-score.

Results: Twenty-seven eligible RCTs of pharmacological therapies, containing 9149 patients, were identified. In our primary analysis, using failure to achieve an average of ≥3 bowel movements (BMs) per week with an increase of ≥1 BM per week over baseline, or an average of ≥3 BMs per week, to define non-response the network meta-analysis ranked naloxone first in terms of efficacy (RR = 0.65; 95% CI 0.52-0.80, P-score 0.84), and it was also the safest drug. When non-response to therapy was defined using failure to achieve an average of ≥3 bowel movements (BMs) per week, with an increase of ≥1 BM per week over baseline, naldemidine was ranked first (RR = 0.66; 95% CI 0.56-0.77, P-score 0.91), and alvimopan second (RR = 0.74; 95% CI 0.57-0.94, P-score 0.71).

Conclusion: In network meta-analysis, naloxone and naldemidine appear to be the most efficacious treatments for OIC. Naloxone was the safest of these agents.

What is already known about this subject?

There is an epidemic of opioid prescribing in the West.

These drugs have deleterious effects on the gastrointestinal tract.

Effective treatments, including μ-opioid receptor antagonists, prokinetics, and secretagogues are available, but their relative effectiveness is uncertain.

What are the new findings?

We identified 27 RCTs of pharmacological therapies in opioid-induced constipation (OIC), containing 9149 patients.

The μ-opioid receptor antagonists naloxone, naldemidine, alvimopan, and subcutaneous methylnaltrexone, as well as the prokinetic prucalopride, were all more effective than placebo for the treatment of OIC.

In our primary analysis, naloxone was ranked as the best drug, and was also the safest.

Naldemidine was the most effective drug when an average of ≥3 bowel movements (BMs) per week with an increase of ≥1 BM per week over baseline was used to define response.

How might it impact on clinical practice in the near future?

Clinicians should consider the use of naloxone and naldemidine in OIC as a first choice when laxatives fail.

Guidelines for the management of OIC should be updated to include this important information.

INTRODUCTION

Chronic constipation affects up to 20% of individuals in the community. [1] Prescribed medications are implicated as a contributing factor in the aetiology of chronic constipation in a substantial proportion of individuals. [2] In the West, there is an epidemic of opioid prescribing, [3, 4] which in the US has led the surgeon general to discourage strongly the prescription of these drugs for non-malignant pain in adults. [5] As well as the risk of long-term addiction and higher rates of death among opioid users, [6] these drugs have undesired actions on the gastrointestinal (GI) tract, due to the location of μ-opioid receptors. Opioids lead to delayed GI transit and hard, infrequent stools, [7] with up to 50% of individuals taking these drugs reporting constipation, which they attribute to opioid use. [8, 9]

Surveys of patients receiving long-term opioid therapy reveal that opioid-induced constipation (OIC) is associated with significant increases in physician visits and sickness-related absence from work, as well as a significantly lower quality of life, compared with opioid users who do not experience constipation. [10, 11] In addition, up to one-third of patients reduce their opioid dosage, or discontinue the drugs altogether, in order to improve their bowel symptoms, which may negatively impact on their pain control. [9] As a result, a substantial proportion of patients with OIC use over the counter or prescription laxatives, in an attempt to alleviate their symptoms. [8] However, a previous Cochrane review revealed that there is little evidence to support a benefit of laxatives in this patient group, [12] which is mirrored by surveys of patients, where less than 50% report a satisfactory effect. [13]

As a result, pharmacological therapies have been developed in an attempt to provide effective therapy for a disorder that can be difficult to treat. The majority of these are drugs that act on μ-opioid receptors, in order to selectively antagonise the GI effects of

opioids. [14] These include methylnaltrexone, naloxone, alvimopan, bevenopran, naldemedine, and naloxegol. However, other agents that have already demonstrated their efficacy in the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation, such as prucalopride and lubiprostone, [15, 16] have also been tested in OIC. Prucalopride is a prokinetic, which is a highly selective 5-hydroxytryptamine-4 receptor agonist, and lubiprostone is a secretagogue, which acts on CIC-2 chloride channels in the intestine. Our previous meta-analysis demonstrated that some of these drugs were efficacious and safe in the treatment of OIC. [14] However, there have been new randomised controlled trials (RCTs) conducted for some of these agents, and several new drugs developed in the intervening 5 years. In addition, there have been no head-to-head studies conducted to enable healthcare providers to judge which of these drugs is likely to be the most effective in treating OIC. We have therefore updated our previous systematic review, [14] but also conducted a network meta-analysis, in order to examine these issues.

METHODS

Search Strategy and Study Selection

We updated a previous meta-analysis studying this issue. [14] A search of the medical literature was conducted using MEDLINE (2012 to December 2017), EMBASE and EMBASE Classic (2012 to December 2017), PUBMED (2012 to December 2017) and the Cochrane central register of controlled trials. We also searched clinicaltrials.gov for unpublished trials, or supplementary data for potentially eligible studies. RCTs examining the effect of pharmacological therapies (methylnaltrexone, naloxone, alvimopan, naldemedine, naloxegol, bevenopran, lubiprostone, prucalopride, naronapride, velusetrag, linaclotide, or plecanatide) in adult patients (>90% of participants over the age of 16 years) with OIC were eligible for inclusion (Box 1). The first period of cross-over RCTs were also eligible for inclusion.

