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Alvimopan is associated with decreased length of stay for both open and laparoscopic segmental colectomy

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ABSTRACT

Background: Alvimopan has been shown to reduce length of stay after bowel resection. Use remains variable among institutions due to cost and efficacy concerns in laparoscopic surgery. Additionally, alvimopan's effects have not been isolated from other medications within enhanced recovery protocols. The aim of this study was to distinguish the relationship between alvimopan use, length of stay, and cost in both open and laparoscopic segmental colectomies.

Methods: The Vizient dataset was queried to identify patients undergoing open and laparoscopic colectomies from 2015 to 2017. Patient demographics and treatment details were collected. Primary outcomes of interest included duration of stay and total direct costs.

Results: In the study, 12,727 patients met inclusion criteria and 3,358 (26.4%) received alvimopan. For both open and laparoscopic groups, alvimopan was associated with decreased length of stay in unadjusted (4.0 vs 6.0 days, $P < .01$ and 3.0 vs 4.0 days, $P < .01$, respectively) and adjusted analysis (effect ratio 0.79, $P < .01$ and 0.85, $P < .01$, respectively). Alvimopan was associated with a 7% decrease in direct cost after adjustment (effect ratio 0.93, $P = .04$), with no cost difference in laparoscopic procedures (effect ratio 0.99, $P = .71$).

Conclusion: Alvimopan use is associated with decreased length of stay for both open and laparoscopic colon resections, decreased cost in open procedures, and no cost difference for laparoscopic procedures.

Introduction

Postoperative ileus (POI) is a temporary impairment in bowel function preventing effective transit of intestinal contents and tolerance of oral intake, and is a common complication following major gastrointestinal (GI) surgery.[1] POI represents a major source of postoperative morbidity and increased length of stay (LOS), resource use, and cost.[2–4] In the United States alone, POI represents a significant economic burden, with annual costs totaling $1.46 billion.[5] Although the pathogenesis of POI is multifactorial, endogenous opioids released due to the stress of surgery and exogenous opioids administered for postoperative pain management play key roles in the development of POI.[6,7] Alvimopan is a peripherally acting μ-opioid antagonist that blocks the effects of opioids on the GI tract without affecting analgesia.[8] Alvimopan has been shown to accelerate recovery of GI function after abdominal surgery, shorten LOS, and reduce POI-related morbidity.[9–13] Given the favorable outcomes associated with alvimopan use, it is often included as a part of institutional enhanced recovery protocols. Enhanced recovery after surgery (ERAS) protocols are multimodal care approaches aiming to standardize medical care and optimize recovery after surgery. They have been demonstrated to improve patient outcomes by reducing LOS, complications, and cost, and are now considered standard of care after colorectal surgery.[14,15]

Although the general principles of enhanced recovery protocols are similar, the exact pharmacologic components are not standardized between institutions and can vary greatly. Alvimopan is not routinely administered at some institutions due to cost concerns, which can exceed $1,000 for a 7-day course, and limited efficacy data in laparoscopic procedures.[10,16] Although a few large national studies have shown reduction in LOS for patients undergoing laparoscopic bowel resections, these studies have either not adjusted for variability in institutional enhanced recovery protocols or patient comorbidities, or do not distinguish between patients

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undergoing small bowel, colon, and rectal resections.[17–19] It remains unclear how the addition of other pharmacologic components in an institution's enhanced recovery protocol may contribute to the improvements associated with alvimopan administration. Therefore, the primary aim of this study was to examine the relationship between alvimopan, LOS, and cost in both open and laparoscopic segmental colectomies in a large national cohort, adjusting for both patient comorbidities and individual medications commonly included as part of enhanced recovery protocols. We hypothesized that alvimopan would be associated with decreased LOS in both open and laparoscopic colectomies after controlling for other pharmacologic components of enhanced recovery protocols.

