Peripherally Acting Mu-Opioid Receptor Antagonists and Postoperative Ileus: Mechanisms of Action and Clinical Applicability

Eugene R. Viscusi, MD*
Tong J. Gan, MD†
John B. Leslie, MD, MBA‡
Joseph F. Foss, MD§
Mark D. Talon, CRNA‖
Wei Du, PhD¶
Gay Owens, PharmD¶

Postoperative ileus (POI), a transient cessation of coordinated bowel function after surgery, is an important health care problem. The etiology of POI is multifactorial and related to both the surgical and anesthetic pathways chosen. Opioids used to manage surgical pain can exacerbate POI, delaying gastrointestinal (GI) recovery. Peripherally acting mu-opioid receptor (PAM-OR) antagonists are designed to mitigate the deleterious effects of opioids on GI motility. This new class is investigational for POI management with the goal of accelerating the recovery of upper and lower GI tract function after bowel resection. In this review, we summarize the mechanisms by which POI occurs and the role of opioids and opioid receptors in the enteric nervous system, discuss the mechanism of action of PAM-OR antagonists, and review clinical pharmacology and Phase II/III POI trial results of methylnaltrexone and alvimopan. Finally, the role of anesthesiologists in managing POI in the context of a multimodal approach is discussed.
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Postoperative ileus (POI) is a transient cessation of coordinated bowel motility that prevents effective transit of intestinal contents or tolerance of oral intake.[1,2] POI occurs universally after bowel resection (BR), often not resolving for 4 days or longer.[3] Clinically, POI is characterized by delayed passage of flatus and stool, bloating, abdominal distension, abdominal pain, nausea, and vomiting and is associated with an increase in postoperative morbidity and length of hospital stay (LOS).[4,5] The etiology of POI is multifactorial and includes the surgical stress response (inhibitory reflexes resulting from sympathetic neural stimulation) and an acute inflammatory response associated with manipulation of the bowel.[4,6–9] Endogenous opioids secreted within the gastrointestinal (GI) tract in response to surgical stress and administration of exogenous opioid-based analgesia can stimulate peripheral opioid receptors within the GI tract, which may exacerbate POI and further delay GI recovery.[4,7,10–13]

The time required to recover GI function often determines the LOS.[14] In the United States, LOS for patients undergoing BR ranges from 5 to 14 days.[15,16] Mean cost per hospital stay has been estimated to be approximately $6000 more for patients with coded POI compared with patients without coded POI.[17] Therefore, accelerating GI recovery after BR via patient management or pharmacologic approaches would represent a clinically important addition to the standard of care. Current management of POI has included the following: nasogastric tube (NGT) insertion, IV hydration and parenteral nutrition, laxatives and off-label use of drugs, such as ceruletide, metoclopramide, somatostatin, and erythromycin.[2,15,18] However, these therapies have either proven inadequate for management of POI, increased risk for additional postoperative complications, or not been

From the *Department of Anesthesiology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania; †Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina; ‡Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, Minnesota; §Cleveland Clinic, Cleveland, Ohio; ‖Department of Anesthesiology, University of Texas Medical Branch, Galveston, Texas; and ¶Adolor Corporation, Exton, Pennsylvania.

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Address correspondence and reprint requests to Eugene R. Viscusi, MD, Department of Anesthesiology, Acute Pain Management Service, Thomas Jefferson University, 111 S. 11th St., Suite G-8490, Philadelphia, PA 19107. Address e-mail to eugene.viscusi@jefferson.edu.

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clinically validated. Accelerated GI recovery has been reported by some health care centers with the use of multimodal care pathways.[1,19–24] These pathways incorporate patient education, the use of less-invasive surgical techniques, and opioid-sparing analgesics or techniques, such as epidural analgesia.[1,19–24] However, some anesthetic pathways and advanced surgical techniques are not feasible for all patients and not available at all institutions.[1,19–24] Previous pharmacologic approaches, such as prokinetic drugs or laxatives, have not been consistently successful for managing POI.[25,26] Furthermore, epidural analgesia has become less popular with the routine application of anticoagulation for venous thromboembolism prophylaxis. A class of drugs known as peripherally acting mu-opioid receptor (PAM-OR) antagonists target one of the main causes of POI: opioid activation of mu-opioid receptors in the GI tract.[1,4] Two drugs in this PAM-OR antagonist class, methylnaltrexone and alvimopan, are under investigation or approved for the management of POI after BR.*[27–31] Methylnaltrexone is currently approved for treatment of opioid-induced constipation in patients with advanced illness[32] and was investigated in Phase III POI trials. Alvimopan was recently approved by the US Food and Drug Administration (FDA) to accelerate the time to upper and lower GI recovery after partial large or small BR with primary anastomosis. We present a brief background of opioid receptors and their role in enteric physiology, the mechanisms of action of PAM-OR antagonists, and a review of published clinical trial data of PAM-OR antagonists in patients undergoing BR. Finally, a discussion is presented on how, as perioperative physicians, anesthesiologists can work within the surgical team to manage POI in this surgical population.

