The Impact of Postoperative Ileus and Emerging Therapies

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ABSTRACT

Postoperative ileus (POI) is a temporary impairment of gastrointestinal (GI) function that follows surgery, especially abdominal laparotomy. The duration of POI is variable, and prolonged POI can delay return to normal function for affected patients. Prolonged POI is associated with increased hospital costs and length of hospital stay. Because no consensus management strategies exist, there is clearly an unmet medical need for effective therapies such as peripherally acting mu-opioid receptor (PAM-OR) antagonists to accelerate GI recovery.

Key words: alvimopan, ADL 8-2698, PAM-OR, peripherally acting mu-opioid receptor antagonist, pharmacoeconomics, postoperative ileus, surgical complications

INTRODUCTION

Postoperative ileus (POI) is a temporary impairment of gastrointestinal (GI) motility that occurs, at least to some degree, after most surgical procedures. The signs and symptoms of POI include abdominal pain and distention, nausea and vomiting, and delayed passage of flatus or stool. The duration of POI may vary, and "prolonged" POI (ileus lasting for three days or more) is associated with delayed enteral feeding and an increased risk of other postoperative morbidities, often resulting in extended hospital stays.

GI recovery is often delayed after surgeries that involve entry into the peritoneum or manipulation of the GI tract. Of the approximately 42.5 million inpatient surgical procedures in the U.S. reported in 2002, approximately 30% were performed on the digestive tract. It is therefore likely that POI delays the return to normal bowel function in many patients. Moreover, the additional costs of managing patients with POI have not been extensively reported, but they may extend into millions of dollars annually. Nonetheless, POI remains underdiagnosed, possibly because treatment options to date have been of limited benefit.

The treatment of POI has been challenging because of its complex and multifactorial etiology. One underlying cause is surgical trauma from manipulation of the bowel, which stimulates a multitude of events that result in reduced GI transit.

For instance, catecholamine neurotransmitters are released in response to local anatomi cal irritation and possibly from associated spinal nerves. Cytokines are released from inflammatory cells during abdominal surgery and may contribute to slowing of GI motility. Locally active hormones, such as substance P and vasoactive intestinal peptide, are also released during abdominal surgery, and their antagonism represents a possible mechanism for reducing the duration of POI.

Inadequate perioperative concentrations of intracellular electrolytes necessary for smooth muscle function, especially potassium, calcium, and magnesium, have been associated with POI.

Last, stimulation of opioid receptors within the GI tract by endogenously secreted and pharmacologically administered opioids has been linked to the pathogenesis of POI. In addition to experiencing pain and discomfort, patients with POI may have an increased risk of postoperative problems, especially pulmonary morbidity, and they are often unable to advance their diet after surgery. These patients may receive nasogastric suction to relieve abdominal pressure, and they may require intravenous hydration and parenteral feeding.

Therefore, POI can impede mobilization, delay hospital discharge, and increase hospital costs and utilization of medical care resources.

Despite their efficacy in treating acute constipation, approved laxatives and prokinetic agents have demonstrated only limited utility in the POI setting. Other approved pharmacological agents for constipation have not been investigated for treating POI. Several strategies, including modified surgical techniques, changes in anesthesia modality, opioid-sparing postoperative analgesia, and optimized multimodal analgesia, have been studied as possible means of accelerating GI recovery. However, few attempts have produced consistent and clinically meaningful benefits for recovery of GI function. Whether the use of alternative modalities of postoperative analgesia would provide meaningful benefits for GI recovery is unknown.

By contrast, combining multiple approaches in a multimodal management plan has yielded promising results. These techniques involve using optimized anesthesia methods and implementing postoperative management protocols that include advancing the diet as tolerated and encouraging ambulation on the first day after surgery. However, the benefits of multimodal management have yet to be confirmed in larger multicenter, randomized, controlled trials and resource-intensive management protocols might not be possible at many treatment centers.

More aggressive postoperative management techniques have been explored, but these have resulted in an increased rate of hospital readmissions in at least one study. Therefore, no single management strategy exists to facilitate GI recovery, and no therapy has been approved by the U.S. Food and Drug Administration (FDA) to reduce the duration of POI.