Materials and Methods

Patients and data acquisition

After institutional review board approval and exempt status notification, the Vizient Clinical Database (Vizient, Inc., Irving, TX)/Resource Manager (CDB/RM) was queried for patients ≥18 years or older undergoing elective laparoscopic or open segmental colectomy between January 1, 2015 and June 30, 2017. The CDB/RM is an analytic platform for performance improvement populated by hundreds of health systems and community hospitals nationwide, including nearly all academic medical centers.[20] Segmental colon resections were defined and classified using International Classification of Diseases, 9th Revision, Clinical Modification (*ICD-9-CM)* and International Classification of Diseases, 10th Revision, Procedure Coding System (*ICD-10-PCS)* codes: open right colectomy (*ICD-10-PCS* codes 0DBF0, 0DBK0 and *ICD-9-CM* code 4573), open left colectomy (*ICD-10-PCS* codes 0DBG0, 0DBM0 and *ICD-9-CM* code 4575), open transverse colectomy (*ICD-10-PCS* code 0DBL0 and *ICD-9-CM* code 4574), open sigmoidectomy (*ICD-10-PCS* code 0DBN0 and *ICD-9-CM* code 4576), laparoscopic right colectomy (*ICD-10-PCS* codes 0DBF4, 0DBK4 and *ICD-9-CM* code 1733), laparoscopic left colectomy (*ICD-10-PCS* codes 0DBG4, 0DBM4 and *ICD-9-CM* code 1735), laparoscopic transverse colectomy (*ICD-10-PCS* code 0DBL4 and *ICD-9-CM* code 1734), and laparoscopic sigmoidectomy (*ICD-10-PCS* code 0DBN4 and *ICD-9-CM* code 1736).

Demographic, procedure related, and outcome variables

All variables were collected at the patient level utilizing the Vizient CDB/RM. Demographic variables included age, sex, race, and comorbidities. Comorbidity information was gathered from the Vizient database in the form of *ICD-9* and *ICD-10-CM* codes of certain secondary diagnoses, such as congestive heart failure, hypertension, and obesity. Procedure-related variables included procedure type and administration of common ERAS-associated pharmacologic agents, including alvimopan, acetaminophen, ketamine, ketorolac, and gabapentin, as well as route of administration. Primary outcomes of interest included LOS and total direct cost. Secondary outcomes included in-hospital mortality, intensive care unit (ICU) admission, and 30-day readmission. LOS was defined as time from index procedure to time of discharge and 30-day readmission was defined as readmission for any reason within 30 days of discharge after the index procedure.

Statistical methods

Patients were stratified into laparoscopic and open procedures. The association between alvimopan use and other variables was assessed with χ^2 tests for categorical variables and t tests for continuous variables. Multivariate linear regression was performed with LOS and total direct cost as the outcomes of interest. Predictors adjusted for in the model included alvimopan use, type of procedure, location of procedure, readmission risk based on the Elixhauser Comorbidity Index, and administration of ERAS-associated medications. Elixhauser Comorbidity Index (readmission and mortality scores) were calculated using presence or absence of individually aggregated *ICD* secondary diagnosis codes. LOS and cost were log-transformed, and random hospital-specific intercept effect was incorporated in adjusted analysis. All statistical analysis was performed by the Department of Biostatistics at the Medical College of Wisconsin.

Results

Study population characteristics

In the study, 12,727 patients met inclusion criteria. In addition, 5,993 (47.1%) of patients were male, 10,002 (78.6%) were white, and average age was 60.3 years. Furthermore, 6,327 (49.7%) underwent open procedures while 6,400 (50.3%) underwent laparoscopic resections. Alvimopan was administered to a total of 3,358 (26.4%) total patients. Within the open group, 1,708 (27.0%), 618 (9.8%), 908 (14.4%), and 3,093 (48.9%) underwent right, transverse, left, and sigmoid colectomy, respectively. Within the laparoscopic group 2,212 (34.6%), 309 (4.8%), 598 (9.3%), and 3,281 (51.3%) underwent right, transverse, left, and sigmoid colectomy, respectively.

