Peripherally Acting μ-Opioid Receptor Antagonists in the Management of Postoperative Ileus: a Clinical Review

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Abstract
Postoperative ileus (POI) and constipation are common secondary effects of opioids and carry significant clinical and economic impacts. μ-Opioid receptors mediate opioid analgesia in the central nervous system (CNS) and gastrointestinal-related effects in the periphery. Peripherally acting μ-opioid receptor antagonists (PAMORAs) block the peripheral effects of opioids in the gastrointestinal tract, while maintaining opioid analgesia in the CNS. While most are not approved for POI or postoperative opioid-induced constipation (OIC), PAMORAs have a potential role in these settings via their selective effects on the μ-opioid receptor. This review will discuss recent clinical trials evaluating the safety and efficacy of PAMORAs, with a focus on alvimopan (Entereg®) and methylnaltrexone (Relistor®) in patients with POI or postoperative OIC. We will characterize potential factors that may have impacted the efficacy observed in phase 3 trials and discuss future directions for the management and treatment of POI.

Keywords Postoperative ileus · Opioid-induced constipation · Opioid analgesics · μ-Receptor antagonists · Alvimopan · Methylnaltrexone

Introduction

Postoperative Ileus

Postoperative ileus (POI) is defined as a delay of normal gastrointestinal (GI) motility after surgery and can be secondary to surgical stress responses (i.e., bowel manipulation and/or resection), neurohormonal dysfunction, inflammation, fluid and electrolyte imbalances, and opioids (both endogenous and exogenous).1–3 Clinical features of POI include bloating, abdominal distention, nausea, vomiting, delay in oral intake, and pain.4 The incidence of POI has been reported in 10 to 30% of patients who have undergone colectomy, cholecystectomy, or other abdominal surgeries.1–5 Multiple factors may affect the incidence of POI, including the type and duration of surgery,6, 7 inflammatory factors induced during surgery,8 and opioid dose5 and duration.9

POI is associated with decreased patient satisfaction, extended hospital length of stay, medical complications, increased hospital costs, subsequent surgical interventions, and higher readmission rates.5, 10, 11 Hospital costs in patients with POI are estimated to be double compared with those who have normal return of bowel function (median total hospital costs, $21,046 vs $10,945).5 As such, accelerating GI recovery after surgery is paramount in improving patient outcomes and decreasing costs.

Strategies to improve rates of POI have changed over time. Traditional approaches to POI prevention include chewing gum, adequate fluid resuscitation, and administration of prokinetic drugs and laxatives.3 However, some of these measures are associated with additional risks or have limited or unproven efficacy.8 More contemporary multimodal strategies, termed enhanced recovery after surgery (ERAS) protocols, aim to limit the stress response to surgery.3 Examples of key interventions of the ERAS protocol are to encourage ambulation, early diet, and multimodal analgesia.3, 12–15 Peripheral μ-opioid receptor
antagonists (PAMORAs) also play a critical role in many ERAS protocols, especially among patients undergoing open surgery.3 Herein, we review the role of μ-opioid receptors in GI motility, the use of PAMORAs after surgery to accelerate GI recovery, and discuss future directions.

**Peripherally Acting μ-Opioid Receptor Antagonists in GI Recovery**

Opioid analgesics are often administered during and after surgical procedures for the management of intraoperative and postoperative pain, respectively.16 In addition to their intended central effect on pain receptors, opioids have an undesired influence peripherally in the GI tract, including decreased gastric motility and emptying, inhibited bowel propulsion, and altered fluid and electrolyte balance.17 Opioids profoundly affect the forward propulsive and coordinated peristaltic activity of the bowel leading to both POI and postoperative opioid-induced constipation (OIC).16, 18 Although OIC and POI are similar, POI involves the loss of forward propulsive motion of the GI tract after surgery.19

Opioid receptors, of which there are 3 main classes (μ, δ, κ), are ubiquitous in the central nervous system (CNS) and enteric nervous system.17 Nonselective μ-opioid receptor antagonists cross the blood-brain barrier and target both central and peripheral μ-opioid receptors.20, 21 For example, the nonselective μ-opioid receptor antagonist naloxone (Narcan®) has a long clinical history of successful use for the treatment of opioid overdose, reversing overdose-induced respiratory depression while reducing symptoms of acute withdrawal in opioid-dependent patients.22 Targeting of both central and peripheral μ-opioid receptors relieves constipation but also reverses opioid analgesia.20, 21