Disclosure: Dr. Wittbrodt is a member of an advisory board for GlaxoSmithKline and Adolor Corporation.
BURDEN OF ILLNESS

The severity of symptoms associated with POI is correlated with its duration.18 Typically, small-intestine function returns within the first day after surgery; stomach function, within the first two postoperative days; and colon function, within three days.2 Therefore, even during normal GI recovery, the transit of fluid and of secretions through the GI tract is disrupted. Abdominal bloating and swelling may result; these problems are often managed with nasogastric suction, which can further delay GI recovery and increase the risk of fever and pulmonary complications.2 Furthermore, the nasogastric tube (NGT) has been associated with significant patient discomfort.18

POI interferes with normal postoperative recovery and can lead to costly sequelae. Persistent abdominal discomfort and GI complications from POI can result in delayed oral feeding,2 with nutritional consequences such as alterations in metabolic state, impaired nitrogen balance, and low levels of essential nutrients at a time of severe metabolic stress postoperatively.20

Prolonged hospital stays while the patient awaits resolution of POI causes not only increased utilization of health care resources but also a delay in the ability to resume activity, with possible financial and social consequences for the patient.21,22 Moreover, prolonged POI is associated with an increased risk of hospital-acquired (nosocomial) infection and pulmonary complications.9 In severe or prolonged cases of POI, re-admission to the hospital or treatment of related complications may become necessary.19,23

PHARMACOECONOMIC IMPACT AND MANAGEMENT STRATEGIES

In today’s health care climate, an increasing emphasis is being placed on shortening the length of hospital stay (LOS) and containing health care costs for inpatient surgery. Management or reduction of POI has been identified as an area in which meaningful benefits can be achieved.6 No consensus guidelines exist for the optimal management of GI recovery, and postoperative management practices remain inconsistent.24 Moreover, numerous pharmacoeconomics data on POI have been compiled since the report by Woods.18 Although each of these studies has been challenged by the current lack of consensus on definitions for POI and the underreporting of POI in most institutions, all of these studies have demonstrated that POI is a statistically significant and profoundly important factor associated with negative outcomes, a prolonged LOS, and an increased use of resources.25–28

Table 1  Prokinetic Agents Investigated for the Treatment of Postoperative Ileus (POI) in Randomized, Controlled Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect on POI Duration</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propanolol (e.g., InnoPran XL, Reliant)</td>
<td>Inconsistent</td>
<td>Cardiovascular and CNS effects limit its use</td>
</tr>
<tr>
<td>Dihydroergotamine mesylate (e.g., Migranal and DHE 45, Valeant)</td>
<td>Inconsistent</td>
<td>Cardiovascular and CNS effects limit its use</td>
</tr>
<tr>
<td>Neostigmine bromide (Prostigmin, ICN)</td>
<td>Inconsistent</td>
<td>GI and cardiac ADEs limit its use</td>
</tr>
<tr>
<td>Erythromycin (e.g., Ery-Tab, Abbott)</td>
<td>No significant effect</td>
<td>Minimal ADEs when used at doses for prokinetic effects</td>
</tr>
<tr>
<td>Cisapride (Propulsid, Janssen)</td>
<td>Decreased in most trials, but inconsistent</td>
<td>Withdrawn from U.S. markets because of cardiac ADEs</td>
</tr>
<tr>
<td>Metoclopramide (Reglan, Schwarz Pharma)</td>
<td>None</td>
<td>Frequent CNS-related ADEs, especially in the elderly, limit its use</td>
</tr>
<tr>
<td>Cholecystokinin</td>
<td>None</td>
<td>Investigational drug; not approved for U.S. market</td>
</tr>
<tr>
<td>Ceruletide (Tymtran, Pfizer)</td>
<td>Decreased</td>
<td>GI ADEs (nausea/vomiting) limit its use</td>
</tr>
<tr>
<td>Vasopressin (e.g., Pitressin, King; Pressyn, Ferring)</td>
<td>None</td>
<td>Cardiovascular and renal ADEs limit its use</td>
</tr>
</tbody>
</table>

ADEs = adverse drug events; CNS = central nervous system; GI = gastrointestinal. Adapted from Holte K, Kehlet H. Drugs 2002;62(18):2603–2615. With permission from Wolters Kluwer Health.13