Open procedure cohort

In patients who underwent an open procedure, 1,446 (22.9%) received alvimopan. Patients receiving alvimopan were older (mean age 61.3 years vs 60.1 years, $P = .01$) and had lower Elixhauser Comorbidity Index readmission (10.2 vs 12.3, $P < .01$) and mortality scores (2.4 vs 3.6, $P < .01$), with no significant differences in sex, race, or types of colectomy performed between the groups. Alvimopan administration was associated with increased utilization of ERAS-associated medications in the first 48 hours of hospitalization, including intravenous (IV) acetaminophen (45.8% vs 27.8%, $P < .01$), oral acetaminophen (52.2% vs 28.1%, $P < .01$), ketamine (22.5% vs 19.6%, $P = .02$), ketorolac (38.0% vs 29.3%, $P < .01$), and gabapentin (41.3% vs 22.1%, $P < .01$; Table I). In unadjusted analysis, alvimopan administration was associated with a decrease in median LOS from 6.0 to 4.0 days ($P < .01$) and lower rates of ICU admission (9.2% vs 14.9%, $P < .01$). There were no significant differences in 30-day readmission or in-hospital mortality. Use of alvimopan was associated with a significant decrease in total direct cost, with a median cost of $9,649.00 compared to $10,114.00 ($P < .01$; Table II).

With unadjusted linear regression, alvimopan administration was associated with a 27% decrease in LOS (effect ratio 0.73, 95% confidence interval [CI] 0.70–0.76, $P < .01$). After adjustment for procedure type, age, sex, race, Elixhauser Comorbidity Index readmission score, and administration of other ERAS-associated medications, alvimopan administration was associated with a 21% decrease in LOS (effect ratio 0.79; 95% CI, 0.76–0.83; $P < .01$). Medications associated with decreased LOS after adjustment included oral acetaminophen (effect ratio 0.87; 95% CI, 0.84–0.90; $P < .01$), ketorolac (effect ratio 0.87; 95% CI, 0.84–0.90; $P < .01$), and gabapentin (effect ratio 0.92; 95% CI, 0.89–0.96; $P < .01$). Intravenous (IV) acetaminophen was significantly associated with increased LOS (effect ratio 1.04; 95% CI, 1.00–1.08; $P = .04$). Ketamine administration was also associated with increased LOS, although this did not meet statistical significance (effect ratio 1.02; 95% CI, 0.99–1.06; $P = .22$). Type of colectomy performed affected LOS. Right and sigmoid colectomies were significantly associated

Table I
Open procedures: Patient characteristics

	Alvimopan use		*P* value
	No (N = 4,881)	Yes (N = 1,446)	
Age, mean (SD)	60.1 (14.8)	61.3 (14.3)	.01
Sex			.22
Male	2,296 (47.0%)	707 (48.9%)	
Female	2,585 (53.0%)	739 (51.1%)	
Race			.16
White	3,830 (78.5%)	1,095 (75.7%)	
Black	610 (12.5%)	196 (13.6%)	
Asian	86 (1.8%)	34 (2.4%)	
Other	251 (5.1%)	81 (5.6%)	
Unknown	104 (2.1%)	40 (2.8%)	
Elixhauser comorbidity index			
Readmit score, mean (SD)	12.3 (13.7)	10.2 (12.8)	<.01
Mortality score, mean (SD)	3.6 (8.4)	2.4 (7.4)	<.01
Type of colon resection			.40
Right colon	1,321 (27.1%)	387 (26.7%)	
Transverse colon	486 (10.0%)	132 (9.1%)	
Left colon	713 (14.6%)	195 (13.5%)	
Sigmoid colon	2,361 (48.4%)	732 (50.6%)	
Medication administration in first 48 h			
Acetaminophen IV	1,356 (27.8%)	662 (45.8%)	<.01
Acetaminophen PO	1,371 (28.1%)	755 (52.2%)	<.01
Ketamine	959 (19.6%)	325 (22.5%)	.02
Ketorolac	1,431 (29.3%)	550 (38.0%)	<.01
Gabapentin	1,080 (22.1%)	597 (41.3%)	<.01

SD, standard deviation; *PO*, per oral.

