Efficacy and Safety of Mu-Opioid Antagonists in the Treatment of Opioid-Induced Bowel Dysfunction: Systematic Review and Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Context. Opioid-induced bowel dysfunction (OBD) is characterized by constipation, incomplete evacuation, bloating, and increased gastric reflux. OBD occurs both acutely and chronically, in multiple disease states, resulting in increased morbidity and reduced quality of life.

Objective. To compare the efficacy and safety of traditional and peripherally active opioid antagonists vs conventional interventions for OBD.

Design. We searched MEDLINE, the Cochrane Central Register of Controlled Trials and EMBASE. Additional reports were identified from the reference lists of retrieved articles.

Study Selection. Studies were included if they were randomized controlled trials that investigated the efficacy of mu-opioid antagonists for OBD.

Data Extraction. Data were extracted by two independent investigators and included demographic variables, diagnoses, interventions, efficacy, and adverse events.

Results of Data Synthesis. Twenty-two articles met inclusion criteria and provided data on 2,352 opioid antagonist-treated patients. The opioid antagonist investigated was alvimopan (eight studies), methylnaltrexone (six), naloxone (seven), and nalbuphine (one). Meta-analysis demonstrated that methylnaltrexone and alvimopan are efficacious in reversing opioid-induced increased gastrointestinal transit time and constipation, and that alvimopan is safe and efficacious in treating postoperative ileus. The incidence of adverse events with opioid antagonists was similar to placebo and generally reported as mild-to-moderate.

Conclusions. Insufficient evidence exists for the safety or efficacy of naloxone or nalbuphine in the treatment of OBD. Long-term efficacy and safety of any of the opioid antagonists is unknown, as is the incidence or nature of rare adverse events. Alvimopan and methylnaltrexone both show promise in treating OBD, but further data will be required to fully assess their place in therapy.

Key Words. Opioid-Induced Bowel Dysfunction; Constipation; Postoperative Ileus; Opioid Antagonist; Meta-analysis

Introduction

Opioids can delay gastric emptying, decrease peristalsis and slow bowel motility [1]. “Opioid-induced bowel dysfunction” (OBD) connotes not only constipation, but also a constellation of...
Opioid Antagonists for Opioid Bowel Dysfunction

635

symptoms including incomplete evacuation; bloating; abdominal distention; and increased gastric reflux [2]. Constipation, in turn, is defined as “the evacuation of hard stools less frequently than is normal for the individual” [3], or as “a symptom (that is, a subjective phenomenon) characterized by diminished frequency of defeation associated with difficulty or discomfort” [4]. Constipation is the most commonly occurring adverse effect of chronic opioid therapy in patients with advanced cancer [5]. It is an almost inevitable consequence of opioid use in malignant and nonmalignant disease states, and one of the side effects of opioids to which few patients develop tolerance.

Postoperative ileus, a temporary impairment of gastrointestinal (GI) tract motility after abdominal or other surgery, is characterized by abdominal distension, lack of bowel sounds, accumulation of gas and fluids in the bowel, and delayed passage of flatus and defeation [6]. It has multifactorial etiologies, including the common use of opioids peroperatively. Postoperative ileus can contribute to pain and discomfort, reduce the ability for patients to take oral nutrition, increase the risk for pulmonary complications and increase length of hospital stay [7].

Opioids therefore can precipitate bowel dysfunction both acutely and chronically, in patients with malignant and nonmalignant disease, and may increase morbidity and reduce quality of life.

Traditional treatment of opioid-induced constipation in patients with chronic or cancer pain includes the use of a stimulant and a stool softener. The long-term effectiveness and safety of such a regimen is unclear. A prokinetic drug, such as metoclopramide, may also be employed to reduce gastric stasis [5]. There are currently no pharmacological agents licensed for the treatment of postoperative ileus. Multimodal interventions, such as the introduction of early enteral nutrition and the use of epidural anesthetics, combined with a reduction in opioid use, have been shown to reduce duration of ileus, but are labor-intensive [7,8]. The use of opioid antagonists, such as naloxone, may directly reduce opioid-induced adverse effects. However, analgesia may also be reversed, and titration to a balance between reduced adverse effects and satisfactory analgesia is required. The site and mechanism of OBD has not been fully elucidated, but is thought to be predominately peripherally mediated [9]. The search for opioid antagonists therefore that act locally in the gut, without reversing analgesia has involved the oral administration of existing antagonists, such as naloxone, and the development of new compounds. To date, no new compound is commercially available. However, two drugs, methylnaltrexone and alvimopan, are at an advanced phase of development.

The purpose of this systematic review and meta-analysis is to compare the efficacy of both traditional nonselective opioid antagonists and newer, peripherally selective antagonists vs placebo or other existing pharmacological or nonpharmacological treatments for OBD and to evaluate adverse events reported in clinical trials.

Methods

Criteria for Considering Studies for This Review

Reports were included in the review if they were randomized controlled trials which investigated the efficacy of mu-opioid antagonists for OBD. Reports were excluded if they were nonrandomized, case reports, clinical observations or were studies that included loperamide as the opioid agonist, as it is not an analgesic.

Types of Participants

Participants of any age and either sex were included. Patients receiving opioids for chronic malignant and nonmalignant pain, or for opioid dependency, and those receiving opioids as part of a postoperative regimen were included. Studies employing healthy volunteers were also included, providing that subjects received both an opioid and an opioid antagonist, and fulfilled all other inclusion criteria.

Types of Interventions

Mu-receptor opioid antagonists, agonist/antagonists, or partial agonists, either peripherally or systemically acting, administered at any dose and by any route.

Types of Outcome Measures

Information about the indication for opioid, number of patients studied, opioid and opioid antagonist drug and dosing regimen, study design (placebo or active control, parallel or crossover), study duration and follow-up, OBD outcome measures and results, withdrawals and adverse events was included.

Primary outcomes included:

1. In experimental models, GI transit time;
2. In studies of constipation, bowel movements (BM): time to, number per time period, total
number, immediate laxation, global assessment, proportion of patients having BM within given time period, weight and ease of;
3. In studies of postoperative ileus, combined endpoints such as: flatus/BM: time to latter; flatus/BM/solid food: time to latter; or solid food/BM: time to latter.

Additional outcomes included:
1. Flatus: time to;
2. Opioid withdrawal symptoms;
3. Pain;
4. Analgesic requirements;
5. Constipation assessment scales;
6. Length of stay: intensive care unit, overall, time to readiness for discharge, time until actual discharge;
7. Requirement for postoperative chest X-ray;
8. Nasogastric tube insertion;
9. Gastric tube reflux volume;
10. Overall satisfaction.

Search Strategy for Identification of Studies
Trials for inclusion in the review were identified by searching MEDLINE (1966 to May Week 2 2006), the Cochrane Central Register of Controlled Trials (CCRCT) (2nd Quarter 2006), and EMBASE (1974–March 2006). Additional reports were identified from the reference lists of retrieved articles. No language restriction was applied. Both the Food and Drug Administration (FDA) and European Medicine Evaluation Agency websites were searched for additional trials. The manufacturers of methylnaltrexone and alvimopan were contacted for information on unpublished trials.

The search strategy employed for MEDLINE was as follows:
1. constipation.mp. or exp Constipation/
2. exp ileus/
3. exp Gastrointestinal motility/or Gastrointestinal Transit/or exp Gastrointestinal Tract/or exp Gastric emptying/
4. exp Colonic Diseases, Functional/
5. 1 or 2 or 3 or 4
6. exp Narcotic antagonists/
7. exp Opioid antagonist/or Receptors, opioid, mu.mp. or Receptors, opioid, kappa.mp. or Receptors, opioid delta.mp. or exp Receptors, Opioid, mu/ai
8. exp Naltrexone/or exp Naloxone/or Methylnaltrexone/or nalmefene/or Alvimopan.mp. or ADL 8-2698.mp. or LY246736.mp.
9. pentazocine/or nalbuphine/or buprenorphine/or dezocine/or butorphanol.mp.
10. 6 or 7 or 8 or 9
11. randomized controlled trial.pt.
12. meta-analysis.pt.
15. random:.ti,ab,sh.
16. (meta-anal: or metaanaly: or meta analy:).ti,ab,sh.
17. ((doubl: or singl:) and blind:).ti,ab,sh.
18. exp clinical trials/
19. crossover.ti,ab,sh.
20. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 5 and 10 and 20
22. limit 21 to humans

This strategy was adapted to the CCRCT and EMBASE databases.

Selection of Studies
Eligibility was initially determined by reading the titles and abstracts retrieved from each search. Full-length articles of potentially eligible studies were obtained and assessed. All abstracts and potentially eligible articles were read by two authors (EM and DB). Disagreements were resolved by discussion, or if persistent, by a third reviewer (DC). The reports were not anonymized in any way prior to assessment.

Data Extraction and Management
Data (as detailed in “Types of outcome measures”) were independently extracted from each study by two authors (EM and DB) using a data extraction sheet. Disagreements were resolved by discussion, or if persistent, by a third reviewer (DC).

Assessment of Methodological Quality of Included Studies
Each report was scored for quality by two authors (EM and DB). The three-item scale devised by the Oxford Group [10] was used to assess study quality. This scoring system employs the following five questions, yielding a maximum possible score of 5 points:

(1a) Is the study randomized? If yes, add 1 point.
(1b) Is there a description of an adequate generation of the random sequence? If yes, add 1 point. If not, deduct 1 point.
(2a) Is the study double blind? If yes, add 1 point.
(2b) Is there an explicit statement that the patients and evaluators were blinded and the treat-
ment was indistinguishable? If yes, add 1 point. If not, deduct 1 point.

(3) Are withdrawals and dropouts described? If yes, add 1 point.

Disagreement between reviewers regarding the score allocated to each trial was resolved by discussion or a third reviewer (DC). Quality scores were not, however, used to weigh the studies in any way.

**Measures of Treatment Effect**

**Dichotomous Data**

Discrete events such as preference for opioid antagonist vs conventional treatment regimens, or the number of patients reporting adverse events were used to calculate absolute risk reduction (ARR, also known as risk difference) using RevMan 4.2.8 software [11–13]. When a statistically significant ARR existed between interventions, numbers needed to treat (NNTs) or numbers needed to harm (NNHs) were derived. Dichotomous outcomes were also presented in terms of both raw numbers and percentages of patients in each study arm benefiting from therapy or suffering adverse events.

**Continuous Data**

Continuous outcomes (e.g., time to first BM, pain intensity, analgesic consumption, intensity of a specific adverse event) were combined using weighted mean differences (WMDs). Meta-analyses were undertaken when appropriate comparable data were available using RevMan 4.2.8 software [11]. We applied a fixed effects model to assess outcomes data unless significant heterogeneity was present, in which case we applied a random effects model.

