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REVIEW

Clinical and Economic Consequences of the Treatment of Postoperative Ileus with Alvimopan

S.Bader, K.Jaroslawski, H.E. Blum and G. Becker

Department of Palliative Care, University Hospital Freiburg, Robert-Koch-Str. 3, D-79106 Freiburg, Germany.
Corresponding author email: sabine.bader@uniklinik-freiburg.de

Abstract: Postoperative ileus (POI) increases morbidity and prolongs hospital stay after bowel resection. Alvimopan is a μ-antagonist designed to counteract gastrointestinal side effects of opiates without impairing analgesia due to its inability to pass the blood brain barrier. Because of its association with myocardial events in a long term study where it was applied to treat opiate-induced constipation, approval by the FDA in 2008 for POI is restricted to short term inpatient use. This review gives an overview about pharmacology, efficacy and economic aspects of alvimopan for the treatment of POI. Alvimopan consistently accelerated gastrointestinal recovery in all moderately well designed trials represented by decreasing the time to first bowel movement and tolerance of solid food after surgery. There is limited evidence about its economic impact by shortening the length of hospital stay. Its role in upcoming multimodal perioperative "fast track" programs cannot be defined from currently available data.

Keywords: Alvimopan, μ-antagonist, opiate antagonist, postoperative ileus

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Introduction

Postoperative ileus (POI) is a complex, well known clinical problem of vague definition and not completely understood multifactorial pathophysiology which can become a significant burden to patients. Peritoneal lesion and physical manipulation on the intestines impair coordinated bowel motility, thereby decreasing the tolerance, propulsion and proper digestion of food. This results in the absence of bowel sounds, flatus and bowel movements during a postoperative period and can lead to distension of the abdomen, intestinal accumulation of fluids and gas, pain, nausea and vomiting. Motility of the gut and its ability to digest recover usually during the first five days after surgery.[1] Prolongation of this period might lead to a nutrition deficit and therefore impair the immune defense. This can lead to delayed wound healing, hence late ambulation, pulmonary atelectasis with pneumonia and deep vein thrombosis with the potency for pulmonary embolism as secondary complications.[2,3] There are no validated patient-reported outcome measures available to evaluate the patients' perception of the problem, but it seems obvious that higher postoperative morbidity might impair individual patients' quality of life and also increase the length of hospital stay, resource use and health care costs for the community.[4,5]

POI is the most common reason for prolongation of length of hospital stay.[6,7] A large US American study using the databases of 160 hospitals revealed that if "paralytic ileus" or "digestive system complication" after abdominal surgery was coded in patients' records, the average length of hospital stay was significantly increased (11.5 versus 5.5 days). The average costs for the hospital stay per affected patient doubled from about 9000 to 18000 USD in 2002. This attributed about 1.46 billion USD to the country's annual health care costs.[8] Therefore, shortening the hospital stay is a desirable accessorial goal of a POI treatment for economic reasons as well.

Pathophysiology

Several pathophysiological mechanisms for this phenomenon have been identified on animal models. Motility disturbance in the stomach wall after surgery has been shown to be associated with disorganized and uncoordinated electrical activity and lack of coordinated propulsion.[9] Changes in fluid balance, hormone levels and electrolyte concentrations during and after surgery might additionally impair peristalsis.[2,10] Stress related elevation of sympathetic activity triggers local and spinal vagal reflexes which inhibit gastrointestinal motility.[11] The apparently close interaction between reactive local inflammation, afferent and efferent sympathicus activation and the release of endogenous opioids is not completely understood but might be crucial to understand how different therapeutic interventions (sympathicus blockade by thoracic epidural analgesia, antiinflammatory drugs, opioid-antagonists) might complement or counteract each other. During the first 24 hours after mechanical manipulation, leucocytes invade the gut wall and secrete inflammatory mediators impairing propulsive smooth muscle activity.[12] Endogenous opiates potentiate the induction of the enzyme nitric oxide synthase in leucocytes and the release of nitric oxide from phagocytes. Nitric oxide is the main inhibitory transmitter of the gut's motor activity.[13] The interaction between opiates and leucocytes over the μ-receptor has also been reported to modulate the immune system in a potentially harmful way.[14,15] On top of those physiological reactions of the body to stress, the use of opioids in post-surgical pain management inhibits propulsive gastrointestinal motility over the same mechanisms as endogenous opioids do.[16,17]

