

# Cost and efficacy examination of alvimopan for the prevention of postoperative ileus

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## ABSTRACT

Opioid analgesics exacerbate ileus through peripheral  $\mu$ -opioid receptor action. Alvimopan, a  $\mu$ -opioid receptor antagonist, has been proposed to alleviate postoperative ileus, leading to decreased time to return of gastrointestinal function and hospital discharge. As opioid-induced motility issues are only one factor affecting postoperative ileus, continued examination of the cost of the use and efficacy of the drug is needed. Data for this study were collected retrospectively from the charts of 55 patients who received an anastomosis and were given alvimopan at Morristown Medical Center between 2010 and 2013 as well as from 58 appropriately matched controls. The billing record and chart for each patient was examined, and information on total hospital charges, age, sex, body mass index, primary diagnosis, procedure type, length of stay (days), time to return of bowel function (hours), and outcomes were recorded for analysis. No difference between patients given alvimopan and controls was observed for the length of hospital stay (4.6 vs 4.8 days) or for time to return of bowel function (68.5 vs 67.3 hours). Total hospital charges were higher for treated patients ( $p=0.0080$ ), averaging \$48 705.15 and \$41 068.80, respectively. Alvimopan was not associated with improved clinical outcome but was associated with an increase in hospital charges within this population.

## INTRODUCTION

With major surgery to the alimentary tract comes the risk of complications. One particularly common complication is the transient cessation of bowel motility and subsequent impairment of function known as postoperative ileus.<sup>1–3</sup> Postoperative ileus can come at great cost to patients and to healthcare providers.<sup>1–4</sup> Patients affected by postoperative ileus often experience increased pain, pulmonary discomfort, and, particularly in prolonged cases, are at risk of serious issues such as aspiration and acute gastric dilation.<sup>5–6</sup> Hospital length of stay (LOS) is often extended, increasing the cost of care and imparting up to an estimated \$1 billion in total additional economic burden per year.<sup>6–8</sup> Postoperative ileus may arise from a sympathetic nervous system reflex and from local inflammation caused by physical interaction with the bowel during surgery.<sup>1</sup> Endogenous opioids can trigger the inhibitory reflex and induce ileus.<sup>1–9</sup> The use of opioid

analgesics following surgery can compound and prolong postoperative ileus.<sup>1–10–12</sup>

It has been proposed that antagonizing  $\mu$ -opioid receptors prevents ileus.<sup>8</sup> Alvimopan is a  $\mu$ -opioid antagonist. It exhibits high receptor affinity and does not cross the blood–brain barrier.<sup>1–13–16</sup> In clinical trials, alvimopan was observed to decrease time to return of gastrointestinal function and to hospital discharge following major abdominal surgery when compared with a placebo.<sup>3–17</sup> The aim of our study was to perform a retrospective review of the efficacy of alvimopan in preventing postoperative ileus in patients who underwent an intestinal anastomosis. Efficacy was measured using factors such as average time to return of bowel function and average hospital LOS. Billing information such as room, equipment, service and pharmaceutical costs were also analyzed to determine any changes in cost of care associated with alvimopan use.

## METHODS

The Institutional Review Board of Morristown Medical Center approved this retrospective study including data from 55 patients, 17 male patients and 38 female patients, who underwent an operation involving an intestinal anastomosis and received alvimopan between the years 2010 and 2013. During preoperative holding, 12 mg alvimopan was administered orally to these patients, then 12 mg orally every 12 hours postoperatively for up to 7 days or until discharge. These patients were matched to 58 appropriate controls from the same time period (19 males, 39 females) for age, gender, diagnosis, comorbidities, surgical approach (open vs laparoscopic), and technique of anastomosis formation (stapled vs hand-sewn). All patients were instructed to engage in bowel preparation, comprising four bisacodyl tablets 2 days before their operation, then a clear liquid diet, one gallon of Golytely, 500 mg of Flagyl, and 1 g of neomycin by mouth 1 day preoperatively. Pain was managed by nurses, physicians, or physician's assistants per the patient's need and at the care provider's discretion. A subjective 1–10 pain score, in conjunction with auscultation of bowel sounds to detect digestive impairment, informed pain management decisions. In some cases, patients receiving alvimopan were matched with multiple controls, as those controls were very



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similar to the treated patients. All patients included in this study were identified from our institution's pre-existing database of intestinal anastomosis operations. Each patient's chart was consulted, from which age, sex, body mass index, primary diagnosis, procedure type, LOS (days), time to return of bowel function (hours to first flatus), and outcomes were recorded for analysis. Continuous data sets were compared using Microsoft Excel and GraphPad Prism software.