Table II
Open procedures: Outcomes

	Alvimopan use		*P* value
	No (N = 4,881)	Yes (N = 1,446)	
LOS (d), median	6.0	4.0	<.01
In-hospital mortality	10 (0.2%)	1 (0.1%)	.74
ICU admission	725 (14.9%)	133 (9.2%)	<.01
30-d readmission	590 (12.1%)	156 (10.8%)	.18
Total direct cost, median	$10,114.00	$9,649.00	<.01

with decreased LOS (effect ratio 0.89; 95% CI, 0.85–0.93; $P < .01$ and effect ratio 0.93; 95% CI, 0.89–0.96; $P < .01$, respectively). Higher Elixhauser readmission scores (effect ratio 1.01; 95% CI, 1.01–1.01; $P < .01$) and older age (effect ratio 1.01; 95% CI, 1.00–1.02; $P = .01$) were associated with increased LOS. Female sex was significantly associated with shorter LOS (effect ratio 0.97; 95% CI, 0.95–1.00; $P = .04$). Race was not associated with a significant difference in LOS (Table III).

Alvimopan was associated with an 11% decrease in cost in unadjusted analysis (effect ratio 0.89; 95% CI, 0.83–0.96; $P < .01$) and a 7% decrease in adjusted analysis (effect ratio 0.93; 95% CI, 0.86–1.00; $P = .04$). Oral acetaminophen (effect ratio 0.90; 95% CI, 0.85–0.96; $P < .01$) and ketorolac (effect ratio 0.95; 95% CI, 0.89–1.00; $P = .05$) were associated with decreased total cost. Gabapentin (effect ratio 0.97; 95% CI, 0.90–1.03; $P = .32$) was also associated with decreased cost, but did not meet statistical significance. IV acetaminophen (effect ratio 1.11; 95% CI, 1.04–1.18; $P < .01$) and ketamine (effect ratio 1.16; 95% CI, 1.09–1.24; $P < .01$) were both associated with increased cost. Right colon resections were associated with decreased costs (effect ratio 0.79; 95% CI, 0.73–0.85; $P < .01$), with no statistically significant cost changes associated with other types of colectomy. Increased Elixhauser readmission score (effect ratio 1.01; 95% CI, 1.01–1.01; $P < .01$) and older age were also associated with increased cost (effect ratio 1.02; 95% CI, 1.01–1.04; $P < .01$). Patient race and sex were not associated with significant differences in cost (Table IV).

Table III
Multivariate analysis of factors associated with LOS after open segmental colon resection

	Effect ratio (95% CI)	*P* value
Age (units of 10 y)	1.01 (1.00–1.02)	.01
Sex (female versus male)	0.97 (0.95–1.00)	.04
Race (non-white versus white)	1.01 (0.98–1.05)	.53
Elixhauser readmission score (units of 1 point)	1.01 (1.01–1.01)	<.01
Type of segmental colon resection		
Right	0.89 (0.85–0.93)	<.01
Transverse	0.97 (0.91–1.02)	.23
Left	Reference	—
Sigmoid	0.93 [0.89–0.96]	<.01
Alvimopan	0.79 (0.76–0.83)	<.01
Acetaminophen IV	1.04 (1.00–1.08)	.04
Acetaminophen PO	0.87 (0.84–0.90)	<.01
Ketamine	1.02 (0.99–1.06)	.22
Ketorolac	0.87 (0.84–0.90)	<.01
Gabapentin	0.92 (0.89–0.96)	<.01

PO, per oral.

Laparoscopic procedure cohort

In patients undergoing laparoscopic procedures, 1,912 (29.8%) received alvimopan. There were no statistically significant differences in age, sex, race, Elixhauser Comorbidity Index mortality scores, or types of colectomy performed between those who received alvimopan and those who did not. Patients receiving alvimopan had a lower Elixhauser readmission score (6.7 vs 7.5, $P = .02$). Alvimopan administration was associated with increased utilization of ERAS-associated medications in the first 48 hours of hospitalization, including IV acetaminophen (46.7% vs 24.7%, $P < .01$), oral acetaminophen (44.2% vs 34.4%, $P < .01$), ketorolac (44.5% vs 37.0%, $P < .01$), and gabapentin (32.3% vs 19.9%, $P < .01$). Although there was increased administration of ketamine in those who received alvimopan (15.5% vs 14.1%), this did not meet statistical significance ($P = .16$; Table V). In unadjusted analysis, alvimopan administration was associated with a decrease in median LOS by 1.0

