Economic Analysis of Alvimopan for Prevention and Management of Postoperative Ileus

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Study Objective. To determine whether alvimopan for prevention of postoperative ileus in patients undergoing small- or large-bowel resection by laparotomy is associated with lower total costs compared with standard care.

Design. Pharmacoeconomic analysis using a formal decision model.

Data Source. Four phase III clinical trials, two pooled analyses, and one meta-analysis.

Patient Population. A cohort of patients who underwent bowel resection with primary anastomosis by laparotomy and received either standardized, accelerated postoperative care (usual care) or usual care plus alvimopan.

Measurements and Main Results. Clinical outcomes, obtained from pooled analyses of published studies, were time to discharge order written, postoperative nasogastric tube insertion, postoperative ileus-related readmission within 7 days, and occurrence of nausea and vomiting. Cost inputs included drugs, nursing labor, readmissions, and hospitalizations. Costs were assessed by determining the net cost of alvimopan use and subsequent reduction in length of stay. Sensitivity and scenario analyses were conducted. Costs for alvimopan were $570 based on an average of 9.5 doses. Given the 18.4-hour mean reduction in time to discharge order written, use of alvimopan reduced hospitalization costs by $2021. Mean difference in overall cost of care, as determined by Monte Carlo simulation, was $1168 (95% certainty interval −$437 to $5879), favoring the use of alvimopan. In the sensitivity analysis, association of alvimopan with lower costs was robust to several changes in key parameters including cost and number of doses of alvimopan, time to discharge order written, readmission rates, and hospitalization cost. In the scenario analyses, alvimopan use yielded a net cost of $226 when no difference in time to discharge order written was assumed. In the scenario analysis using data from a study that did not enforce opioid use, alvimopan resulted in a cost saving of $65/patient.

Conclusion. Alvimopan was cost saving for prevention of postoperative ileus in patients undergoing bowel resection by laparotomy, although these potential cost savings were highly dependent on a difference in time to discharge order written. This finding is not applicable to the less-invasive laparoscopic surgical approach for which quality data on alvimopan use are lacking. Limitations of this analysis included use of time to discharge order written as a proxy for length of stay and difficulty interpreting study results due to inconsistent reporting and conduct of the clinical trials evaluating alvimopan. More research is needed to determine the cost-effectiveness of alvimopan.
Postoperative ileus is a transient cessation of coordinated bowel motility that prevents effective transit of intestinal contents and/or tolerance of oral intake after surgical intervention. Postoperative ileus is common when bowel or nearby structures are manipulated during surgery. Clinical symptoms include delayed and incomplete gastric emptying, abdominal distention, pain, nausea, and vomiting. Complications include atelectasis, pneumonia, and delayed enteral nutrition, ambulation, and wound healing. Recovery time varies from days to weeks. Recovery is complicated by the use of opioids, which can also decrease gastric motility. Postoperative ileus is responsible for causing considerable morbidity in some patients.

Postoperative ileus is a major contributor to delaying hospital discharge after abdominal surgery, increasing length of stay by approximately 2–3 days. In one analysis, 3% of patients undergoing colon and rectum surgeries were readmitted for bowel obstruction and ileus. Postoperative ileus significant enough to be coded in billing records has been associated with substantial increases in length of stay, as well as $8000–10,000/patient in additional costs. Overall, postoperative ileus is estimated to cost the United States health care system $1.46 billion annually.

Alvimopan is a peripherally acting μ-opioid antagonist that has been demonstrated to accelerate upper and lower gastrointestinal recovery after bowel surgery in patients expected to receive opioids for postoperative pain management. Specifically, alvimopan reduces the need for nasogastric tube reinsertion and the occurrence of nausea and vomiting in patients undergoing laparotomy. Alvimopan has also been found to decrease time to discharge order written. Although readmissions due to postoperative ileus were not statistically significantly different in any of the clinical trials, alvimopan reduced the proportion of patients requiring hospitalization for any cause in a pooled analysis. However, with an estimated cost of up to $840/patient, using alvimopan typically results in a substantial addition to the immediate cost of therapy. As a result of this immediate cost, a potential for cardiovascular complications with long-term use, and concerns about off-label use, institutions may restrict or refuse the use of alvimopan.