International Database Studies

European studies have revealed that although POI is an underrecognized condition, its economic and humanistic impacts are an international problem, especially for patients undergoing GI surgery. An analysis of four separate national databases of European hospitals revealed that although POI is known to be common,1–3 it has been reported in a relatively small proportion of at-risk surgical patients.4 Patients with reported POI had more prolonged hospital stays in each country assessed (median LOS increases of 10 to 14.5 days, by coun-
try) and worse outcomes, compared with patients without reported POI, for approximately a 10-fold increase in mortality rates in each country.29

Moreover, a covariate-adjusted analysis of surgical patients in Germany revealed that POI of more than five days’ duration was an independent variable that significantly correlated with an increased LOS.30 The analysis included the patient’s age, the type of surgery, the presence of tumors, the type of hospital unit, the surgeon’s specialty, the American Society of Anesthesiology’s classification, and the presence of anastomotic leaks. This finding was especially meaningful, given that POI of more than five days’ duration was reported in 52% to 75% of patients after colonic surgery in Germany.29

In an international study of 1,082 patients who underwent colonic resection, patterns of GI recovery were found to be generally similar in Europe and in the U.S.; however, important differences were observed in patient management.31 Notably, 20% of patients were still unable to tolerate a solid diet six to eight days after surgery (depending on the country); thus, all countries included patients who were at an increased risk for prolonged LOS because of delayed GI recovery. However, patients who had undergone colonic resection in Europe were typically discharged from the hospital five to eight days after GI recovery; patients in the U.S. were typically discharged approximately three days after GI recovery.31 Therefore, accelerating GI recovery may have an especially profound effect on LOS in the U.S.

Studies in the United States

Increases in hospital costs and utilization of resources for patients with POI have been reported in two assessments of U.S. hospital records.

In the first analysis, Saunders and colleagues25 used the Premier Perspective® Database, a large national database of hospital discharge records. They identified patient records according to surgical categories (open laparotomy, incisional procedures, non-incisional procedures, thoracic procedures, and orthopedic procedures) and “coded POI” diagnoses using International Classification of Disease-9 (ICD-9) codes (560.1 [paralytic ileus] and 997.4 [digestive system complication]).

In the second analysis, Salvador and associates26 used records from a single university hospital and identified (1) surgical patients who had undergone specific procedures, namely, total abdominal hysterectomy (TAH) and hemicolectomy, and (2) prolonged POI by a review of patients’ charts. Although these analyses used different surgical populations and different criteria for identifying the POI populations, both arrived at the same conclusion: POI is extremely costly to the U.S. health care industry.

In the report by Saunders et al.,25 the incidence of coded POI was 4.25% for the overall study population (N = 806,081) of patients treated in 2002. Open laparotomy was associated with the highest rate of coded POI (9.01%), compared with 3.61% for incisional procedures, 2.39% for non-incisional procedures, 1.44% for orthopedic procedures, and 1.57% for thoracic procedures. The incidence of coded POI in the patients undergoing open laparotomy is consistent with that reported in a small-scale study of open-laparotomy patients at a university hospital (10.5%).27

Without adjusting for baseline status, the researchers found that coded POI was associated with a statistically significant increase of four days in mean LOS (9.3 days vs. 5.3 days for patients with no coded POI; P < .001) and a significant increase of $6,300 in mean total hospital costs ($18,000 vs. $11,700 for patients without coded POI; P < .001) in the overall study population.25 This large incremental cost from coded POI could be related to increases in supportive procedures (e.g., NGT reinsertion, hydration, and parenteral feeding), laboratory assessments, an increased LOS, and a higher number of hospital readmissions.

If the incidence of POI and related costs from this trial are applied to the 42.5 million inpatient surgeries that were reported in 2002, this would translate into more than $11 billion in increased hospital costs from patients with coded POI (i.e., 42.5 million patients times 4.25% of patients with coded POI multiplied by $6,300 in increased mean costs per patient with coded POI).

Two further analyses of the open-laparotomy patients from the Saunders study25 have been presented. Wang et al.32 assessed risk factors for this patient group and calculated the increased burden of coded POI after open laparotomy on national health care resources. They reported a 20% increase in the risk of coded POI for each one-hour increase in operating room time and that opioid-based patient-controlled analgesia (PCA), which has been reported to deliver better postoperative pain control,33,34 was associated with a 39% increase in the risk of coded POI. This is consistent with an earlier report that PCA is associated with an increased incidence of prolonged POI in patients undergoing colectomy.35 This correlation is especially important because PCA is an emerging trend in postoperative pain management in the U.S.36

For the open-laparotomy patients, coded POI was associated with an additional 12.6 days’ LOS and $1,763 in total hospital costs above those recorded for patients without coded POI. This analysis calculated that the national burden of coded POI for open laparotomies was approximately 370,000 extra days of hospitalization and $253 million in total hospital costs.