Patients' billing information was examined. Room charges, drug and pharmacy charges, surgical and medical supply charges, laboratory charges, pathology and cytology charges, imaging charges, minor surgery charges, operating room charges, anesthesia charges, non-surgical service charges, therapy charges (physical and occupational), emergency department charges, and EKG charges were recorded. Patients with incomplete billing information and their matched case or control were removed from this portion of the study. Fifty pairs were analyzed for this portion.

## RESULTS

Between 2010 and 2013, a total of 55 (17 male, 38 female) patients undergoing an intestinal anastomosis at Morristown Medical Center were given alvimopan. They were matched with 58 controls (19 male, 39 female). In the alvimopan group, 44 had their pain managed with opioids while 43 control patients had their pain managed with opioids. A Fisher's test found no significant association between alvimopan and opiate use. The most common primary diagnoses were malignant tumors and diverticulitis. The most common procedures were right colectomies, sigmoid colectomies, and low anterior resections (table 1). Complications between the two cohorts were not

significantly different, with the most common complications being ileus, deep vein thrombosis, and cardiac complications.

Using a Student's t-test, no significant difference between patients given alvimopan and controls was observed for the average length of hospital stay (4.6 vs 4.8 days;  $p=0.7198$ ) or for the average time to return of bowel function (68.5 vs 67.3 hours;  $p=0.8251$ ). An examination of average hospital charges revealed significantly higher charges in the alvimopan group ( $p=0.0080$ , table 2).

Patients who received alvimopan were more likely to have greater charges for medical and surgical supplies ( $p=0.0016$ ), pathology and cytology services ( $p=0.0042$ ), operating room charges ( $p=0.0241$ ), and therapy charges ( $p=0.0441$ ). These results were determined using one-tailed Student's t-tests.

To check for confounding, we stratified the patients in the cost-of-care analysis by the year they were admitted to determine if inflation accounted for these increased costs and analyzed the distribution using one-way ANOVA. It was found that alvimopan use was significantly associated with year ( $p<0.0001$ ). While the cases and controls were both from the same time period spanning 2010 to 2013, the distribution of the alvimopan cohort was concentrated toward the later years. Total cost ( $p=0.0132$ ), supply cost ( $p=0.0022$ ), pathology and cytology services ( $p=0.0015$ ), and operating room cost ( $p<0.0001$ ) were also significantly associated with year. There was no significant difference in costs associated with therapy when stratified by year ( $p=0.3659$ ).

## DISCUSSION

Our study appears to be in disagreement with the findings of the clinical trials reported in the literature. No significant difference was observed between cohorts in return to bowel function, nor in average LOS. These analyses fail to observe the same effect of alvimopan on decreasing time to return of bowel function and LOS that the clinical trials did.<sup>3 17 18</sup> Furthermore, without the decreased LOS but with the additional drug and service charges, alvimopan-treated patients were charged significantly more than controls, also in contrast to the literature.<sup>19</sup>

One possible explanation in the discrepancy between the clinical trials of alvimopan and our study's results is that clinical trials occur in carefully controlled settings where conditions are as identical as possible for the cases and controls, and ours was a 'real-world' efficacy study. However,

**Table 1** Summary of patient characteristics, primary diagnoses, and procedure types for the control and alvimopan-treated groups

	Control (n=58)	Alvimopan (n=55)
Patient characteristics		
Age (mean±SD)	64.7±13.1	65.2±13.75
Male:female sex	19:39	17:38
BMI (kg/m <sup>2</sup> ±SD)	26.4±5.85	28.3±6.63
Primary diagnosis (no. of cases (%))		
Diverticulitis	23 (39.7%)	22 (40.0%)
Benign tumor	6 (10.3%)	7 (12.7%)
Malignant tumor	27 (46.6%)	24 (43.6%)
Crohn's disease	2 (3.4%)	2 (3.6%)
Procedure type (no. of cases (%))		
Ileocolic resection	2 (3%)	2 (4%)
Right colectomy	14 (24%)	14 (25%)
Extended R colectomy	1 (2%)	1 (2%)
Left colectomy	5 (9%)	5 (9%)
Sigmoid colectomy	15 (26%)	13 (23%)
Low anterior resection	14 (24%)	13 (23%)
Hartmann's reversal	4 (7%)	4 (7%)
Ileostomy reversal	3 (5%)	3 (5%)
Colostomy reversal	0 (0%)	1 (2%)

**Table 2** Summary of significant differences in charges between patients in the control and patients who received alvimopan

	Control	Alvimopan
Total charges	\$44 630.62	\$50 868.08**
Surgical supplies*	\$7207.62	\$8706.33**
Pathology and cytology charges*	\$793.94	\$1091.79**
Operating room charges*	\$7443.82	\$8152.56*
Physical and occupational therapy*	\$198.76	\$368.58*

Significance determined using one-tailed t-tests.