**Time-to-Event Data**

Hazard ratios (HRs) derived from time-to-event data, such as time to first BM/solid food, were combined if appropriate by employing a random effects model using methods described by Sutton et al. [14].

**Unit of Analysis Issues**

Crossover trials were combined in analyses with parallel trials. Sensitivity analyses, where crossover trials were removed, were conducted where possible.

**Dealing with Missing Data**

No attempts were made to contact authors for missing patient data. If patient data were missing, analyses were based on patient populations in which outcomes were reported. Discrepancies between number of patients enrolled and number of patients in whom outcomes were reported were noted in the “Table of included studies.” Where studies reported statistics based on intention-to-treat (ITT) or modified ITT populations, available case analyses were performed [15].

**Assessment of Heterogeneity**

We assessed statistical heterogeneity using the I² statistic. The I² statistic is a reliable and robust test to quantify heterogeneity, as it does not depend on the number of trials or on the between-study variance. I² measures the extent of inconsistency among studies’ results, and can be interpreted as the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error. An I² value of greater than 50% is considered to indicate substantial heterogeneity [16]. We also assessed heterogeneity by visually studying forest plots. Where possible, subanalyses or sensitivity analyses were performed in an attempt to explain heterogeneity.

**Assessment of Reporting Biases**

No attempt was made to assess reporting bias. The inclusion of abstracts, searching of FDA and European Medicine Evaluation Agency websites, and direct contact with manufacturers for unpublished studies was undertaken in an attempt to minimize publication bias.

**Results**

**Overview of Included Studies**

The literature search generated 399 citations (MEDLINE, 112; CENTRAL, 57; EMBASE 230), of which 47 were selected for retrieval of the full article. Neither EMBASE nor CCRCT provided additional articles to those generated by the MEDLINE search. Neither the FDA nor the European Medicine Evaluation Agency websites provided information relevant to our search.

Twenty-two of the 47 retrieved articles met inclusion criteria and provided data on 2,352 opioid antagonist-treated patients. A QUOROM (Quality of Reporting of Meta-analyses) flow diagram (Figure 1) shows an overview of the study selection process.

All included studies are presented in the Tables of Included Studies, which, in turn, are divided according to the type of population investigated. Meta-analyses are presented according to the
outcomes assessed. The opioid antagonist investigated was alvimopan in eight studies, methylnaltrexone in six studies, naloxone in seven studies, and nalbuphine in one. All studies were placebo-controlled trials and none employed an active control. The study population was healthy volunteers in 10 studies (all measured GI transit time, Table 1), postoperative patients in six studies (Table 2), patients receiving chronic opioid therapy in four studies (malignant or nonmalignant pain and methadone maintenance, Table 3), and, mechanically ventilated, intensive care patients in two studies (receiving opioids, but not having undergone GI surgery, Table 4). Twelve studies had a parallel design and 10 were crossover studies. Study duration varied from less than 24 hours (single-dose trials) to 35 days, and was related to the populations and outcomes studied: those conducted in healthy volunteers measuring GI transit were mostly short single-dose trials; those involving surgical patients and measuring postoperative ileus lasted approximately 1 week; and studies enrolling patients receiving chronic opioid therapy and measuring resolution of constipation were routinely carried out over a week or longer. Numbers of patients enrolled also varied according to the populations and outcomes measured, and to the drug intervention. Trials assessing alvimopan use in postoperative ileus enrolled on average 386 patients, whereas those investigating naloxone reversal of opioid-related constipation enrolled on average 18 patients.

**Study Quality**

The quality of studies as assessed by the Oxford score varied widely from 1 (lowest quality) to 5 (highest quality). Three trials scored 1 point, two scored 2 points, eight scored 3 points, seven scored 4 points, and two trials scored 5 points. Quality was not related to disease state studied, but was related to opioid antagonist administered: studies employing methylnaltrexone had the highest quality (median score = 4), followed by alvimopan and naloxone (median score = 3) and nalbuphine (one study, Oxford score = 1).

**Meta-analyses of Efficacy Outcomes**

In the studies where alvimopan was administered, means and standard deviations were not routinely reported. Attempts were made to obtain them by contacting both the authors of each study and the manufacturer of the drug. No further data were supplied by either; therefore, the following meta-analyses are based only on data reported in the original articles.

**GI Transit Time**

Eight studies assessed GI transit time by measuring breath hydrogen levels post ingestion of lactulose. Five studies enrolled healthy volunteers and administered methylnaltrexone [17–20] or alvimopan [21]. Three studies enrolled patients in the immediate postoperative period [22], subjects receiving methadone maintenance [23] and patients with cancer [24]. The intervention in the latter studies was methylnaltrexone [23], nalbuphine [22] or naloxone [24]. We had sufficient data to combine the five studies where methylnaltrexone was administered (Figure 2). On average, GI transit time in patients receiving methylnaltrexone was reduced by 59 minutes vs placebo (95% CI: −75 to −42). Mean transit times ranged from 54 to 110 minutes in the methylnaltrexone arms, whereas in the placebo arms times ranged from 125 to 163 minutes. The results appeared to be homogenous ($\Gamma^2 = 0\%$) despite their being derived from mixed populations. Both the statistical
<table>
<thead>
<tr>
<th>Trial</th>
<th>Design, Duration, Intervention</th>
<th>Numbers Enrolled/Completed</th>
<th>Outcomes</th>
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<th>Adverse Events</th>
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<tbody>
<tr>
<td>Barr et al. 2000 [26]</td>
<td>Crossover, placebo-controlled, 4 days each treatment (10-day washout). Alvimopan oral 3 mg three times daily.</td>
<td>Alvimopan period: 7/11 Placebo period: 7/11</td>
<td>Colonic motility: 24 radio-opaque markers ingested orally on days 1–3. Number of markers in each colonic segment on day 5 multiplied by factors: cecum/ascending = 6, hepatic flexure = 5, transverse = 4, splenic flexure = 3, descending = 2, rectosigmoid = 1, and summed. BMs weighed (days 1–4). Pupil diameter measured before and 4 hours after first dose of morphine.</td>
<td>Total marker score: alvimopan 140 ± 88 vs placebo 248 ± 88 (P &lt; 0.01); stool weight: alvimopan 223 ± 178 g vs placebo 35 ± 63 g (P &lt; 0.05). Alvimopan did not antagonize pupil constriction after morphine: alvimopan 0.7 ± 0.8 mm vs placebo 0.7 ± 1 mm.</td>
<td>Not listed.</td>
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<td>Gonenne et al. 2005 [27]</td>
<td>Parallel, placebo-controlled, 72-hour study with intervention on days 2–3. Alvimopan oral 12 mg twice daily.</td>
<td>Alvimopan plus codeine group: 18/18 Codeine plus placebo group: 20/18 Alvimopan plus placebo group: 17/17 Placebo group: 19/19</td>
<td>Gastric emptying (t&lt;sub&gt;GE&lt;/sub&gt;), small-bowel transit (t&lt;sub&gt;SB&lt;/sub&gt;), colonic transit (geometric center); scintigraphy using 99 m-labeled technetium egg meal and 111-labeled indium charcoal delivered to proximal colon via delayed-release capsule. Primary end points: colonic transit—geometric center of colonic counts at 24 hours (% ascending colon x1% + transverse colon x2% + descending colon x3% + rectosigmoid x4% × stool x5%), time for 50% ascending colon emptying.</td>
<td>Gastric emptying: placebo group 130 minutes vs codeine group 160 minutes (P &lt; 0.05 vs placebo) vs alvimopan/codeine group 180 minutes (P &lt; 0.05 vs placebo). Small bowel transit t&lt;sub&gt;SB&lt;/sub&gt;: codeine delayed (P &lt; 0.05); alvimopan reversed. Mean colonic geometric center at 4 hours: placebo/placebo 0.67 ± 0.13 (SE); alvimopan/placebo 0.15 ± 0.13 (P &lt; 0.05 vs placebo); alvimopan/codeine 0.69 ± 0.12; similar results at 24 and 48 hours.</td>
<td>All adverse events mild to moderate. Number of participants with any adverse event (n/N): Placebo group 18/18; Alvimopan group 8/17; Codeine group 14/18; Alvimopan/codeine group 15/19.</td>
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<td>Hawkes et al. 2001 [28]</td>
<td>Crossover, placebo-controlled, 9 days each treatment (2-week washout). Naloxone oral 10 mg twice daily.</td>
<td>Baseline period: 12/12 Codeine period: 12/12 Naloxone period: 12/12 Naloxone + Codeine period: 12/12</td>
<td>Whole-gut transit time: 20 encapsulated markers swallowed each day for 4 days and time to BM noted. Mean whole-gut transit time = (s1 + s2 + s3 + s4)/ (s1 × time lapse in hours between ingestion of these markers and passage of stool, and so on for each set of markers.</td>
<td>GI transit: codeine increased transit time in 8/12 subjects. Overall: Control period 53.1 ± 3.03 (SE); codeine 57.3 ± 5.18 (P = 0.46 vs control); naloxone 42.1 ± 3.69 (P = 0.005 vs control); naloxone plus codeine 40.7 ± 3.96 (P = 0.024 vs control). For eight “codeine responders”: control period 50.4 ± 3.02; codeine 66.2 ± 4.21 (P = 0.001 vs control); naloxone 41.4 ± 5.08 (P = 0.034 vs control); naloxone plus codeine 42.4 ± 5.44 (P = 0.2 vs control).</td>
<td>Mild abdominal pain (control N = 2, codeine N = 5, naloxone N = 1, codeine plus naloxone N = 2); abdominal swelling (codeine plus naloxone N = 2); urgency to defecate (naloxone N = 2, codeine plus naloxone N = 3) (N/12 in each case).</td>
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<td>Trial</td>
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<td>Liu et al. 2000 [21]</td>
<td>Crossover, placebo-controlled, &lt;24 hours each treatment (minimum 5-day washout). Alvimopan oral 2 mg × 2 (2 hours and 30 minutes before lactulose).</td>
<td>Alvimopan plus morphine period: 14/14 Placebo plus morphine period: 14/14 Placebo period: 14/14</td>
<td>GI transit time: lactulose hydrogen breath test (oral lactulose 10 g suspended in 100 ml tap water collected every 15 minutes).</td>
<td>GI transit time (minutes): baseline 69 ± 33; morphine 103 ± 37 (P = 0.005 vs baseline); morphine plus Alvimopan 76 ± 30 (P &gt; 0.3 vs baseline).</td>
<td>None.</td>
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<td>Murphy et al. 1997 [25]</td>
<td>Crossover, placebo-controlled, 3 hours each treatment (minimum 7-day washout). Methylnaltrexone IV 0.3 mg/kg.</td>
<td>Placebo period: 11/11 Morphine period: 11/10 Morphine plus methylnaltrexone period: 10/10</td>
<td>Gastric emptying; directly by noninvasive electric bioimpedance method, indirectly by acetaminophen absorption technique (area under serum concentration curve determined by gastric emptying rate).</td>
<td>Gastric emptying: bioimpedance, time to empty half the stomach (minutes): placebo 5.5 ± 1.9; morphine 21.3 ± 9.0 (P &lt; 0.03 vs placebo); methylnaltrexone plus morphine 7.4 ± 3.0 (P &lt; 0.04 vs morphine) acetaminophen absorption AUC (mg/L/h): placebo 1078 ± 295; morphine 502 ± 395 (P &lt; 0.05 vs placebo); morphine plus methylnaltrexone 798 ± 481 (P &lt; 0.05 vs morphine).</td>
<td>Nausea (VRS, 1 = no nausea, 10 = worst possible nausea); highest scores after morphine alone (P &lt; 0.014 at 50 minutes vs saline). Three patients vomited after morphine, N = 1 vomited with methylnaltrexone plus morphine. No nausea or vomiting with saline.</td>
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<td>Nimmo et al. 1979 [29]</td>
<td>Crossover, placebo-controlled, 24 hours each treatment (minimum 7-day washout). Naloxone IV 1.2 mg.</td>
<td>Pentazocine period: 4/4 Pentazocine plus naloxone period: 4/4 Baseline period: 4/4</td>
<td>Gastric emptying; time to empty half-ingested dose of acetaminophen (method not specified); peak plasma acetaminophen concentration; time to peak plasma concentration.</td>
<td>Mean time (minutes) to empty half ingested dose of acetaminophen: control 13.0 ± 3.5 (SE); pentazocine 97.3 ± 17.6 (P &lt; 0.02 vs control); pentazocine plus naloxone 27.8 ± 7.6 (NS vs control, P value not specified). Mean peak plasma acetaminophen concentration (mcg/ml): control 23.8 ± 1.9 (SE); pentazocine 10.8 ± 0.6 (P &lt; 0.05 vs control); pentazocine plus naloxone 15.0 ± 1.8 (P &lt; 0.05 vs control). Mean time to peak concentration (minutes): control 22.5 ± 1.3 (SE); pentazocine 160.0 ± 16.3 (P &lt; 0.01 vs control); pentazocine plus naloxone 25.0 ± 1.8 (NS vs control, P value not specified).</td>
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<td>Trial Design, Duration, Intervention</td>
<td>Placebo plus placebo period</td>
<td>Placebo plus morphine period</td>
<td>Methylnaltrexone plus morphine period</td>
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<td><strong>Yuan et al. 1996 [17]</strong></td>
<td>Placebo plus placebo period: 14/12</td>
<td>Placebo plus morphine period: 12/12</td>
<td>Methylnaltrexone plus morphine 0.05 mg/kg period: 12/12</td>
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<td>Crossover, placebo-controlled, 7 hours each treatment (minimum 7-day washout). Methylnaltrexone IV 0.45 mg/kg single dose.</td>
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<td><strong>Yuan et al. 1997 [18]</strong></td>
<td>Placebo plus placebo period: 14/14</td>
<td>Placebo plus morphine period: 14/14</td>
<td>Methylnaltrexone plus morphine period: 14/14</td>
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<td>Crossover, placebo-controlled, 7 hours each treatment (minimum 7-day washout). Methylnaltrexone oral 19.2 mg/kg.</td>
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<td>Crossover, placebo-controlled, 7 hours each treatment (minimum 7-day washout). Methylnaltrexone oral enteric-coated 3.2 mg/kg capsule.</td>
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<td><strong>Yuan et al. 2002 [20]</strong></td>
<td>Placebo period: 13/12</td>
<td>Morphine period: 13/12</td>
<td>Morphine plus methylnaltrexone period: 13/12</td>
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<td>Crossover, placebo-controlled, 7 hours each treatment (minimum 7-day washout). Methylnaltrexone SC methylaltrexone 0.1 mg/kg or 0.3 mg/kg.</td>
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Oral-cecal transit time: lactulose hydrogen breath test. Pain: cold-pressor test assessed at 30, 70, 110, and 170 seconds after forearm immersed in cold water; VRS (0 = not painful or bothersome at all; 10 = extreme pain or bothersomeness). Pharmacokinetic data.