So far, the efficacy of traditional approaches to prevent prolonged POI, such as the placement of nasogastral tubes, infusion of high fluid amounts, early mobilisation and the application of laxatives has not been proven in controlled trials. Some interventions have even been shown to be harmful.[2]

Attempts are made to treat POI pharmacologically, but a recent Cochrane review revealed that there are few medical treatments in discussion. They are not sufficiently supported in their efficacy by reliable randomised controlled trials to be recommended in routine clinical use.[18]

One pharmacodynamic approach is the blockade of the opioid-induced inhibition of propulsive motoractivity in the gut which is mainly mediated through μ-receptors.[19–21] Alvimopan (Adolor Corp, Exton, PA), a synthetic, oral, peripherally active μ-antagonist, has been shown to be highly effective in mice, counteracting morphium-induced reduction of gastrointestinal motility.[22] It revealed promising results in several phase II and III trials by antagonising the inhibitory effect of opiates to the

motility of the gut without impairing pain relief or causing withdrawal symptoms.[23–26] Alvimopan also reversed codein-induced colonic transit delay in healthy volunteers.[27]

In the United States, alvimopan has received Food and Drug Administration approval for preventing postoperative ileus by accelerating the time to upper and lower gastrointestinal recovery following partial large or small bowel resection with primary anastomosis in May 2008. It is restricted to inpatient and short term use because it has been associated with a higher risk for myocardial infarction in a trial for long term use against opiate-induced constipation.

This review aims to present and critically appraise the evidence of safety and efficacy of alvimopan in clinical use to prevent POI and its economic implication for health care costs. The search strategy for literature is described in Table 1.

Table 1. Literature retrieval, modified from Deibert.[45]

Search strategy for literature retrieval
We performed a literature search using OVID's interface of the following databases: OVID MEDLINE, including Medline in Process and other non indexed citations (1950–2011), Cochrane Database of Systematic Reviews (4. Quarter 2010), Cochrane Central Register of Controlled Trials (4. Quarter 2010), BIOSIS Previews (1969–2011). The databases were searched by a two step strategy. Step one revealed articles identified by the terms 'alvimopan', 'ADL 8-2698' and 'LY246736' and in step two we searched for articles about postoperative ileus and combined the results. The searches were limited to clinical trials, humans only. In addition, searches were performed in NLM's PubMed (1966–2011) and on the internet using science-specific search engines Scirus and Google Scholar with the search terms 'alvimopan', 'ADL 8-2698' 'LY246736', 'constipation', 'intestinal obstruction', and 'postoperative ileus'. For identifying further trials we went to several trials registers, including Current Controlled Trials Ltd., (http://www.controlled-trials.com), World Health Organisation International Clinical Trials Registry Platform ICTRP (http://www.who.int/trialsearch), National Institutes of Health Randomized Trial Records (http://clinicaltrials.gov) and Pharmaceutical Industry Clinical Trials Database, initiated by the Association of the British Pharmaceutical Industry (http://www.abpi.org.uk). Last date of search was March 31st 2011. In addition, reference lists of articles retrieved were screened for relevant publications. To reveal publications about economic aspects of Alvimopan an additional search was conducted with the search terms 'Alvimopan' and 'economics'.