Senagore and coauthors37 also analyzed risk factors for coded POI and outcomes after open laparotomy. Their analysis confirmed the findings of the Wang report32 that an increased duration of surgery and PCA corresponded with an increased risk of coded POI. However, they also identified advanced age, severe or most severe disease, and the use of epidural opioids as additional risk factors. Along with the financial costs, coded POI was associated with a profound impact on patient outcomes: the in-hospital mortality rates were 2.7% for patients with coded POI, which was significantly higher than the 2.3% rate of in-hospital mortality that was reported for the patients without coded POI.

Salvador et al.26 analyzed medical records for patients who underwent TAH or hemicolectomy at one university hospital. They reported that prolonged POI (ileus lasting for three days or more, as identified by chart review) occurred in approximately 18% of the TAH patients and in 30% of the hemicolectomy patients. This study assessed both humanistic and pharmacoeconomic effects.

Prolonged POI was associated with 1.2 days of abdominal distention for patients undergoing TAH and 3.4 days for those
undergoing hemicolectomy. The median duration of hospital LOS was increased by 3.5 days for TAH patients and by 7.5 days for hemicolectomy patients.

Prolonged POI was also associated with increases of $4,786 for TAH and $13,346 for hemicolectomy in median total hospital costs, compared with the costs for patients without prolonged POI. Although the increased costs per case of prolonged POI are smaller for TAH than for hemicolectomy, TAH is performed much more often. For example, if prolonged POI occurred at a similar rate and with a similar increase in cost in the 420,000 women who undergo TAH each year,38 this condition would be associated with more than $360 million in additional health care costs for TAH procedures alone each year.

In a small study of 88 patients, Artinyan et al.39 compared postoperative morbidity after colorectal surgery. They observed that POI lasting for more than five days was correlated with morbidity more than POI lasting for more than three days in this setting. The analysis identified estimated blood loss, total surgery time, and total postoperative narcotic dose as independent variables that correlated with the duration of POI. It is interesting that four patients (4.5%) required surgical or endoscopic intervention as a result of POI.

**Physician and Postoperative Management Surveys**

Although multimodal therapies might accelerate GI recovery,40,41 these methods have not been widely adopted or uniformly implemented. Moreover, although both early postoperative removal of the NGT and early oral nutrition result in faster postoperative GI recovery and increased patient comfort,42–47 these practices have not been instituted in most treatment centers.

Recent assessments of clinical practice have revealed inconsistencies between the current understanding of POI and how it is being managed in the clinical practice setting. In a study of patients who underwent elective colon surgery, the NGT was left in situ in 63% of patients after surgery in U.S. hospitals.24 This study included more than 260 hospitals in France, Germany, Italy, Spain, the U.S., and the United Kingdom. In the overall population of patients (N = 950), fewer than 20% were able to tolerate solid food before the third day after surgery.

This study also provided further support for the importance of NGT removal to facilitate GI recovery: the LOS was shorter for patients when the NGT was removed on the day of surgery (mean LOS, 14.1 days) than when it was removed one to five days after surgery (mean LOS, 15 to 17 days).

Similarly, a European survey of national physician practices revealed that 66% to 94% of surgeons had no standard procedure for managing patients with POI.18 Indeed, the most common approaches varied according to country; these measures included rehydration, re-insertion of the NGT, and administration of laxatives or enemas, although none of these approaches has demonstrated consistent efficacy for POI.13

Physicians are generally aware that POI can occur, but they do not agree about which symptoms should prompt intervening therapy. A survey of 230 European surgeons revealed that the majority would consider intervention in the event of abdominal distention or vomiting.49 The surgeons were concerned that such symptoms would be associated with increased rates of infection and anastomotic failure. Only 16% to 65% of surgeons, by country, would consider intervention for POI based on the presence of abdominal pain.49 despite earlier reports that POI can contribute to postoperative abdominal pain.1–3,6,12–14,18 One reason why surgeons might be less likely to intervene for patients with POI is that the benefits from currently available therapies have been limited or inconsistent.13