A diagnosis of OIC was based on a history of constipation associated with the onset of opioid analgesic use. Studies recruiting patients with organic or chronic idiopathic constipation were ineligible. Trials using any dose of pharmacological therapy were considered eligible, and agents could be compared with each other, or with placebo. Only trials that used a minimum duration of 2 weeks of treatment were considered, in order not to overestimate the efficacy of one pharmacological therapy relative to another, meaning that we excluded three RCTs deemed eligible for the previous version of this meta-analysis. [17, 18, 19] Studies had to report a dichotomous assessment of overall response to therapy. First and senior authors of studies were contacted to provide additional information on trials, where required. The search strategy is provided in the supplementary materials.

There were no language restrictions, and abstracts identified by the initial search were evaluated independently by two investigators for eligibility. All potentially relevant papers were obtained and evaluated in detail. Foreign language papers were translated, where required. Abstract books of conference proceedings between 2012 and 2017 were hand-searched to identify potentially eligible studies published only in abstract form. Bibliographies of all identified relevant studies were used to perform a recursive search of the literature. Articles were assessed independently by two investigators using pre-designed eligibility forms, according to the pre-defined eligibility criteria. Disagreements between investigators were resolved by discussion.

Outcome Assessment

The primary outcome assessed was the efficacy of pharmacological therapies, compared with each other or with placebo, in OIC in terms of failure to respond to therapy, with the endpoints of interest used to define response reported below. Secondary outcomes included adverse events occurring as a result of therapy (overall numbers, as well as individual adverse events including diarrhoea, abdominal pain, nausea, or reversal of analgesia).

Data Extraction

All data were extracted independently by two investigators on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (response or no response to therapy). Many of the included eligible RCTs used different primary endpoints. However, due to the multitude of endpoints reported within the individual trials, we were able to assess the efficacy of therapies according to the following four dichotomous endpoints to define response to treatment:

reporting an average of ≥3 bowel movements (BMs) per week with an increase of ≥1 BM per week over baseline; reporting an average of ≥3 BMs per week; reporting any clinical improvement in symptoms; or reporting the need for use of rescue laxatives. For all included studies the following data were also extracted for each trial, where available: country of origin, setting (primary, secondary, or tertiary care), number of centres, criteria used to define OIC, proportion of female patients, and dose and duration of therapy. Data were extracted as intention-to-treat analyses, with drop-outs assumed to be treatment failures (i.e. no response to therapy), wherever trial reporting allowed. If this was not clear from the original article we performed an analysis on all patients with reported evaluable data.

Quality Assessment and Risk of Bias

Two investigators performed this independently at the study level. Disagreements were resolved by discussion. The Cochrane handbook was used to assess risk of bias, [20] by recording the method used to generate the randomisation schedule and conceal treatment allocation, whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes.

Data Synthesis and Statistical Analysis

A network meta-analysis was performed using the frequentist model, using the statistical package “netmeta” (version 0.9-0, https://cran.r-project.org/web/packages/netmeta/index.html) in R (version 3.4.2), and reported according to the PRISMA extension statement for network meta-analyses, [21] in order to explore indirect treatment comparisons of the efficacy and safety of each medication. Network

meta-analysis results usually give a more precise estimate, compared with results from standard, pairwise analyses, [22, 23] and can also rank treatments to inform clinical decisions. [24]

We examined the symmetry and geometry of the evidence by producing a network plot with node and connection size corresponding to the number of study subjects and studies respectively. We produced a comparison adjusted funnel plot to explore publication bias of all available comparisons, versus placebo, using Stata version 14 (Stata Corp., College Station, TX, USA). Symmetry around the effect estimate line indicates the absence of publication bias, or small study effects. [25] We produced a pooled RR with 95% CIs to summarise the effect of each comparison tested, using a random effects model as a conservative estimate. There were no indirect comparisons between the active treatment groups, so we were unable to perform consistency modelling to check correlation between direct and indirect evidence. [26] Global statistical heterogeneity across all comparisons was assessed using the I^2 measure from the "netmeta" statistical package. The I^2 measure ranges between 0% and 100%, and is typically considered low, moderate, and high for values of 25% to 49%, 50% to 74%, and ≥75% respectively. [27] We ranked the treatments according to their P-score. The P-score is a value between 0 and 1, with a higher score indicating a greater probability of the treatment being ranked as best. [28] However, the magnitude of the P-score should be considered, as well as the treatment rank. The mean value of the P-score is always 0.5, so if treatments cluster around this value they are likely to be of similar efficacy. In our primary analysis we combined an average of ≥3 BMS per week with an increase of ≥1 BM per week over baseline and an average of ≥3 bowel movements (BMs) per week, but also analysed these separately. The number needed to treat (NNT), with a 95% CI, was calculated for each drug compared with placebo using the formula NNT = 1 / (control event rate x (1 – RR)).