ENTERIC NEUROPHYSIOLOGY

The enteric nervous system (ENS) is the neural network that supplies the digestive tract and mediates complex reflex activity in the GI tract independently of the central nervous system (CNS). The ENS processes information from sensory receptors, regulates neural reflex activities, and coordinates the complex motor patterns in the GI tract responsible for mixing and propulsive movements and the secretory functions.[33] Additionally, extrinsic neural pathways also connect with the ENS and modulate its function.[34,35] Extrinsic sensory neurons travel in spinal and vagal afferent nerves, transmitting information to the CNS.[34] Efferent fibers of the sympathetic (inhibitory) and parasympathetic (excitatory) nervous systems synapse with nerve fibers in the ENS and modulate motor activity.[8,34] Therefore, because of its complex interconnecting neural networks and sophisticated functions, the ENS is often referred to as the brain in the GI tract.[33]

Three types of neurons mediate the regulation of ENS functions: sensory neurons, interneurons, and motor neurons.[34,36] Enteric sensory neurons receive sensory information from sensory receptors in the intestinal epithelium, mucosa, and muscle.[34,36] Interneurons serve as conduits between the sensory and motor neurons and between different motor neurons to allow the ENS to function as an intercommunicating network in the intestinal plexuses.[34] Excitatory and inhibitory motor neurons work in concert to mediate effective peristalsis through interaction and control of smooth muscle cells, epithelial cells, glands, and blood vessels.[34,36] The inflammatory response to manipulation of the intestines during abdominal surgery can also influence GI motility.[6] Immune cells infiltrate the intestines and secrete proinflammatory cytokines, resulting in decreased smooth muscle function and GI dysmotility.[4]

OPIOID RECEPTORS IN THE CNS AND ENS

Opioid receptors are G protein-coupled receptors that mediate a wide variety of physiologic effects through the binding of endogenous opioid peptides and exogenous opioids. The three primary opioid receptor types (mu, δ, and kappa) are ubiquitous in the CNS and ENS.[11] Mu-opioid receptors are the primary mediators of opioid analgesic effects in the CNS (mu_1) and GI-related effects in the GI tract (mu_2).[11] In the CNS, mu-opioid receptors are enriched in the cerebral cortex, striatum, and hippocampus in the brain.[37] The central effects mediated by opioids in

Table 1. Effects of Opioids on the Gastrointestinal Tract

Pharmacologic action	Clinical effect
Decreased gastric motility and emptying	Decreased appetite, increased gastroesophageal reflux
Decreased pyloric tone	Nausea and vomiting
Decreased enzymatic secretion	Delayed digestion; hard, dry stools
Inhibition of small and large bowel propulsion	Delayed absorption of medication, straining, incomplete evacuation, bloating, abdominal distension, constipation
Increased fluid and electrolyte absorption	Hard, dry stools
Increased nonpropulsive segmental contractions	Spasms, abdominal cramps, pain
Increased anal sphincter tone	Incomplete evacuation

Data from Refs. 11, 41, and 42.

*Ludwig K, Enker WE, Delaney CP, Wolff BG, Du W, Fort JG, Cherubini M, Cucinotta J, Techner L. Gastrointestinal recovery in patients undergoing bowel resection: results of a randomized trial of alvimopan and placebo with a standardized accelerated postoperative care pathway. Arch Surg 2008;143:1098–105.

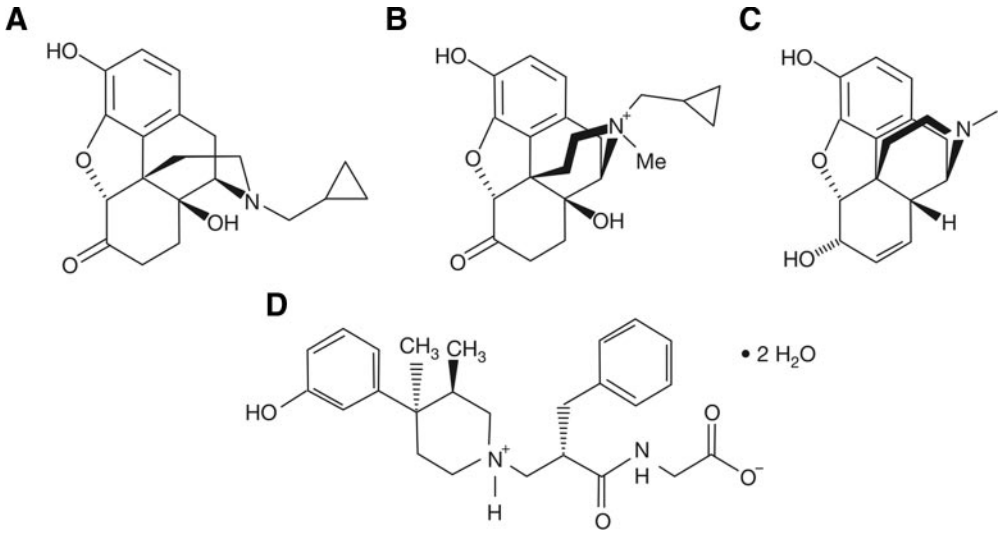

Figure 1. Structural formulas of naltrexone (A), methylnaltrexone (B), morphine (C), and alvimopan (D).

the CNS include not only analgesia but also euphoria, sedation, and respiratory depression.[38]