Oral-cecal transit time (minutes): baseline 104.6 ± 31.1; morphine 163.3 ± 39.8 minutes ($P < 0.01$ vs baseline); methylnaltrexone plus morphine 106.3 ± 39.8 ($P = 0.56$ vs baseline).

Pain: differences in pain intensity and pain bothersomeness ratings in all four immersion time points: $P < 0.001$ for both morphine and morphine plus methylnaltrexone vs control. Differences between morphine and methylnaltrexone plus morphine NS.

Oral-cecal transit time: placebo plus placebo period: 114.6 ± 37.0 minutes; placebo plus morphine period: 158.6 ± 50.2 minutes ($P < 0.001$ vs placebo period); methylnaltrexone plus morphine period: 110.4 ± 45.0 minutes ($P = 0.28$ vs baseline, $P < 0.005$ vs placebo plus morphine).

No adverse events occurred at any dose of methylnaltrexone.

Oral-cecal transit time (minutes): baseline (placebo): 96.7 ± 54.1; morphine 155.0 ± 53.6 ($P = 0.014$ vs baseline); morphine plus methylnaltrexone 93.3 ± 56.0 ($P = 0.009$ vs morphine only; $P = 0.55$ vs baseline).

Oral-cecal transit time (minutes): 0.1 mg/kg methylnaltrexone: baseline 85 ± 20.5; morphine 155 ± 27.9 ($P < 0.01$ vs baseline); methylnaltrexone plus morphine 110 ± 41.0. 0.3 mg/kg methylnaltrexone: baseline 140 ± 58.2 ($P < 0.01$ vs baseline); methylnaltrexone plus morphine 108 ± 59.6 ($P < 0.05$ vs morphine).

Subjective ratings: methylnaltrexone significantly decreased morphine-induced changes.

Subjective effects: 12 item questionnaire (flushing, stimulated, numb, drunken, difficulty in concentrating, drowsy, coasting or spaced out, turning of stomach, skin itch, dry mouth, dizzy, and nauseous): 5-point scale (0 = not at all; 4 = extremely) completed at 0 hour, 5 minutes, postmorphine injection (~20 minutes) and 180 minutes postmorphine. Ratings of 12 items summed.

See Results.

AUC = area under the curve; BM = bowel movement; GI = gastrointestinal; NS = not statistically significant; SE = standard error; VRS = verbal rating score.

All results mean ± SD unless otherwise stated.
<table>
<thead>
<tr>
<th>Trial</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Delaney et al. 2005 [30]</td>
<td>Parallel, placebo-controlled, 7 days maximum. Alvimopan oral 6 or 12 mg 2 hours prior to surgery, then twice daily beginning on postoperative day 1.</td>
<td>Bowel resection (N = 303); radical hysterectomy (N = 32); simple hysterectomy (N = 22) Alvimopan 6 mg group: 152/128 Alvimopan 12 mg group: 146/107 Placebo group: 153/121</td>
<td>Primary efficacy endpoint: time to recovery of GI function (later of time of first tolerating solid food or time to pass first flatus or BM) Secondary efficacy endpoint: time to recovery of GI function (later of time of first tolerated solid food, or time to first BM) Pain: postoperative VAS (anchors not defined); opioid consumption Time to hospital discharge readiness or actual discharge</td>
<td>Primary efficacy endpoint: mean time to GI recovery: alvimopan 12 mg, 92.8 hours (HR = 1.28, ( P = 0.059 ) vs placebo); alvimopan 6 mg, 86.2 hours (HR = 1.45, ( P = 0.003 ) vs placebo); placebo group 100.3 hours. Bowel resection or radical hysterectomy patients only: alvimopan 12 mg, 101.3 hours (HR = 1.29, ( P = 0.073 ) vs placebo); alvimopan 6 mg, 94.5 hours (HR = 1.51, ( P = 0.004 ) vs placebo); Placebo group, 111.4 hours. Simple hysterectomy patients only: similar times to recovery in all groups (53 hours vs 56 hours vs 58 hours, alvimopan 12 mg, 6 mg, placebo, respectively). Secondary efficacy endpoint: alvimopan 12 mg, 104 hours (HR = 1.31, ( P = 0.057 ) vs placebo); alvimopan 6 mg, 100 hours (HR = 1.46, ( P = 0.007 ) vs placebo); placebo group, 115 hours Time to first BM: alvimopan 12 mg, 87 hours (HR = 1.47, ( P = 0.006 ) vs placebo); alvimopan 6 mg, 85 hours (HR = 1.55, ( P = 0.002 ) vs placebo); Placebo group, 102 hours Readiness for discharge: alvimopan 12 mg, 98 hours (HR = 1.54, ( P = 0.004 ) vs placebo); alvimopan 6 mg, 97 hours (HR = 1.61, ( P &lt; 0.001 ) vs placebo); Placebo group, 112 hours. Antagonism of analgesia? No.</td>
<td>Mean maximum VAS scores for nausea, vomiting, and abdominal distension similar among all groups (not listed). Most common treatment emergent adverse events: nausea and vomiting. Vomiting reduced by 53% ( (P &lt; 0.001) ), constipation reduced by 53% ( (P = 0.04) ) in alvimopan 12 mg group vs placebo. Nausea the only adverse event leading to discontinuation of study drug that occurred with ≥2% higher frequency in alvimopan groups vs placebo group.</td>
</tr>
<tr>
<td>Freye &amp; Helle 1988 [22]</td>
<td>Parallel, placebo-controlled, 4 hours Nalbuphine 0.1 mg/kg at end of surgery (route not specified).</td>
<td>Various nongastrointestinal surgeries Nalbuphine group:?/20 Placebo group:?/20</td>
<td>Gastro-cecal transit time: lactulose hydrogen breath test—transit complete when threefold increase in exhaled hydrogen compared to preoperative measurement. Pain: VAS (scale not specified).</td>
<td>Gastro-cecal transit time (minutes): nalbuphine 380 ± 89.6 vs placebo 270 ± 53.5 (( P &lt; 0.01 )). Pain: increased in nalbuphine group at 10 and 20 minutes vs placebo (3.5 vs 1.8 and 2.5 vs 1.4, ( P &lt; 0.005 )), lower at 120 and 240 minutes (0.7 vs 1.4 and 0.7 vs 1.1, ( P &lt; 0.05 )). Antagonism of analgesia? Yes: from 0 to 20 minutes.</td>
<td>Vomiting, agitation/anxiety, hypoventilation, blood pressure, and heart rate changes measured, but not listed or discussed.</td>
</tr>
<tr>
<td>Study</td>
<td>Design Description</td>
<td>Pain VAS (anchors not specified)</td>
<td>Time to recovery of GI function</td>
<td>Time to: readiness for hospital discharge based on recovery of GI function alone (determined by investigator)</td>
<td>Time until ready for discharge (median)</td>
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<td>Lee et al. 2001 [33]</td>
<td>Parallel, placebo-controlled, 48 hours Naloxone epidural 0.206 µg/kg/h (added to existing epidural).</td>
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<td>Taguchi et al. 2001 [31]</td>
<td>Parallel, placebo-controlled, 7 days maximum. Alvimopan oral 1 mg or 6 mg twice daily.</td>
<td>Partial colectomy (N = 15); total abdominal hysterectomy (N = 63) Alvimopan 1 mg group: 27/18 Alvimopan 6 mg group: 26/26 Placebo group: 26/22</td>
<td>Time to first flatus and first BM (h) Pain: VAS 100 cm; total daily consumption of opioid</td>
<td>Time to first postoperative passage of flatus and feces Pain: VAS during rest and coughing.</td>
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<tr>
<td>Viscusi et al. 2006 [8]</td>
<td>Parallel, placebo-controlled, 7 days maximum. Alvimopan oral 6 mg or 12 mg twice daily.</td>
<td>Bowel resection (N = 437); radical total abdominal hysterectomy (N = 109); simple total abdominal hysterectomy (N = 91). Alvimopan 6 mg group: 220/187 Alvimopan 12 mg group: 222/184 Placebo group: 224/176</td>
<td>Time to recovery of GI function, determined by three-component (flatus, BM, and toleration of solid food) composite endpoint; and two-component composite endpoint (BM, solid food).</td>
<td>Time to recovery of GI function, three-component composite endpoint; alvimopan did not accelerate recovery compared with placebo (6 mg): HR = 1.20, P = 0.080; 12 mg: HR = 1.24, P = 0.038. After adjustment for significant covariates (sex/surgical duration), benefits significant for both doses (6 mg: HR = 1.24, P = 0.037; 12 mg: HR = 1.26, P = 0.028).</td>
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Discharge order written: 6 mg: HR = 1.31 (14.2 hours earlier) vs placebo, P = 0.008; 12 mg: HR = 1.28 (15.2 hours earlier) vs placebo, P = 0.015. Postoperative pain: no significant differences in opioid consumption or pain scores between groups Antagonism of analgesia? No.
### Table 2 Continued