Pharmacology

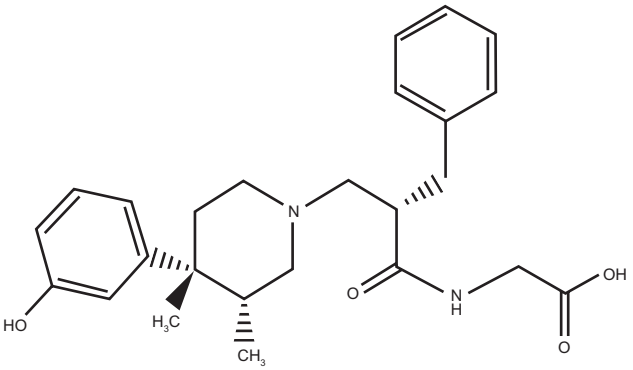
Alvimopan (Table 2) is a zwitterionic molecule, a quaternary highly selective long acting opiate antagonist with negligible activity at the δ- and κ-receptors and high binding affinity for the μ-receptor. It does not pass the blood brain barrier because of its high polarity and size.[22] Pain reduction through opiates is primarily mediated by μ-receptors located in the central nervous system and therefore not affected by alvimopan.[2,15,28] None of the trials presented reported any reduction on opiate-based pain control.

Orally taken, alvimopan becomes partially metabolized by the gut flora into its primary amid metabolite ADL 08-0011 which is absorbed. ADL 08-0011 exhibits affinity to and activity on the μ-receptor in vitro and in vivo equally to alvimopan. Its clinical effect after the application of the primary drug alvimopan is unknown.[29] Unlike alvimopan, ADL 08-0011 has a tendency to accumulate when alvimopan is applied 12 mg b.i.d. after multiple doses. It shows a wide range in most pharmacokinetic variables. They depend on different factors of the individual subject like race, geographic habitat, presence of inflammatory bowel disease (IBD) or co-medication like antibiotics and acid blockers. This might be due to differences in the gut microflora because the metabolization of alvimopan into ADL 08-0011 depends on bacterial processes. Since most surgical patients will receive antibiotic treatment ADL 08-0011 will be significantly less (about 81% less) absorbed and is therefore expected to not play a clinical role in the efficacy of alvimopan for the treatment of postoperative ileus.[30]

No clinically relevant differences in pharmacokinetic behavior have been noticed among those different subgroups of patients for alvimopan itself. In a meta-analysis of a series of clinical trials to explore its pharmacokinetics in different groups of patients and healthy volunteers, there was no variation in pharmacokinetic function depending on weight, gender, height, body mass index, presence of inflammatory bowel disease, renal function, concomitant antibiotic use, acid blocker use or P-glycoprotein inhibitor use.[30]

Oral bioavailability of alvimopan in humans is low (6%) to begin with and decreases with higher doses.[15,30] That suggests that the absorption might be a saturable process.[30] Food curtails the rate and extent of absorption, which may be due to a shorter transit time through the gut. Alvimopan's low intestinal absorption

Table 2. Pharmacokinetic descriptives of alvimopan.[30,31,46]

	Alvimopan/entereg 2-([(2S)-2-([(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl)-3-phenylpropanoyl]amino)acetic acid ADL 08–2698 SB767905
Molecular weight	460.1Da
Structure	
Route	Oral (Bioavailability in humans 6%)
tmax h	1.5–3 (after 12 mg single oral dose, decreased slightly by age, increased slightly by slower gastrointestinal passage)
t1/2 h	2.4–5.5 h (after 6–24 mg single oral doses in healthy volunteers)
Receptor	High affinity to μ-receptor (Kd 0.35 nM in vitro), 30-fold less potency at κ and δ receptors
Cmax ng/ml	About 10 ng/ml (range 5–16) after a 12 mg single oral dose, absorption decreases insignificantly with age
AUC ng/h*ml	46.1 (SD 19.1)
Elimination	Elimination 65% biliary and about 35% renal, reabsorption in the gut, no accumulation at the dosage of 12 mg twice daily, therefore no dose adaption for renal or hepatical impairment, plasma clearence 254 l/h,
Active metabolite	Active primary amid metabolite ADL 08-0011, metabolized by gut flora, clinical outcome not affected by metabolism

rate per time decreases in surgical patients, but plasma concentration and absolute extent of absorption increase, probably because of a slower gastrointestinal passage and therefore longer residence time of the drug in the gut. A slightly higher plasma concentration in elderly subjects was minor compared to inter-subject variability and might therefore be clinically irrelevant.[30,31]