We also performed analyses to assess the overall safety of each medication, including overall numbers of adverse events, as well as occurrence of diarrhoea, abdominal pain, nausea, or reversal of analgesia. We then performed a series of a priori subgroup analyses to test the robustness of our primary results. Firstly, we included only those studies with a low risk of bias. Secondly, we included only those studies with treatment duration of ≥6 weeks, to account for a more prolonged response that may better reflect "real-world" use. Finally, we repeated our primary analysis using a Bayesian model to assess the robustness of our findings. We compared the relative efficacy of therapies for our primary outcome using the "mvmeta" commands in Stata, using a random effects model. We ranked the treatments according to their surface under the cumulative ranking curve (SUCRA) value. The SUCRA value is the equivalent to the P-score used in the frequentist model of our primary analyses. [28]

RESULTS

The search strategy generated 2523 citations, 48 of which appeared to be relevant to the systematic review and were retrieved for further assessment (Figure 1). Of these, 21 were excluded for various reasons, leaving a total of 27 eligible articles, [29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55] which reported 27 separate placebo-controlled trials, containing a total of 9149 patients. Twenty-two of these RCTs, reported in 22 articles, [29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50] studied the effect of μ-opioid-receptor antagonists in OIC, three assessed lubiprostone, [51, 52, 53] and two prucalopride. [54, 55] We did not identify any trials of naronapride, velusetrag, linaclotide, or plecanatide in OIC. Five of the 22 trials of μ-opioid-receptor antagonists used naloxone, [29, 30, 31, 32, 33] four used methylnaltrexone, with endpoints of interest reported in six separate articles, [34, 35, 36, 37, 38, 39] five used naldemidine, reported in four articles, [40, 41, 42, 43] four used alvimopan, [44, 45, 46, 47] two naloxegol, reported in one article, [48] and two bevenopran. [49, 50] All studies were published in English, and agreement between investigators for trial eligibility for the 48 articles retrieved was excellent (Kappa statistic = 0.87). Detailed characteristics of individual RCTs are provided in Table 1. Risk of bias for all included trials is reported in Supplementary Table 1. Only 11 trials, reported in 11 articles, [30, 31, 33, 35, 37, 39, 40, 43, 45, 51, 52] were at low risk of bias. We obtained data for four of the RCTs from clinicaltrials.gov. [49, 50, 53, 55] We did not identify any trials making head-to-head comparisons of one drug versus another, meaning that direct evidence was only available in comparison with placebo. Active medications could therefore only be compared with each other using an indirect evidence meta-analysis. Data concerning failure to achieve clinical improvement, need for rescue laxatives, and safety are provided for the reader in the supplementary materials.

Table 1. Characteristics of Randomised Controlled Trials of Pharmacological Therapies Versus Placebo in Opioid-induced Constipation.

Study	Country, number of centres, and setting	Patient group studied	Criteria used to define opioid-induced constipation	Number of patients (% female)	Number of patients assigned to active drug, dosage, schedule, and duration of therapy	Outcomes reported
Thomas 2008 [34] and Chamberlain 2009 [38]	USA and Canada, 27 sites, primary and secondary care	Advanced illness (life expectancy ≥1 month), laxative refractory	Stable opioid regimen for ≥2 weeks, <3 BMs* in previous week, and no clinically meaningful BM within 48 hours before first study dose	134 (56.7)	63 patients received methylnaltrexone 0.15mg/kg subcutaneously o.d.† on alternate days for 2 weeks	≥3 BMs per week Clinical improvement Need for rescue laxatives

Michna 2011 [35] and Iyer 2011 [39]	USA, multiple sites, setting not reported	Chronic non-malignant pain, not laxative refractory	Opioid dose equivalent to >50mg/day of morphine for ≥2 weeks, <3 rescue-free BMs per week associated with ≥1 of: hard or lumpy stools, straining, or incomplete evacuation	460 (60.2)	298 patients received methylnaltrexone 12mg subcutaneously o.d. or on alternate days for 4 weeks	≥3 BMs per week ≥3 BMs per week with an increase of ≥1 BM per week from baseline Clinical improvement Need for rescue laxatives
Bull 2015 [36]	Multi-national, 60 sites, secondary and tertiary care	Advanced illness (life expectancy ≥1 month), not laxative refractory	<3 BMs in previous week, and no clinically meaningful BM within 24 hours before first study dose	230 (48.7)	116 patients received methylnaltrexone 8 or 12mg subcutaneously on alternate days for 2 weeks	Need for rescue laxatives
Rauck 2017 [37]	USA, 117 sites, setting not reported	Chronic non-malignant pain, laxative refractory	Opioid dose equivalent to ≥50mg/day of morphine for ≥2 weeks, <3 rescue-free BMs per week associated with ≥1 of: Bristol stool form 1 or 2, straining, or incomplete evacuation on ≥25% of BMs	804 (62.9)	603 patients received methylnaltrexone 150, 300, or 450mg orally o.d. for 4 weeks, then as required for 8 weeks	≥3 BMs per week with an increase of ≥1 BM per week from baseline

