Postoperative ileus negatively impacts patient outcomes and healthcare utilization, increasing both postoperative length of stay and healthcare costs. In efforts to optimize perioperative care, efforts have been placed into developing tools to minimize postoperative ileus. Alvimopan (Entereg®) was developed to meet this need. Alvimopan has permitted accelerated return of bowel function after abdominal surgery in select patients. Alvimopan has the potential to significantly improve clinical and financial results, and research is ongoing to determine effective further applications of this medication.

Keywords: alvimopan • enhanced recovery pathways • entereg • postoperative ileus

Postoperative ileus (POI) is defined as the transient cessation of coordinated bowel motility after surgical intervention, which prevents effective transit of intestinal contents and/or tolerance of oral intake [101]. Organ recovery following major abdominal surgery generally occurs in less than 24 h for small bowel, 24–48 h for the stomach and 48–120 h for the colon [1,2]. Thus, return of normal bowel function is expected within three to five days for laparoscopic and open surgery, respectively. When this fails to occur within this expected time frame, POI is clinically diagnosed. Out of the 22 million inpatient surgeries performed annually in the USA, an estimated 2.7 million are complicated by a delay in return of bowel function [3]. POI is especially common following colorectal surgery, occurring in up to 25% of patients [4].

The pathophysiology of POI remains poorly understood, but involves a complex interaction of neurologic, hormonal, inflammatory and mechanical factors regulating the GI tract [1,5,6]. Direct bowel manipulation, edema from surgery, and inhaled anesthetics have all been shown to impact postoperative bowel function [2,7,8]. In addition, narcotic analgesics, common in the perioperative period, peripherally bind to receptors within the GI tract and slow motility [9,10]. These effects are most pronounced in the colon, as there is less intrinsic enteric stimulation than in other parts of the GI tract [11].

There are proven clinical and financial implications of POI [12]. For patients, nausea, vomiting and abdominal discomfort are the most common complaints; these symptoms contribute to patient morbidity, frustration and reduced quality of life. POI is a major driver of delayed hospital discharge, increased length of stay (LOS), and the resulting healthcare utilization [13,14]. The effects on healthcare costs have also been documented. POI has been estimated to account for 6.25% of total hospital costs in the USA, and review of the Health Care Financing Administration’s 1999–2000 database estimated POI contributes US $1.14 billion annually [101,102].

This review discusses current evidence for the use of alvimopan (Entereg®, Adolor and GlaxoSmithKline, PA, USA) as a pharmacologic adjunct to reduce POI in patients undergoing bowel resections. A systemic PubMed search was performed with the keywords “alvimopan” combined with “postoperative ileus”, “bowel resection”, "enhanced recovery pathways" and "clinical trial outcomes".
‘laparoscopy’ and ‘recovery pathway’. Additional relevant publications were identified from the references of selected studies, and from the authors’ personal databases. Inclusion of papers was decided by consensus of the authors with a focus on large scale and sound Phase II and III studies in open and laparoscopic bowel resections.

Enhanced recovery pathways & laparoscopic surgery
Effective methods to reduce POI and LOS have been developed. To date, the most effective method in reducing POI and its associated LOS is laparoscopic colorectal surgery. Several randomized-controlled trials, systematic reviews, and large-scale trials have proven the benefits of laparoscopic colorectal surgery in accelerating gastrointestinal recovery and shorter average LOS by 2–3 days following colorectal surgery [15–21]. While laparoscopic surgery may decrease the incidence of POI through decreased bowel manipulation and sympathetic stimulation, it does not eliminate the problem [16, 22]. Standardized fast track or enhanced recovery pathways (ERP) have also successfully reduced LOS. Protocols exist for multiple fields of surgery, and incorporate elements including reduction in perioperative fluids, early oral refeeding, early mobilization, minimization of narcotics, and pharmacologic treatment of ileus to reduce time to return of bowel function [23, 24, 103]. ERP have demonstrated consistent reductions in POI and hospital LOS when compared to open surgery [16, 23, 25]. Several studies have shown that the implementation of an ERP reduced LOS from 7–10 days to approximately 4 days following colorectal surgery [16, 17, 19, 26–28]. The combination of laparoscopy with an ERP further optimizes short-term outcomes and healthcare utilization. Both randomized controlled and single-institution studies demonstrated additional significant reductions in mean LOS using laparoscopy with a standardized ERP [16–21].