At the time of undertaking this study, we identified only a single economic analysis of alvimopan in the literature. By comparing only the cost of alvimopan and the cost offsets associated with a reduced length of stay, this analysis showed that alvimopan would be expected to reduce costs. However, significant limitations existed in the methodology used in this analysis, bringing into question the validity of the report’s results. Most important, there was a lack of clarity as to how the cost analysis was developed, and the results were not explored sufficiently by sensitivity analyses.

Given the cost of alvimopan and the need for a more detailed, comprehensive cost-consequence analysis for formulary decision makers, we developed a decision model designed to assess total costs and cost offsets associated with alvimopan use in patients undergoing small- or large-bowel resection by laparotomy and scheduled to receive opioids.

**Methods**

We constructed a formal decision model to assess costs from the health care system perspective. We adhered to the methods recommended by the Panel on Cost-Effectiveness in Health and Medicine and guidelines from the International Society for Pharmacoeconomic and Outcomes Research.
Comparison Groups and Alvimopan Dosing

In this analysis, we compared a standardized, accelerated postoperative care pathway (usual care) with usual care plus alvimopan. The standardized accelerated postoperative care pathway consisted of removal of the nasogastric tube no later than noon on postoperative day 1, introduction of liquid diet and ambulation on postoperative day 1, and introduction of solid food by postoperative day 2. This multimodal approach to accelerate recovery is regarded as best practice in postoperative management of patients undergoing major bowel surgeries.\(^\text{20–23}\)

The alvimopan comparison group was based on the following regimen: alvimopan 12 mg administered 30 minutes to 5 hours before surgery, followed by subsequent maintenance doses of 12 mg given every 12 hours for a maximum of 7 days postoperatively (i.e., maximum of 15 total doses).

Patient Population

We performed the analysis targeting patients undergoing partial small- or large-bowel resection with primary anastomosis by laparotomy and scheduled to receive postoperative pain management with intravenous opioid-based patient-controlled analgesia. The time horizon considered for this evaluation was the duration of hospitalization.

Model Design

We used a decision tree (Figure 1) to assess the net cost of using alvimopan 12 mg versus usual care. The design of both comparison groups was identical. Based on the published results of four randomized clinical trials, we identified length of stay as a primary cost driver in our model.\(^\text{9, 11–13}\) However, time to discharge order written was used as a proxy for length of stay in all four clinical trials.\(^\text{9, 11–13}\) We therefore had to use time to discharge order written in our model rather than the preferable terminal outcome of length of stay. From those studies, we also identified adverse outcomes associated with a considerable cost (i.e., a cost sufficient to potentially alter the expected value of alvimopan in the decision model) and included them in the decision tree. Specifically, we included postoperative nasogastric tube insertion, postoperative ileus-related readmission within 7 days, and occurrence of nausea and vomiting.

Other clinical outcomes of the trials, such as all-cause readmission within 10 days, time to recovery of gastrointestinal function, and time to readiness for discharge, were originally considered but were determined to be irrelevant or have insufficient evidence linking them to important clinical or economic terminal outcomes. In particular, the time to gastrointestinal recovery was measured as a composite end point defined as the later of the following events: tolerance of solid food, first bowel movement, or first flatus. We deemed that this composite outcome served as an intermediate to length of stay and did not add information beyond our existing proxy for length of stay.

Model Inputs

We conducted a thorough literature review of the PubMed database (through September 10, 2011 [no starting date specified]) by using the following search terms: alvimopan, phase III trial, bowel, resection, postoperative, and ileus. First, published randomized clinical trials of alvimopan were obtained and reviewed. We then identified two pooled analyses and a meta-analysis of the trials to support our model inputs of the clinical outcomes.\(^\text{10, 14, 18}\) Clinical inputs were selected from one of the pooled analyses\(^\text{10}\) (Table 1), as this analysis likely presents the most accurate

![Figure 1](Image)