Preclinical studies have localized all three opioid receptor types in the myenteric and submucosal plexuses of the ENS on muscular and secretory motor neurons and interneurons.[11,39] Activation of opioid receptors in the ENS inhibits the release of neurotransmitters from excitatory motor neurons and stimulates neurotransmitter release from inhibitory motor neurons, resulting in nonpropulsive motility.[13] Endogenous peptides, such as dynorphin and enkephalin, are produced and act locally.[40] Under normal conditions, endogenous opioid peptides may play a role in modulating GI motility patterns; however, under periods of surgical stress, secretion of these peptides can interfere with GI patterns and may contribute to POI.[12,13] Exogenous opioids (e.g., morphine) administered for analgesic purposes may also cause various opioid side effects, such as pruritus and urinary retention, and can activate the peripheral mu-opioid receptors in the GI tract. The adverse GI effects of exogenous opioid treatment include nausea, vomiting, altered fluid dynamics, inhibited gastric emptying, inhibited intestinal coordinated propulsive activity and increased transit time, all of which may contribute to POI (Table 1).[11,41,42]

PAM-OR ANTAGONISTS

Clinical Pharmacology

The PAM-OR antagonists methylnaltrexone and alvimopan were designed to mitigate the peripheral GI-related adverse effects of opioids while maintaining centrally based analgesia. Indeed, at clinically relevant concentrations, methylnaltrexone and alvimopan do not readily cross into the CNS.

Methylnaltrexone is a highly polar derivative of the opioid antagonist naltrexone (17-[cycloproylmethyl]-4,5α-epoxy-3,14-dihydroxymorphinanium-6-one). Unlike naltrexone, methylnaltrexone does not readily cross the blood–brain barrier because of the substitution of a polar methyl group (Fig. 1).[41] Both naltrexone and methylnaltrexone are structurally similar to morphine. Methylnaltrexone binds to mu-opioid receptors with a K_i ranging from 26 nM to 110 nM and has a rapid dissociation rate from the mu-opioid receptor ($t_{1/2}$ = 0.46 min).[43] *In vitro* binding assays demonstrated that methylnaltrexone is a partial agonist at all three opioid receptors (mu, δ, and kappa).[44] When administered IV to patients every 6 h for 72 h consecutively, methylnaltrexone (0.3 mg/kg) was present at a mean plasma concentration of 14 ng/mL 6 h after the final dose.[45] The mean steady-state volume of distribution for methylnaltrexone ranges from 1.8 L/kg to 2.6 L/kg.[45] Methylnaltrexone can be metabolized to naltrexone by demethylation; however, this does not appear to occur appreciably in humans at clinical doses.[46,47] Approximately, 40%–60% of methylnaltrexone is excreted in the urine within 24 h of IV administration.[45,47]

Alvimopan is a trans-3,4-dimethyl-4-(3-hydroxyphenyl) piperidine.[48] Alvimopan is a large molecular weight zwitterion with high polarity and does not cross the blood–brain barrier at clinically relevant concentrations.[48,49] Alvimopan binds with high affinity to mu-opioid receptors (K_i = 0.4 nM) and, compared with methylnaltrexone, has a higher affinity for and slower dissociation rate ($t_{1/2}$ = 30–44 min) from the mu-opioid receptor *in vitro*.[43,44] The *in vitro* binding affinity of alvimopan was the most selective at the mu-opioid receptor compared with other opioid receptors (pK_i = 9.6, 8.6, and 8.3 at the mu-, δ-, and kappa-opioid receptors, respectively).[44] However, it is not known whether the high affinity for the mu-opioid receptor or slower dissociation rate of alvimopan is related to clinical efficacy.[43]

Alvimopan has limited bioavailability and is rapidly absorbed (T_{max} = 2 h) after oral administration of a single dose.[50,51] Mean peak plasma concentrations of 9 ng/mL were observed after 6 days of 12-mg twice-daily oral dosing, and the mean volume of alvimopan distribution after oral administration ranged from 11

to 98 L (0.24–2 L/kg), similar to that of methylnaltrexone.[45,51] After multiple doses of alvimopan 12 mg, there was little or no accumulation at steady-state.[51] Alvimopan is converted by intestinal microflora to an active primary amide hydrolysis metabolite, ADL 08-0011, that is not required for efficacy in the management of POI.† Similar to alvimopan, recent evidence from an *in vitro* study suggested that ADL 08-0011 acted as an inverse agonist at mu- and δ-opioid receptors and as a partial agonist at kappa-opioid receptors (pK_i = 9.6, 7.8, and 7.5 at the mu-, δ-, and kappa-opioid receptors, respectively), although the clinical implications cannot be evaluated at this time.[44] Mu-opioid receptors have been identified in both submucosal and myenteric ganglia; therefore, alvimopan or its active metabolite present in the circulation may contribute to efficacy in the management of POI. However, the relative contributions of systemic versus local concentrations of alvimopan have yet to be determined.[52] Elimination of alvimopan occurs through biliary and renal excretion; alvimopan excreted into the bile undergoes further metabolism and is then eliminated in the feces.[53] Alvimopan is well tolerated in elderly and renal-impaired patients.[50,54] No overall differences in safety have been observed in older patients; however, a greater sensitivity to alvimopan in these patients cannot be excluded.[55]