Table IV
Multivariate analysis of factors associated with total direct cost after open segmental colon resection

	Effect ratio (95% CI)	*P* value
Age (units of 10 y)	1.02 (1.01–1.04)	<.01
Sex (female versus male)	1.00 (0.96–1.05)	.93
Race (non-white versus white)	0.97 (0.91–1.02)	.24
Elixhauser Readmission Score (units of 1 point)	1.01 (1.01–1.01)	<.01
Type of segmental colon resection		
Right	0.79 (0.73–0.85)	<.01
Transverse	0.95 (0.87–1.04)	.30
Left	Reference	—
Sigmoid	0.98 (0.92–1.05)	.64
Alvimopan	0.93 (0.86–1.00)	.04
Acetaminophen IV	1.11 (1.04–1.18)	<.01
Acetaminophen PO	0.90 (0.85–0.96)	<.01
Ketamine	1.16 (1.09–1.24)	<.01
Ketorolac	0.95 (0.89–1.00)	.05
Gabapentin PO	0.97 (0.90–1.03)	.32

PO, per oral.

Table V
Laparoscopic procedures: Patient characteristics

	Alvimopan use		*P* value
	No (N = 4,488)	Yes (N = 1,912)	
Age, mean (SD)	60.3 (14.1)	60.2 (13.5)	.98
Sex			.67
Male	2,089 (46.5%)	907 (47.1%)	
Female	2,399 (53.5%)	1,011 (52.9%)	
Race			.07
White	3,583 (79.8%)	1,494 (78.1%)	
Black	443 (9.9%)	234 (12.2%)	
Asian	90 (2.0%)	34 (1.8%)	
Other	234 (5.2%)	99 (5.2%)	
Unknown	138 (3.1%)	51 (2.7%)	
Elixhauser comorbidity index			
Readmit score, mean (SD)	7.5 (11.0)	6.7 (10.2)	.02
Mortality score, mean (SD)	1.0 (6.4)	0.8 (5.8)	.70
Type of colon resection			.11
Right colon	1,575 (35.1%)	637 (33.3%)	
Transverse colon	208 (4.6%)	101 (5.3%)	
Left colon	398 (8.9%)	200 (10.5%)	
Sigmoid colon	2,307 (51.4%)	974 (50.9%)	
Medication administration in first 48 h			
Acetaminophen, IV	1,107 (24.7%)	892 (46.7%)	<.01
Acetaminophen, PO	1,542 (34.4%)	845 (44.2%)	<.01
Ketamine	634 (14.1%)	296 (15.5%)	.16
Ketorolac	1,661 (37.0%)	851 (44.5%)	<.01
Gabapentin	892 (19.9%)	617 (32.3%)	<.01

SD, standard deviation; *PO*, per oral.

days (3.0 vs 4.0 days, $P < .01$). There were no significant differences in ICU admission, 30-day readmission, and in-hospital mortality between the groups. Use of alvimopan was associated with a significant decrease in total direct cost, with a median cost of $8,268.50 vs $8,441.00 ($P < .01$; Table VI).