PAMORAs aim to mitigate the risk of POI while maintaining analgesia in patients receiving postoperative opioids by selectively inhibiting peripheral μ-opioid receptors.23 The effects of PAMORAs are limited to the periphery given their polarity, large structure, and low lipid solubility that prevents them from crossing the blood-brain barrier.24 As such, selective antagonism of the GI μ-opioid receptors blocks the peripheral effects of opioids, while maintaining the analgesic effects of opioids in the CNS.23, 25

Most of the approved PAMORAs are not indicated for POI or postoperative OIC, but they may have a role in the management of postoperative bowel dysfunction by virtue of their abovementioned mechanism of action.19 Currently, alvimopan and methylnaltrexone have the most significant data supporting their use for POI. Other PAMORAs, such as naloxegol, are less thoroughly studied with only small series demonstrating some efficacy for POI.26

**PAMORAs for POI**

**Alvimopan (Entereg®)**

Alvimopan is the only PAMORA indicated to accelerate the time to upper and lower GI recovery following partial bowel resection surgery with primary anastomosis (Table 1).27 It is limited to 15 total doses, which can only be administered in the hospital.27 Dosing guidelines recommend one 12-mg capsule 30 min to 5 h before surgery and one 12-mg capsule twice daily beginning the day after surgery until discharge for a maximum of 7 days.27 In clinical studies for the management of POI, alvimopan was administered orally (alvimopan 6 and/or 12 mg) preoperatively and continued following surgery.28–33

**Alvimopan and GI Recovery**

The safety and efficacy of alvimopan has been evaluated in patients undergoing major abdominal surgery, including bowel resection,34–38 hysterectomy,30, 31, 33 and radical cystectomy.34 The primary efficacy endpoint for the earlier alvimopan efficacy studies was time to recovery of GI function as demonstrated by the endpoint GI3.29, 31, 32 GI3 is a composite endpoint determined by the time that a patient first tolerated solid food (a marker for upper gastrointestinal function recovery) and the time that a patient first passed flatus or had a bowel movement (a marker for lower gastrointestinal recovery).29–32 However, the GI3 endpoint did not demonstrate statistically significant differences compared with placebo in every alvimopan study (Table 2).29, 31, 33 Post hoc analysis of the data suggested that a secondary endpoint, GI2, was more objective. The GI2 endpoint is the same as the GI3 endpoint but eliminates flatus as a marker for lower GI recovery. Flatus has been found to be subjective and highly variable.29–32 As such, GI2 was preferentially utilized in subsequent alvimopan studies.28, 29, 32, 33 Indeed, across most studies, time to the GI2 endpoint, regardless of whether it was a primary or secondary endpoint, was reduced in the alvimopan group compared with that in the placebo group.28, 29, 33 Overall, alvimopan shortened the time to GI recovery and time to readiness for discharge (Table 2).28, 30, 32, 35

**Alvimopan and Hospitalization**

The effect of alvimopan has also been studied in large databases in order to evaluate the effects on length of stay and postoperative complications. For example, the Premier Perspective database is an observational propensity-matched cohort study that includes hospitalized postsurgical patients from a network of more than 400 hospitals.36 Using this database, Steele and colleagues evaluated the effect of alvimopan on clinical outcomes and healthcare utilization in
patients undergoing bowel resection. Compared with matched cohorts (n = 18,559), patients receiving alvimopan (n = 18,559) had significantly reduced postoperative length of stay (mean ± standard deviation, 4.62 ± 2.45 days vs 5.24 ± 3.35 days; P < 0.001). In addition, alvimopan was associated with significantly reduced postoperative GI complications, urinary tract infections, and postoperative infections (all P < 0.001). Cardiovascular, pulmonary, and thromboembolic events were also significantly reduced in the alvimopan group when compared with those in matched controls (P < 0.001). The authors noted that these improved outcomes may have been a result of shorter hospital length of stays and the implementation of ERAS protocols.