\* $p<0.05$ ; \*\* $p<0.01$ .

our results still differ from a similar analysis of real-world efficacy of alvimopan. Vora *et al*<sup>20</sup> engaged in a study of a population of similar size. In this case, patients were undergoing cystectomy and urinary diversion. Preoperative preparations were largely the same in both of our studies with the exception of our use of bisacodyl. While the alvimopan cohorts in both of our studies reported similar prevalence of ileus, our controls varied greatly in the incidence of ileus. We noted a 3.6% incidence of ileus. Meanwhile, Vora *et al*<sup>20</sup> reported a 26.2% incidence. We believe that this difference may come from the differences in pain management strategies. Patients in Vora *et al* study received opioids through patient-controlled anesthesia (PCA) pumps or an epidural infusion with fentanyl. None of the patients in our study received opioids via PCA and only two patients—one in the alvimopan group, one in the control group—were prescribed transdermal fentanyl patches only to continue a therapy that had been initiated prior to their operation. Opioids were administered by care providers taking special care to avoid overdose and ileus. This meticulous and iterative process of pain management may be an effective strategy for the reduction of ileus and a source of confounding.

We employed one-tailed t-tests in our cost analysis because physicians and staff have observed higher costs for patients receiving alvimopan which has not been analyzed statistically prior to this study. Our detailed cost analysis of the increased cost associated with alvimopan use found that the increase in the cost of care was not due to alvimopan, but rather an increase in cost from other sections. We considered these results to be reasonable at first under the possible explanation that some providers may have a preference to use novel products and procedures (like alvimopan) which may, piecemeal, increase the total cost of care. However, our analysis with regard to year found that alvimopan was more likely to be prescribed in later years. While all patients were selected for admission between 2010 and 2013, the distribution of patients receiving alvimopan was concentrated toward the later years. This analysis also found that all of the costs found to be significantly associated with alvimopan use are also significantly associated with time—with the exception of therapy-related costs. The costs related to therapy were not significantly associated with time but were associated with alvimopan use, meaning they were not confounded by time while the aforementioned variables were.

In examining these results, we have formed a new hypothesis. The increases in cost associated with either time or alvimopan use may be explained by a hospital-wide shift toward accelerated recovery. While it is not official hospital policy, many healthcare providers at Morristown Medical Center adhere to the guidelines of Enhanced Recovery After Surgery (ERAS) Society<sup>21</sup> and the number of providers who reportedly adhere to these guidelines has noticeably increased. The use of alvimopan and physical therapy are both indicated in the ERAS guidelines for colorectal surgery and it would stand to reason that as ERAS becomes more popular, more patients would be receiving these services and others. Accelerated recovery would also warrant quicker return of pathology results which may result in greater associated costs. These guidelines also promote postoperative ambulation. This is a component of

the physical therapy which our patients receive following their operations, and we see that this is significantly associated with alvimopan use and increased cost, further supporting this new hypothesis. ERAS and related guidelines and philosophies of care may also promote novel operations with better outcomes and faster recovery times which may also be costlier. Physicians who did not prescribe their patients alvimopan are not following the ERAS guidelines as they are written and may not be adopting other portions of the guidelines, potentially resulting in lower costs of care. This could be the subject of a multidisciplinary study to examine any significant changes in the cost of care associated with ERAS or related guidelines in all surgical fields.

Aside from the conjectures made in this discussion, it is unclear exactly why the patients treated with alvimopan in this study did not enjoy the benefits reported following its use elsewhere. It is possible that the contribution of opioid analgesic-induced impairment of bowel motility to the total pathology of postoperative ileus is not always significant enough in the multifactorial nature of the phenomenon for its blockage to always have a noticeable effect. One would expect the randomized nature of the literature trials as well as their relatively large cross-trial sample size to have accounted for this possibility, which highlights our study's largest weakness: its retrospective design and limited sample size.

Matching our alvimopan-treated patients to controls for age, gender, indication, surgical approach, and anastomotic technique should alleviate this weakness to some degree. Though the evidence in the literature does point toward the efficacy and cost-effectiveness of alvimopan, our lack of observation of an effect and the subsequent increased economic burden of the treatment does suggest another look at the use of this drug, perhaps over a longer timeframe. While we cannot attribute the entirety of the additional cost to the use of alvimopan, this discrepancy is slightly concerning and further supports more analysis.

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