Liu 2002 [29]	USA, 1 site, secondary care	Chronic non-malignant and malignant pain, laxative status not reported	Onset of constipation corresponding to use of opioids and on a stable dose of opioids	9 (55.6)	6 patients received naloxone 2 or 4mg orally t.i.d.± for 3 weeks	Clinical improvement
Simpson 2008 [30]	4 European countries, multiple sites, primary and secondary care	Chronic non-malignant pain, not laxative refractory	Opioid dose equivalent to ≥20mg/day to ≤50mg/day of oxycodone, and constipation caused or aggravated by an opioid	322 (60.9)	162 patients received oxycodone PR‡ /naloxone PR orally in a 2:1 fixed dose ratio for 12 weeks	≥3 BMs per week at 4 weeks Need for rescue laxatives at 4 weeks
Meissner 2009 [33]	Germany, 28 sites, secondary and tertiary care	Chronic non-malignant pain, not laxative refractory	Stable oxycodone dose (40, 60, or 80mg/day) with concomitant constipation	202 (62.9)	152 patients received naloxone 10, 20, or 40mg orally o.d. for 4 weeks	Need for rescue laxatives
Lowenstein 2009 [32]	Multi-national, multiple sites, secondary care	Chronic non-malignant pain, not laxative refractory	Stable oxycodone dose (60 to 80mg/day) with <3 BMs per week caused or aggravated by opioids	265 (68.3)	130 patients received oxycodone PR/naloxone PR orally in a 2:1 fixed dose ratio for 12 weeks	≥3 BMs per week Clinical improvement Need for rescue laxatives

Sanders 2015 [31]	UK and Germany, 10 sites, setting not reported	Chronic non-malignant pain, not laxative refractory	Stable opioid dose for ≥1 month, and <3 BMs per week associated with ≥1 of: hard or small stools, straining, or incomplete evacuation on ≥25% of BMs	40 (52.5)	32 patients received naloxone 2.5, 5, 10, or 20mg orally o.d. for 3 weeks then b.i.d.§ for 3 weeks	Clinical improvement
Paulson 2005 [44]	USA, 22 sites, secondary and tertiary care	Chronic non-malignant pain or opioid-dependent, not laxative refractory	Stable opioid dose for ≥1 week of ≥10mg morphine or equivalent, and <3 BMs per week associated with ≥1 of: hard or lumpy stools, straining, sensation of obstruction, or incomplete evacuation	168 (58.3)	114 patients received alvimopan 0.5 or 1mg orally o.d. for 3 weeks	Clinical improvement
Webster 2008 [45]	Multi-national, 113 sites, secondary and tertiary care	Chronic non-malignant pain, not laxative refractory	Stable opioid dose for ≥1 month of ≥30mg morphine or equivalent and history of decreased BMs since starting opioids, with ≥1 of: hard stools, straining, or incomplete evacuation on 25% of BMs	522 (63.8)	393 patients received alvimopan 0.5mg b.i.d., 1mg o.d., or 1mg b.i.d. orally for 6 weeks	≥3 BMs per week Clinical improvement

Irving 2011 [46]	Multi-national, 153 sites, secondary and tertiary care	Chronic non-malignant pain, laxative status not reported	Stable opioid dose for ≥1 month of ≥30mg morphine or equivalent and history of decreased BMs since starting opioids, with ≥1 of: hard stools or straining	485 (64.0)	321 patients received alvimopan 0.5mg o.d. or 0.5mg b.i.d. orally for 12 weeks	≥3 BMs per week with an increase of ≥1 BM per week from baseline Clinical improvement Need for rescue laxatives
Jansen 2011 [47]	Multi-national, 148 sites, secondary and tertiary care	Chronic non-malignant pain, laxative status not reported	Stable opioid dose for ≥1 month of ≥30mg morphine or equivalent and history of decreased BMs since starting opioids, with ≥1 of: hard stools or straining	518 (63.0)	346 patients received alvimopan 0.5mg o.d. or 0.5mg b.i.d. orally for 12 weeks	≥3 BMs per week with an increase of ≥1 BM per week from baseline Need for rescue laxatives

Webster 2017 [41]	USA, 49 sites, setting not reported	Chronic non-malignant pain, laxative refractory	Stable opioid dose for ≥1 month of ≥30mg morphine or equivalent and <3 BMs per week associated with ≥1 of: hard or small stools, straining, sensation of obstruction, or incomplete evacuation on ≥25% of BMs	244 (68.4)	183 patients received naldemedine 0.1, 0.2, or 0.4mg orally o.d. for 4 weeks	≥3 BMs per week with an increase of ≥1 BM per week from baseline Clinical improvement Need for rescue laxatives
Katakami 2017a [42]	Japan and South Korea, 102 sites, setting not reported	Chronic malignant pain, laxative refractory	Stable opioid dose and ≤5 BMs during a 14 day run-in period associated with ≥1 of: hard stools, straining, sensation of obstruction, or incomplete evacuation on 25% of BMs	227 (40.1)	170 patients received naldemedine 0.1, 0.2, or 0.4mg orally o.d. for 2 weeks	≥3 BMs per week with an increase of ≥1 BM per week from baseline Clinical improvement Need for rescue laxatives