In a recent subanalysis of patients who underwent bowel resection from the Premier Perspective database, alvimopan (n = 15,719) reduced the incidence of POI (P < 0.001), POI-related readmission (P < 0.01), and length of hospital stay (P < 0.001) compared with matched controls (n = 37,229). Cardiovascular complications and in-hospital mortality were reduced in patients at risk for POI who received alvimopan compared with matched controls. Similarly, in a study of patients undergoing radical cystectomy, the prolonged length of stay (≥ 7 days) was significantly lower for patients receiving alvimopan compared with that for those receiving placebo (32.9% vs 51.5%; P < 0.01).

Conflicting data, however, have been reported regarding the utility of alvimopan in patients undergoing surgery with intestinal anastomosis. In a recent small retrospective analysis of alvimopan (n = 55) and matched controls (n = 58), the authors found no significant difference in length of hospital stay (4.6 vs 4.8 days; P = 0.72) or mean time to return to bowel function (68.5 vs 67.3 h; P = 0.83). This study demonstrated that patients treated with alvimopan incurred significantly greater charges for medical and surgical supplies, pathology and cytology services, operating room charges, and therapy charges (P < 0.05). However, these increases in costs were largely associated with surgical time and a shift in hospital-wide accelerated recovery efforts; they may also be due to differences in surgical complexity between groups. Nevertheless, this suggests that patient selection is important in deciding who should receive ERAS interventions, including PAMORAs, such as alvimopan.

Alvimopan Safety

In the majority of studies evaluating the safety and efficacy of alvimopan, the exclusion criteria prohibited preoperative use of opioids. As such, alvimopan is contraindicated in patients who are taking therapeutic doses of opioids for greater than 7 days before starting alvimopan.
Table 2  Summary of efficacy data from alvimopan and methylnaltrexone pivotal clinical trials²⁸, ²⁹, ³¹–³³, ⁴¹–⁴³