Alvimopan is mainly fecally eliminated without major hepatic metabolization and renal impairment is of no clinical relevance for its plasma level. No dose adaption has to be made for patients with renal or hepatic insufficiency.[15]

Clinical Trials

Seven randomized placebo controlled clinical trials have been identified and shall be presented here to demonstrate the efficacy of alvimopan in clinical practice (Table 3).[32]

In 2001 Taguchi published the first trial where 78 patients received either placebo, 1 mg or 6 mg of alvimopan two hours before open abdominal surgery (15 hysterectomy, 63 partial colectomy) and twice daily up to the first bowel movement or until hospital discharge, in order to evaluate the effect of this intervention on the postoperative recovery of gastrointestinal function. He reported a significant shortening of the time to first flatus, first bowel movement and hospital discharge only for the 6 mg group. There was a significant reduction in nausea and vomiting without any impairment of analgesia or occurrence of other side effects. The trial was well designed, but conducted at a single site where patients underwent a strict treatment with patient-controlled intravenous opiate-based analgesia, early diet, early removal of the nasogastric tube and fast mobilization, which might be one reason, why the overall median time to discharge was much shorter than national average.[33]

Table 3. Alvimopan for postoperative ileus (modified from Becker[32]).

	Design	Patients	Intervention	Outcome
Taguchi 2003	RCT, parallel group	n = 78 15 hysterectomy 63 part colectomy	1. Placebo 2. 1 mg Alvimopan 3. 6 mg Alvimopan 2 Hours before and b.d.i. until first bowel movement or discharge	Significant decrease for group 3 compared to 1 in the time until 1. First flatus (70 hrs > 49 hrs) ($P = 0.03$) 2. First bowel movement (111 hrs > 70 hrs) ($P = 0.01$) 3. Hospital discharge (91 hrs > 68 hrs) ($P = 0.03$) Significantly less nausea and vomiting in group 3 no difference in pain, itching, abdominal cramping, use of opioids
Herzog 2006	RCT, parallel group	n = 519 only hysterectomy	1. Placebo (n = 106) 2. Alvimopan 12 mg (n = 413) 2 Hours before surgery and b.d.i.for postoperative day 1–7	In treatment group: 1. Nausea and vomiting not significantly higher but mainly on the first postoperative day, 2 2. Constipation was not significantly lower 3. Significantly accelerated GI-2 recovery, because of significantly earlier first bowel movement (hazard ratio, 2.33; $P < .001$) by 22 hours
Delaney 2005	RCT, parallel group	n = 451	1. Placebo (n = 153) 2. Alvimopan 6 mg (n = 150) 3. Alvimopan 12 mg (n = 146) 2 Hours before surgery and b.d.i.for max. postoperative day 1–7	Group 3 vs 1: 1. Mean time to gastrointestinal recovery significantly reduced (hazard ratio = 1.45; $P = 0.003$), 2. Mean time to the hospital discharge order significantly accelerated (hazard ratio = 1.50; $P < 0.001$), 14 hrs earlier Smaller not significant reduction seen with alvimopan 12 mg Incidence of nausea and vomiting reduced by 53 percent in the alvimopan 12-mg group
Wolff 2004	RCT parallel group	n = 469 451 bowel resection 18 radical hysterectomy	1. Placebo (n = 165) 2. Alvimopan 6 mg (n = 169) 3. Alvimopan 12 mg (n = 176) 2 Hours before surgery and b.d.i. for max. postoperative day 1–7	Group 2 vs 1: 1. Time to recovery of GI function accelerated (hazard ratio [HR] = 1.28; $P < 0.05$) mean difference 15 hrs Group 3 vs 1 1. Time to recovery of GI function accelerated (HR = 1.54; $P < 0.001$), mean difference 22 hours, 2. The time to hospital discharge order written significantly accelerated (HR = 1.42; $P = 0.003$) with a mean difference of 20 hours The incidence of adverse events was similar among treatment groups, no change in pain scores