Katakami 2017b COMPOSE-4 [43]	Japan, 70 sites, setting not reported	Chronic malignant pain, not laxative refractory	Stable opioid dose and ≤5 BMs during a 14 day run-in period associated with ≥1 of: hard stools, straining, sensation of obstruction, or incomplete evacuation on 25% of BMs	193 (38.3)	97 patients received naldemedine 0.2mg orally o.d. for 2 weeks	≥3 BMs per week with an increase of ≥1 BM per week from baseline
Hale 2017 COMPOSE-1 [40]	Multi-national, 68 sites, setting not reported	Chronic non-malignant pain, not laxative refractory	Stable opioid dose for ≥1 month of ≥30mg morphine or equivalent and ≤3 BMs per week associated with ≥1 of: hard or lumpy stools, straining, sensation of obstruction or blockage, or incomplete evacuation on ≥25% of BMs	547 (60.4)	274 patients received naldemedine 0.2mg orally o.d. for 12 weeks	≥3 BMs per week with an increase of ≥1 BM per week from baseline
Hale 2017 COMPOSE-2 [40]	Multi-national, 69 sites, setting not reported	Chronic non-malignant pain, not laxative refractory	Stable opioid dose for ≥1 month of ≥30mg morphine or equivalent and ≤3 BMs per week associated with ≥1 of: hard or lumpy stools, straining, sensation of obstruction or blockage, or incomplete evacuation on ≥25% of BMs	553 (60.5)	277 patients received naldemedine 0.2mg orally o.d. for 12 weeks	≥3 BMs per week with an increase of ≥1 BM per week from baseline

Chey 2014 KODIAC-04 [48]	USA and Europe, 115 sites, setting not reported	Chronic non-malignant pain, 54.6% of patients laxative refractory	Stable opioid dose for ≥1 month of ≥30 to 1000mg morphine or equivalent and <3 BMs per week associated with ≥1 of: hard or lumpy stools, straining, sensation of obstruction, or incomplete evacuation on ≥25% of BMs	641 (61.3)	427 patients received naloxegol 12.5 or 25mg orally o.d. for 12 weeks	≥3 BMs per week with an increase of ≥1 BM per week from baseline Need for rescue laxatives
Chey 2014 KODIAC-05 [48]	USA and Europe, 142 sites, setting not reported	Chronic non-malignant pain, 53.2% of patients laxative refractory	Stable opioid dose for ≥1 month of ≥30 to 1000mg morphine or equivalent and <3 BMs per week associated with ≥1 of: hard or lumpy stools, straining, sensation of obstruction, or incomplete evacuation on ≥25% of BMs	696 (63.4)	464 patients received naloxegol 12.5 or 25mg orally o.d. for 12 weeks	≥3 BMs per week with an increase of ≥1 BM per week from baseline Need for rescue laxatives
Singla 2012 [50]	USA, number of sites and setting not reported	Chronic non-malignant pain, not laxative refractory	<3 BMs per week associated with ≥1 of: hard or lumpy stools, straining, sensation of obstruction, or incomplete evacuation on ≥25% of BMs	131 (48.1)	88 patients received bevenopran 0.1 or 0.25mg orally o.d. for 4 weeks	≥3 BMs per week with an increase of ≥1 BM per week from baseline

Techner 2012 [49]	USA, number of sites and setting not reported	Chronic non-malignant pain, not laxative refractory	<3 BMs per week associated with ≥1 of: hard or lumpy stools, straining, sensation of obstruction, or incomplete evacuation on ≥25% of BMs	81 (69.1)	40 patients received bevenopran 0.25mg orally o.d. for 4 weeks	≥3 BMs per week with an increase of ≥1 BM per week from baseline
Cryer 2014 [51]	USA and Canada, 79 sites, primary, secondary, and tertiary care	Chronic non-malignant pain, not laxative refractory	Stable opioid dose for ≥1 month and <3 BMs per week associated with ≥1 of: hard or very hard stools, straining, or incomplete evacuation on ≥25% of BMs	439 (64.4)	221 patients received lubiprostone 24mcg orally b.i.d for 12 weeks	≥3 BMs per week Need for rescue laxatives
Jamal 2012 [52]	USA and Europe, 103 sites, primary, secondary, and tertiary care	Chronic non-malignant pain, not laxative refractory	Stable opioid dose for ≥1 month and <3 BMs per week associated with ≥1 of: hard or very hard stools, straining, or incomplete evacuation on ≥25% of BMs	431 (63.1)	214 patients received lubiprostone 24mcg orally b.i.d for 12 weeks	≥3 BMs per week with an increase of ≥1 BM per week from baseline Need for rescue laxatives

NCT00597428 (unpublished) [53]	USA and Canada, 114 sites, primary, secondary, and tertiary care	Chronic non-malignant pain, not laxative refractory	Stable opioid dose for ≥1 month and <3 BMs per week associated with ≥1 of: hard or very hard stools, straining, or incomplete evacuation on ≥25% of BMs	437 (61.1)	223 patients received lubiprostone 24mcg orally b.i.d for 12 weeks	≥3 BMs per week
Sloots 2010 [54]	Multi-national, 60 sites, secondary and tertiary care	Chronic non-malignant pain, not laxative refractory	Constipation secondary to chronic daily opioid use	196 (61.2)	130 patients received prucalopride 2 or 4mg orally o.d. for 4 weeks	≥3 BMs per week Clinical improvement
NCT01117051 (unpublished) [55]	Belgium, number of sites and setting not reported	Chronic non-malignant pain, not laxative refractory	Constipation secondary to chronic daily opioid use	174 (72.8)	88 patients received prucalopride 1 or 2mg orally o.d. for up to 12 weeks	≥3 BMs per week

*BM; bowel movement

†o.d.; once-daily

±t.i.d.; three times daily

‡PR; prolonged release

§b.i.d.; twice-daily

Efficacy

Failure to Achieve an Average of ≥3 BMs per Week with an Increase of ≥1 BM per Week Over Baseline, or an Average of ≥3 BMs per Week