With unadjusted linear regression, alvimopan administration was associated with a 19% decrease in LOS (effect ratio 0.81; 95% CI 0.78–0.84; $P < .01$). After adjustment for procedure type, age, sex, race, Elixhauser Comorbidity Index readmission score, and ERAS-associated medications, alvimopan administration was associated with a 15% decrease in LOS (effect ratio 0.85; 95% CI, 0.82–0.88; $P < .01$). Other medications associated with decreased LOS after adjustment included oral acetaminophen (effect ratio 0.90; 95% CI, 0.87–0.92; $P < .01$) and ketorolac (effect ratio 0.88; 95% CI, 0.85–0.90; $P < .01$). Gabapentin (effect ratio 0.97; 95% CI, 0.94–1.01; $P = .12$), IV acetaminophen (effect ratio 0.99; 95% CI, 0.96–1.03; $P = .68$), and ketamine (effect ratio 1.00; 95% CI, 0.97–1.04; $P = .84$) were not associated with significant change in LOS. Increased Elixhauser Comorbidity Index readmission scores were associated with longer LOS (effect ratio 1.01; 95% CI, 1.01–1.01; $P < .01$), as was older age (effect ratio 1.02; 95% CI, 1.01–1.03; $P < .01$) and non-white race (effect ratio 1.04; 95% CI, 1.01–1.07; $P = .02$). Female sex (effect ratio 0.97; 95% CI, 0.95–1.00; $P = .02$) was associated with shorter LOS. Right and sigmoid colectomies were also associated with shorter LOS (effect ratio 0.93; 95% CI, 0.89–0.97; $P < .01$ and effect ratio 0.95; 95% CI, 0.91–0.99; $P = .02$, respectively; Table VII).

Table VI
Laparoscopic procedures: Outcomes

	Alvimopan use		*P* value
	No (N = 4,488)	Yes (N = 1,912)	
LOS (d), median	4.0	3.0	<.01
In-hospital mortality	10 (0.2%)	1 (0.1%)	.13
ICU admission	193 (4.3%)	84 (4.4%)	.87
30-day readmission	326 (7.3%)	124 (6.5%)	.26
Total direct cost, median	$8,441.00	$8,268.50	<.01

Table VII
Multivariate analysis of factors associated with length of stay after laparoscopic segmental colon resection

	Effect ratio (95% CI)	*P* value
Age (units of 10 y)	1.02 (1.01–1.03)	<.01
Sex (female versus male)	0.97 (0.95–1.00)	.02
Race (non-white versus white)	1.04 (1.01–1.07)	.02
Elixhauser readmission score (units of 1 point)	1.01 (1.01–1.01)	<.01
Type of segmental colon resection		
Right	0.93 (0.89–0.97)	<.01
Transverse	0.96 (0.90–1.02)	.20
Left	Reference	—
Sigmoid	0.95 (0.91–0.99)	.02
Alvimopan	0.85 (0.82–0.88)	<.01
Acetaminophen IV	0.99 (0.96–1.03)	.68
Acetaminophen PO	0.90 (0.87–0.92)	<.01
Ketamine	1.00 (0.97–1.04)	.84
Ketorolac	0.88 (0.85–0.90)	<.01
Gabapentin	0.97 (0.94–1.01)	.12

PO, per oral.

For patients undergoing laparoscopic procedures, alvimopan was not associated with significant cost difference in both unadjusted (effect ratio 0.99; 95% CI, 0.92–1.07; $P = .81$) and adjusted analysis (effect ratio 0.99; 95% CI, 0.92–1.06; $P = .71$). Administration of IV acetaminophen was associated with a 17% increase in cost (effect ratio 1.17; 95% CI, 1.09–1.25; $P < .01$). No other medications (oral acetaminophen, ketamine, ketorolac, or gabapentin) were associated with statistically significant cost differences. Laparoscopic right colectomy was associated with decreased cost (effect ratio 0.90; 95% CI, 0.83–0.98; $P = .01$), while sigmoid colectomy was associated with increased cost (effect ratio 1.10; 95% CI, 1.02–1.19; $P = .01$). Higher Elixhauser Comorbidity Index scores (effect ratio 1.01; 95% CI, 1.00–1.01; $P < .01$) and increased age (effect ratio 1.02; 95% CI, 1.01–1.03; $P = .03$) were associated with increased total cost. Sex and race were not significantly associated with change in cost (Table VIII).

