



# The Evolving Multimodal Management Plan for Postoperative Ileus

## APPLICATIONS IN PRACTICE: EDUCATIONAL RESOURCE NEWSLETTER

**P**ostoperative ileus (POI) is the temporary impairment of coordinated bowel motility that occurs for a variable period following surgery.<sup>1,2</sup> POI is most commonly associated with abdominal surgeries, although it may be a consequence of other surgical procedures as well. This transient pause in normal bowel function that prevents effective transit of intestinal contents and/or tolerance of oral intake is considered a normal response to the stress and tissue injury associated with a surgical procedure. Different parts of the gastrointestinal tract recover at different times following surgery; the small intestine within the first 24 hours, followed by the stomach between 24 and 48 hours, and the colon between 48 and 120 hours.<sup>3,4</sup> For the patient, POI may be associated with delayed passage of flatus and stool, increased postoperative pain, increased nausea and vomiting, prolonged time to resumption of normal diet, delay in postoperative mobilization, increased risk of complications, and prolonged hospitalization. The duration of POI is

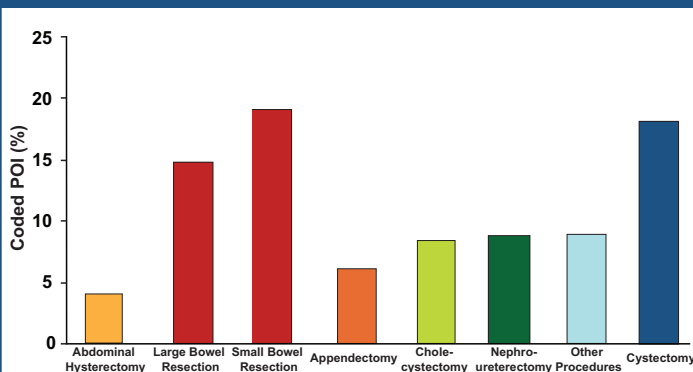
variable, but for many patients undergoing abdominal surgery, untreated POI can last beyond 5 days.<sup>5</sup>

There are numerous risk factors for POI including the surgical site, extent of bowel manipulation, operation duration, patient characteristics, and opioid use. Neurogenic, inflammatory, and pharmacological components all contribute to the pathophysiology of POI. Inhibitory neural reflexes and sympathetic hyperactivity impact GI motility. Cytokines and other inflammatory mediators are elicited through the activation of pathways associated with the inflammatory response to surgical manipulation, and these factors also modulate GI motility. Corticotropin-releasing hormone is another element of the stress response that contributes to POI. Exogenously-administered opioids, as well as endogenously-generated enkephalins and endorphins, have significant direct effects on the GI tract that negatively impact motility. The incidence of POI varies depending on the type of surgery (Figure 1).

that the incidence of POI may be higher due to underreporting of POI cases. Chang et al evaluated records for 304 consecutive patients who underwent radical cystectomy from 1995 to 2000, and identified 54 with POI (18%).<sup>6</sup> POI was the most common minor complication following surgery for this patient population.

Postoperative ileus clearly presents an unfavorable burden on the patient, but it is also a burden on the health care system. Recovery of GI function is a

Figure 1: Incidence of POI for Common Abdominal/Pelvic Surgeries<sup>2</sup> (Adapted)



Based on HCFA Data 1999-2000 for all surgeries except cystectomy; cystectomy data from Chang et al.<sup>6</sup>

Large and small bowel resections are associated with the highest incidence of POI (14.9 and 19.2%, respectively) according to an analysis of Health Care Financing Administration data from 1999-2000.<sup>2</sup> Some authors have suggested

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**Table 1: Management Options for Postoperative Ileus<sup>2</sup> (Adapted)**