**Figure 1.** Decision analysis model developed to assess the net cost of using alvimopan plus usual care versus usual care alone to prevent postoperative ileus in patients undergoing small- or large-bowel resection by laparotomy. Collapsed branches of the tree (++) are repeats of those shown with different probabilities. The square represents root node, circles represent change nodes, and triangles represent terminal nodes. NGT = nasogastric tube.
estimates available for the effectiveness of alvimopan. Table 1 shows the estimates and proportions reported by each of the studies for outcomes relevant to the model. Table 2 shows the inputs actually used in the base case of the model and the associated sources. The drug cost of alvimopan was estimated by using 80% of the average wholesale price reported in the 2010 Red Book. In the base-case analysis, the mean number of alvimopan doses (9.5) observed in one of the pooled analyses was used (Table 1). Costs of postoperative ileus-related readmission and per-day hospitalization (used to calculate the cost saving associated with the reduction in time to discharge order written) were taken from a systematic review of published studies on the economic burden of postoperative ileus. To estimate resources used in nasogastric tube insertion, we solicited information regarding equipment used (Bard tube and suction canister [Bard Medical, Covington, GA]) and nursing time required from an expert panel of four surgical nurses. The total cost of nursing labor was determined by multiplying average salaries (as reported by the U.S. Bureau of Labor Statistics) by the duration of time to perform insertion obtained from surveying a panel of experts.

For the purpose of our decision model, costs associated with nausea and vomiting were assumed to involve only the antiemetic drug costs and excluded nominal costs such as emesis basins. Given the current guideline recommendations to use an antiemetic agent from a different pharmacologic class in patients with postoperative nausea and vomiting who do not respond to the first drug, we assumed ondansetron and prochlorperazine, both generically available, as the antiemetic agents used in nausea and vomiting, respectively, and estimated these generic drug prices based on 50% of the average wholesale price. All cost data were inflation adjusted to the end of 2010 using the consumer price index for medical care or hospital and related services.

**Sensitivity and Scenario Analyses**

We performed various sensitivity analyses to account for uncertainty in the model assump-

| Variable                              | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 | Pooled Analysis 1 | Pooled Analysis 2 |
|---------------------------------------|---------|---------|---------|---------|---------|-------------------|-------------------|
| No. of Patients                       | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 | Pooled Analysis 1 | Pooled Analysis 2 |
| Usual care                            | 145     | 303     | 224     | 149     | 292     | 695               | 383               |
| Alvimopan                             | 138     | 307     | 222     | 165     | 297     | 714               | 397               |
| Mean alvimopan 12-mg doses (mean)     | NR      | NR      | NR      | 11.6    | 8.9     | 9.3               |                   |
| Time to discharge order written (hrs) | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 | Pooled Analysis 1 | Pooled Analysis 2 |
| Usual care                            | 122     | 138     | 126.2   | 146     | 220.7   | 142.9             | 146.8             |
| Alvimopan                             | 115     | 120     | 126.2   | 126     | 214.8   | 124.9             | 128.4             |
| Difference                            | 7       | 18      | 15.2    | 20      | 5.9     | 18.0              | 18.4              |
| Nausea (%)                            | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 | Pooled Analysis 1 | Pooled Analysis 2 |
| Usual care                            | 68      | 66.2    | 54.0    | 64.2    | 8       | 65                | 60.2              |
| Alvimopan                             | 58.9    | 57.8    | 50.2    | 54.5    | 10      | 56                | 51.1              |
| Vomiting (%)                          | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 | Pooled Analysis 1 | Pooled Analysis 2 |
| Usual care                            | 32      | 24.6    | 25.0    | 25.5    | 8       | 27                | 26.1              |
| Alvimopan                             | 15      | 14.0    | 20.8    | 19.9    | 5       | 19                | 19.6              |
| Readmitted for postoperative ileus (%)| Study 1 | Study 2 | Study 3 | Study 4 | Study 5 | Pooled Analysis 1 | Pooled Analysis 2 |
| Usual care                            | NR      | 1.9     | 11.2    | ~8      | NR      | NR                | 11.7d             |
| Alvimopan                             | NR      | 0.9     | 8.6     | ~4      | NR      | NR                | 7.7d              |
| Nasogastric tube reinstertion (%)      | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 | Pooled Analysis 1 | Pooled Analysis 2 |
| Usual care                            | 6.9     | 10.3    | 8.2     | 14.8    | NR      | NR                | 12.2              |
| Alvimopan                             | 7.2     | 6.0     | 5.5     | 4.8     | NR      | NR                | 6.8               |