Discussion

This study demonstrates at the national level that alvimopan administration is associated with reduced LOS for patients undergoing segmental colon resections, regardless of open or laparoscopic approach. Ours is the first on a national level to attempt to

Table VIII
Multivariate analysis of factors associated with total direct cost after laparoscopic segmental colon resection

	Effect ratio [95% CI]	*P* value
Age (units of 10 y)	1.02 (1.01–1.03)	.03
Sex (female versus male)	0.97 (0.93–1.02)	.21
Race (non-white versus white)	1.01 (0.95–1.07)	.79
Elixhauser Readmission Score (units of 1 point)	1.01 (1.00–1.01)	<.01
Type of segmental colon resection		
Right	0.90 (0.83–0.98)	.01
Transverse	1.09 (0.97–1.23)	.14
Left	Reference	—
Sigmoid	1.10 (1.02–1.19)	.01
Alvimopan	0.99 (0.92–1.06)	.71
Acetaminophen IV	1.17 (1.09–1.25)	<.01
Acetaminophen PO	0.99 (0.94–1.05)	.78
Ketamine	1.06 (0.99–1.14)	.11
Ketorolac	0.98 (0.93–1.03)	.41
Gabapentin	1.00 (0.94–1.07)	.91

PO, per oral.

adjust for both patient comorbidities (using the Elixhauser Comorbidity Index) and the effects of common ERAS medications. ERAS protocols have been shown to improve LOS and perioperative comorbidity in elective colorectal surgery; however, there are currently no guidelines recommending inclusion of specific components. Thus, protocols are highly variable depending on individual institutional policy and studies are limited by lack of information regarding implementation and compliance.[21] Within the limitations of our data set, it was impossible to account for all aspects of an ERAS protocol or stratify patients by inclusion or exclusion in an ERAS protocol. We therefore attempted to control for the pharmacologic component of ERAS protocols by adjusting for common ERAS-associated medications, such as oral and IV acetaminophen, ketamine, ketorolac, and gabapentin. By doing so, we think we were able to better isolate the alvimopan-associated effect size and reduce the chances that alvimopan administration was simply a surrogate marker for being enrolled in an ERAS protocol.

Despite the additional cost of medication administration for alvimopan, we noted a slight benefit in total direct cost for patients undergoing open procedures who received alvimopan, and no significant change in cost for patients undergoing laparoscopic procedures. This is likely a result of the shorter LOS associated with alvimopan use noted in both open and laparoscopic groups. It is unclear why there was no cost benefit for laparoscopic patients in our study when previous studies have demonstrated a cost benefit with alvimopan use in both open and laparoscopic procedures.[19,22] One possibility is that any benefit may have been decreased by the overall shorter LOS for the laparoscopic group versus open, and the increased drug costs or cost of laparoscopic supplies. Additionally, it may be that alvimopan is more impactful in patients undergoing open surgery who experience more pain and require more opioid pain medications. Notably our cost analysis does not include the cost savings to the institution or the potential revenue in allowing for additional throughput of patients.

Other significant variables affecting LOS and cost included Elixhauser Comorbidity Index readmission score, age, and type of segmental colectomy performed. For every 1-point increase in Elixhauser readmission score, the associated cost and LOS increased by 1% for both laparoscopic and open procedures. For every 10-year increase in age, the associated LOS increased by 1% and cost by 2% in open procedures, with a 2% associated increase in LOS and cost in laparoscopic procedures. It is unsurprising that older patients with more comorbidities were more likely to have a longer and more expensive hospital admission in comparison to a younger and healthier cohort. Similarly, right colon resections were associated with the shortest LOS and cost, consistent with the decreased complexity in performing this operation compared to left and sigmoid colectomies.

Although the primary aim of our study was to assess the impact of alvimopan on LOS and total direct cost, our results also provided insight into the use of other medications commonly included as part of enhanced recovery protocols. Ketorolac and oral acetaminophen were associated with decreased LOS in both open and laparoscopic groups, with associated decrease in costs for open surgery and no change in costs for laparoscopic procedures. In contrast, IV acetaminophen and ketamine were associated with increased cost for both laparoscopic and open groups, without any corresponding improvement in LOS. This suggests ketorolac and oral acetaminophen may be most beneficial to include as part of enhanced recovery protocols, whereas IV acetaminophen and ketamine were associated with neither cost nor LOS benefit.