Management Option	Benefit
Patient education and optimization	Reduce preoperative anxiety, enhance postoperative recovery
Limited nasogastric tube use	Allows resumption of oral intake
Early oral/enteral/sham feeding	Gastrocolic reflex, stimulation of GI hormones Counteracts catabolism Improves immune function Hastens wound healing
Laxatives	Help to induce bowel movement
Early ambulation	Helps to prevent post-op complications such as clots, atelectasis, pneumonia
Laparoscopic surgery	Reduced manipulation and trauma of the bowel leads to less sympathetic activation and inflammation, reduced pain and associated opioid use, earlier ambulation, reduced need for nasogastric tube, earlier resumption of diet
Epidural anesthesia/analgesia	Synergistically block inhibitory sympathetic reflexes; epidural analgesia reduces systemic opioid requirement thus minimizing opioid-related adverse effects
Opioid-sparing analgesia	Minimizing the use of opioids reduces associated GI effects; anti-inflammatory effects of NSAIDs
Peripheral opioid antagonism	Reverse GI effects of opioids without compromising postoperative analgesia

determining factor prior to postsurgical hospital discharge. For patients with prolonged POI, longer hospitalization means additional demands on personnel, hospital beds, and associated resources. An economic analysis of POI associated with abdominal surgery reported by Goldstein et al<sup>7</sup> used data from a 2002 national database. These investigators identified 8.5% (142,026) of the procedures with coded POI. The average length of stay for coded POI was 11.5 days compared with 5.5 days without coded POI, and the mean costs per hospital stay were \$18,877 and \$9,460, respectively. The projected cumulative annual costs for coded POI (total hospitalization and readmission costs) were \$1,464,167,173.

With the multifactorial etiology of POI, a multimodal approach incorporating several individual management strategies applied simultaneously can help to accelerate recovery and reduce the duration and morbidity of POI (Table 1).<sup>2</sup>

invasive surgical techniques may contribute to the reduced duration of POI as demonstrated in a number of studies comparing laparoscopy and open surgery.<sup>1</sup> A meta-analysis of 22 studies (2965 patients) of colorectal surgery demonstrated a significant reduction in postoperative pain as assessed by visual analog scale (first postoperative day), earlier passage of flatus (-1 day), earlier bowel movement (-0.9 days), and shortened hospital length of stay (-1.5 days) associated with laparoscopic compared with open surgery.<sup>8</sup> Limitations associated with laparoscopic surgery include the specialized training required for performing such surgeries, and further, not all procedures are amenable to the laparoscopic approach.

Intraoperative inhaled or intravenous anesthetics can temporarily inhibit GI motility. The adjunctive use of epidural anesthesia with general anesthesia may help to minimize these GI effects by

The components of a multimodal approach may include patient optimization and education, minimally invasive surgical techniques (where appropriate), epidural anesthesia/analgesia, opioid sparing analgesia, limited use of postoperative nasogastric (NG) tubes, early oral/enteral feeding, early ambulation, and peripheral opioid antagonism. Reduction of surgical stress with less

blocking inhibitory sympathetic reflexes, preventing the release of afferent pain neurotransmitters, and increasing splanchnic blood flow. Patient-controlled analgesia (PCA) with intravenous opioids is very effective for the control of postoperative pain, but has direct inhibitory effects on GI motility. Opioids decrease gastric motility, inhibit small and large intestinal propulsion, and have other GI effects that contribute to the abdominal discomfort associated with POI. Numerous studies have demonstrated a reduction in the duration of postoperative ileus with epidural analgesia in the postoperative period compared with systemic opioids.<sup>9</sup> Not all patients are inclined to use epidurals, and trained personnel are required for expert placement. As will be discussed later, another approach to the adverse effects of opioids on the GI tract is the use of peripheral opioid antagonists, which negate such effects without compromising analgesia. Minimizing the postoperative opioid burden with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is another component of a multimodal approach to POI. Analgesic and anti-inflammatory properties of NSAIDs are beneficial for patients with POI, and a randomized, double-blind study of morphine PCA with or without ketorolac in 79 patients who underwent colorectal surgeries demonstrated a 29% reduction in morphine use, earlier first bowel movement, and earlier ambulation in those patients receiving the morphine/ketorolac combination.<sup>10</sup>

The routine use of nasogastric tubes for gastric decompression following abdominal surgery has been challenged by evidence that suggests that NG tubes do not hasten the return of bowel function, increase patient comfort, or reduce hospital stay. A meta-analysis by Nelson et al of 33 studies and 5,240 patients revealed that patients without routine NG tube use had significantly earlier return of bowel function, a significant reduction in pulmonary complications, and a shorter length of hospital stay compared with patients using NG tubes.<sup>11</sup> Anastomotic leak was not different between the two groups.