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design, Duration, Intervention</th>
<th>Surgery, Numbers Enrolled/ Completed</th>
<th>Outcomes</th>
<th>Results</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolff et al. 2004 [32]</td>
<td>Parallel, placebo-controlled, 7 days maximum</td>
<td>Laparotomy for large bowel resection (N = 395), small bowel resection (N = 56) or radical hysterectomy (N = 18); Colon or rectal cancer (54%); Crohn's disease (11%); Ostomy reversal (7%); Intestinal polyps (6%); Uterine cancer (4%)</td>
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<td></td>
<td>Alvimopan oral 6 mg or 12 mg twice daily</td>
<td>Alvimopan 6 mg group: 169/155, Alvimopan 12 mg group: 176/165, Placebo group: 165/149</td>
<td>Primary efficacy endpoint: time to recovery of GI function (later of time of first tolerating solid food or time to pass first flatus or BM) Primary efficacy endpoint: time to recovery of GI function (later of time of first tolerating solid food, or time to first BM) Pain: VAS (anchors not defined); opioid consumption. Time to hospital discharge</td>
<td>Primary efficacy endpoint: mean time to GI recovery: alvimopan 12 mg, 98 hours (HR = 1.54, P &lt; 0.001 vs placebo); alvimopan 6 mg, 105 hours (HR = 1.28, P &lt; 0.05 vs placebo); placebo group 120 hours Secondary efficacy endpoint: alvimopan 12 mg, 105 hours (HR = 1.67, P &lt; 0.001 vs placebo); alvimopan 6 mg, 113 hours (HR = 1.38, P = 0.013 vs placebo); placebo group, 133 hours Time to hospital discharge: alvimopan 12 mg, 126 hours (HR = 1.42, P = 0.003 vs placebo); alvimopan 6 mg, 133 hours (HR = 1.25, P = 0.070 vs placebo); Placebo group, 146 hours Pain: VAS; similar among all groups (data not listed). Postoperative opioid consumption: alvimopan 12 mg, 27.1 mg; alvimopan 6 mg, 33.6 mg (statistically significant, but P not listed vs placebo); Placebo group, 27.0 mg. Antagonism of analgesia? No (although data not reported).</td>
<td>Most common treatment emergent adverse events: nausea and vomiting; similar among all groups. Treatment emergent postoperative ileus: placebo group, 15.8% vs alvimopan 6 mg, 8.3% (P = 0.043 vs placebo) vs alvimopan 12 mg, 6.3% (P = 0.005 vs placebo). Treatment emergent adverse events leading to discontinued treatment: placebo group 4.2% vs alvimopan 6 mg, 2.4% vs alvimopan 12 mg, 3.4%, of which nausea and vomiting were the most common reasons.</td>
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</tbody>
</table>

BM = bowel movement; HR = hazard ratio; GI = gastrointestinal; NGT = nasogastric tube; VAS = visual analog scale.

All results mean ±SD unless otherwise stated.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Design, Duration, Intervention</th>
<th>Indication for Opioid, Numbers Enrolled/Completed</th>
<th>Outcomes</th>
<th>Results</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu &amp; Wittbrodt 2002 [34]</td>
<td>Parallel, placebo-controlled, 3 weeks Naloxone oral 2 mg or 4 mg three times daily (doses ranged from 1.7% to 10% of daily opioid dose)</td>
<td>Chronic pain (malignant and nonmalignant) Naloxone 2 mg group: 3/3 Naloxone 4 mg group: 3/2 Placebo group: 3/2</td>
<td>Constipation Assessment Scale (0–2, 2 = most severe): eight symptoms rated—abdominal distention/bloating, change in amount of gas passed rectally, less frequent bowel movements (BM/week), oozing liquid stool, rectal fullness or pressure, rectal pain with bowel movement, smaller stool size, urge but inability to pass stool. Short Form Brief Pain Inventory: overall pain levels, analgesic requirements, interference of pain on quality of life. All data recorded for 3 days prior to intervention, then daily throughout intervention.</td>
<td>Constipation: frequency: 6/6 naloxone patients reported improved bowel frequency vs baseline. 1/3 patients receiving placebo improved bowel frequency. Trend toward less constipating symptoms in naloxone patients. 4/6 naloxone patients satisfied with bowel habits vs 0/3 placebo. Pain: naloxone 3/6 required increased analgesia (N = 1, complete reversal with naloxone 4 mg) vs placebo 2/3 (due to increased tumor size and placebo effect). Antagonism of analgesia? naloxone 2 mg group: 2/3; naloxone 4 mg group: 1/3.</td>
<td>Diarrhea (naloxone N = 1), anxiety (naloxone N = 2), cramping (naloxone N = 1; placebo N = 1); jitteriness (naloxone N = 1).</td>
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<tr>
<td>Paulson et al. 2005 [35]</td>
<td>Parallel, placebo-controlled, 35 days (treatment and follow-up) Alvimopan oral capsule(s) 0.5 mg or 1 mg daily</td>
<td>Nonmalignant pain (N = 148) or opioid dependence (N = 20) Alvimopan 0.5 mg group: 58/54 Alvimopan 1 mg group: 56/47 Placebo group: 54/51</td>
<td>Constipation: proportion of patients with at least 1 BM within 8 hours of intervention each day for 21 days averaged across all patients; Median time to BM; total weekly number of BMS during baseline, treatment and follow-up. Overall patient satisfaction: percentage of patients reporting improvement in quality of BMs (better or much better than usual). Pain: VAS (0–100); median opioid consumption (morphine equivalent doses).</td>
<td>Overall (21 days) proportion of patients having a BM within 8 hours of study medication on each day: alvimopan 1 mg group 54% vs alvimopan 0.05 mg group 43% vs Placebo group 29% (P &lt; 0.001 both active groups vs placebo). Median time to BM: alvimopan 1 mg group 3 hours vs alvimopan 0.5 mg group 7 hours vs placebo group 21 hours (HRs: alvimopan 1 mg group vs placebo group: 2.29; P &lt; 0.01; alvimopan 0.5 mg group vs placebo group: 1.36; P = 0.12). Mean (95% CI) weekly number of BMs (weeks 1, 2 and 3, respectively): alvimopan 1 mg group: 6.4 (7.3–9.4), 6.9 (6.1–7.8), 6.4 (5.4–7.3) vs alvimopan 0.5 mg group: 5.8 (4.8–6.9), 5.6 (4.8–6.4), 5.2 (4.3–6.1) vs placebo group: 5.5 (4.4–6.6), 5.0 (4.2–5.9), 5.5 (4.5–6.4).</td>
<td>At least one adverse event: alvimopan 0.5 mg group 37% vs alvimopan 1 mg group 48% vs placebo group 33%. Most common adverse events: cramping, nausea, vomiting, diarrhea, flatulence. Exacerbation of baseline pain: alvimopan 1 mg group (N = 2).</td>
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</table>
Overall patient satisfaction: alvimopan 1 mg group 70% vs alvimopan 0.5 mg group 58% vs placebo group 50%, $P = 0.046$, alvimopan 1 mg group vs placebo group).

“Modest” decreases in severity of straining, cramping, and rectal pain, softening of stool, and decreased frequency of anorectal obstruction, with incomplete evacuation vs placebo (data not listed, dose not specified, $P = 0.002$).

Pain: opioid consumption and VAS pain intensity scores remained consistent throughout the study for all groups. Antagonism of analgesia? No (but see adverse events).