| Study      | Study design                                  | Type of surgery                                      | Constipation type | Drug administration                                      | Endpoint(s)                                      | Treatments                      | Endpoint result |
|------------|-----------------------------------------------|-----------------------------------------------------|-------------------|----------------------------------------------------------|-------------------------------------------------|---------------------------------|-----------------|
| Wolff et al. 2004 | Phase 3, randomized, double-blind, placebo-controlled | • Partial bowel resection with primary anastomosis  
• Radical hysterectomy | POI        | • Oral  
• 2 h before surgery  
• After surgery, BID until discharge or for maximum of 7 days | Mean GI3, hour  
Mean GI2, hour  
Mean hospital discharge order written, hour | • Placebo  
• Alvimopan 6 mg  
• Alvimopan 12 mg  
• Placebo  
• Alvimopan 6 mg  
• Alvimopan 12 mg  
• Placebo  
• Alvimopan 6 mg  
• Alvimopan 12 mg  
• Placebo  | 120  
105; P < 0.05  
98; P < 0.001  
133  
113; P = 0.013  
105; P < 0.001  
146  
133; P = 0.070  
126; P = 0.003 |
| Delaney et al. 2005 | Phase 3, randomized, double-blind, placebo-controlled | • Segmental colon resection  
• Simple or radical hysterectomy | POI        | • Oral  
• 2 h before surgery  
• After surgery, BID until discharge or for maximum of 7 days | Mean GI3, hour  
Mean hospital discharge order written, hour | • Placebo  
• Alvimopan 6 mg  
• Alvimopan 12 mg  
• Placebo  
• Alvimopan 6 mg  
• Alvimopan 12 mg  
• Placebo  
• Alvimopan 6 mg  
• Alvimopan 12 mg  
• Placebo  | 100.3  
86.2; P = 0.003  
92.8; P = 0.059  
122  
108; P < 0.001  
115; P = 0.17  
224  
220; P = 0.037*  
221; P = 0.028* |
| Viscusi et al. 2006 | Phase 3, randomized, placebo-controlled, parallel group | • Bowel resection or total abdominal hysterectomy | POI        | • Oral  
• 2 h before surgery  
• After surgery, BID for 7 days | Mean GI3, hour  
Mean hospital discharge order written, hour | • Placebo  
• Alvimopan 6 mg  
• Alvimopan 12 mg  
• Placebo  
• Alvimopan 6 mg  
• Alvimopan 12 mg  
• Placebo  
• Alvimopan 6 mg  
• Alvimopan 12 mg  
• Placebo  | 55.4  
53.5; P = NS  
92.0  
71.8; P < 0.001  
68.6  
66.3; P = NS  
92.6 (3.06)  
84.2 (2.37); P = NS  
87.8 (2.68); P = NS  
109.5 (3.41)  
95.2 (2.40); P < 0.001  
98.8 (2.71); P = 0.008  
112  
92; P < 0.001  
98  
82; P = NR  
138  
120; P < 0.001 |
| Herzog et al. 2006 | Phase 3, randomized, double-blind, placebo-controlled | • Simple hysterectomy | POI        | • Oral  
• 2 h before surgery  
• After surgery, BID for 7 days | Mean GI3, hour  
Mean hospital discharge order written, hour | • Placebo  
• Alvimopan 12 mg  
• Placebo  
• Alvimopan 12 mg  
• Placebo  
• Alvimopan 12 mg  
• Placebo  
• Alvimopan 12 mg  
• Placebo  | 55.4  
53.5; P = NS  
92.0  
71.8; P < 0.001  
68.6  
66.3; P = NS  
92.6 (3.06)  
84.2 (2.37); P = NS  
87.8 (2.68); P = NS  
109.5 (3.41)  
95.2 (2.40); P < 0.001  
98.8 (2.71); P = 0.008  
112  
92; P < 0.001  
98  
82; P = NR  
138  
120; P < 0.001 |
| Buchler et al. 2008 | Phase 3, randomized, double-blind, placebo-controlled | • Small or large bowel resection with primary anastomosis | POI        | • Oral  
• 2 h before surgery  
• After surgery, BID until discharge or for a maximum of 7 days | Mean GI3 (SE), hour  
Mean GI2 (SE), hour  
Mean hospital discharge order written, hour | • Placebo  
• Alvimopan 12 mg  
• Placebo  
• Alvimopan 12 mg  
• Placebo  
• Alvimopan 12 mg  
• Placebo  
• Alvimopan 12 mg  
• Placebo  | 55.4  
53.5; P = NS  
92.0  
71.8; P < 0.001  
68.6  
66.3; P = NS  
92.6 (3.06)  
84.2 (2.37); P = NS  
87.8 (2.68); P = NS  
109.5 (3.41)  
95.2 (2.40); P < 0.001  
98.8 (2.71); P = 0.008  
112  
92; P < 0.001  
98  
82; P = NR  
138  
120; P < 0.001 |
| Ludwig et al. 2008 | Phase 3b, randomized, double-blind, placebo-controlled | • Small or large bowel resection with primary anastomosis | POI        | • Oral  
• 30 to 90 min before surgery  
• After surgery, BID until discharge or for up to a maximum of 7 days | Mean GI2, hour  
Mean hospital discharge order written, hour | • Placebo  
• Alvimopan 12 mg  
• Placebo  
• Alvimopan 12 mg  
• Placebo  
• Alvimopan 12 mg  
• Placebo  
• Alvimopan 12 mg  
• Placebo  | 55.4  
53.5; P = NS  
92.0  
71.8; P < 0.001  
68.6  
66.3; P = NS  
92.6 (3.06)  
84.2 (2.37); P = NS  
87.8 (2.68); P = NS  
109.5 (3.41)  
95.2 (2.40); P < 0.001  
98.8 (2.71); P = 0.008  
112  
92; P < 0.001  
98  
82; P = NR  
138  
120; P < 0.001 |
| Study          | Study design                                      | Type of surgery    | Constipation type | Drug administration | Endpoint(s)                                                                 | Treatments                          | Endpoint result |
|---------------|--------------------------------------------------|--------------------|-------------------|---------------------|-----------------------------------------------------------------------------|-------------------------------------|-----------------|
| Methylnaltrexone | Anissian et al. 2012 Phase 2, randomized, double-blind, placebo-controlled | Orthopedic surgery | Acute-onset OIC   | SC, QD for up to 4 or 7 days | Median time to first bowel movement, hour | Placebo, Methylnaltrexone 12 mg | 50.9, 15.8; P = 0.02 |
| Viscusi et al. 2013 Phase 2, randomized, double-blind, placebo-controlled | Segmental colectomy | POI                  | IV                | Within 90 min after surgery, Every 6 h thereafter until patient tolerates solid food for 24 h, is discharged, or for a maximum of 7 days | Mean time to first bowel movement (SD), hour | Mean discharge eligibility (SD), hour | Placebo, Methylnaltrexone 0.30 mg/kg | 118.1 (10.3), 98.0 (5.7); P = 0.038 |
| Yu et al. 2011 Phase 3, randomized, double-blind, placebo-controlled (2 studies) | Segmental colectomy | POI                  | IV                | Within 90 min after surgery, Every 6 h thereafter until 24 h after the return of bowel function, discharge, or for a maximum of 10 days | Median time to first bowel movement, days: Study 1 | Median time to first bowel movement, days: Study 2 | Placebo, Methylnaltrexone 12 mg, Methylnaltrexone 24 mg | 4.23, 4.14; 3.88, 4.52; 4.61, P = NS |