**Figure 1** Peripherally acting mu-opioid receptor (PAM-OR) antagonists. PAM-OR antagonists bind to mu-opioid receptors within the gastrointestinal (GI) tract, blocking the effects of endogenous opioids and opioid analgesics on GI motility. In contrast, centrally mediated opioid analgesia is not affected. (Reproduced with permission from GlaxoSmithKline and Adolor Corporation.)
**EMERGING THERAPIES**

Individual postoperative GI recovery protocols in hospitals are not standardized, but some centers have reported accelerated GI recovery with multimodal regimens involving opioid-sparing analgesia, standardized general anesthesia, early oral nutrition and ambulation, and patient education. However, aggressive management techniques to accelerate GI recovery and reduce LOS have sometimes resulted in increased rates of readmission.

An emerging therapeutic option for the management of POI involves blocking opioid signaling via the mu-opioid receptors in the GI tract. However, mu-opioid receptors within the central nervous system (CNS) are responsible for opioid analgesia. Therefore, the optimal opioid antagonist for treating POI would specifically block the effects of opioids in the gut (bowel dysfunction) without disturbing the analgesic effects of opioids in the CNS (Figure 1). The development of effective peripherally acting mu-opioid receptor (PAM-OR) antagonists would allow for continued treatment of patients with the gold standard of pain management—opioids—while reducing the inhibitory effects of endogenously released or pharmaceutically administered opioids on GI motility.

Several opioid antagonists have been investigated for their effects on bowel motility but have not yet demonstrated utility in the POI setting. The opioid antagonist naloxone reverses opioid effects on the gut but has limited utility in patients who are receiving opioid analgesia because it can enter the CNS and reverse central opioid effects. *Nalmefene glucuronide*, a mu-opioid receptor antagonist, demonstrated GI selectivity in rodent models, but it precipitated signs and symptoms consistent with opioid withdrawal in humans. In contrast, *methylnaltrexone*, a PAM-OR antagonist, does not cross the blood–brain barrier and can reverse reductions in bowel motility associated with the administration of opioid analgesics without affecting opioid analgesia.

Methylnaltrexone significantly reduced mouth-to-cecum transit time in several small trials in patients receiving chronic opioid therapy with morphine or methadone. None of the published studies of methylnaltrexone evaluated patients in the immediate postoperative period, but phase 2 studies to assess its role in POI are currently under way.

**Alvimopan** (Entereg, Adolor/GlaxoSmithKline), a novel PAM-OR antagonist, has the highest reported affinity for mu-opioid receptors of all PAM-OR antagonists studied to date. Moreover, it is an oral agent, a form that might improve the convenience of therapy.

Alvimopan recently became the first PAM-OR antagonist to show significant benefits for postoperative GI recovery after bowel resection or TAH in three randomized, placebo-controlled, phase 3 efficacy trials and one phase 3 safety trial. Moreover, this agent was well tolerated, with no clinically meaningful differences in adverse-event profiles between alvimopan and placebo. Neither alvimopan 6 mg nor alvimopan 12 mg compromised opioid analgesia, as evidenced by similar pain scores and analgesic usage between treatment groups of patients and placebo groups.

A total of 1,627 patients scheduled for bowel resection or TAH were randomly selected to receive alvimopan 6 mg, 12 mg, or placebo in three large phase 3, multicenter efficacy trials (Table 2). Because there is currently no consensus endpoint for capturing GI recovery, these trials assessed many parameters of GI and general recovery.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Randomized Patients (No.)</th>
<th>Dose Level (mg)</th>
<th>Mean Time to Written Hospital Discharge Order (Hours)</th>
<th>P Value for Cox Hazard Ratio versus Placebo*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolff et al.63</td>
<td>165</td>
<td>0†</td>
<td>146</td>
<td>—</td>
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<tr>
<td></td>
<td>169</td>
<td>6</td>
<td>133</td>
<td>.070</td>
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<td></td>
<td>176</td>
<td>12</td>
<td>126</td>
<td>.003</td>
</tr>
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<td>Delaney et al.64</td>
<td>153</td>
<td>0†</td>
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<td>152</td>
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<td>146</td>
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<td>115</td>
<td>.171‡</td>
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<tr>
<td>Viscusi et al.65</td>
<td>224</td>
<td>0†</td>
<td>126</td>
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<td></td>
<td>229</td>
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<tr>
<td></td>
<td>222</td>
<td>12</td>
<td>111</td>
<td>.015</td>
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</tbody>
</table>

* Significance was assessed via the Hochberg step-up method to adjust for multiple comparisons.
† The 0-mg group was the placebo control arm.
‡ The difference is not considered statistically significant.