In all studies, alvimopan 12 mg was given 2 hours before surgery, then twice/day.  
NR = not reported.  
Methods for pooling data not given. Includes only patients undergoing bowel surgery. Includes studies 1–4.  
Excludes patients undergoing total abdominal hysterectomy. Includes studies 1, 3, and 4.  
Time to discharge order written not provided for each treatment group. Mean study time to discharge order written presented, along with difference. Mean value provided for reference.  
Postoperative ileus-specific readmission rates not reported. Values are total readmission rates.
tions and to address the variability of published data. We did several 1-way and multiway sensitivity analyses over low and high estimates of select variables (Table 2). Each variable was subjected to a 1-way sensitivity analysis. The range over which each variable was varied was chosen based on the 95% confidence interval as reported in the studies that provided the base-case estimates. Where confidence intervals were not available (i.e., doses of alvimopan), we chose the triangular distribution and inputted the range from a pooled analysis\textsuperscript{10} for the extreme values (i.e., 1–15 doses). Specifically, we used the following distributions: beta for event probabilities, log-normal for hospital costs including readmission and nursing time, triangular for number of doses of alvimopan, and normal for the difference in time to discharge order written between the alvimopan and usual care groups. Monte Carlo simulation was then used to evaluate the overall uncertainty of the model result in the base case. All analyses were performed by using TreeAge Pro 2009 (TreeAge Software, Inc., Williamstown, MA).

In addition, several scenario analyses were conducted to address shortcomings identified in the literature supporting alvimopan use. A European study\textsuperscript{24} assessing alvimopan use in post-operative ileus observed a much lower efficacy of alvimopan than did the other four studies\textsuperscript{9, 11–13} Because of potential heterogeneity in the results, specifically a lower utilization of opioids and differences in the European health care system (demonstrated by a longer time to discharge), all European study subjects were omitted from subsequent meta-analyses.\textsuperscript{9–14, 18, 24}

We therefore conducted two scenario analyses using estimates from one European study\textsuperscript{24} to populate the model. In the first scenario analysis, only the base-case estimates for number of alvimopan doses, time to discharge order written, and the probabilities of nausea and vomiting were replaced with those from the European study.\textsuperscript{24} Since nasogastric tube reinsertion and