Alvimopan

■ Background & pharmokinetics
Pharmacologic adjuncts have been attempted to further reduce or eliminate POI [29, 30]. Beta blockers, neostigmine and cisapride were all trialed to speed return of bowel function; results were mixed and significant side effects, notably cardiovascular events and abdominal cramping, limited their efficacy and use [31, 32]. While successful in managing postoperative nausea and emesis, metoclopramide was not effective in reducing POI [33]. Newer medications have aimed to counteract the gastrointestinal slowing caused by endogenous and exogenous narcotics. The most promising and clinically proven medication to date is alvimopan.

Alvimopan is a systemically absorbed, peripherally acting µ-opioid antagonist with high affinity for human µ-opioid receptors. Due to its size and structure, this drug does not cross the blood-brain barrier and thus provides selective opioid antagonism within the GI tract without affecting the efficacy of centrally acting analgesia [34]. The drug was approved by the US FDA in May 2008 for patients scheduled to undergo small or large bowel resection via laparotomy [35]. Contraindications include chronic opioid use, bowel obstruction and severe renal or hepatic failure. Recommended dosing is 12 mg by mouth within 2 h of surgery, then twice daily until discharge for a maximum of 7 days (15 doses). Alvimopan has been proven safe and generally well tolerated; the most common side effects are dyspepsia, hypokalemia, back pain and urinary retention [36–38, 104]. In early studies with long-term, low-dose use, there was an observed, but insignificant increase in cardiovascular events [36, 37]. However, no causative link has ever been established and the effect has not been reproduced in any other study, or noted in any short-term use study. To ensure the safety of the drug, alvimopan carried a black box warning and is approved under a Risk Evaluation and Mitigation Strategy, which limits use to short term (less than 15 doses) and inpatients in hospitals enrolled in the Entereg Access Support & Education program [105]. Because of this limited availability, it has not been universally implemented into many standard ERPs, but rather is used as an adjunct to them, when available for appropriate patients. Contraindications include chronic opioid use, bowel obstruction, and severe renal or hepatic failure.

■ Cost–effectiveness
The cost benefits of alvimopan have been evaluated when hospital LOS was reduced about 1 day. A cost analysis study of the US studies estimated the average cost of the addition of alvimopan to be $558, with a mean reduction in hospitalization by 1.2 days, and a mean savings of $879–977 per patient [26]. Analysis using a national database showed a significant reduction in total hospital costs of $2345 per patient with the addition of alvimopan (p < 0.0001) [38]. The cost reduction remained significant when open and laparoscopic cases are analyzed separately, with savings of $3218 (p < 0.0001) and $1382 (p = 0.0008) respectively. When analyzing prospective and historical data, Absher et al. confirmed cost savings of both open ($997 per case) and laparoscopic cases ($531 per case) [39].

■ Alvimopan & open colorectal surgery
Multiple randomized-controlled trials support the use of alvimopan for patients undergoing open colorectal surgery to reduce time to gastrointestinal recovery. Major Phase II and III studies are summarized in Table 1. Taguchi et al. published the results of the first double-blind prospective trial of use of alvimopan in 78 postoperative patients in 2001 [40]. In this Phase II single-institution study, patients undergoing elective total abdominal hysterectomy or open surgery
colocotomy was excluded. Postoperative management was identical to the previous study. In total, 469 patients were enrolled with the vast majority undergoing large (84%) or small (12%) bowel resections. Results showed a significant decrease in time to gastrointestinal recovery in both treatment arms, with a decrease of 15 h in the 6-mg alvimopan group (p = 0.05) and 22 h for those receiving 12 mg (p < 0.001). As with previous studies, pain scores and adverse events were similar between groups. In addition, significantly fewer patients in the 12-mg alvimopan group required nasogastric tube placement compared with placebo. Viscusi conducted a separate trial with a similar design [42]. While initial results did not show significant change in time to bowel function, pain scores, or adverse events between groups, alvimopan significantly reduced time to gastrointestinal recovery by 7.5 h for the 6-mg group (p = 0.037) and 9.9 h for 12 mg (p = 0.008).

Analysis of pooled data from the three US studies showed a clear benefit from alvimopan in terms of return of bowel function [43]. All 1212 patients from the previous studies undergoing bowel resection were compared, showing significantly decreased time to return of bowel function (GI-3) of 12.4 and 14.8 h for both 6- and 12-mg alvimopan groups, respectively (p = 0.001 and p < 0.001).