Clinical Trials of PAM-OR Antagonists for the Management of POI

The IV formulation of methylnaltrexone and the oral formulation of alvimopan are currently under investigation or approved for the management of POI after BR (Table 2).*[27–31,56] Phase II and Phase III alvimopan trials included both patients undergoing BR or total abdominal hysterectomy.*[27–29,31,56–58] However, upon pooled analysis, clinically meaningful benefit was only noted in patients who underwent BR, very likely because of the relatively short stay of total abdominal hysterectomy patients and a high censoring rate because of the large proportion of patients leaving the hospital before bowel movement (BM).[57,59] Therefore, results are only reported for the BR patient population. Of note, all patients (placebo and alvimopan groups) in alvimopan Phase III trials were managed with a standardized, accelerated, postoperative care pathway intended to facilitate GI recovery.[27–29,31] This pathway included removal of the NGT, if used, by noon on postoperative day 1. A liquid diet and ambulation were encouraged on postoperative day 1, and a solid diet was encouraged on postoperative day 2. Patients in all methylnaltrexone trials reported herein received opioid-based IV patient-controlled analgesia (PCA).[30] Patients in all alvimopan North American trials received postoperative opioid-based IV-PCA,*[27–29] and patients in the non-US trial were scheduled to receive opioids either by IV-PCA or by bolus parenteral administration.[31]

Efficacy Profiles

Phase III studies with subcutaneous methylnaltrexone focused on the treatment of opioid-induced bowel dysfunction (OBD) in chronic opioid users.[60] However, Phase II studies demonstrated the ability of IV methylnaltrexone to antagonize the GI effects of opioids in healthy volunteers and chronic opioid users.[60] A single IV injection of methylnaltrexone prevented morphine-induced increase in oral-cecal transit time in healthy volunteers.[61] In this study, methylnaltrexone reduced oral-cecal transit times to premorphine injection baselines without affecting the analgesic effects of morphine on pain intensity and pain bothersome ratings.[61]

In a pilot study (n = 4) in patients with chronic methadone use and constipation, IV methylnaltrexone (0.05–0.45 mg/kg) significantly reduced GI transit times; however, immediate adverse GI effects (e.g., immediate laxation and abdominal cramping) were reported, suggesting that this population is more sensitive to lower doses of methylnaltrexone than patients not receiving chronic opioids.[62] Further studies of patients with chronic methadone use revealed that 2 days of IV methylnaltrexone (0.1 mg · kg^{-1} · day^{-1}) treatment produced immediate laxation in patients using methadone.[63] The mean change in oral-cecal transit time was significantly greater after treatment with methylnaltrexone (77.7 ± 37.2 min; baseline, 132.3 min) compared with patients in the placebo-treated group (1.4 ± 12 min; baseline, 126.8 min; $P < 0.001$).[63]

Results of a Phase II trial examining IV methylnaltrexone for accelerating recovery of GI function in patients (n = 65) undergoing segmental colectomy via laparotomy were recently reported.[30,64] Patients received methylnaltrexone 0.3 mg/kg ≤90 min after surgery and every 6 h until first toleration of solid food or hospital discharge for a maximum of 7 postoperative days. Mean time to GI recovery (Fig. 2A), measured by first toleration of solid food (Fig. 2B) or first BM (Fig. 2C), whichever occurred first, was accelerated by 27 h in the methylnaltrexone group compared with the placebo group (methylnaltrexone 0.3 mg/kg, 124 h; placebo, 151 h; P = 0.06).[30] Moreover, mean time to eligibility for hospital discharge was accelerated by 30 h in the methylnaltrexone group compared with placebo (methylnaltrexone 0.3 mg/kg, 119 h; placebo, 149 h; P = 0.03; Fig. 2D). Confirmatory Phase II/III trials were undertaken to validate these results.[30,65] Preliminary results from the two Phase III trials demonstrated that treatment with IV methylnaltrexone 12 or 24 mg every 6 h in patients recovering from segmental colectomy surgical procedures failed to achieve the primary end point, reduction in time to

†Foss J, Schmith VD, Fort JG, Du W, Techner L. Pharmacokinetics of alvimopan and its amide hydrolysis metabolite: effect of perioperative antibiotic use in patients undergoing laparotomy. Poster presented at American College of Clinical Pharmacy Annual Meeting, St. Louis, MO, October 26–29, 2006.

Table 2. Summary of PAM-OR Antagonist Clinical Trials for the Management of POI

Trial	Trial level	Population	Dose and schedule	SAPC pathway use	Outcome
Methylnaltrexone					
Viscusi et al.[30]	Randomized, double-blind, placebo-controlled Phase II	BR (n = 65)	0.3 mg/kg IV ≥90 min after surgery and every 6 h for 7 days	ND	Accelerated time to first BM, toleration of liquids, and hospital discharge eligibility
Alvimopan					
Wolff et al.[29]	Randomized, multicenter, double-blind, placebo-controlled Phase III	BR (n = 472) TAH (n = 25)	6 or 12 mg orally ≥2 h before surgery and BID after surgery	Yes	Accelerated time to GI-3 and GI-2 recovery and DCO written
Delaney et al.[27]	Randomized, multicenter, double-blind, placebo-controlled Phase III	BR (n = 303) TAH (n = 129)	6 or 12 mg orally ≥2 h before surgery and BID after surgery	Yes	Accelerated time to GI-2 recovery, first BM, toleration of solid food, discharge eligibility, and DCO written
Viscusi et al.[28]	Randomized, multicenter, double-blind, placebo-controlled Phase III	BR (n = 437) TAH (n = 200)	6 or 12 mg orally ≥2 h before surgery and BID after surgery	Yes	Accelerated time to GI-3 and GI-2 recovery, first BM, discharge eligibility, and DCO written
Buchler et al.[31]	Randomized, multicenter, double-blind, placebo-controlled Phase III	BR (n = 883)	6 or 12 mg orally 2 h before surgery and BID after surgery	Yes	Accelerated time to GI-2 recovery
Ludwig et al.[a,b,c]	Randomized, multicenter, double-blind, placebo-controlled Phase III	BR (n = 654)	12 mg orally 30 to 90 min before surgery and BID after surgery	Yes	Accelerated time to GI-2 and GI-3 recovery and DCO written