(*Continued*)

Table 3. (*Continued*)

	Design	Patients	Intervention	Outcome
Viscusi 2005	RCT, parallel group	n = 615 418 bowel resection 197 hysterectomy	1. Placebo (n = 224) 2. Alvimopan 6 mg (n = 220) 3. Alvimopan 12 mg (n = 221) 2 Hours before surgery and b.d.i.for max. postoperative day 1–7	After adjustment for significant covariates (sex/surgical duration), Alvimopan did accelerate 1. GI-3 compared with placebo (6 mg: HR = 1.24, $P = 0.037$; 12 mg: HR = 1.26, $P = 0.028$). Alvimopan accelerated time to 1. GI-2 (6 mg: HR = 1.37, $P = 0.008$; 12 mg: HR = 1.33, $P = 0.018$) and 2. DCO (6 mg: HR = 1.31, $P = 0.008$; 12 mg: HR = 1.28, $P = 0.015$). Adverse events were similar between groups.
Ludwig 2008	RCT, parallel group	n = 654 only bowel resection	1. Placebo (n = 325) 2. Alvimopan 12 mg (n = 329) **30–90 Minutes** before surgery and b.d.i. for max. postoperative day 1–7	Alvimopan, 12 mg accelerated significantly 1. GI-2 recovery, 2. GI-3 recovery, and 3. Time to hospital discharge compared with a standardized accelerated postoperative care pathway alone (hazard ratio = 1.5, 1.5, and 1.4, respectively; $P < .001$ for all). Opioid consumption was comparable between groups Alvimopan was associated with reduced postoperative ileus-related morbidity compared with placebo.
Bücheler 2008	RCT, parallel group	n = 738 only bowel resection	1. Placebo (n = 242) 2. Alvimopan 6 mg (n = 248) 3. Alvimopan 12 mg (n = 251) 2 Hours before surgery and b.d.i.for max. postoperative day 1–7 NSAID allowed	Alvimopan (6 mg,12 mg)significantly reduced mean time to tolerate solid food (14.3 hrs, 10.7 hrs) in all patients Only patients receiving PCA experienced decrease in time to GI-2 which reached statistical significance (post hoc analysis) Adverse events similar in all groups

In a gynecological multi-center trial patients underwent simple total abdominal hysterectomy and perceived either placebo or 12 mg alvimopan at least two hours before the scheduled operation and twice daily for postoperative days 1–7. Time to first bowel movement was significantly decreased. The medication was given beyond hospital discharge and patients kept diaries to report further side effects. The exact method of data collection was not reported. Overall, the most common adverse events were nausea, vomiting and constipation. Nausea and vomiting were insignificantly more frequent in the treatment group on the first postoperative day but not different later on, whereas constipation tended to be improved by alvimopan.[34]

As part of a phase III clinical development program, four independent multi-center trials comprising more than 2000 patients in North America have been conducted and finally led to the approval of the drug by the FDA in May 2008. Two of these studies had received funding from the pharmaceutical company involved and some co-authors were employees of these sponsors. The quality of following trials was rated as moderate by a recent Cochrane review due to methodological or reporting deficiencies.[18] Not enough details about the method of randomization and blinding were provided and the intention to treat principle was not properly applied in any of those trials. None of the trials had provided information if the proportional hazards assumption had been violated or fulfilled. Pooling data of those American trials

in a meta-analysis of this Cochrane review confirmed, that alvimopan shortens the time between surgery and first bowel movement, time to reach GI-2 and time to tolerate solid food. It also reduces the length of hospital stay (Table 4). The analysis did not detect a significant dose-response in efficacy of the drug.[18]

Most trials were comprised of patients receiving partial intestinal surgery or hysterectomy excluding laparoscopic interventions. Postoperative analgesia for all subjects was patient-controlled intravenous opiate application and clinical management included early ambulation, removal of the nasogastric tube earlier than noon of and first fluid diet intake on the first day after surgery. None of these trials reported any impairment of analgesia measured by opiate consumption and visual analog scale (VAS) pain scores. No difference in adverse effects was noticed unless mentioned below. Most of them showed a reduction in time to bowel recovery and time to hospital discharge.