**Table 1. Summary of major Phase II/III alvimopan studies in open surgery.**

<table>
<thead>
<tr>
<th>Trial (year)</th>
<th>Phase</th>
<th>Enrolled (n)</th>
<th>Alvimopan dosages versus placebo (mg)</th>
<th>Gastrointestinal recovery (hazard ratio)</th>
<th>Discharge (hazard ratio)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taguchi et al. (2001)</td>
<td>II</td>
<td>78</td>
<td>1 6</td>
<td>1.2 (p = 0.59) 2.9 (p = 0.01)</td>
<td>1.2 (p = 0.48) 2.0 (p = 0.008)</td>
<td>[40]</td>
</tr>
<tr>
<td>Delaney et al. (2005)</td>
<td>III</td>
<td>451</td>
<td>6 12</td>
<td>1.45 (p = 0.003) 1.28 (p = 0.059)</td>
<td>1.50 (p &lt; 0.001) 1.18 (p = 0.17)</td>
<td>[41]</td>
</tr>
<tr>
<td>Wolff et al. (2004)</td>
<td>III</td>
<td>469</td>
<td>6 12</td>
<td>1.28 (p &lt; 0.05) 1.54 (p &lt; 0.001)</td>
<td>1.25 (p = 0.070) 1.42 (p = 0.003)</td>
<td>[27]</td>
</tr>
<tr>
<td>Viscusi et al. (2006)</td>
<td>III</td>
<td>665</td>
<td>6 12</td>
<td>1.24 (p = 0.037) 1.26 (p = 0.028)</td>
<td>1.36 (p = 0.002) 1.30 (p = 0.010)</td>
<td>[42]</td>
</tr>
<tr>
<td>Buchler et al. (2008)</td>
<td>III</td>
<td>911</td>
<td>6 12</td>
<td>1.22 (p = 0.042) 1.13 (p = 0.20)</td>
<td>1.08 (p = 0.47) 1.07 (p = 0.49)</td>
<td>[44]</td>
</tr>
</tbody>
</table>
In addition, time to tolerance of solid food and first bowel movement (GI-2 recovery) was reduced 15 and 18.3 h respectively as was time to discharge order, which was reduced by 16 and 18.4 h (p < 0.001 for all). There was no change in pain scores, opioid usage or adverse events. Need for nasogastric tube, prolonged ileus and hospital readmission rates were lower in both treatment groups compared with placebo.

A multicenter European trial conducted at 70 hospitals across 11 countries evaluated patients undergoing bowel resection [44]; results showed a nonsignificant decrease in GI-3 recovery for both treatment groups (p = 0.042 and p = 0.20). Notably, this study varied from the others with much lower use of opioid analgesia with some patients receiving none at all. The difference between the results of this study and those in North America is likely related to the fact that there was such wide difference in practices between different centers in different countries, even within the constraints of a well structured trial. Even so, pooled analysis of the European study, the three US studies, and an additional American trial still demonstrated alvimopan significantly speeded GI-3, GI-2 and time to discharge in all subgroups regardless of gender, age or ethnicity (p < 0.05 for all) [45]. This analysis also showed retained benefits in subgroups receiving antibiotics, proton pump inhibitors, histamine antagonists and those that underwent mechanical bowel preparation, all interventions that had previously been reported to decrease the drugs pharmacokinetics [46]. An additional meta-analysis demonstrated similar benefits of alvimopan over placebo with no increase in pain scores or adverse events [47]. Most recently, a pooled post hoc responder analysis of the multicenter, randomized, controlled, double-blind, Phase III trials found alvimopan significantly accelerated the proportion of patients who achieved GI-2 and GI-3 recovery on each postoperative day (p < 0.001 for each) and decreased LOS (mean for alvimopan, 5.2 days; mean for placebo, 6.2 days) compared with a standardized accelerated postoperative care pathway [48]. Furthermore, there was a small number needed to treat (NNT = 7) to achieve risk reduction in POI and reduced LOS in one patient.

Despite these demonstrations of the benefits of alvimopan in open colorectal surgery, some are still concerned that the benefit of the medication may be overshadowed by a greater reduction in POI and hospital stay provided from implementation of an ERP [15,22,23]. This may or may not be true, and alvimopan has yet to be evaluated in comparison to the ‘European style’ ERP including a thoracic epidural. The randomized trials all used a perioperative care pathway based on that used in one of the earliest colorectal ERP paper by Delaney and colleagues in 2001 [25]. In this paper Delaney achieved a LOS of 4.3 days for patients having major open colorectal surgery without epidurals, as good as any open ERP program since then, with or without epidurals. The nonsignificant results of the European study may be related to opioid sparing, but may also be related to variability between centers [44]. While clearly effective at reducing POI and LOS for open surgery, future studies will likely evaluate its role as ERP continue to evolve.