PAM-OR = peripherally acting mu-opioid receptor; POI = postoperative ileus; SAPC = standardized accelerated postoperative care; BR = bowel resection; IV = intravenous; ND = not disclosed; BM = bowel movement; TAH = total abdominal hysterectomy; BID = twice daily; GI-3 = time to first toleration of solid food and first flatus or bowel movement; GI-2 = time to first toleration of solid food and first bowel movement, based on last to occur; DCO = hospital discharge order.

[a] Ludwig K, Enker WE, Delaney CP, Wolff BG, Du W, Fort JG, Cherubini M, Cucinotta J, Techner L. Gastrointestinal tract recovery in patients undergoing bowel resection: results of a randomized trial of alvimopan and placebo with a standardized accelerated postoperative care pathway. Arch Surg 2008;143:1098–105.

[b] Leslie JB, Steinbrook RA, Viscusi E, Du W, Techner L. Alvimopan oral dosing 30 to 90 minutes before and twice daily after bowel resection accelerates gastrointestinal recovery. Poster presented at the American Society of Anesthesiologists Annual Meeting, Chicago, IL, October 14–18, 2006.

[c] Ludwig K, Enker WE, Delaney CP, Wolff BG, Du W, Fort JG, Cherubini M, Cucinotta J, Techner L. Accelerated gastrointestinal recovery and reduced length of stay following modified preoperative dose timing with alvimopan: results of a large, randomized, placebo-controlled study in partial bowel resection. Poster presented at the 92nd Annual Clinical Congress of the American College of Surgeons, Chicago, IL, October 8–12, 2006.

recovery of GI function, defined as time to first BM, compared with placebo.[66,67]

The efficacy of alvimopan in GI recovery after laparotomy for BR or hysterectomy has been examined in four randomized, double-blind, placebo-controlled, parallel-group, Phase III trials in the United States and Canada,*[27–29] and one double-blind, placebo-controlled, Phase III trial outside of North America (Table 3).[31] All five trials evaluated the efficacy of alvimopan in restoring GI function by the use of a composite assessment of upper and lower GI function recovery: GI-2 recovery, defined as time to first toleration of solid food and first BM, with recovery time measured by the event that happened last. GI-2 recovery was evaluated by *post hoc* analysis in the first Phase III study[29] and as primary or secondary end points in all other studies.*[27–29,31] The modified intent-to-treat population included all randomized and treated patients who received protocol-specified surgery (in this case, BR) and who had at least one on-treatment evaluation for flatus, BM, or solid food.[57] Patients were excluded from eligibility if they were pregnant, currently using opioids or receiving an acute course of opioids (greater than three doses) <1 wk before study entry, experiencing complete bowel obstruction, undergoing total colectomy, colostomy, ileostomy, or ileal pouch-anal anastomosis, or had a history of total colectomy, gastrectomy, gastric bypass, short bowel syndrome, or multiple previous abdominal operations performed by laparotomy.[57] After completion of the initial studies and discussion with colorectal surgeons, a review of the data revealed that GI-2 recovery, which excludes time to first flatus, was a more appropriate assessment of GI function in BR