In the trial reported by Delaney et al, the mean time to gastrointestinal recovery and hospital discharge was reduced by alvimopan, but surprisingly only reached statistical significance for 6 mg and not for 12 mg. The authors implied that the statistics were attenuated because a high number of patients in the 12 mg alvimopan group discontinued study and treatment for gastrointestinal adverse events which were not further specified. The incidence of nausea and vomiting was reduced by 53% in the alvimopan 12 mg group.[35]

Wolff et al detected a dose-response concerning the time to discharge from the hospital. Only the 12 mg alvimopan group had a significantly shorter stay of about 22 hours less than the placebo group. They also reported a slightly higher daily opioid consumption rate for the patients who took 6 mg alvimopan (33.6 mg) than in the placebo (27.0 mg) and the 12 mg group (27.1 mg). This was statistically significant but not judged as clinically relevant by the authors.[28]

In the trial presented by Viscusi, GI-3 (tolerance of solid food and first bowel movement or first flatus completed) results did only reach statistical difference after adjusting for relevant covariates like sex and duration of surgery.[36]

Using a pooled data analysis of these last three trials, Delaney showed a dose-response of alvimopan for gastrointestinal recovery after bowel resection (GI-2 = time to first toleration of solid food and first bowel movement and GI-3 = time to first toleration of solid food and first flatus or bowel movement) and also for time to hospital discharge. In a subgroup analysis, females and patients older than 65 only benefitted from 12 mg alvimopan concerning the time to reach GI-3.[37]

Therefore the next trial was performed with only 12 mg alvimopan versus placebo and showed that a shortening of the time between first application of the drug from more than two hours to 30–90 minutes before surgery did not have any impact on its effect on bowel recovery. Most adverse effects were fewer in the alvimopan group and for nausea and vomiting this decrease even reached statistical significance.[38]

In 2008, a trial with a similar design and 738 patients was presented by Bücheler et al. It was conducted in 11 countries outside of America. Contrary to the trials conducted in North America, patients were not restricted to PCA and allowed to take NSAID as postoperative pain control. The trial showed a reduction of time to gastrointestinal recovery (GI-2 and GI-3) without reaching statistical significance. By post hoc analysis this decrease in recovery time reached statistical significance in the subgroup of patients receiving patient-controlled analgesia per intravenous opiate-infusion. These patients also showed a significantly higher consumption of opioids in the first 48 hours after surgery. All American patients had received PCA. In the European trial only the patient subgroup with PCA profited significantly from the treatment. This implies a restriction of alvimopan's effectiveness in patients who receive this kind of analgesia and the clinical outcome in all

Table 4. Pooled data analysis of four RCTs in North America by Cochrane review.[18,28,35,36,38]

	Hazard ratio for alvimopan 12 mg	Hazard ratio for alvimopan 6 mg
First bowel movement	1.74 (95% CI 1.20, 2.34)	1.60 (95% CI 1.32, 1.92)
Time to reach GI-2	1.59 (95% CI 1.33, 1.90)	1.41 (95% CI 1.22, 1.63)
Time to toleration of solid food	1.14 (95% CI 1.00, 1.29)	1.57 (95% CI 1.04, 2.37)
Length of hospital stay	1.31 (95% CI 1.2,1.43)	1.38 (95% CI 1.22, 1.57)

studies might be mainly caused by antagonizing the effect of exogenous opiates.[39]

All trials quoted have a similar set up and comprise a small spectrum of clinical situations. Even if in these settings alvimopan has shown to be effective, more evidence is needed to evaluate its role in everyday clinical use. Because of strict exclusion criteria in all of those trials, no patients on chronic opiate therapy have been researched. Only the European trial allowed the postoperative use of NSAID which were taken by 69% of those patients. Anti-inflammatory drugs have shown to be effective in postoperative pain management and have an effect on POI by either sparing opioid consumption or by reducing the inflammation process in the gut wall which impairs propulsive motoractivity. They could therefore influence the effect of opiates and alvimopan.[40] More research is needed on postoperative ileus for other visceral surgical and anesthetic procedures. No trials have been performed on patients undergoing laparoscopic procedures and epidural local anesthesia, which are both common procedures to improve surgical outcome concerning POI in so called multimodal "fast track" enhanced recovery programs.[41]