BID twice daily, IV intravenous, NR not reported, NS not significant, OIC opioid-induced constipation, POI postoperative ileus, QD once daily, SD standard deviation, SE standard error, SC subcutaneous

* After adjustment for multiple comparisons
alvimopan label warns that recent exposure to opioids may increase the risk of abdominal pain, nausea, vomiting, and diarrhea since patients recently exposed to opioids may be more sensitive to the effects of PAMORAs.\textsuperscript{27}

The duration of treatment with alvimopan is limited to short-term use in the hospital (15 doses) as noted in the boxed warning within the label.\textsuperscript{27} As such, an FDA risk evaluation and mitigation strategy is required to ensure that alvimopan use is restricted to the hospital setting.\textsuperscript{27} Secondly, the box warning also states that the incidence of MI was greater in patients receiving alvimopan compared with those receiving placebo in a 12-month study of patients treated with opioids for chronic noncancer pain.\textsuperscript{25} The increased incidence of MI and cardiovascular events with long-term treatment was not significantly different between treatment groups, but there was a numeric difference noted between groups.\textsuperscript{39} MI and cardiovascular events were suffered by 7 (1.3\%) and 14 (2.6\%) patients who received alvimopan, respectively, compared with 0 (0\%) and 3 (1.1\%) patients who received placebo, respectively. All events occurred in patients who were at a high risk for or had established cardiovascular disease.\textsuperscript{39}

While this was originally thought to be an overall function of the drug class, subsequent phase 3 and dedicated long-term safety studies of alvimopan in POI have failed to identify any increased risk for cardiovascular adverse events.\textsuperscript{36, 37} Importantly, unlike the increased cardiovascular risks observed in the 12-month study, there was no increased risk of MI observed in short-term trials (up to 7 days) with alvimopan.\textsuperscript{27}

**Methylnaltrexone (Relistor®)**

Methylnaltrexone (formulated as a subcutaneous [SC] and oral dosage) is a PAMORA indicated for the treatment of OIC in adults with chronic noncancer pain, including patients with chronic pain related to prior cancer who are on a stable opioid dose.\textsuperscript{40} SC methylnaltrexone is also indicated for the treatment of OIC in adults with advanced illness or active cancer who require an increase in opioid dose for palliative care (Table 1).\textsuperscript{40}

For OIC in patients with chronic noncancer pain, methylnaltrexone is given as an SC injection of 12 mg SC once daily or an oral 450-mg dose in the morning. For patients with advanced illness, the SC methylnaltrexone dosage is based on body weight and administered once every other day as needed.\textsuperscript{40} Patients who weigh 38 to <62 kg should receive an 8-mg dose, and patients who weigh 62 to 114 kg should receive a 12-mg dose. Those who fall outside this weight range should receive a dose of 0.15 mg/kg.\textsuperscript{40}

While neither the injection nor the oral formulation of methylnaltrexone is indicated for POI or postoperative OIC,\textsuperscript{40} trials have been conducted in the postsurgical setting for both potential indications.\textsuperscript{41–43} These studies and their results are summarized in Table 2 and discussed below.