Sykes 1996 [24] Crossover, placebo-controlled. Phase I: 2 days each treatment arm; Phase II: unspecified Phase I: naloxone oral 4-hourly for total daily dose of 0.5–20% of total daily dose of analgesic opioid; Phase II: naloxone oral at 10–80% of morphine dose

<table>
<thead>
<tr>
<th>Trial</th>
<th>Indication for Opioid, Numbers Enrolled/Completed</th>
<th>Outcomes</th>
<th>Results</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cancer pain (various malignancies)</td>
<td>Constipation: Phase I: small bowel transit time—lactulose/hydrogen breath test; Phase II: stool frequency; subjective reports of ease of defecation. Pain: 4-point scale (0 = no pain, 3 = severe pain).</td>
<td>Overall patient satisfaction: alvimopan 1 mg group 70% vs alvimopan 0.5 mg group 58% vs placebo group 50%, $P = 0.046$, alvimopan 1 mg group vs placebo group). “Modest” decreases in severity of straining, cramping, and rectal pain, softening of stool, and decreased frequency of anorectal obstruction, with incomplete evacuation vs placebo (data not listed, dose not specified, $P = 0.002$). Pain: opioid consumption and VAS pain intensity scores remained consistent throughout the study for all groups. Antagonism of analgesia? No (but see adverse events).</td>
<td>Nausea (N = 1), withdrawal (N = 1), abdominal discomfort (N = 5); all after receiving naloxone, all in Phase II—no placebo comparison.</td>
</tr>
<tr>
<td></td>
<td>Sykes 1996 [24] Crossover, placebo-controlled. Phase I: 2 days each treatment arm; Phase II: unspecified Phase I: naloxone oral 4-hourly for total daily dose of 0.5–20% of total daily dose of analgesic opioid; Phase II: naloxone oral at 10–80% of morphine dose</td>
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Overall: naloxone at doses of 10% or less of morphine dose produced no laxative effect in any of 14 patients, but produced laxation in 9/12 when used at 20% or more. Two generalized withdrawals occurred. 5 mg of naloxone or less produced laxation in 6/8 patients in whom this represented at least 20% of the morphine dose. 6–10 mg dose was effective in 2/3 patients. Doses > 10 mg caused withdrawal in one patient and laxation in another.

Antagonism of analgesia? Yes (N = 1).

<table>
<thead>
<tr>
<th>Yuan et al. 2000 [23]</th>
<th>Parallel, placebo-controlled, 2 days. Methylnaltrexone IV up to 0.365 mg/kg</th>
<th>Methadone maintenance program</th>
<th>Methylnaltrexone group: 11/11 Placebo group: 11/11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral-cecal transit time change from baseline; hydrogen breath test (oral lactulose 10 g suspended in 100 ml tap water); immediate laxation; defecation during or within 1 minute of infusion; BM frequency and consistency; overall satisfaction with respect to bowel movement. Withdrawal symptom questionnaire: items included yawning, lacrimation, rhinorrhea, perspiration, tremor, piloerection, and restlessness (VRS 0 = none, 3 = severe).</td>
<td>Oral-cecal transit time (change from baseline, minutes): methylnaltrexone −77.7 ± 37.2 vs placebo −1.4 ± 12.0 (P &lt; 0.001); immediate laxation: day 1, methylnaltrexone N = 10 vs placebo N = 0 (P &lt; 0.001); day 2, methylnaltrexone N = 11 vs placebo N = 0 (P &lt; 0.001); 7/9 placebo group disappointed with BM satisfaction vs 0/11 in methylnaltrexone group.</td>
<td>No opioid withdrawal observed in any subject. Antagonism of analgesia? No.</td>
<td>No significant adverse events. Mild to moderate abdominal cramping without discomfort: 11/11 methylnaltrexone group vs 0/11 placebo group; mild lightheadedness (N = 1 methylnaltrexone group); mild diarrhea (N = 1 methylnaltrexone group).</td>
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</table>

BM = bowel movement; HR = hazard ratio; VAS = visual analog scale; VRS = verbal rating scale. All results mean ± SD unless otherwise stated.
Table 4  Intensive care unit patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design, Duration, Intervention</th>
<th>Numbers Enrolled/ Completed</th>
<th>Outcomes</th>
<th>Results</th>
<th>Adverse events</th>
</tr>
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<tbody>
<tr>
<td>McNicol et al. 2003 [42]</td>
<td>Parallel, placebo-controlled, 5–10 days. Naloxone via gastric tube 8 mg every 6 hours.</td>
<td>Naloxone group: 38/38 Placebo group: 43/43</td>
<td>Constipation: time to first defecation. ICU and hospital stay time. Need for propulsive medication, fentanyl and norepinephrine. Gastric tube reflux: daily amount of fluid flowing passively back through gastric tube. Frequency of pneumonia.</td>
<td>Naloxone group: 38/38 Placebo group: 43/43</td>
<td>Constipation: time to defecation (hours); naloxone 72 (62–84) (median [interquartile range]) vs placebo 73 (50–81), ( P = 0.37 ). Gastric tube reflux volume (ml): naloxone 54 (0–162) (median [interquartile range]) vs placebo 129 (48–245), ( P = 0.03 ). Pain: fentanyl requirements (mcg/kg/h): naloxone 7 (6.2–8.6) (median [interquartile range]) vs placebo 6.5 (5.2–7.9), ( P = 0.15 ). Hospital stay (days): naloxone 24 (16–33) (median [interquartile range]) vs placebo 23 (14–34), ( P = 0.92 ). Pneumonia: naloxone, ( N = 13 ) vs placebo, ( N = 24 ), ( P = 0.04 ).</td>
</tr>
<tr>
<td>Meissner et al. 2003 [42]</td>
<td>Parallel, placebo-controlled, 5–10 days. Naloxone via gastric tube 8 mg every 6 hours.</td>
<td>Naloxone group: 38/38 Placebo group: 43/43</td>
<td>Constipation: time to first defecation. ICU and hospital stay time. Need for propulsive medication, fentanyl and norepinephrine. Gastric tube reflux: daily amount of fluid flowing passively back through gastric tube. Frequency of pneumonia.</td>
<td>Naloxone group: 38/38 Placebo group: 43/43</td>
<td>Constipation: time to defecation (hours); naloxone 72 (62–84) (median [interquartile range]) vs placebo 73 (50–81), ( P = 0.37 ). Gastric tube reflux volume (ml): naloxone 54 (0–162) (median [interquartile range]) vs placebo 129 (48–245), ( P = 0.03 ). Pain: fentanyl requirements (mcg/kg/h): naloxone 7 (6.2–8.6) (median [interquartile range]) vs placebo 6.5 (5.2–7.9), ( P = 0.15 ). Hospital stay (days): naloxone 24 (16–33) (median [interquartile range]) vs placebo 23 (14–34), ( P = 0.92 ). Pneumonia: naloxone, ( N = 13 ) vs placebo, ( N = 24 ), ( P = 0.04 ).</td>
</tr>
<tr>
<td>Meissner et al. 2004 [43]</td>
<td>Parallel, placebo-controlled, 4–8 days. Naloxone via gastric tube 8 mg four times daily.</td>
<td>Naloxone group: 7/17 Placebo group: 7/22</td>
<td>Incidence of esophagogastric mucosal lesions: Savary-Miller score. Gastric reflux, enteral nutrition volume, frequency of prokinetic drug administration.</td>
<td>Naloxone group: 7/17 Placebo group: 7/22</td>
<td>Incidence of esophagogastric mucosal lesions: naloxone, ( N = 4 ) (24%) gastritis vs placebo, ( N = 9 ) gastritis, N = 1 esophagitis, N = 4 both (64% of group positive for lesions, ( P = 0.02 ). Less prokinetic use in naloxone group ( (P = 0.03) ). Trend for tolerance of greater enteral feedings in naloxone group. Antagonism of analgesia? Not stated.</td>
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</table>

ICU = intensive care unit.

Figure 2  Results of the meta-analysis of oral-cecal transit time (minutes): opioid antagonist vs placebo. Data are presented as the mean (95% CI) gastrointestinal transit times (minutes) for opioid antagonists vs placebo (fixed effects model). Size of the data markers corresponds to the weight of the study in the meta-analysis. WMD = weighted mean difference.
significance and the magnitude of the difference between methylnaltrexone and placebo was similar when the one study carried out in patients receiving methadone was removed from the meta-analysis. The four remaining methylnaltrexone studies all had a crossover design. The three additional studies were not combined as they employed different intervention drugs (alvimopan, nalbuphine, and naloxone), enrolled different populations (postoperative patients and patients with cancer), and produced clearly heterogenous outcomes. Alvimopan reduced transit time (76 minutes vs placebo 103 minutes, 95% CI = −52 to −2); nalbuphine increased transit time (380 minutes vs placebo 270 minutes; 95% CI = 64–156); and naloxone did not produce a statistically significant change (164 minutes vs placebo 176 minutes; 95% CI = −48 to 24).

Two studies assessed time to empty 50% of gastric contents in healthy volunteers and tested either methylnaltrexone [25] or naloxone [24]. Both were crossover studies. Methylnaltrexone and naloxone accelerated opioid-delayed emptying time by 14 minutes (95% CI: −20 to −8) and 70 minutes (95% CI: −107 to −32), respectively, vs placebo. In both studies combined, using a fixed effects model, emptying time was reduced by 15 minutes (95% CI: −21 to −10). However, the I2 statistic (87.8%) and inspection of the forest plot suggest considerable heterogeneity between the studies. When a random effects model was employed, the aggregate effect from both studies was no longer statistically significant.

Four studies in healthy volunteers presented data on outcomes (e.g., positioning of colonic markers) that we were not able to meta-analyze [26–29]. Two studies demonstrated that alvimopan reversed opioid-induced increases in GI transit [26,27]. The other two studies also demonstrated improvement in GI transit outcomes in patients administered the nonselective opioid antagonist naloxone [28,29]. Given the heterogeneity of the interventions and outcomes data and the limited information provided on adverse events, it was not possible to make any firm conclusions based on these four studies.

Postoperative Ileus

Five studies investigated opioid antagonist use in patients at risk of developing postoperative ileus. Four studies administered alvimopan [8,30–32] and one naloxone [33]. All studies had a parallel group design. In the alvimopan studies, the primary outcome was either time to first BM or flatus [31] or a composite measure of time to passage of flatus or stool and tolerating solid food [8,30,32]. Similarly, the naloxone study investigated time to first postoperative passage of flatus and feces. The alvimopan studies reported most outcomes as HRs derived from time-to-event variables, whereas the naloxone study presented means and standard deviations.

Secondary outcomes included pain (visual analog scale [VAS] intensity), opioid consumption, time to readiness for hospital discharge, insertion of a nasogastric tube, and need for chest X-ray.