**Table 2** Phase 3 Randomized, Placebo-Controlled Efficacy Trials of Alvimopan for Postoperative Ileus

**EMERGING THERAPIES**

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Each dose of alvimopan significantly accelerated the time to the first bowel movement or the time to the first bowel movement and tolerance of solid food in all three trials. Notably, both doses of alvimopan reduced the time to the writing of the hospital discharge order (DCO) and, at least one dose level of alvimopan in each trial reduced the time to the DCO that reached statistical significance compared with placebo.

The mean time to the written DCO ranged from 122 to 146 hours (five to six days) after the completion of surgery for the...
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placebo groups. Alvimopan 6 mg reduced the time to the written DCO by 13.2 to 14.2 hours, and alvimopan 12 mg reduced this time by 7.2 to 19.5 hours, compared with placebo.

In the pooled subset of patients undergoing bowel resection, the decreased time to the DCO was even more pronounced. These results suggest that alvimopan can reduce LOS after bowel resection or TAH and may therefore reduce mean hospital costs. Moreover, more benefits, in terms of reduced postoperative GI morbidity and lower rates of hospital readmission, were reported for alvimopan than for placebo.

A pooled analysis of postoperative morbidity in all patients in the alvimopan phase 3 efficacy trials found the following:67

- significant reductions in the rates of postoperative NGT re-insertion (5.5% for alvimopan 6 mg, 5.6% for alvimopan 12 mg, 9.6% for placebo)
- POI as a serious adverse event (1.9% for alvimopan 6 mg, 1.5% for alvimopan 12 mg, 5.4% for placebo)
- hospital readmission (6.0% for alvimopan 6 mg, 7.1% for alvimopan 12 mg, 11% for placebo)
- the proportion of patients who remained in the hospital for seven days or more after surgery (18.8% for alvimopan 6 mg, 15.7% for alvimopan 12 mg, 29.3% for placebo)

A key strength of the alvimopan phase 3 POI studies is that all patients in the treatment and placebo arms received a multimodal therapy protocol (accelerated care pathway) that is practiced at some specialized centers to facilitate GI recovery.51 This protocol includes removal of the NGT by noon on the day after surgery on day one, encouragement of ambulation and offering of liquids on day one, and offering of solid food on day two. Therefore, the acceleration of GI recovery observed with alvimopan was above and beyond any GI recovery benefits that might have occurred from the implementation of multimodal therapy.

Alvimopan has also demonstrated efficacy in patients with bowel dysfunction during opioid therapy. Oral alvimopan (0.5 and 1 mg daily) significantly increased the incidence of bowel movements within eight hours of administration, the number of weekly bowel movements, and overall satisfaction without compromising centrally mediated opioid analgesia in patients with bowel dysfunction who were receiving chronic opioid therapy.68

One limitation of oral alvimopan is that it is useful only in patients with existing enteral access. No parenteral form of alvimopan has been studied to date.

CONCLUSION

Postoperative ileus is a widely recognized but highly undertreated condition that exacts a large toll on health care resources. No FDA-approved treatment for POI currently exists, and none of the available prokinetic agents has demonstrated promise in this setting.13

An updated management strategy may improve overall outcomes, and the integration of new treatment regimens into multimodal care pathway programs has the potential to reduce the incidence and severity of POI. Successful resolution of POI will benefit both the patient and the health care system by increasing patient comfort, reducing postoperative complications, and decreasing hospital LOS and the requirement for readmission.

Emerging pharmacotherapies for POI, including PAM-OR antagonists such as alvimopan, have shown a promising effect on the duration of POI in phase 3 studies.53–66 The results of ongoing research in this area of postoperative care are anticipated to further define the role of such agents in the management of POI.

REFERENCES