Table 2: Methylnaltrexone for POI

Endpoint	Methylnaltrexone (0.3 mg/kg IV) (N = 33)	Placebo (N = 32)	P-value*
Full liquids	70 ± 9	100 ± 19	0.05
1st BM	97 ± 6	120 ± 10	0.01
GI recovery	124 ± 9	151 ± 16	0.06
Discharge eligible	119 ± 7	149 ± 17	0.03
Actual discharge	140 ± 6	165 ± 16	0.09

Values represent mean time in hours ± standard error; \* 1-sided<sup>20</sup>

to determine the true efficacy of gum chewing for POI, however for those individuals who are not at risk of choking due to swallowing difficulties, this inexpensive intervention may be beneficial.

Early ambulation is consistently

included in a multimodal approach for patients following bowel resection surgeries. Mobilization is clearly beneficial for the prevention of lower extremity thromboembolism and other postoperative complications, but the theory that early ambulation alone should enhance the resumption of normal bowel function and reduce the duration of POI is not supported by the literature.<sup>17,18</sup>

The gastrointestinal effects of opioids include inhibition of enteric nerve activity, inhibition of propulsive motor activity, inhibition of secretory activity, and alterations in immune cell function.<sup>19</sup> These effects are mediated primarily by opioid binding to  $\mu$  receptors in the GI tract.

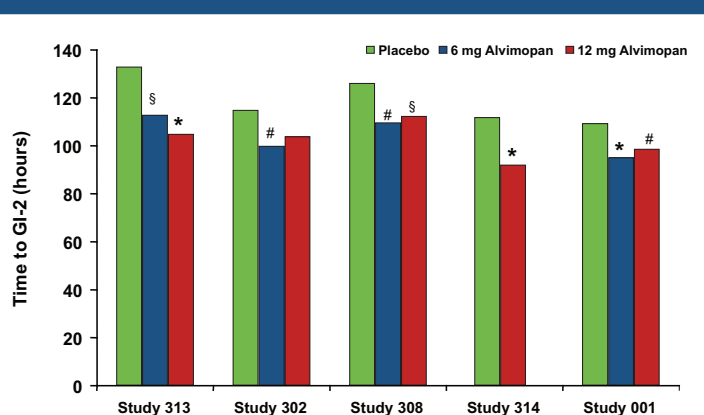
Methylnaltrexone and alvimopan are agents that antagonize opioid binding at  $\mu$  receptors, but do not cross the blood brain barrier, and therefore they do not compromise the analgesic effects of opioids. The efficacy and safety of methylnaltrexone for POI was evaluated in a Phase 2 study of 65 patients undergoing segmental colectomy.<sup>20</sup>

Patients were randomized to treatment with methylnaltrexone (0.3 mg/kg IV) or placebo within 90 minutes of the end of surgery, and then every 6 hours for a maximum of 7 days. Patients treated with methylnaltrexone had significantly earlier time to tolerance of full liquids, first bowel movement, and discharge eligibility compared with placebo-treated patients (Table 2).

A recent phase 3 trial of methylnaltrexone for postoperative ileus in patients undergoing segmental colectomy did not demonstrate an advantage for the treatment group.<sup>21,22,23</sup> A similar trial with ventral hernia repair has been completed, but we are awaiting the presentation of data.<sup>24</sup> In a study of methylnaltrexone for opioid-induced constipation, abdominal pain, flatulence, and nausea were reported more frequently for patients treated with methylnaltrexone (0.15 mg/kg subcutaneously every other day for 2 weeks) than patients treated with placebo.<sup>25</sup>

Alvimopan has been studied for the treatment of postoperative ileus in multiple phase 3 studies, and was approved by the FDA in 2008 to accelerate the restoration of normal bowel function in adult patients who have undergone partial large or small bowel resection surgery.<sup>5,26,27,28,29,30</sup> For phase 3 studies, patients were