There were 22 RCTs, reported in 20 separate articles, [30, 32, 34, 35, 37, 40, 41, 42, 43, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55] randomising 5212 patients to active treatment and 3288 to placebo, included in this analysis. The network plot is provided in Supplementary Figure 1. There were moderate levels of global statistical heterogeneity (I^2 = 58.8%). The comparison adjusted funnel plot for publication bias, or other small study effects, showed symmetry around the zero line (Supplementary Figure 2). Naloxone was ranked as the most effective treatment (P-score 0.84), and was significantly more effective than placebo in two RCTs (RR 0.65; 95% CI 0.52 to 0.80, NNT = 4; 95% CI 3 to 8) (Figure 2). Naldemedine (five RCTs, RR 0.67; 95% CI 0.59 to 0.77, NNT = 5; 95% CI 4 to 7), alvimopan (three RCTs, RR 0.67; 95% CI 0.57 to 0.80, NNT = 5; 95% CI 4 to 8), subcutaneous methylnaltrexone (two RCTs, RR 0.74; 95% CI 0.58 to 0.94, NNT = 6; 95% CI 4 to 26), and prucalopride (two RCTs, RR 0.74; 95% CI 0.58 to 0.96, NNT = 6; 95% CI 4 to 39) were also significantly more effective than placebo (Figure 2). On indirect comparison of active treatments, significant differences were seen with naloxone compared with oral methylnaltrexone or lubiprostone; naldemedine compared with naloxegol, oral methylnaltrexone, or lubiprostone; and alvimopan compared with lubiprostone (Table 2).

We performed a series of pre-specified subgroup analyses. When considering only studies with a low risk of bias, there were nine RCTs included, reported in eight articles, [30, 35, 37, 40, 43, 45, 51, 52] randomising 2539 patients to active treatment and 1732 to placebo. Alvimopan was ranked as the best treatment (one RCT, P-score 0.89; RR

Table 2. League Table of Results for Failure to Achieve an Average of ≥3 BMs per Week with an Increase of ≥1 BM per Week Over Baseline or an Average of ≥3 BMs per Week.

Naloxone									
0.97 (0.75; 1.25)	**Naldemedine**								
0.96 (0.73; 1.27)	0.99 (0.80; 1.24)	**Alvimopan**							
0.88 (0.64; 1.21)	0.91 (0.69; 1.19)	0.91 (0.68; 1.23)	**Methylnaltrexone SC**						
0.87 (0.62; 1.22)	0.90 (0.68; 1.20)	0.91 (0.66; 1.23)	0.99 (0.70; 1.41)	**Prucalopride**					
0.83 (0.60; 1.16)	0.86 (0.64; 1.15)	0.86 (0.63; 1.17)	0.95 (0.67; 1.34)	0.95 (0.66; 1.37)	**Bevenopran**				
0.76 (0.58; 1.01)	0.79 (0.63; 0.99)	0.79 (0.62; 1.02)	0.87 (0.65; 1.17)	0.88 (0.64; 1.19)	0.92 (0.68; 1.25)	**Naloxegol**			
0.71 (0.51; 0.99)	0.74 (0.56; 0.97)	0.74 (0.55; 1.00)	0.81 (0.58; 1.14)	0.82 (0.57; 1.16)	0.86 (0.60; 1.22)	0.93 (0.69; 1.26)	**Methylnaltrexone**		
0.71 (0.55; 0.92)	0.73 (0.60; 0.90)	0.74 (0.58; 0.93)	0.81 (0.61; 1.07)	0.81 (0.60; 1.10)	0.85 (0.63; 1.15)	0.93 (0.74; 1.17)	1.00 (0.75; 1.33)	**Lubiprostone**	
0.65 (0.52; 0.80)	0.67 (0.59; 0.77)	0.67 (0.57; 0.80)	0.74 (0.58; 0.94)	0.74 (0.58; 0.96)	0.78 (0.61; 1.01)	0.85 (0.71; 1.01)	0.91 (0.71; 1.17)	0.92 (0.79; 1.07)	**Placebo**

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects.

compared with placebo = 0.58; 95% CI 0.42 to 0.79) (Supplementary Figure 3). There was moderate global statistical heterogeneity (I^2 = 70.2%). When restricting to studies with treatment duration of ≥6 weeks 13 RCTs were included, reported in 11 articles, [32, 37, 40, 45, 46, 47, 48, 51, 52, 53, 55] randomising 3981 patients to active treatment and 2531 to placebo. Naloxone was the highest ranked treatment (one RCT, P-score 0.89; RR compared with placebo = 0.66; 95% CI 0.53 to 0.84), with low global statistical heterogeneity (I^2 = 36.2%) (Supplementary Figure 4). Results for our primary analysis were almost identical when a Bayesian model was used, although bevenopran moved from being ranked sixth to being ranked third.