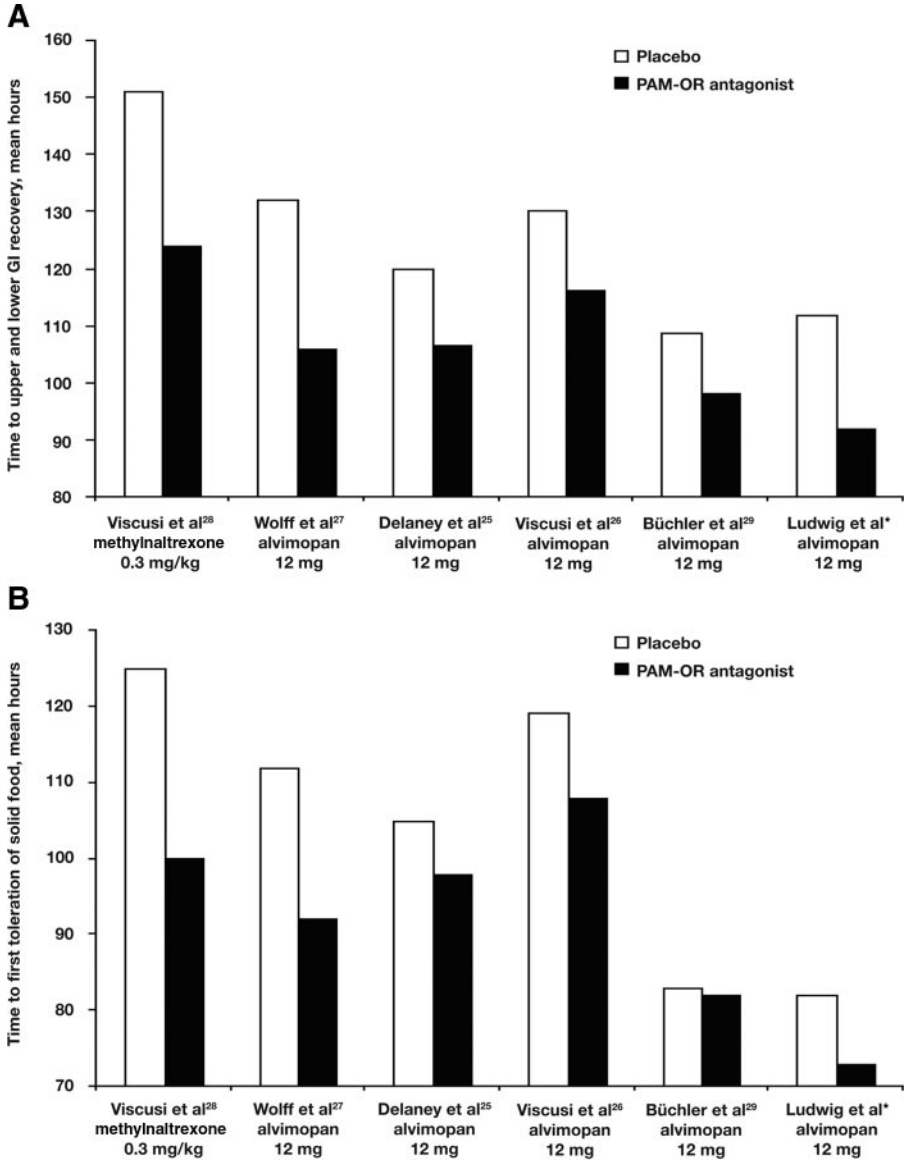

Figure 2. Time to upper and lower GI recovery in PAM-OR antagonist efficacy trials (bowel resection population). Time to composite upper and lower GI recovery (A), first toleration of solid food (B), first BM (C), and readiness or eligibility for hospital discharge (D) are reported. Upper and lower GI recovery was defined as time to first toleration of solid food *or* first BM, with time to recovery based on the first event to occur in the methylnaltrexone trial, and time to first toleration of solid food *and* first BM, with time to recovery based on the last event to occur in the alvimopan trials. GI = gastrointestinal; PAM-OR = peripherally acting mu-opioid receptor; BM = bowel movement. See data from Refs. 27–31 and Ludwig et al.*

patients because GI-3 recovery (defined as time to first toleration of solid food and time to first BM or first flatus) is subject to greater variability in comparison with BM, in part, because of patient-reported subjectivity of flatus.[57] Indeed, although alvimopan 12 mg statistically significantly accelerated GI-2 recovery compared with placebo in all Phase III efficacy trials with the exception of one dose in one trial,[27] a similar significant acceleration of GI-3 recovery was not observed in all Phase III clinical trials.*[27–29,31] Time to hospital discharge order (DCO) written was also a secondary end point in the alvimopan trials. Pooled or meta-analyses of results for these clinical trials have been the subject of several recent publications.[59,68–70]

In the Phase III North American BR trials, patients scheduled to receive opioid-based IV-PCA received oral alvimopan 6–12 mg or placebo ≥30 min before surgery and twice daily after surgery until hospital discharge for a maximum of 7 postoperative days (Table 3).*[27–29] In these trials, patients undergoing BR who received alvimopan 12 mg showed significant acceleration in mean time to recovery of GI function as assessed by GI-2 (13–26 h sooner) as well as accelerated mean time to DCO written (13–19 h sooner) compared with placebo. The mean proportion of patients with postoperative NGT insertion was 4.3%–9.8% lower in the alvimopan-treated group than the placebo group in all North American trials with the exception of one, in which no significant difference in NGT insertion was observed.[27] In all of the trials, a standardized accelerated care pathway was used to facilitate GI recovery in all patients, and patients received postoperative opioid-based IV-PCA.*[27–29]

In the European Phase III trial that investigated alvimopan for accelerated recovery of GI function in patients undergoing BR (n = 705), the study design varied from the North American trials.[31] Patients were not required to use opioid-based IV-PCA, and nonsteroidal antiinflammatory drugs and other non-opioid analgesia were allowed.[31] In patients who received