Figure 2: Alvimopan Phase 3 Studies: GI Recovery

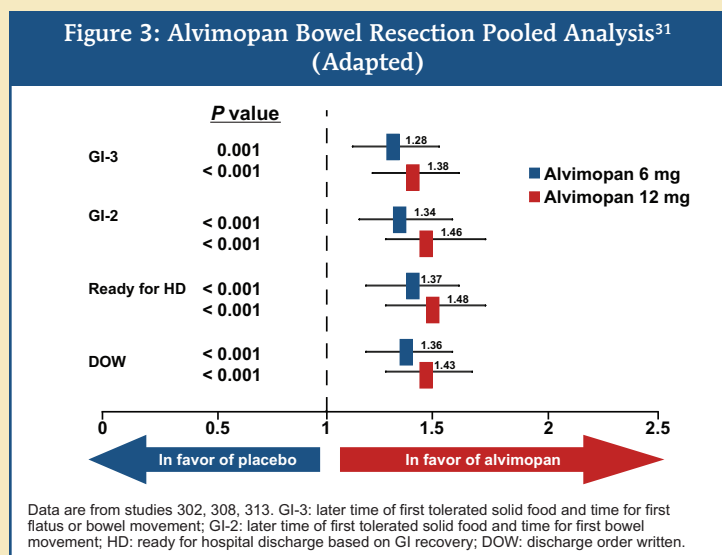


\*P < 0.001; #P < 0.01; §P < 0.02; Studies 313, 302, 308 include bowel resection and hysterectomy; studies 314, 001 bowel resection only; all studies conducted in North America except 001, which was conducted in Europe and New Zealand. GI-2: later time of first tolerated solid food and time for first bowel movement.<sup>5,26,27,28,29</sup>

The authors concluded that “routine nasogastric decompression does not accomplish any of its intended goals and so should be abandoned in favor of selective use of the nasogastric tube.” Removal of an NG tube also eliminates a barrier to enteral nutrition. Early feeding can stimulate GI motility through the gastrocolic reflex and the stimulation of gastrointestinal hormones. Kehlet and Holte presented data from 7 studies comparing early feeding vs traditional feeding on the duration of postoperative ileus.<sup>12</sup> Significant reduction of ileus was reported in 3 of the 7 studies, although the benefit was modest. Several authors have reported meta-analyses of early versus later enteral feeding following colorectal, gynecologic or abdominal surgeries.<sup>13,14,15</sup> Each of these analyses reported slightly reduced length of stay with early feeding, and supported the safety of early nutrition in each of the patient populations. Importantly, there was no benefit demonstrated by restricting postoperative oral nutrition. Gum chewing (a form of sham feeding) has also been evaluated as a means to stimulate gastrointestinal motility and reduce the duration of POI. A recent review identified 9 clinical trials with 437 patients in which gum chewing was compared with standard care following elective intestinal surgery.<sup>16</sup> Each of the outcome measures was significantly reduced in patients who chewed gum compared with traditional care (time to flatus, -14 hr; time to bowel movement, -23 hr; length of hospital stay, -1.1 days). Rigorous investigation is required

randomized to treatment with alvimopan (6 or 12 mg) or placebo, with the first dose given preoperatively between 5 hours and 30 minutes prior to surgery, and postoperatively BID up to 7 days or until hospital discharge. Patients in the alvimopan studies were scheduled for postoperative analgesia with opioid-based patient-controlled analgesia (epidurals and NSAIDs were excluded). Endpoints included indices of GI recovery (GI-2, GI-3), time to discharge order written (DOW), and safety. GI-3 is the later time of first tolerated solid food and the time for first flatus or bowel movement; GI-2 is the later time of first tolerated solid food and the time to first bowel movement. **Figure 2** presents GI recovery results from 5 alvimopan studies. Studies 313, 302, and 308 included both bowel resection and hysterectomy patients, whereas data from studies 314 and 001 are for bowel resection patients only.

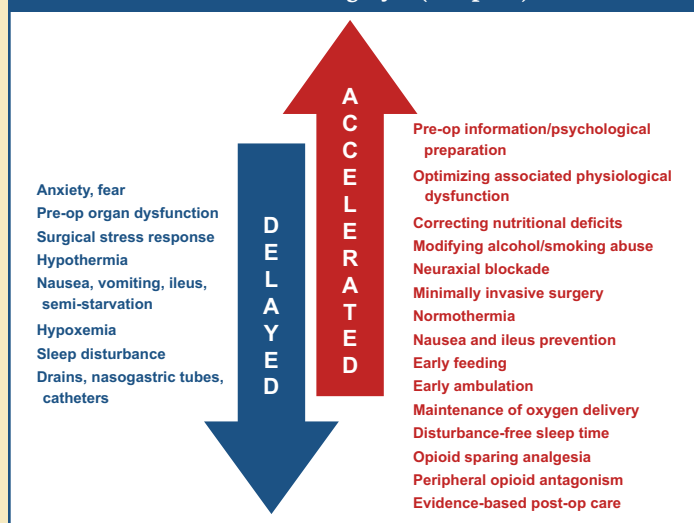
Treatment with alvimopan (both 6 and 12 mg doses) resulted in a reduction in time to GI-2 compared with placebo. Pooled retrospective analysis of bowel resection patients from studies 302, 308, and 313 demonstrated a significant reduction in GI recovery, readiness for hospital discharge based on GI recovery, and time to discharge order written for both 6 and 12 mg doses of alvimopan compared with placebo (**Figure 3**).<sup>31</sup>