The alvimopan studies reported sufficient information to allow us to combine the following outcomes for both a 6 mg and 12 mg dose: GI-3 (the later of two events: time that patient first tolerates solid food, or time the patient first passes flatus or has a BM); GI-2 (the later of the patient tolerating solid food or having a BM); time to first BM; time to first solid food, time to readiness for discharge; and time to actual discharge order written. The results of these meta-analyses are listed in Table 5. The combined outcomes demonstrate that alvimopan is superior to placebo for all outcomes except first solid food, where alvimopan shows a trend toward superiority. The results also indicate that there is no advantage to increasing the dose of alvimopan from 6 to 12 mg. Taguchi reported outcomes (time to first flatus, BM, liquids and solids, and time to readiness for and actual discharge) for 26 patients receiving a 1 mg dose of alvimopan. Because of the small sample size, the confidence intervals around the point estimate for each outcome are too wide to show significant differences between this dose and 6 or 12 mg. However, there is a trend toward superior efficacy in both the 6 and 12 mg doses vs 1 mg for most outcomes.

The alvimopan studies also reported the numbers of patients requiring chest X-ray or insertion of a nasogastric tube. In the former outcome, a dose of 6 mg resulted in a 6% ARR (95% CI: −11 to −1), whereas the 12 mg dose produced a non-statistically significant reduction of 4%. In total, 77 of 720 (11%) patients receiving alvimopan required an X-ray vs 57 of 369 (15%) receiving placebo. Both 6 and 12 mg doses resulted in a 4% reduction in insertion of nasogastric tube (95% CI: −7 to −1). In each case, 6% of those receiving alvimopan required insertion vs 10% of those administered placebo. For both outcomes, only the nasogastric data for 12 mg of alvimopan appeared heterogenous (I2 = 64%). Using a random effects model for this outcome, the data were no longer statistically significant.
The single study of epidural naloxone reported earlier flatus and first BM vs placebo [33]. It was not possible to compare measures of efficacy for oral alvimopan and epidural naloxone because of the different manner in which outcomes were presented. However, one study for each intervention presented postoperative maximum VAS pain scores vs placebo in a manner that permitted meta-analysis [31,33]. The respective studies demonstrated no difference in pain scores between epidural naloxone and placebo or oral alvimopan and placebo, suggesting that neither intervention antagonized analgesia. In addition, the three other studies administering alvimopan to postoperative patients all reported no difference in maximum VAS scores for all doses vs placebo. All four alvimopan studies measured opioid consumption. In all but two cases, opioid consumption was similar between active and placebo groups. Delaney [30] reported a statistically significant difference between placebo and 12 mg alvimopan (25.6 mg vs 31.6 mg) and Wolff [32] reported a statistically significant difference between placebo and 6 mg alvimopan (27 mg vs 33.6 mg). The studies were not combinable because of nonreporting of standard deviations.

### Constipation

Four studies investigated opioid antagonist use in patients with constipation because of chronic opioid usage. Two studies administered naloxone [24,34], one alvimopan [35], and one methylnaltrexone [23]. All were parallel studies except for Sykes [24], which employed a crossover design. Indications for opioid use included cancer pain, noncancer pain, and methadone maintenance. Assessment of constipation varied among studies and included composite scales, proportion of patients with a BM within a specified time period, small bowel transit time, stool frequency, and overall satisfaction. Possible reversal of analgesia was assessed by using the Short Form Brief Pain Inventory, VAS pain intensity, and withdrawal scales.

The studies reported sufficient data to allow us to analyze three separate measures of efficacy; number of patients with a BM within a specified time period; BMs per week; and number of patients satisfied with BMs. The studies by Paulson and Yuan [23,35] investigated number of patients reporting a BM within 8 hours or immediate laxation, respectively. The former study enrolled patients with cancer pain, noncancer pain, and opioid dependency and administered alvimopan. The latter study enrolled patients receiving methadone maintenance and administered methylnaltrexone. The meta-analysis demonstrated significant heterogeneity ($\Gamma^2 = 98.4\%$). However, individually both studies showed statistically significant improvement for antagonist vs placebo. Fifty-four percent of patients receiving alvimopan had a BM vs 30% of those receiving placebo, which translates to an NNT of 4.2 (95% CI: 2.4–16.7). One hundred percent of patients receiving methylnaltrexone had immediate laxation vs none in the placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Combined Number of Patients Receiving Alvimopan*</th>
<th>Combined Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI-3†</td>
<td>516</td>
<td>1.29 (1.13–1.48)</td>
</tr>
<tr>
<td>GI-2‡</td>
<td>516</td>
<td>1.40 (1.20–1.62)</td>
</tr>
<tr>
<td>First bowel movement</td>
<td>387</td>
<td>1.57 (1.33–1.87)</td>
</tr>
<tr>
<td>First solid food</td>
<td>387</td>
<td>1.41 (1.00–2.00)</td>
</tr>
<tr>
<td>Hospital discharge order written</td>
<td>542</td>
<td>1.53 (1.19–1.95)</td>
</tr>
<tr>
<td>Readiness for hospital discharge based solely on GI recovery</td>
<td>349</td>
<td>1.41 (1.20–1.66)</td>
</tr>
<tr>
<td>12 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI-3†</td>
<td>524</td>
<td>1.44 (1.23–1.69)</td>
</tr>
<tr>
<td>GI-2‡</td>
<td>524</td>
<td>1.43 (1.24–1.65)</td>
</tr>
<tr>
<td>First bowel movement</td>
<td>359</td>
<td>1.48 (1.23–1.77)</td>
</tr>
<tr>
<td>First solid food</td>
<td>359</td>
<td>1.16 (0.97–1.39)</td>
</tr>
<tr>
<td>Hospital discharge order written</td>
<td>524</td>
<td>1.29 (1.14–1.47)</td>
</tr>
<tr>
<td>Readiness for hospital discharge based solely on GI recovery</td>
<td>322</td>
<td>1.36 (1.15–1.60)</td>
</tr>
</tbody>
</table>

* Combined numbers based on modified intention to treat populations except where unavailable; in which case safety populations used.
† The time to recovery of GI function—a composite end point that represents full (upper and lower) GI recovery—defined by the latter of the following two events: time that the patient first tolerates solid food, or time that the patient first passes flatus or a bowel movement.
‡ Time to first tolerance of solid food or first bowel movement, whichever occurred last (end point excludes flatus). GI = gastrointestinal.
group, which translates to an NNT of 1 (95% CI: 0.86–1.2). When both studies are combined using a fixed effects model the use of an opioid antagonist produces an NNT of 2.7 (95% CI: 1.9–4.8). However, when a random effects model is employed to adjust for between-study heterogeneity, the combined effect observed in the two studies is no longer statistically significant.

Three studies assessed number of BMs per week [24,34,35]. Only the study by Paulson enrolled more than 10 patients. Each of the three studies demonstrated a statistically insignificant trend toward improvement with opioid antagonist vs placebo. When the three studies are combined, the improvement achieves statistical significance, with patients receiving an opioid antagonist having 1.4 BMs more per week than those receiving placebo (95% CI: 0.2–2.5). When sensitivity analysis is performed to remove the crossover study by Sykes, the improvement is still statistically significant (WMD: 1.2; 95% CI: 0.03–2.9).

Lastly, three studies assessed patient satisfaction [23,34,35]. All three studies showed a significant improvement in patients’ satisfaction with their BMs when receiving opioid antagonist vs placebo, with methylnaltrexone appearing to demonstrate the greatest improvement (100% of patients satisfied vs 22% of patients receiving placebo) [23]. Using a fixed effects model, the three studies combined demonstrated a statistically significant improvement in satisfaction, with 75% of patients receiving opioid antagonist satisfied vs 44% of those receiving placebo. This translates to an NNT of 3.1 (95% CI: 2.1–6.2). Both the forest plot and the I² statistic (84.8%) suggest that considerable between-study heterogeneity exists. However, the combination of studies using a random effects model continues to show a significant improvement in satisfaction for patients receiving an opioid antagonist.

Two studies assessed numbers of patients reporting reversal of analgesia by capturing any increases in baseline pain intensity [34,35]. Neither study defined the increment in pain intensity VAS that was considered to indicate reversal. Separately and in combination, neither study showed any difference between opioid antagonist and placebo in number of patients reporting reversal.

Meta-analyses of Safety Data

Twenty-nine different adverse events were reported, of which 19 were reported in a similar manner by more than one article, thereby making meta-analysis possible. Safety data were meta-analyzed by incidence or severity of adverse event, and where possible subanalyzed by intervention and disease state. Where articles reported an absence of adverse events they were not added to the analysis. Where data for different dosage strengths were provided, incidence or severity was analyzed for each strength. Although most data were reported as incidence rather than severity, authors often described severity as mild-to-moderate, or not serious. Analysis failed to show a difference between opioid antagonist and placebo except for the following adverse events.

Nausea

Meta-analysis using a fixed effects model demonstrated a statistically significant reduction in incidence of nausea when alvimopan 12 mg was administered to postoperative patients. In total, 293 of 543 (54%) patients receiving alvimopan 12 mg complained of nausea vs 331 of 542 (61%) receiving placebo, resulting in an ARR of 7% (95% CI: −13 to −1). There appeared to be a dose-dependent reduction in nausea for alvimopan, although the difference in incidence between 12 mg and 6 mg was marginal. The fixed effects model also showed an overall class effect for opioid antagonists (alvimopan and naloxone) in various disease states with a 6% reduction in absolute risk (95% CI: −10 to −2). However, inspection of the forest plot suggests that in the single studies of alvimopan administered to different populations (constipation, healthy volunteers) and in the single study of naloxone administered to healthy volunteers, there was no reduction in incidence of nausea, suggesting heterogeneity of effect. When a random effects model was employed to account for heterogeneity, the studies administering alvimopan 12 mg in postoperative patients continued to demonstrate the same reduction in incidence of nausea, but the overall class effect was slightly lower (5% reduction in risk) (Figure 3).

Sensitivity analysis involving removal of the one crossover study [25] made no difference to the magnitude or statistical significance of either model.

Meta-analysis using a fixed effects model also demonstrated a reduction in severity of nausea when a study of methylnaltrexone administered to healthy volunteers [25] and a study of alvimopan administered to postoperative patients [31] were combined. Despite the different drugs and populations, the data appeared to be homogeneous. The overall effect was a WMD in the
severity of nausea of 15% (95% CI: −25 to −4). If sensitivity analysis is performed to remove the crossover study [25], the single study of alvimopan administered to postoperative patients is still statistically significant with a WMD of 20% (95% CI: −35 to −5).