| Variable                                | Base | Low  | High | Scenario | Sources                  |
|-----------------------------------------|------|------|------|----------|--------------------------|
| **Clinical inputs**                     |      |      |      |          |                          |
| Time to discharge order written (hrs)   |      |      |      |          |                          |
| Alvimopan                               | 128.4| 53.0 | 265.0| 214.8    | Base-case: pooled analysis 2\textsuperscript{10} |
| Usual care                              | 146.8| 67.0 | 280.0| 220.7    | Scenario: study 5\textsuperscript{24} |
| Nausea (%)                              |      |      |      |          |                          |
| Alvimopan                               | 51.1 | 46.0 | 56.0 | 10.0     | Base-case: pooled analysis 2\textsuperscript{10} |
| Usual care                              | 60.2 | 35.0 | 65.0 | 8.0      | Scenario: study 5\textsuperscript{24} |
| Vomiting (%)                            |      |      |      |          |                          |
| Alvimopan                               | 19.6 | 15.8 | 23.4 | 5.0      | Base-case: pooled analysis 2\textsuperscript{10} |
| Usual care                              | 26.1 | 21.8 | 30.4 | 8.0      | Scenario: study 5\textsuperscript{24} |
| NGT reinsertion (%)                     |      |      |      |          |                          |
| Alvimopan                               | 6.8  | 4.8  | 8.4  | 6.8      | Base-case: pooled analysis 2\textsuperscript{10} |
| Usual care                              | 12.2 | 9.1  | 13.9 | 12.2     | Scenario: study 5\textsuperscript{24} |
| Readmission (%)                         |      |      |      |          |                          |
| Alvimopan                               | 1.00 | 0.26 | 1.70 | 1.00     | Base-case: pooled analysis 2\textsuperscript{10} |
| Usual care                              | 2.00 | 0.97 | 3.05 | 2.00     | Scenario: study 5\textsuperscript{24} |
| **Cost inputs**                         |      |      |      |          |                          |
| Alvimopan 12mg                           |      |      |      |          |                          |
| Cost/dose ($)                           | 60.00| 37.50| 75.00| 60.00    | 2010 Red book\textsuperscript{16} |
| No. of doses                            | 9.5  | 5.0  | 14.0 | 11.6     | Base-case: pooled analysis 2\textsuperscript{10} |
|                                        |      |      |      |          | Scenario: study 5\textsuperscript{24} |
| NGT reinsertion                         |      |      |      |          |                          |
| Nursing wage ($/hr)                     | 31.31| 23.00| 50.00| 31.31    | Bureau of labor statistics\textsuperscript{25} |
| Nursing time (hrs)                      | 0.26 | 0.18 | 0.34 | 0.26     | Expert opinion            |
| NGT ($)\textsuperscript{a}             | 12.59| 7.78 | 20.73| 12.59    | --                       |
| Nausea treatment                        |      |      |      |          |                          |
| Ondansetron ($/dose)\textsuperscript{b} | 0.56 | 0.56 | 1.20 | 0.56     | 2010 Red book\textsuperscript{16} |
| Vomiting treatment                      |      |      |      |          |                          |
| Prochlorperazine ($/dose)\textsuperscript{b} | 1.3  | 1.50 | 1.80 | 1.50     | 2010 Red book\textsuperscript{16} |
| Postoperative hospital cost ($/day)     | 1910 | 192  | 7755 | 1910     | Economic burden studies\textsuperscript{8, 26} |
| Readmission cost ($)                    | 29,094| 6365 | 109,187| 29,094   | Economic burden studies\textsuperscript{8, 26} |

\textsuperscript{1}Alvimopan dosage 12 mg 2 hours before surgery, then twice/day.

\textsuperscript{2}NGT = nasogastric tube.

\textsuperscript{a}Includes Bard tube and suction canister.

\textsuperscript{b}Costs of treating nausea and vomiting were assumed to consider only antiemetic agents.

\textsuperscript{c}Postoperative ileus-related readmission within 7 days.
readmission for postoperative ileus were not evaluated in the European study, the probabilities of the outcomes were set equal to the base-case alvimopan values, using estimates from one of the pooled analyses. In the second scenario analysis, we assumed that alvimopan produced no benefit with respect to reducing the need for nasogastric tube reinsertion or postoperative ileus-related readmission, and the model inputs were set equal to usual care. These two scenarios represent the two possible extremes for the effectiveness of alvimopan.

Results

Base Case

In the base-case model, the added drug costs for alvimopan were estimated at $570/person, and there was an estimated cost offset of $2021 resulting from reduced length of stay (as proxied by time to discharge order written) with alvimopan use. Additional cost offsets were realized by reductions in the need for gastric tube reinsertion, nausea, vomiting, and postoperative ileus-related readmissions. Overall, the use of alvimopan resulted in a total cost of $11,084. In comparison, usual care resulted in a total cost of $12,271. Hence, in the base case, alvimopan use was associated with an average savings of $1187/person.

Sensitivity Analysis on the Base Case

The stability of the base case depended primarily on two variables: cost of a hospital day and mean time to discharge. The mean cost of a hospital day created the most variability in the model. Usual care became the preferred option (i.e., total cost less than that of alvimopan) when the cost of a hospital day was reduced below a threshold of $362/day. Similarly, when the difference in time to discharge order written between alvimopan and usual care was reduced to 3.5 hours, usual care became the less costly preferred option. Other variables (the cost and probability of postoperative ileus-related readmission, and the number of doses and cost of alvimopan) were not able to change the base-case results when varied in a univariate manner.