Time to discharge order written was  $\geq 16$  hours earlier for patients treated with alvimopan (both doses) compared with placebo. The most commonly reported adverse events associated with alvimopan treatment were anemia, hypokalemia, constipation, heartburn, and flatulence. Further investigation is required to evaluate the efficacy of alvimopan in patients who receive epidurals or NSAIDs for postoperative analgesia.

Alvimopan has also been studied in patients taking opioids for chronic non-cancer pain. A 12-month study in which patients were treated with either alvimopan (0.5 mg) or placebo BID reported an imbalance in the number of reports of myocardial infarction in patients treated with alvimopan (1.3%) compared with placebo (0).<sup>30,32</sup> Following thorough evaluation of these safety data, the FDA concluded that the serious cardiovascular adverse events occurred in patients at high risk for cardiovascular disease; that myocardial infarction did not appear to be linked to the duration of dosing; this serious adverse event was not observed in other alvimopan studies (including POI studies in bowel resection patients treated with 12 mg BID for up to 7

**Figure 4: Factors That Impact Recovery Following Abdominal Surgery<sup>34</sup> (Adapted)**



days); and a causal relationship has not been established between alvimopan and myocardial infarction. In keeping with a risk-management program, alvimopan is only available to hospitals that enroll in the Entereg Access Support and Education (E.A.S.E.™) program.<sup>33</sup> The following is required of participating hospitals: a) limit use of alvimopan to short term, inpatient use; b) patients will not receive more than 15 doses of alvimopan; c) alvimopan will not be dispensed to patients following hospital discharge; and d) the hospital will not transfer alvimopan to unregistered hospitals.

Numerous factors can contribute to either delayed or accelerated recovery following elective surgery (**Figure 4**).

The goals of a multimodal approach for patients at risk for the development of POI are to enhance the recovery of bowel function, reduce POI-related morbidity, improve patient outcomes, and reduce the length of hospital stay. Several studies have documented the success of a multimodal/fast-track approach for colorectal surgeries with reduced duration of postoperative ileus and length of hospital stay.<sup>34,35,36,37,38,39,40,41</sup> However, according to the results of a multinational survey, evidence-based strategies that are part of a multimodal approach following colonic surgeries are not consistently

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applied clinically in the United States and Europe.<sup>42</sup> Among the barriers to the implementation of multimodal protocols are lack of awareness, skepticism, institutional limitations, time involved, insufficient expertise or staff support, reimbursement or liability issues, and the engagement of a multidisciplinary team.<sup>40</sup> Surgeons, anesthesiologists, pharmacists, nurses, and support personnel can work together as a team for the proactive prevention and treatment of POI. Communication, commitment, organization, motivation, and time from all team members are crucial for the success of this approach. A systematic transfer of patient information through each phase of hospital care is required to maintain continuity of the multimodal approach. Successful implementation of a multimodal approach to bowel resection procedures is associated with many desirable outcomes, and importantly will result in improved patient care.

One of the elements of this educational resource is a worksheet to use as a tool for the evaluation of your current practices with patients who are at risk for the development of POI. It is hoped that this tool will help you to identify measures that could be incorporated into your approach to optimize patient outcomes and recovery.



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## CME/CPE INFORMATION: NEWSLETTER

### Needs Statement/Target Audience

This activity is intended for colon/rectal surgeons, general surgeons, anesthesiologists, health-system pharmacists, medical/surgical nurses, and other healthcare professionals who manage postoperative ileus (POI).

### Educational Activity Learning Objectives

Upon completion of this activity, the participants should be able to:

- Describe the prevalence, pathophysiology, and defining criteria for postoperative ileus (POI)
- Distinguish evidence-based therapeutic options for the management of POI
- Describe how to implement a multimodal management plan in your institution for patients undergoing bowel resection procedures to improve time to bowel recovery

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