One weakness of our study involves limitations in our data set regarding details of medication administration. Although we could assess which medications were administered each day of a patient's hospitalization, we were unable to distinguish details regarding frequency (one-time, as needed, or scheduled) and dose of administration. We assumed that alvimopan was only given at the recommended standardized dose and frequency, and only for on-label use. Our data set also did not include information regarding baseline preoperative opioid use, which would make patients ineligible for alvimopan and may contribute to complications, possibly confounding our results.

Additionally, we did not have information regarding indication for medications administered. Although commonly used as part of ERAS protocols, IV acetaminophen and ketorolac may also be used as rescue medications for patients with uncontrolled pain. We attempted to control for this possibility by restricting inclusion to medications administered on the day of and day after surgery, as medications administered as part of an enhanced recovery protocol would most likely be given early during the hospitalization and in a scheduled fashion. Although this may have confounded the results of our analysis for IV medications, oral medications (acetaminophen and gabapentin) and ketamine are not typically used for rescue purposes and are less likely to be affected. Additional limitations to this study include its retrospective nature and weaknesses associated with large administrative databases, including potential for coding error and inability to assess data quality.

In conclusion, using a large national administrative cohort, we demonstrated that alvimopan use was associated with reduced LOS, regardless of open or laparoscopic approach. Furthermore, administration of alvimopan was associated with decreased costs in those undergoing open procedures and cost-neutral in those undergoing a laparoscopic procedure. Finally, alvimopan was associated with the greatest reduction in LOS for both open and laparoscopic colectomies when compared to other common ERAS medications.

Conflict of interest/Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Discussion

Dr Ian Paquette (Cincinnati, Oh): I enjoyed your talk, and thank you for the invitation to come here and discuss this paper. I have a couple of comments and 2 questions.

I think this work is important because we are trying to improve the outcomes of colorectal patients, and in doing so we sometimes add additional costs. Alvimopan costs about $125 per day. It is nice to see some data showing lower net costs of a hospitalization in the setting of using this medication. Often hospital pharmacy and administration can be a barrier to using these agents.

I think this paper is a nice addition because there's a lot of data that shows this seems to work in open cases. There are some studies, particularly one from the Mayo Clinic, that shows some benefit in the laparoscopic patients, but I think we needed some more data on its use in laparoscopy.

The real reason I think this needed to be done is because we can find a lot of studies in the literature, particularly with large databases, showing that length of stay is lower with this drug. But when I read those studies, I think it's just a marker that those patients that received this drug were on an ERAS protocol and those who didn't get this drug were not on the protocol, so I like that you separated that out and tried to examine other drugs.

This also highlights a lot of the variability on how we take care of patients in the United States. There is a large variability in which medications are used, and very different processes of care are used.

A couple of simple questions. I always look for differences in the patient groups when I try to see if a study like this is valid. I noticed that the comorbidity score was a little bit lower in the patients that received this drug. Could you just explain the Elixhauser index and tell us what goes into that and whether a difference of a score of 1 or 2 points is really clinically significant? I suspect it's not.

Lastly, what do we do with this, and what do you do with this now? At Medical College of Wisconsin, how do you use this drug? Do you use in the lap cases and in open cases? And if you do use it, do you have any kind of criteria for when it should be stopped? Do you keep it through the whole hospitalization? Or is this something that you just use until GI function recovers, and then stop the drug? Because we are talking about $125 a day, and these are discussions that the pharmacists and the administrators are going to want to have if you want to use a drug like this.

I appreciate your comments. Thank you.

Rachel Henning: Thank you, Dr Paquette. Regarding your first question, 29 separate comorbidities were taken into account to create the comorbidity score, and all of these are individually weighted. These scores can range from negative 19 to a positive 89, and in all our multivariate analyses, comorbidity index is found to be statistically significant with a 1-point change in the comorbidity index causing a 1% increase in both cost and length of stay.

Concerning your second question, in Milwaukee, we use alvimopan with every elective segmental colectomy for both open and laparoscopically unless they are on a narcotic preoperatively, and we use it until 7 days postoperatively or until they are discharged home.

Dr Tina Yen (Milwaukee, WI): I have a question of the audience. For people who do bowel surgery, who uses alvimopan? Looks like not many.