The Monte Carlo simulation conducted on the base case resulted in a mean and median difference in costs of $1168 and $630, respectively. The 95% certainty interval (the interval containing 95% of the observations, removing 2.5% of the observations from each tail of the distribution) was −$437 to $5879. The 80% certainty interval ranged from −$194 to $3008, and 19.6% of all observations fell below $0. Given our distribution inputs for the Monte Carlo simulation, it was not certain that alvimopan would be truly cost saving.

Scenario Analyses

When model inputs for number of alvimopan doses, time to discharge order written, probability of experiencing nausea, and probability of vomiting were set to values observed in the European phase III trial, the use of alvimopan resulted in a total cost of $18,084 compared with the usual care cost of $18,149 (difference $65). When the other model inputs of nasogastric tube reinsertion and probability of readmission were set equal to the base-case values for usual care (i.e., no difference observed), the use of alvimopan resulted in a total cost of $18,375, more costly than usual care by $226.

Discussion

Our analysis provides a much more detailed and comprehensive breakdown of the overall costs associated with alvimopan than the previously published analyses. In our base-case analysis, alvimopan was likely cost saving, as was the case in two previously published cost analyses. Alvimopan achieves a net cost saving in our model, provided time to discharge is reduced by an average of at least 3.5 hours. However, in the Monte Carlo simulations, the 80% certainty interval included $0, indicating a potential that alvimopan may not be cost saving given uncertainty in the underlying parameters of the model. Furthermore, when looking at our scenario analysis including the results of the European study, it appeared that alvimopan could increase the total cost of care. This has important policy implications for institutions that do not uniformly enforce patient-controlled opioid analgesia for postoperative pain management, as described below.

Our analysis is primarily limited by the strength of the data available in existing publications. One pooled analysis well described statistical methods, including an analysis of the between-treatment effects among the three included clinical trials. The other pooled analysis included an additional study but did not sufficiently describe the methods used for pooling data or whether any validity analyses were conducted. However, both pooled analyses excluded the...
large European phase III study\textsuperscript{24} in which alvimopan outcomes were not as favorable as outcomes in the North American studies. Inclusion of the European study’s findings would have considerably reduced the differences seen in length of stay between alvimopan and usual care, possibly but not likely impacting the statistical significance of the findings.

Furthermore, inconsistencies in the numbers of included subjects between the two pooled analyses bring into question the validity of these results. Specifically, the number of subjects and reasons for exclusion in one pooled analysis appear well documented (Table 1).\textsuperscript{10} The pooled results and economic analysis in the other pooled analysis\textsuperscript{18} included an additional study,\textsuperscript{11} but the total number of subjects analyzed is greater than that of both pooled analyses and the additional study combined. In addition, the reported rates of nausea and vomiting do not appear consistent between the pooled analyses, even with data from the additional study. Because of these limitations in that pooled analysis,\textsuperscript{18} we chose to use the results of the other pooled analysis\textsuperscript{10} as the base-case inputs for our model.

As stated in the previous reports,\textsuperscript{10, 18} clinical practice in U.S. and European hospitals differed in relation to use of opioids during these clinical trials, and hospital length of stay was longer for the European study subjects.\textsuperscript{29–31} These differences have also been shown between Canadian and U.S. hospitals.\textsuperscript{31–33} Despite these differences, Canadian study subjects remained in the pooled analyses whereas those in the European study were excluded. Furthermore, significant issues with using randomized clinical trials in economic analyses\textsuperscript{31} were not addressed in the sensitivity analysis by the authors of one of the pooled analysis.\textsuperscript{18} Clinical trials notoriously attempt to standardize care in ways that are different from usual clinical practice to reduce heterogeneity and improve the effect size. The North American studies mandated use of patient-controlled opioid analgesia as well as placing restrictions on nonopioid analgesics, while promoting discharge after achievement of the gastrointestinal recovery outcomes.\textsuperscript{18} In many large, urban, European hospitals, acute pain clinicians promoted and monitored patient-controlled analgesia.\textsuperscript{34, 35} Thus, the differences observed in the European study may have had more to do with the study design that allowed more freedom for variability in pain management than with regional discrepancies in clinical practice. Given the uncertainty raised by this possibility, we chose to conduct an additional scenario analysis using data from the European study\textsuperscript{24} to provide formulary decision makers with additional information on which to base their decisions.