Failure to Achieve an Average of ≥3 BMs per Week with an Increase of ≥1 BM per Week Over Baseline

There were 14 separate RCTs, reported in 12 articles, [35, 37, 40, 41, 42, 43, 46, 47, 48, 49, 50, 52] which randomised 3802 patients to active treatment and 2209 to placebo, providing data for this analysis. The network plot is provided in Supplementary Figure 5. There were moderate levels of global statistical heterogeneity (I^2 = 70.6%). The comparison adjusted funnel plot for publication bias, or other small study effects, showed symmetry around the zero line. From the network meta-analysis naldemedine was ranked as the most effective treatment in terms of this endpoint (P-score 0.91), and was significantly more effective than placebo (five RCTs, RR 0.66; 95% CI 0.56 to 0.77) (Figure 3). Alvimopan (two RCTs, RR 0.74; 95% CI 0.57 to 0.94) was also significantly more effective than placebo. On indirect comparison of active treatments, there were no significant differences seen (Supplementary Table 2).

Failure to Achieve an Average of ≥3 BMs per Week

There were nine separate RCTs, [30, 32, 34, 35, 45, 51, 53, 54, 55] which randomised 1708 patients to active treatment and 1241 to placebo, providing data for this analysis. The network plot is provided in Supplementary Figure 6. There was no statistical heterogeneity (I^2 = 0%). With only nine studies, there were too few to assess for risk of publication bias, or other small study effects. Alvimopan was ranked as the most effective treatment in terms of this endpoint (P-score 0.96), and was significantly more effective than placebo (one RCT, RR 0.58; 95% CI 0.48 to 0.70) (Figure 4). Naloxone (two RCTs, RR 0.65; 95% CI 0.56 to 0.75), subcutaneous methylnaltrexone (two RCTs, RR 0.75; 95% CI 0.64 to 0.88), and prucalopride (two RCTs, RR 0.75; 95% CI 0.62 to 0.92) were also significantly more effective than placebo (Figure 4). On indirect comparison of active treatments, significant differences were seen with alvimopan compared with subcutaneous methylnaltrexone or lubiprostone; and with both naloxone and subcutaneous methylnaltrexone compared with lubiprostone (Supplementary Table 3).

DISCUSSION

In terms of our primary endpoint, this systematic review and network meta-analysis demonstrated that some μ-opioid-receptor antagonists, including naloxone, naldemidine, alvimopan, and subcutaneous methylnaltrexone, as well as the prokinetic prucalopride, were all more effective than placebo for the treatment of OIC. Of these drugs, naloxone was ranked as the most likely to be superior to placebo, and was significantly better than subcutaneous methylnaltrexone and lubiprostone. Naldemidine was the next best drug, and was superior to naloxegol and methylnaltrexone. Naloxone remained the best drug in some of our subgroup analyses, including when only RCTs with a treatment duration of ≥6 weeks were considered in the analysis, and in terms of reducing the need for rescue laxatives. However, when failure to achieve an average of ≥3 BMs per week with an increase of ≥1 BM over baseline was used to define non-response to therapy, which is a more rigorous endpoint, naldemidine was the drug ranked first. In terms of safety, naloxone was the drug ranked first in terms of safety, and lubiprostone last.

We performed a contemporaneous and exhaustive literature search, which included searching the "grey" literature and clinicaltrials.gov, allowing us to analyse data from 27 RCTs of μ-opioid-receptor antagonists, lubiprostone, or prucalopride versus placebo, containing 9149 patients with OIC. In addition, the literature search, eligibility assessment, and data extraction were undertaken independently by two reviewers. We used an intention-to-treat analysis, wherever trial reporting allowed, and pooled data with a random effects model, to provide a more conservative estimate of the efficacy and safety of individual pharmacological therapies in OIC. Finally, we attempted to contact authors of individual studies and accessed clinicaltrials.gov in order to obtain extra information, where required.

Limitations include the fact that only 11 of the RCTS were at low risk of bias, and original authors did not respond to all our queries concerning the methodology used in individual studies. This may mean the efficacy of pharmacological therapies in OIC has been overestimated. [56] The vast majority of trials recruited individuals in secondary or tertiary care, or did not report the study setting, so involved individuals may not be generalisable to OIC patients consulting in primary care. There were moderate levels of global statistical heterogeneity in some of our analyses, although the comparison adjusted funnel plot for the primary outcome from the network was symmetrical, and not suggestive of publication bias, although two of the trials we identified had not been published as either full papers or conference abstracts, [53, 55] and were only identified during our search of clinicaltrials.gov. Finally, there were limited data for naloxegol, bevenopran, and prucalopride. In the case of naloxegol, it should be pointed out that the two phase III RCTs included a total of 1337 patients, [48] and we identified a phase II trial of the drug, but dichotomous data were not reported, and we could not obtain these either from the authors or from clinicaltrials.gov. [57] Phase III RCTs using bevenopran failed to recruit, and were therefore abandoned, meaning that development of the drug was discontinued, and a phase III RCT of prucalopride, which our search identified, [55] was terminated prematurely based on a business priority decision, meaning firstly that there are unlikely to be any further studies of these two drugs, and secondly that the efficacy of both may have been overestimated in the network meta-analysis.

Our network meta-analysis could also be criticised due to the absence of trials making direct comparisons between pharmacological therapies, meaning that all our conclusions were derived from data making indirect treatment comparisons. However, we believe it is unlikely that pharmaceutical companies would ever conduct head-to-head RCTs of these agents. Even if such a study were to be conducted, it is more than likely it

would be designed as a non-inferiority trial, rather than a superiority trial. This is a similar situation to other functional disorders, such as chronic idiopathic constipation, where the only trial to date that has compared two active drugs was designed as a non-inferiority trial. [58] This is the advantage of network meta-analyses, which can circumvent problems such as these, in order to provide a credible ranking system of the likely efficacy and tolerability of all available treatment options for OIC. The results of our study are therefore likely to be important for both patients and policy makers, in order to help inform treatment decisions.