**Methylnaltrexone Efficacy and Safety**

A double-blind, randomized, parallel-group, placebo-controlled phase 2 study was performed to assess the safety and efficacy of SC methylnaltrexone in patients with acute-onset OIC after orthopedic surgery.\textsuperscript{41} In this small study, patients received once-daily medication, either methylnaltrexone 12 mg (n = 18) or placebo (n = 15), for up to 4 or 7 days.\textsuperscript{41} At 2 and 4 h postinjection, a significantly higher percentage of methylnaltrexone-treated patients achieved laxation (bowel movement) versus placebo (2 h, 33.3\% vs 0\%; P = 0.021; 4 h, 38.9\% vs 6.7\%; P = 0.046) (Table 2).\textsuperscript{41} Time to response was also significantly reduced with SC methylnaltrexone treatment versus placebo (median 15.8 h vs 50.9 h, P = 0.02).\textsuperscript{41} In addition, the rates of adverse events (AEs) were similar between the 2 groups, with 33.3\% and 26.7\% of patients in the SC methylnaltrexone and placebo groups, respectively, reporting at least 1 treatment-emergent AE.\textsuperscript{41} Most AEs reported were GI-related and considered to be possibly related to the study medication.\textsuperscript{41} No cardiac AEs were reported and no safety signals or pattern of concern was visualized by ECG,\textsuperscript{41} suggesting that methylnaltrexone exposure does not share the same cardiac risks and precautions as alvimopan. These results demonstrated that SC methylnaltrexone was effective in improving GI recovery and was generally well-tolerated in patients with acute-onset OIC.\textsuperscript{41}

Another phase 2, double-blind, randomized, controlled trial conducted in adults with POI after undergoing segmental colectomy showed that intravenous (IV) methylnaltrexone (0.30 mg/kg in 50 mL of saline; n = 33), compared with placebo (n = 32), significantly decreased the time to first bowel movement.\textsuperscript{42} The study medication was administered within 90 min following the surgical procedure and was repeated every 6 h until solid food was tolerated for 24 h; the patient was discharged, or the patient had received treatment for a maximum of 7 days.\textsuperscript{42} Compared with placebo, IV methylnaltrexone significantly accelerated the mean time to first bowel movement by 20 h (98.0 vs 118.1 h; P = 0.038) and reduced the mean time to discharge eligibility by 33 h (116.1 vs 148.7 h; P = 0.049).\textsuperscript{42} In this study, methylnaltrexone was generally well-tolerated. In fact, GI AEs, including nausea, vomiting, and abdominal pain, were more frequently reported in the placebo group compared with those in the IV methylnaltrexone group.\textsuperscript{42} Notably, the incidence of POI was reduced 2-fold in IV methylnaltrexone–treated patients compared with those receiving placebo (6\% vs 16\%).\textsuperscript{42}

In a recent retrospective analysis of patients who underwent robotic-assisted radical cystectomy for bladder cancer, length of hospital stay, time to flatus and bowel movement, a composite of GI symptoms, episodes of severe pain,
and daily opioid utilization were evaluated comparing SC methylaltrexone (8 mg in patients < 65 kg and 12 mg in patients ≥ 65 kg; n = 29) with controls (n = 29). The median length of hospital stay was significantly reduced with methylaltrexone treatment compared with the control group (4 vs 7 days, P < 0.01), which contributed to a significant reduction in the total cost of hospital stay by more than $10,500 USD per patient. The use of methylaltrexone did not impact daily opioid usage or daily pain scores. In fact, there was a reduction in the number of severe pain episodes observed in methylaltrexone-treated patients. Although there were no significant differences in the median time to flatus or bowel movement between patients who received methylaltrexone compared with those patients in the control group, patients receiving methylaltrexone had significantly fewer GI complications (methylaltrexone cohort [10.3%] vs no methylaltrexone cohort [44.8%], P < 0.01). The authors suggested that this finding may imply that the reduction of GI symptoms (bloating, distention, or discomfort) may be a factor in accelerated patient discharge.