Economic Aspects

In controlled settings of the RCTs presented above in North America, alvimopan shortened the length of hospital stay significantly to approximately a day less than the placebo. A post hoc economic base-case and sensitivity analysis of those trials combining alvimopan and hospital costs for each patient assigned a reduction of mean estimated hospital costs of 879-$977USD to patients who received alvimopan compared to those treated with placebo.[42]

There was no effect of alvimopan on length of hospital stay found in the European study. LOS was 3–4 days longer in the European placebo group than in the American equivalent indicating that regional differences in multimodal care pathways and discharge management might play a big role for this clinical and economic outcome. The placebo group's mean length of stay was still shorter than registered in several European countries according to a recent survey, also implying that other factors in the study design with its standardized clinical procedures might play a role in shortening the time until discharge.[43]

From the clinical point of view POI is a multifactorial phenomenon. To prevent it might involve an intelligent combination of different interventions. Whether or not clinical benefit of alvimopan translates into cost reducing effects by shortening of hospital stays or decreasing readmission rates independently from the health care setting cannot be deducted from the evidence of these RCTs. RCTs are designed with standardized procedures and conducted in homogeneous health care settings to evaluate clinical effects especially in early stages of drug development. Even if secondary endpoints of potential economic interest like LOS are reported, the size and mechanism of their impact cannot be transferred directly to real life situations nor to other organizational environments. Any contribution to this outcome by the trial's standardized procedure is hard to isolate. The fact that in all these trials the LOS was significantly shorter than in "real life statistics" demonstrates this problem very well. Economic evaluation of medical interventions therefore has to be done in the individual health care system to obtain relevant quantitative results.

In 2008, after the restricted approval of the FDA and the introduction of alvimopan into clinical practice in the USA, Absher et al conducted an open label, multi-hospital prospective study on 108 patients with a retrospective chart review (91 patients) comparing length of hospital stay and post-operative morbidity judged by rates of nasogastric tube insertion and hospital readmission rate within 30 days for patients receiving alvimopan while undergoing bowel resection.[44] Contrary to the RCTs mentioned above, patients who underwent laparoscopic procedures (LBR) were included and there were no clinical pathways nor restrictions for postoperative analgesia specified as inclusion criterion. Most patients in both groups again received PCA, which seems to be the routine method of choice in the US. Hospital LOS was 1.2 days (5.6 days) shorter in the alvimopan group than in the retrospective cohort (6.8 days) with no difference between open and laparoscopic surgery. For patients over the age of 70 this effect was even larger with an average difference of 3.2 days less. Mean costs the authors assigned to any additional day in the hospital for the control group were 1357USD for patients undergoing open (OBR) and 938USD for laparoscopic surgery (LBR). Costs for a single dose of alvimopan including labor cost (2.5USD) was

Table 5. Executive summary.

Clinical problem	• Postoperative ileus (POI) prolongs length of hospital stay • POI is followed by higher postoperative morbidity • Limited efficacy of current treatments
Mechanism of action	• Alvimopan blocks μ-receptors in the gut • Counteracts opiate-induced inhibition of gastrointestinal recovery • Increases propulsary smooth-muscle activity in the gut
Pharmacokinetics	• Tmax 1.5–3 h • T1/2 = 2.4–5.5 h • Limited to the periphery, too polar to pass blood-brain barrier • Only 6% oral bioavailability • Active metabolites ADL 08-0011 clinically not relevant • 65% fecal, 35% renal elimination • No danger of accumulation
Clinical efficacy for POI	• Significantly shorter time to gastrointestinal recovery • Significantly shorter time until hospital discharge (ca.20 h) *Only proven for patients receiving patient controlled intravenous opiate-based analgesia*
Safety and tolerability	• Associated with myocardial ischemia in long term use for opiate-induced constipation, therefore only inpatient, short term use • No accumulation • Reduction of nausea and vomiting, but data not significant • No reduction of pain control • No sufficient data on long and medium term usage
Dosage and administration	12 mg 30 min-5 hrs before surgery, twice daily afterwards for maximum of seven days until first bowel movement
License	FDA approval in May 2008 to prevent POI in bowel resection surgery, limited to inpatient use and a maximum of 15 capsules
Economic aspects	Further research needed