Vomiting
As with the analysis of the incidence of nausea, the number of patients who vomited was statistically significantly reduced in postoperative patients administered alvimopan 12 mg, as well as in all patients administered alvimopan when all populations (healthy volunteers, constipation) and different drugs were included in the analysis. Again, there appears to be a slight dose dependency for the effect of alvimopan on reduction of the incidence of vomiting. Class effect statistical significance disappeared when a random effects model was used to account for between-study heterogeneity (I² = 57%). In the postoperative population administered alvimopan 12 mg, 103 of 543 patients vomited (19%) vs 147 of 542 (27%) patients receiving placebo. This translates to a 9% ARR (95% CI: −16 to −1) when a random effects model is employed.

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**Figure 3** Results of the meta-analysis of incidence of nausea: opioid antagonist vs placebo. Data are presented as risk difference or absolute risk reduction (95% CI) in incidence of nausea, e.g., −0.09 is equal to a 9% absolute reduction in risk of nausea occurring in the opioid antagonist group vs placebo (random effects model). Size of the data markers corresponds to the weight of the study in the meta-analysis. RD = risk difference.

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Again, in a similar manner to the nausea meta-analysis, sensitivity analysis involving removal of the one crossover study [25] made no difference to the magnitude or statistical significance of either model.

**Abdominal Cramping**

In a single study enrolling patients with opioid-induced constipation, all 11 of those administered methylnaltrexone reported mild abdominal cramping vs none of 11 administered placebo [23]. No overall class effect was seen in the 11 trials that reported incidence of cramping, and no other drug in any other condition produced an increase in abdominal symptoms vs placebo. Removal of the single crossover study from this analysis [28] did not affect the results.

**Diarrhea**

A single study of alvimopan administered to patients with constipation showed an increase in the incidence of diarrhea in those patients vs patients receiving placebo [35]. Six of 56 (11%) patients receiving alvimopan complained of diarrhea vs none of 54 receiving placebo. This translates to an absolute increase in risk of 11% (95% CI: 2–19) and an NNH of 9 (95% CI: 5–50). There was no difference in incidence of diarrhea in any other populations (postoperative ileus, healthy volunteers) or with different antagonists (methylnaltrexone, naloxone).

**Constipation**

In contrast to the dose dependency for other adverse events observed with alvimopan, 6 mg but not 12 mg reduced the incidence of constipation when two studies of postoperative patients were combined [8,30]. Twenty-two of 370 (6%) patients administered alvimopan 6 mg reported suffering from constipation vs 39 of 377 (10%) administered placebo, translating to an ARR of 4% (95% CI: −8 to −1).

**Postoperative Ileus**

When a fixed effects model was used to combine three studies of alvimopan 12 mg administered to postoperative patients a statistically significant reduction in the incidence of ileus was seen [8,30,32]. Thirty-six of 543 (7%) patients receiving alvimopan vs 60 of 542 (11%) receiving placebo reported suffering from ileus, translating to an ARR of 5% (95% CI: −8 to −1). When data for a dose of 6 mg from the same three studies were combined, the reduction in ileus was not significant. The higher dose data appeared to be borderline heterogenous ($\Gamma^2 = 58\%$) and when a random effects model was employed, the analysis was no longer statistically significant. The authors did not report how ileus was defined.

**Anxiety/Jitteriness**

If the outcomes anxiety and jitteriness are combined, a single study [34] showed an increased incidence in patients with constipation administered naloxone vs those administered placebo. The study population was very small, however. Three of six patients (50%) receiving naloxone vs none of three receiving placebo reported this combined outcome. The small sample size is reflected in the wide confidence intervals for increase in absolute risk (50%; 95% CI: 1–99) and NNH (2; 95% CI: 1.01–100).

**Oliguria**

Meta-analysis of data from two studies [8,32] demonstrated a tendency toward reduction in incidence of oliguria. When data from both doses were combined, an overall effect of ARR of 4% (95% CI: −7 to −1) was observed. Seventy-six of 786 patients (10%) receiving alvimopan suffered from oliguria vs 104 of 778 (13%) receiving placebo. The results appeared to be homogenous ($\Gamma^2 = 0\%$).

**Treatment-Related Withdrawals**

Postoperative patients administered 6 mg of alvimopan were less likely to withdraw from the study because of their treatment than those receiving placebo [8,30,32]. Thirty-one of 539 patients (6%) receiving alvimopan withdrew vs 59 of 542 (11%) receiving placebo, which translates to an ARR of 5% (−8 to −2). Differences on treatment-related withdrawals did not differ significantly for the higher dose of 12 mg vs placebo, or for alvimopan or naloxone in other conditions, although analysis showed a marginal overall class effect that persisted when a single crossover study was removed [29].

**Serious Adverse Events**

Both alvimopan 6 mg and 12 mg demonstrated a 5% ARR in serious adverse events vs placebo in postoperative patients when a fixed effects model was used. However, in both cases, there was evidence of heterogeneity of data ($\Gamma^2 > 80\%$). When a random effects model was employed, the reduction at both doses was no longer significant. Removal of the single crossover study did not affect the overall analysis [28].
An overall reduction in rehospitalization was seen when data from both 6 mg and 12 mg doses of alvimopan were combined in postoperative patients. Forty-nine of 786 patients receiving alvimopan (6%) were rehospitalized vs 76 of 778 (10%) receiving placebo. The data appeared to be homogenous ($I^2 = 0\%$).

**Discussion**

Our objective in this review was to compare the efficacy and safety of both traditional nonselective opioid antagonists and newer, peripherally selective antagonists vs placebo or other existing pharmacological or nonpharmacological treatments for OBD. We hypothesized that the newly developed peripherally acting opioid antagonists would have similar efficacy as nonselective antagonists in reversing opioid-induced constipation or postoperative ileus, but would be less likely than nonselective antagonists to reverse centrally mediated opioid effects such as analgesia.

**Efficacy**

**GI Transit Time**

Our analyses demonstrate that methylnaltrexone reverses opioid-induced increases in GI transit time. Limited data suggest that reversal occurs not only in healthy volunteers, but also in patients with opioid-induced constipation. The four methylnaltrexone studies performed in healthy volunteers had a crossover design. While there are disadvantages and potential biases to employing a crossover design, we considered that the studies employed sufficient washout periods to prevent carry over of effect from one intervention to the next. Also, as the subjects were healthy volunteers, there should be little change in their health status in the period between interventions. It is not possible to make firm conclusions regarding the efficacy of any other opioid antagonist in any particular condition or disease state, or to make comparisons between antagonists. The between-study heterogeneity that exists in the meta-analysis could be a consequence of actual differences in efficacy among the opioid antagonists, but equally could be due to the single studies and low enrollment numbers for the remaining antagonists. Limited data suggest that alvimopan reduces transit time in postoperative patients, naloxone has a similar effect in healthy volunteers, and nalbuphine increases transit time in postoperative patients. The data on time to 50% gastric emptying time were also heterogenous, probably as a consequence of differences in the methods used to measure transit.

A more challenging question relates to the clinical significance of a 59-minute reduction in GI transit time. Both constipation and postoperative ileus are multifactorial and have multiple symptoms. The fact that the majority of studies measuring GI transit used healthy volunteers further prevents us from generalizing their conclusions to clinical settings that may not be poised to translate each decrement of GI transit time into correspondingly quicker times to hospital discharge. The one methylnaltrexone study that enrolled patients in a methadone maintenance program with chronic constipation demonstrated that reductions in GI transit time were accompanied by a laxation response in all patients [23].

**Postoperative Ileus**

The four studies employing alvimopan as the opioid antagonist for postoperative ileus had a combined intention to treat population of 1,586 patients. These studies therefore provided the most robust data on which to base clinical conclusions. The naloxone study enrolled 43 patients.

Evaluating the effectiveness of therapeutic agents for postoperative ileus is challenging because the definition of ileus and methods for assessment are not clear [9]. This lack of uniformity may explain why studies measured multiple outcomes and why some of those outcomes were derived from composite endpoints. However, our meta-analyses of HRs derived from these multiple outcomes demonstrated that alvimopan was more effective than placebo for all except time to solid food. The authors of the four studies also provided mean or median differences for the majority of outcomes, but did not supply sufficient data (either in the manuscript or in direct communication) to allow us to meta-analyze these differences. The clinical significance of an HR is not intuitive to many clinicians. The HR describes the relative risk of the complication, or in our case benefit, based on comparison of event rates. A value of greater than 1 (one) indicates that the benefit is more likely to occur in the opioid antagonist group within a given time period. Spruance et al. make a good analogy: the difference between hazard-based and time-based measures is analogous to the odds of winning a race and the margin of victory [36]. If we extrapolate their analogy to our analysis, in the largest of the studies [8], the HR
The studies that measured postoperative ileus did so in only three different surgeries: bowel resection, hysterectomy, and gastrectomy. It remains to be determined whether the positive results seen in these studies translate to other postoperative populations.

A limitation of many reports included in this review is their restriction of study populations to receive systemic opioids for postoperative pain management. Major abdominal and thoracic surgeries increasingly employ epidural mixtures containing local anesthetics, whose use is known to accelerate return of intestinal function [37–39]. Therefore, the advantage achieved by opioid antagonists observed in these studies might be reduced if it were compared with currently employed epidural analgesic mixtures.

**Constipation**

In common with measures of GI transit time, and in contrast to the studies of postoperative ileus, a small number of heterogenous studies with low patient enrollment were available for the meta-analysis of constipation outcomes.

Comparison of number of patients reporting a BM within a specified time period favored intravenous methylnaltrexone over alvimopan [23,35]. However, this comparison should be interpreted with caution, given the limited numbers of patients, the difference in study populations, and the fact that methylnaltrexone was administered intravenously (one would expect the marketed drug to be available in oral formulation).

In a similar manner, the three studies assessing number of BMs per week appeared to favor naloxone [24,34] over alvimopan [35]. Again though, the naloxone studies recruited a low number of subjects (16 in total), all of whom were administered opioids for pain, vs the alvimopan study, which enrolled 110 patients with either pain or opioid addiction. It should also be noted that patients receiving alvimopan actually had more mean BMs per week than those in either of the naloxone studies: the WMD was less because patients receiving placebo had a relatively high number of BMs per week in the alvimopan study. Last, none of the studies show statistically significant differences between antagonist and placebo when taken in isolation.

It is, again, difficult to make firm conclusions based on the three studies of patient satisfaction, for reasons similar to those outlined for the two previous outcomes. Unlike the measure of number of BMs per week, however, all three studies

(odd of winning the race) for GI-3 is 1.28 and corresponds to a reduction in time (margin of victory) to first solid food/BM/flatus of 15 hours for alvimopan 6 mg vs placebo. Similarly, the GI-2 HR of 1.38 corresponds to a reduction in time to first solid food and BM of 20 hours, and the HR of 1.25 corresponds to the hospital discharge order being written 13 hours earlier in patients receiving 6 mg alvimopan. However, even if we were able to translate the combined HRs into mean differences in e.g., time to first BM, the clinical significance of these differences is still unclear. Does a reduction in time to first BM translate to a reduction in morbidity? The reduction in time to hospital discharge (or readiness for hospital discharge) may offer some insight. Perhaps, if the authors had listed numbers of patients discharged on each postoperative day, this would have given us a better indicator of cost-effectiveness and reduction in morbidity. In addition, the results of the outcomes “requirement for nasogastric tube insertion” or “requirement for a chest X-ray” suggest that alvimopan reduces the incidence of postoperative complications.