**Alvimopan & laparoscopic surgery**

The role of alvimopan in laparoscopic abdominal surgery is less clear. Laparoscopy is now used in more than 40% of bowel resections, and the use is continuing to expand [20,49]. Laparoscopy significantly reduces LOS (p < 0.0001) and total hospital costs (p = 0.0007) compared with open colectomy patients [16]. To date, the existing literature has shown mixed results of alvimopan’s efficacy in laparoscopic surgery with some demonstrating similar reductions in POI and LOS as seen in open cases, while others showed no significant benefit. In a retrospective case series review of 165 patients, Itawi et al. found alvimopan significantly decreased hospital LOS by 1.55 days and POI from 20 to 2% (p < 0.0001) when added to a standard ERP in elective laparoscopic colectomy patients [50]. Then, a national matched-cohort study of over 7000 patients found postoperative LOS and direct hospital costs were lower for all alvimopan patients and the laparoscopic cohort specifically after bowel resection (p ≤ 0.0008 for each) [38].

However, other studies demonstrated no measurable benefit. A recent case-matched study from our unit evaluating outcomes of 100 elective laparoscopic segmental colectomy patients with and without alvimopan found no significant reduction in LOS (p = 0.84), but a significant reduction in the rate of POI in the alvimopan group (p = 0.04) [51]. The nonsignificant difference may have been related to the fact that LOS was so short in the placebo group, and the authors’ opinion is that when a fully optimized ERP is used in conjunction with minimally invasive surgery and standardized discharge criteria, then changes in LOS may not be achieved. Another multi-armed study of 282 patients confirmed the benefit in open cases, but also failed to show significant decrease in LOS or POI in laparoscopic cases [52]. Thus, the use of laparoscopy and ERP could reduce LOS to the point that no further benefit can be obtained with the addition of alvimopan in this population. Further prospective studies should be performed to determine if a true benefit exists in laparoscopic patients.

**Future perspective**

The benefits of alvimopan in open bowel resections is well established and it has become implemented in conjunction with many standard ERPs. While national data suggest a potential benefit in laparoscopic surgery, further prospective and large-scale randomized control trials are
needed before definitive recommendations can be made. The efficacy of alvimopan in conjunction with epidural opioid anesthesia after bowel resections has not been studied, and its benefit in patients using epidural based ERP could also bear evaluation. Finally, the role of alvimopan in abdominal surgeries other than bowel resections, as well as use in conditions such as chronic constipation, requires further investigation to elucidate other potential benefits of the drug.

**Financial & competing interests disclosure**

The authors have no relevant affiliations or financial involvement with any organization or entity with any financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

**Executive summary**

**Background**

- Postoperative ileus is a common and costly complication following abdominal surgery.

**Enhanced recovery pathways & laparoscopic surgery**

- Standardized fast-track or Enhanced Recovery Pathways and laparoscopic surgery have been shown to reduce postoperative ileus and hospital length of stay.

**Alvimopan**

- Alvimopan (Entereg®) is a peripherally acting μ-opioid antagonist that clinically reduces the duration of postoperative ileus.
- Alvimopan is currently approved in the USA for patients undergoing small or large bowel resection via laparotomy at approved hospitals.
- Alvimopan has been shown to safely and significantly reduce time to gastrointestinal recovery, length of hospitalization and healthcare costs in patients undergoing open bowel resections.
- The demonstrated benefits were determined using a nonepidural enhanced recovery pathways placebo group, and have yet to be confirmed in epidural based enhanced recovery pathways.
- The role of alvimopan in laparoscopic surgery is less clear as current studies show conflicting results in terms of the reduction of postoperative ileus and hospital length of stay.

**Future perspective**

- Further prospective and large-scale, randomized trials are needed to make definitive recommendations for use with laparoscopic bowel resections and non-bowel resection cases.

**References**

Papers of special note have been highlighted as:

- of interest
- of considerable interest


Meta-analysis showing enhanced recovery pathways reproducibly and safely reduces hospital length of stay and optimizes healthcare utilization.
Review: Clinical Trial Outcomes


41 First Phase II trial to show significant benefit of alvimopan.


46 Analysis of all Phase III data, showing effectiveness in all subgroups.


50 Post hoc responder analysis of Phase III trials.

Alvimopan & enhanced recovery pathways in colorectal surgery


### Websites


102 Consensus summary of current postoperative ileus data, including the current definition of postoperative ileus, “the transient cessation of coordinated bowel motility after surgical.”

103 ERAS society guidelines.
www.erasociety.org/index.php/eras-guidelines

104 Entereg – Adverse Reactions (2012).
www.entereg.com/content/adverse_reactions

105 Entereg Initial rems approval (2008).