65USD and patients took an average of 9.7 doses for OBR and 7.7 for LBR. The netto reduction of costs per patient receiving alvimopan were calculated to be 997USD for OBR and 531USD for LBR.

There was a significant decrease in the rate of reinsertion of nasogastric tubes for the alvimopan group with an Odds Ratio of 0.1 (95% CI 0.02, 0.47), but no difference in the hospital readmission rate. NSAID were significantly more often applied in the alvimopan group. No association with a shorter LOS was detected for the use of NSAID neither by univariate nor by multivariate analysis. With regard to the restriction of alvimopan use it was important to notice that no incidence of myocardial ischemia or sudden death were reported in the alvimopan group.

Even if this study is weakened through lots of potential biases by nature due to its design (no blinding, no randomization, cohorts limited in comparability because of their baseline characteristics and retrospective analysis, no rigorous method of adverse event reporting, etc.) and underpowered nor suited to detect clinical events, it shows a certain congruence at least in its clinical outcome with the RCTs and describes an economic benefit of the usage of alvimopan in this health care system.

More research focusing on prospective randomized trials with validated tools evaluating financial impact in different health care systems has to be done to further assess the economic role alvimopan might play by preventing POI.

Conclusion

Results from trials retrieved for this review concerning POI prevention using alvimopan have to be interpreted with caution. Some trials' designs cannot completely exclude biases because of deficiencies in statistical analysis and some authors' potential conflicts of interest.

There is clear evidence that alvimopan significantly shortens the time to first bowel movement, time to tolerance of solid food and time to hospital discharge after open bowel resection or abdominal hysterectomy for patients receiving patient-controlled opiate-based pain control (Table 5). There is no clear proof for a dose-response

in its efficacy, but in several analyses the 12 mg dosage showed better results than 6 mg, especially in women and patients over 65.[37] The drug has to be applied between 5 hours and 30 minutes before and twice daily after surgery until gastrointestinal recovery. Short term usage of alvimopan is safe and does not impair pain management. No myocardial events have been associated with alvimopan in this setting but further monitoring for this serious adverse effect is indispensable.

Because the data available are limited to specific clinical situations, they don't allow for a clear recommendation of the use of alvimopan in preventing POI in general. That the effect of alvimopan could only be shown on patients on PCA suggests that its effect might mainly be based on antagonizing exogenous opiates on the gut wall but also, that it could be the key to escape the restraint to avoid opiates to prevent POI at all costs. Lately, so called "fast track" multimodal strategies for faster recovery after abdominal surgery have shown to reduce the length of hospital stay significantly.[41] They include the preference of laparoscopic procedures for less manipulation on the gut and the use of midthoracic epidural analgesia to interrupt sympathical reflexes. They promote the use of NSAID and COX2-inhibitors against inflammation to reduce opiate request. Only one of the trials retrieved has included patients on any of these therapies. These limited data do not provide enough evidence to judge the efficacy of alvimopan in combination with those interventions. Since their mechanism of action might interfere in a complementing or counteracting way with the effect of alvimopan further research has to focus on combining alvimopan with these procedures to evaluate and specify the drug's future role in abdominal surgery.

The economic impact of alvimopan by shortening the length of hospital stay is shown with limited evidence mainly in the health care system of the USA. The external validity of these results for other health care settings focussing on different multimodal management strategies for abdominal surgery is low and more studies have to be specifically designed to evaluate this aspect in different countries.

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Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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