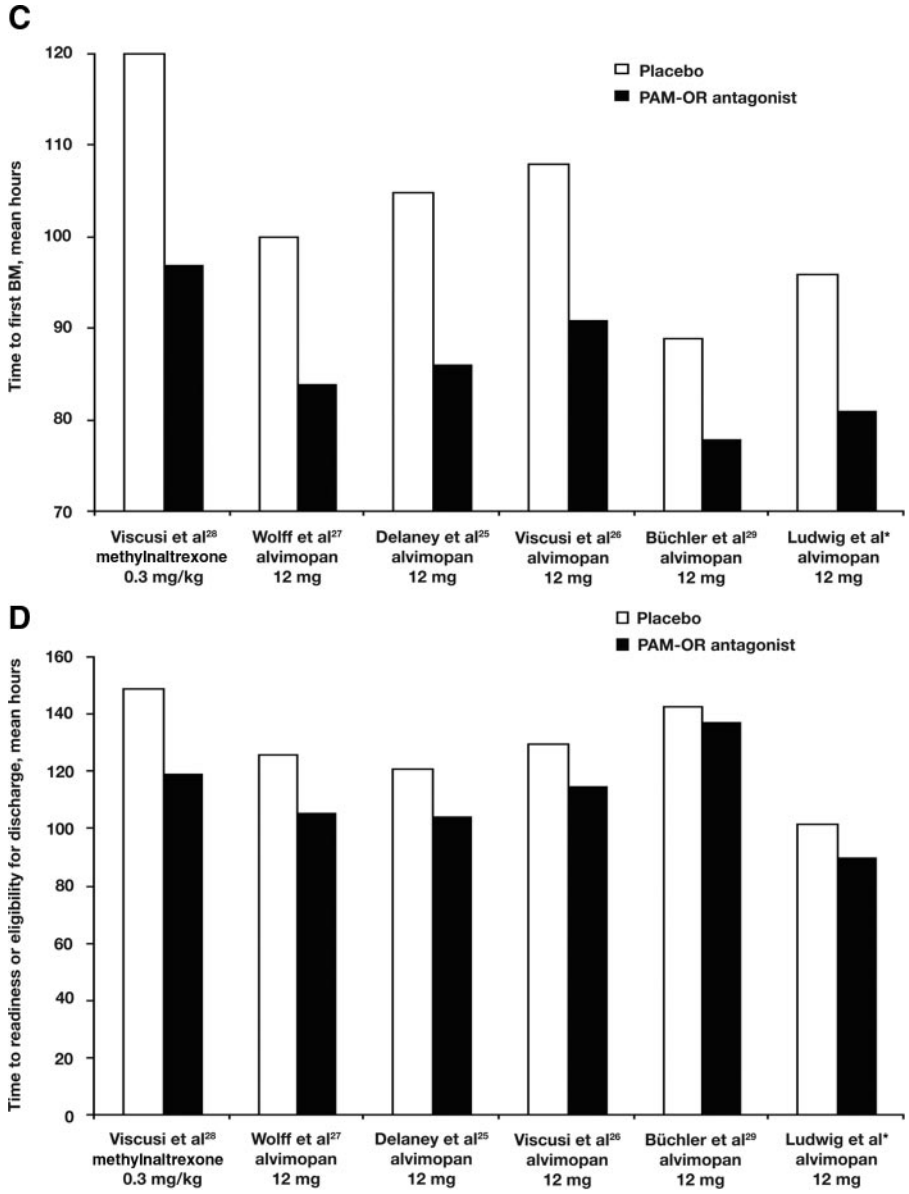

Figure 2. (*Continued*).

Table 3. Effects of Alvimopan on Acceleration of GI-2 and DCO Written From Phase III Efficacy Trials (BR Only)

	GI-2					DCO written				
	Placebo, KM mean hours	Alvimopan, 12 mg, KM mean hours	Difference, KM mean hours	HR	*P*	Placebo, KM mean hours	Alvimopan, 12 mg, KM mean hours	Difference, KM mean hours	HR	*P*
Wolff et al.[29]	132	106	26	1.63	<0.001	147	128	19	1.42	<0.05
Delaney et al.[27]	120	107	13	1.40	<0.05	143	130	13	1.29	0.084
Viscusi et al.[28]	130	116	14	1.37	<0.05	149	128	21	1.56	<0.001
Buchler et al.[31]	109	98	11	1.30	<0.05	—[a]	—	—	—	—
Ludwig et al.[b,c,d]	112	92	20	1.53	<0.001	138	120	18	1.40	<0.001

GI-2 = time to gastrointestinal recovery; DCO = discharge order; BR = bowel resection; KM = Kaplan–Meier; HR = hazard ratio; n/a = not applicable.

[a] Time to DCO written in the European trial is not comparable with North American trials because of regional differences in criteria used for discharge decisions (see text for details).

[b] Ludwig K, Enker WE, Delaney CP, Wolff BG, Du W, Fort JG, Cherubini M, Cucinotta J, Techner L. Gastrointestinal tract recovery in patients undergoing bowel resection: results of a randomized trial of alvimopan and placebo with a standardized accelerated postoperative care pathway. Arch Surg 2008;143:1098–105.

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[d] Ludwig K, Enker WE, Delaney CP, Wolff BG, Du W, Techner L. Accelerated gastrointestinal recovery and reduced length of stay following modified preoperative dose timing with alvimopan: results of a large, randomized, placebo-controlled study in partial bowel resection. Poster presented at the 92nd Annual Clinical Congress of the American College of Surgeons, Chicago, IL, October 8–12, 2006.