### Potential Factors Contributing to Lack of Efficacy of Methylaltrexone in the Treatment of POI in Phase 3 Trials

The efficacy demonstrated in phase 2 trials could not be replicated in larger phase 3 trials. These phase 3 efficacy results were unexpected given the promising data from several phase 2 trials, but multiple factors may have contributed to the perceived lack of efficacy, some of which are reviewed here (Table 3).

| Table 3 | Potential factors contributing to lack of efficacy of methylaltrexone in the treatment of POI in phase 3 trials |
|---------|---------------------------------------------------------------|
| Total amount of opioid administered to patients is not reported and may not have been sufficient to activate μ-opioid receptors |
| Multimodal treatment approaches and postoperative care may not have been matched between treatment groups |
| Endpoint selection may factor into observed lack of efficacy |
| Prior use of opioids may have saturated μ-opioid receptors, leading to ineffective methylaltrexone treatment |
| Dosing was inconsistent across studies; IV methylaltrexone may not be the best route of administration for POI |
| Genetic polymorphisms and concomitant drug usage may produce interpatient variability |

Although data on the use of methylaltrexone in POI or postoperative OIC without new safety concerns, suggesting that methylaltrexone is safe and effective to use in the long term.

### Long-term Use and Effects on Survival in Methylaltrexone Studies for OIC

Long-term use of methylaltrexone in patients with noncancer pain and OIC who received SC methylaltrexone 12 mg daily for 48 weeks was assessed in a phase 3 open-label trial. A significant increase in mean weekly bowel movement rate change from baseline (P < 0.001) was observed through the entire 48-week period. Similar to other studies of shorter duration, GI-related AEs were the most commonly reported AEs (i.e., abdominal pain 24.0%, diarrhea 16.4%, nausea 15.1% of patients). These rates are consistent with a long-term open-label study that found that GI-related AEs ranged from 15.5 to 19.3%. This study demonstrated that SC methylaltrexone provided consistent long-term treatment for OIC without new safety concerns, suggesting that methylaltrexone is safe and effective to use in the long term.
A retrospective post hoc analysis of data pooled from 2 independent randomized, placebo-controlled clinical trials of SC methylnaltrexone in patients with advanced terminal cancer and OIC assessed whether treatment could influence survival. This analysis demonstrated that SC methylnaltrexone significantly increased the median overall survival compared with placebo (76 days, 95% confidence interval [CI] 43–109, vs 56 days, 95% CI 43–69; \( P = 0.033 \)), indicating that methylnaltrexone may have an impact beyond relief of constipation, including a direct effect of methylnaltrexone on cellular targets related to the morphine receptor. Morphine antagonists have been shown to reduce tumor growth in several cancers in vivo models.

### Other PAMORAs

Naloxegol and naldemedine are two other PAMORAs indicated for the treatment of OIC in patients with chronic noncancer pain, but do not have an indication for POI. Although no studies have been conducted in POI treatment, a small study has been published in POI prevention. In an active comparator analysis, perioperative administration of naloxegol was compared with alvimopan among adult patients with bladder cancer who underwent a radical cystectomy. Among 130 patients, no differences were observed between those receiving naloxegol or alvimopan with respect to the development of POI or hospital length of stay. The authors postulated that although no other studies have been conducted with naloxegol, this active comparator study may help support the use of naloxegol as a less expensive alternative to alvimopan. To date, data evaluating the use of naldemedine for OIC in the surgical setting or for the treatment or prevention of POI have not been published.

### Future Direction

Presently, with the exception of the small naloxegol versus alvimopan analysis, direct comparisons between PAMORAs are not possible because comparator studies between these agents have not been performed. Head-to-head studies are needed to make definitive conclusions as protocols and endpoints differ among the various studies.

The pathophysiology of POI is multifactorial and not exclusively related to opioid ligands. Therefore, a multimodal treatment strategy that takes into account inhibition of \( \mu \)-opioid receptors with PAMORAs, while including a variety of techniques or interventions with other mechanisms of action, may be needed. It is likely that the use of PAMORAs concurrently with these adjunct therapies will result in clinically meaningful acceleration of GI recovery after surgery beyond what can be achieved by any single intervention alone.

### Conclusions

Pharmacologic options for the treatment or prevention of POI are limited. Currently, alvimopan is the only PAMORA approved for POI that improves GI recovery after surgery and reduces the length of hospital stay. Although methylnaltrexone is not indicated for POI, studies have shown that it effectively reverses unwanted opioid-induced GI side effects while preserving CNS-mediated analgesia in specific surgical settings. Further studies with methylnaltrexone are warranted to determine its utility in prevention and/or treatment of POI. Given the inconsistencies observed between current studies, future trial designs should be carefully considered in order to evaluate efficacy.

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