It is unclear what is the most effective dose of alvimopan. The ideal dose of a drug achieves an optimal balance between efficacy and safety. Our analyses did not show a consistent statistically significant difference across outcomes between the 6 mg and 12 mg doses for either safety or efficacy.

The one study conducted with epidural naloxone reported statistically significant improvements in time to first flatus and BM of 35 hours and 38 hours, respectively. These numbers compare favorably with those reported in the alvimopan studies, but are derived from a different population (subtotal gastrectomy) and from a smaller sample size. This intervention also requires the epidural administration of a drug.

If ileus (or constipation) is a primarily peripherally mediated adverse effect of opioids, and analgesia mostly centrally mediated, we should expect both peripherally selective and nonselective opioid antagonists to reverse OBD, but only nonselective antagonists to reverse analgesia. However, while data (opioid consumption and VAS pain scores) from the alvimopan studies seem to confirm this hypothesis, the one study of epidural naloxone surprisingly showed no difference in analgesia between the naloxone and placebo groups. This could be a result of chance in a small sample size, or may be due to naloxone having dose-dependent effects, i.e., reversal of ileus at a lower dose than that required to reverse analgesia.
showed a significant difference in preference for antagonist over placebo. The differences between studies may have been confirmed by higher patient enrollment (i.e., a genuine difference in efficacy exists among drugs), but equally could be explained by differences in the way that patient satisfaction was measured, or because of heterogeneous populations.

When assessing the number of patients reporting reversal of analgesia, the study administering naloxone is too small for us to ascertain whether there is no difference between naloxone and placebo or whether the study is insufficiently powered to demonstrate a difference [34]. The larger numbers enrolled in the alvimopan trial suggest that alvimopan does not cause reversal of analgesia in this population.

It is possible that our analyses of efficacy may have been confounded by the different opioids administered in each trial. Different opioids may have varying effects on the GI system [40,41]. The heterogeneity of dosage regimens and routes of administration among studies prevented us from performing any subanalyses based upon opioid administered. However, in all studies that reported the opioid and dose used, the same regimen was administered to both active and placebo arms.

Two studies that assessed outcomes or data that we were not able to include in our analyses merit discussion, as they assessed mechanically ventilated patients in the intensive care unit receiving opioids for analgesia/sedation [42,43]. Both studies employed naloxone and assessed various outcomes including gastric reflux, constipation, and pneumonia (Table 4). Based on limited data, the studies suggest that naloxone reduces both gastric reflux and the incidence of pneumonia without reversing analgesia or causing an increase in opioid requirements. Further investigation in this critical population is merited.

**Safety**

One would usually expect incidence or severity of adverse events to be equivalent or higher in active treatment groups vs placebo. The results from many of the present safety analyses show the opposite, suggesting that these outcomes are in fact measures of efficacy rather than of safety. This assumption would particularly seem to hold for GI-related adverse events. The majority of studies show a reduction, or trend to reduction, in incidence and severity of nausea and in the incidence of constipation, postoperative ileus, and vomiting. Conversely, and as might be expected, GI symptoms such as diarrhea and abdominal cramping occur more commonly in some of the arms receiving opioid antagonist than in those receiving placebo. It is possible that patients would be willing to risk the occurrence of diarrhea and cramping in order to obtain relief from those adverse events related to constipation. Interestingly, a prior study in which ultra-low doses of the nonselective opioid antagonist naloxone were coadministered with morphine during postoperative patient-controlled analgesia also demonstrated a reduction in nausea [44].

In a similar manner to GI-related events, adverse events such as treatment-related withdrawals, serious adverse events, rehospitalization, and death may reflect an intervention’s efficacy as much as its safety. The present meta-analyses of the first three of these outcomes, where incidence is lower in the treatment group, appear to confirm this for certain populations. Meta-analysis of numbers of patients dying during a study period did not demonstrate a difference. This could be because no difference exists between opioid antagonist and placebo, but equally could be a result of study populations being too small to adequately describe a rare event, or because duration of studies was insufficient to capture long-term toxicity.

The other 16 adverse events reported could broadly be categorized as pertaining to the central nervous system, cardiovascular and electrolyte abnormalities, and miscellaneous. Only two meta-analyses, those of anxiety and oliguria, demonstrated a difference between opioid antagonist and placebo. Patients administered naloxone had an increased incidence of anxiety or jitteriness, perhaps demonstrating centrally mediated opioid antagonism, but the number of patients enrolled was insufficient to make firm conclusions regarding naloxone or to extrapolate any conclusion to other antagonists. A reduction in incidence of oliguria was seen when data from two strengths of alvimopan were combined in two studies of postoperative ileus. The difference in incidence was statistically significant but clinically marginal. The possibility also exists that if one analyses multiple adverse events, by chance one analysis will show a difference when none exists.

Most of the safety data come from the alvimopan studies. Many of the methylnaltrexone articles reported “no serious adverse events” or “no adverse events of clinical importance” in either group. The lack of adverse event data in these studies may reflect a milder adverse event profile.
for methylnaltrexone over alvimopan. However, the absence of data in both the methylnaltrexone and placebo arms suggests that differences may be due to the smaller study populations, or because the investigators in the methylnaltrexone studies used different criteria or thresholds for defining events. Last, most methylnaltrexone trials were carried out in healthy volunteers. Adverse events were rarely reported in naloxone studies. Again, this is likely a consequence of limited patient enrollments, and also because of the generally low quality of these studies, rather than any actual differences in adverse event profiles.

Some general observations can be made from the included studies. Measures of both efficacy and safety do not consistently show a class effect for opioid antagonists. Even in those analyses where a statistically significant overall effect is demonstrated, heterogeneity clearly exists between studies with different drugs and/or study populations. It may be inappropriate to combine such heterogeneous data. Equally, there is insufficient evidence for us to make comparisons between any of the antagonists for either safety or efficacy. Therefore, we cannot confirm our hypothesis that antagonists whose site of action is restricted to the periphery have a similar efficacy to nonspecific antagonists, but a lower incidence of side effects.

None of the studies compared an opioid antagonist with another antagonist, an alternative pharmacological regimen, or a nonpharmacological intervention. Therefore, the efficacy or safety of these compounds relative to other interventions is unknown. We can only make comparisons based on similar studies with alternative interventions. Studies involving alternative pharmacotherapies for patients with constipation because of cancer pain and chronic noncancer pain are too heterogeneous to make any meaningful comparisons within these alternative therapies, or between them and opioid antagonists [5]. Other compounds currently being developed, such as the chloride channel activator lubiprostone, may also show efficacy in both opioid-induced constipation and postoperative ileus, but have thus far not been tested in these populations [45].

Alvimopan is the first drug whose manufacturers have sought FDA approval for use in postoperative ileus. However, small studies with prokinetic agents, laxatives, nonsteroidal anti-inflammatory drugs (NSAIDs), and GI hormone analogs, have been conducted in this setting [39]. The majority of these studies either failed to show a benefit, were nonrandomized, or reported unacceptable side effect profiles. One small study involving ketorolac demonstrated a benefit in postoperative ileus, but as NSAIDs are a standard component of postoperative regimens, the use of an opioid antagonist in place of an NSAID is unlikely [46]. Comparison with nonpharmacological interventions, such as nasogastric decompression, early ambulation, and early feeding or multimodal accelerated care pathways, is also difficult, given that such interventions are increasingly considered standard postoperative practice and that trials investigating such interventions studied different populations and measured widely different outcomes [39]. In addition, the alvimopan studies incorporated these accelerated care pathways for both intervention and placebo arms, suggesting that alvimopan will be used in addition to, rather than instead of, such pathways.

Both efficacy and adverse event profiles can change over time. None of the study durations exceeded 35 days. Clearly, for investigation of GI transit time or in postoperative patients, a short study duration is appropriate. However, although the studies involving patients with constipation were generally carried out over the longest time period, patients with chronic pain may require treatment for months or years. It is not possible from the available studies to determine whether efficacy or safety varies over time for these patients. Additionally, these studies enrolled few patients. Results from multicenter, long-term, postmarketing studies of COX-2 inhibitors have demonstrated that rare adverse events may only be seen with chronic administration in large populations. Therefore, despite the seemingly mild adverse event profile demonstrated with opioid antagonists, it is not prudent to claim that this class of drugs is safe for all patients or with chronic use.

Finally, our systematic review and meta-analysis shares limitations common to all analyses of heterogeneous data [47–49]. Negative studies often go unpublished and we are only able to analyze the data which investigators chose to assess and present. As detailed in our Methods section, we attempted to minimize potential bias by contacting authors for unpublished studies and clarification of data, and by searching drug regulatory websites.

**Conclusion**

Insufficient evidence exists for either a class effect of opioid antagonists (with the exception of the outcomes BMs per week and patient satisfaction)
or for the superiority of any antagonist over another in OBD. Insufficient evidence exists regarding the safety or efficacy of the nonselective opioid antagonist naloxone or the mixed/lantagonis agonist nalbuphine in treatment of opioid-induced constipation or postoperative ileus. Limited data in patients with constipation and in experimental models demonstrate that methylnaltrexone is efficacious in reversing opioid-induced increased GI transit time and constipation. Data from three large phase III trials support the efficacy and short-term safety of alvimopan use in several outcomes related to postoperative ileus, although the clinical significance of these improved outcomes is unclear. Limited data also support the efficacy of alvimopan in treating opioid-induced constipation.

Long-term efficacy and safety of any of the opioid antagonists is unknown, as is the incidence or nature of rare adverse events.

Alvimopan and methylnaltrexone both show promise in treating OBD, but further data including that from postmarketing and cost-effectiveness studies and from trials in wider populations will be required to fully assess their place in therapy.

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References

21. Liu SS, Hodgson PS, Carpenter RL, Fricke JR Jr. ADL 8-2698, a trans-3,4-dimethyl-4-(3-hydroxyphenyl) piperidine, prevents gastrointestinal effects


48 Naylor CD. Meta-analysis and the meta-epidemiology of clinical research: Meta-analysis is an important contribution to research and practice but it's not a panacea (Editorial). BMJ 1997;317:617–9.