At the time of our previous meta-analysis there had been no guidelines from national or international organisations to aid Gastroenterologists in the treatment of OIC, [14] despite the fact that patients with constipation, who may have opioids as a precipitating cause, are often seen in Gastroenterology outpatient departments. However, a group of experts in the field have made recent recommendations based on the current available evidence. [59] The authors noted that there was no evidence for any benefit of lifestyle modifications or dietary changes in patients with OIC. In terms of laxatives, it was felt that indirect evidence favoured the use of bisacodyl, sodium picosulfate, polyethylene glycol, or senna first-line, but that there was insufficient evidence for the use of either lubiprostone or prucalopride. A treatment algorithm was proposed, which included the use of laxatives first-line, with co-prescription of a μ-opioid receptor antagonist in those in whom there is no improvement in the symptoms of OIC.

Less than 50% of patients with OIC report a satisfactory therapeutic effect of laxatives, [13] and this is supported by evidence from an updated Cochrane review, which failed to demonstrate any evidence of a beneficial effect of laxatives in OIC. [12] As a result, there is a clear need for cost-effective treatments, particularly given the continued increase in opioid prescribing worldwide. [3, 4] This is especially relevant to Gastroenterologists, as up to 20% of patients with chronic abdominal pain disorders will be

given opioids. [60] In support of our observation from the primary analysis that naloxone was the drug with the best efficacy and safety profile, there have been two cost-utility analyses of combination oxycodone / naloxone, conducted from a UK and Canadian perspective, in patients with moderate to severe pain and OIC. [61, 62] In both of these studies, combination oxycodone / naloxone was associated with a gain in quality-adjusted life years (QALYs), compared with oxycodone alone. The cost per QALY in the UK study was £5841, with a probability of over 96% that oxycodone / naloxone would be cost-effective at a cost per QALY of £20,000. In the Canadian study the cost per QALY ranged from $2178 to $7732. Similarly, naloxegol was cost-effective in a UK population with OIC, with a cost per QALY of £10,849, and a 91% probability of being cost-effective at a cost per QALY of £20,000, [63] but the drug was only effective in our analyses in terms of reducing the need for rescue laxatives. Although there have been cost-effectiveness analyses of lubiprostone and prucalopride, [64, 65] which have demonstrated both are likely to be cost-effective, these have been conducted in patients with chronic idiopathic constipation, rather than OIC.

In summary, our network meta-analysis suggested that, in terms of our primary analysis, naloxone was the drug with the best efficacy profile, and was also the least likely to cause adverse events. In our secondary analyses, naloxone remained most effective in terms of reducing the need for rescue laxatives, and was the second most effective drug when failure to achieve an average of ≥3 BMs per week was used to define non-response. However, naldemidine was the most efficacious drug when failure to achieve an average of ≥3 BMs per week with an increase of ≥1 BM over baseline was used to define non-response, which is probably a more rigorous endpoint, and in terms of rates of clinical improvement. All of this, together with evidence from the pharmacoeconomic literature demonstrating that naloxone is highly likely to be cost-effective, lends weight to either

naloxone or naldemidine being the clinician’s first choice of pharmacological therapy for OIC when laxatives fail.

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Specific author contributions: PL, NEB, DMB and ACF conceived and drafted the study. ACF and PL collected all data. ACF and NEB analysed and interpreted the data. ACF, PL, and NEB drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

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Box 1.

Randomised controlled trials.

Adults (>90% of participants aged >16 years) receiving opioid or opiate drugs.

Diagnosis of opioid-induced constipation based on either clinical symptoms, a physician's opinion, or meeting specific diagnostic criteria specified by study investigators, supplemented by negative investigations where trials deemed this necessary.

Compared pharmacological therapies (methylnaltrexone, naloxone, alvimopan, naldemedine, naloxegol, bevenopran, lubiprostone, prucalopride, naronapride, velusetrag, linaclotide, or plecanatide,) with each other, or placebo.

Minimum duration of therapy of 2 weeks.

Dichotomous assessment of overall response to therapy.

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FIGURE LEGENDS

Figure 1. Flow Diagram of Assessment of Studies Identified in the Systematic Review.

Figure 2. Forest Plot of the Indirect Evidence for Failure to Achieve an Average of ≥3 BMs per Week with an Increase of ≥1 BM per Week Over Baseline, or an Average of ≥3 BMs per Week.

I^2 for global statistical heterogeneity = 58.8%.

Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

Direct comp. is the number of direct comparisons of the indicated medication versus placebo.

Figure 3. Forest Plot of the Indirect Evidence for Failure to Achieve an Average of ≥3 BMs per Week with an Increase of ≥1 BM per Week Over Baseline.

I^2 for global statistical heterogeneity = 70.6%.

Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

Direct comp. is the number of direct comparisons of the indicated medication versus placebo.

Figure 4. Forest Plot of the Indirect Evidence for Failure to Achieve an Average of ≥3 BMs per Week.

I^2 for global statistical heterogeneity = 0%.

Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first. Direct comp. is the number of direct comparisons of the indicated medication versus placebo.