Alvimopan was compared with the standard of care for managing postoperative ileus in clinical trials, namely, nasogastric tube insertion, early administration of intravenous fluids and solid food, and encouragement of early ambulation. In recent studies, chewing gum has been shown to improve time to first bowel movement and to reduce hospital length of stay after appendectomy,\textsuperscript{36} radical cystectomy for bladder cancer,\textsuperscript{37} and abdominal surgery.\textsuperscript{38} Results of a meta-analysis suggest that given its safety profile and beneficial effects, chewing gum should be offered to select patients after assessment of mental status and aspiration risk.\textsuperscript{38} Studies are needed to assess whether alvimopan is superior to chewing gum and if the addition of alvimopan to chewing gum results in further reductions in length of stay or other benefits.

The use of laparoscopy, a less invasive surgical procedure, has also been shown to reduce postoperative surgical complications including gastrointestinal recovery time, vomiting, and hospital length of stay.\textsuperscript{15, 39, 40} Decreased manipulation of the bowels and less pain and subsequent opioid use are likely factors in these findings. In the phase III clinical trials evaluating alvimopan, only patients who underwent laparotomy were enrolled. One retrospective analysis evaluating the use of alvimopan in patients undergoing either open or laparoscopic bowel resection suggested that similar benefits may be observed in those undergoing laparoscopic surgery.\textsuperscript{28} However, this study used an open-label design and retrospective analysis with insufficient sample size (given the results observed in prospective clinical trials) and had substantial and important differences in baseline patient characteristics. Nonopioid use was higher in the alvimopan group, and total exposure to opioids (total dose given) was not controlled for in the analyses. Given these serious limitations, it remains unclear whether alvimopan results in improvements in postoperative ileus-related outcomes in patients undergoing laparoscopic surgery.

Limitations

There are several important limitations to our pharmacoeconomic analysis. As mentioned above, inconsistent reporting of clinical and economic outcomes in meta-analyses, differences in the conduct of clinical trials, and
difficulty interpreting these results were a major concern. In an effort to overcome these limitations, we made a written request for data from the manufacturer of alvimopan but received no response. Without access to primary data from the clinical trials, we attempted to address these issues using sensitivity analyses to provide formulary administrators with the most information possible on which to base their decisions.

We were unable to quantify benefits of alvimopan in terms of an effectiveness or utility measure such as quality-adjusted life-years gained, due to the relatively minor impact of the drug on outcomes that affect these measures. There may be willingness by some to pay an additional amount for a drug that decreases vomiting and improves patient satisfaction by reducing the need for a nasogastric tube, rehospitalization, and decreased length of stay. However, because of the small potential gains associated in these outcomes by alvimopan, these benefits were not included in our analysis.

We did not consider the potential increased risk of bowel perforation or other adverse events in our analysis. Most documented adverse events associated with alvimopan use appeared to be either minor or no different from those in control subjects. In the case of bowel perforation, this rare event is unlikely to significantly affect the economic analysis, but should be considered carefully by clinicians as it changes the risk:benefit ratio of alvimopan. More research is needed to determine the incidence, severity, and consequences of this potentially serious complication.

Finally, a factor limiting the accuracy of these findings pertained to the use of time to discharge order written instead of the actual time to discharge. This was necessary due to the use of this surrogate marker in the primary sources of data. Although it is not clear that this difference biases the results in any way, using the actual time to discharge would have been a more appropriate way to determine changes in the length of stay.

Conclusion

Alvimopan is a potentially useful drug in the treatment of patients undergoing bowel resection surgery by laparotomy. The drug is likely to reduce hospital length of stay and total cost of care in this population, although limitations exist in published reports that raise questions regarding the certainty of these findings. Research is needed to determine the effects of alvimopan when chewing gum is used as part of the postsurgical regimen or when surgery is performed using laparoscopic procedures.

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