alvimopan 12 mg, mean time to GI-2 recovery was accelerated by 11 h in the alvimopan group compared with the placebo group. A *post hoc* subset analysis of patients who received opioid-based IV-PCA (commonly used in the United States) revealed that mean time to GI-2 recovery was accelerated by 15 h in the alvimopan group compared with the placebo group, similar to results observed in North American Phase III trials.[31] Thus, it appears alvimopan demonstrated the largest benefit in patients receiving opioid-based IV-PCA. In addition, a comparison of the placebo groups between trials indicated that the time to hospital DCO written was on average 3–4 days longer in the European trial than in the North American trials. This disparity is believed to reflect differences in social and financial pressures that contribute to discharge decisions in the two regions and, thus, makes comparisons in hospital LOS and time to DCO written between the North American and European trial difficult.[31]

Recently, alvimopan received FDA approval "to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis."[55] This indication establishes a role for alvimopan in the management of POI after partial BR; no trials have addressed the role of alvimopan in the prevention or treatment of POI. The recommended dosage for alvimopan is 12 mg administered from 30 min to 5 h before surgery followed by 12 mg twice daily for up to 7 days for a maximum of 15 in-hospital doses.[55] The POI clinical development program initially included multiple alvimopan doses (6 or 12 mg), and a clear dose-response effect was not demonstrated in all clinical trials. However, analysis of pooled clinical trial results demonstrated a more consistent and robust treatment effect of alvimopan 12 mg compared with alvimopan 6 mg in patients undergoing BR.[57,68] For example, in a pooled analysis of the first three Phase III trials, alvimopan 6 mg accelerated GI-2 recovery by 15 h (HR = 1.34; $P < 0.001$) compared with placebo, whereas alvimopan 12 mg accelerated GI-2 recovery by 18 h (HR = 1.46; $P < 0.001$).[68]

Table 4. Effects of Alvimopan on Opioid Consumption and VAS Pain Scores in Pooled Analysis of Data from Phase III Efficacy Trials

	Placebo (n = 695)	Alvimopan 12 mg (n = 714)
Opioid consumption, mean MSEs (P value)		
Preoperative	18.9	19.9 (0.308)
Intraoperative	28.3	29.2 (0.591)
Daily postoperative	28.8	27.2 (0.290)
Mean daily VAS pain scores (P value)[a]	29.1	29.2 (0.913)

Data from Ref. 71 and Viscusi ER, Steinbrook RS, Du W, Techner L. Alvimopan accelerates gastrointestinal recovery and decreases length of hospital stay after bowel resection (BR) without compromising opioid-based analgesia. Poster presented at the 81st Clinical and Scientific Congress of the International Anesthesia Research Society, Orlando, FL, March 23–27, 2007.

MSE = morphine sulfate equivalent; VAS = visual analog scale.

[a] VAS pain scores as reported in three Phase III trials.[27–29]

Safety Profiles

Methylnaltrexone did not antagonize morphine-induced analgesia in healthy volunteers.[61] Furthermore, in the Phase II methylnaltrexone POI trial (0.3 mg/kg, IV), no differences in pain scores were reported between patients receiving methylnaltrexone or placebo, suggesting that methylnaltrexone did not reverse opioid analgesia.[30] In Phase III alvimopan trials, opioid consumption and pain scores were comparable between alvimopan and placebo groups, indicating that opioid analgesia was not reversed by alvimopan (Table 4).*[27–29,71]

Methylnaltrexone was well tolerated in the Phase II POI trial, and the most commonly reported adverse events were fever (methylnaltrexone, 38%; placebo, 33%) and nausea (methylnaltrexone, 30%; placebo, 63%). Transient orthostatic hypotension has been reported in Phase I studies in healthy volunteers receiving ≥0.64 mg/kg IV methylnaltrexone; however, orthostatic hypotension is unlikely to occur at the therapeutic doses being investigated (0.3 mg/kg).[60,72] Methylnaltrexone (0.05–0.45 mg/kg) caused laxation and abdominal cramping within minutes of IV administration but did not result in systemic opioid withdrawal among patients receiving chronic opioid therapy.

Approximately 2600 patients were treated with a single dose of alvimopan preoperatively followed by twice-daily administration beginning on postoperative day 1 until hospital discharge or up to 7 days.[57] Among patients who underwent BR, 999 patients received alvimopan 12 mg and 986 patients received placebo, and the most commonly reported treatment-emergent adverse events were nausea (alvimopan 12 mg, 43.3%; placebo, 49.8%), vomiting (alvimopan 12 mg, 14.1%; placebo, 21.2%), hypertension (alvimopan 12 mg, 12.6; placebo, 11.9), and abdominal distension (alvimopan 12 mg, 12.0%; placebo, 13.9%). The incidence of POI as a treatment-emergent adverse event was lower in the alvimopan-treated group than in the placebo group (alvimopan 12 mg, 6.0%; placebo, 11.5%).[57] Per the label, the use of alvimopan is not recommended in patients with severe hepatic impairment or patients with end-stage renal disease.[55]

Results from a long-term safety study of alvimopan 0.5 mg twice daily for the treatment of OBD in patients with chronic noncancer pain demonstrated a numeric imbalance in reports of myocardial infarction.[73] These preliminary findings lead to the suspension of Phase III safety and efficacy studies in patients with OBD (a chronic indication), pending full analysis of the data. In contrast, no imbalance in severe adverse events was observed in worldwide population data from the POI trials (an acute indication).[57] Cardiovascular events were reported in 50 of 2610 (2%) patients in the alvimopan group and 39 of 1365 (3%) patients in the

placebo group.[57] Patients who experienced a cardiovascular event were generally older (≥65 yr of age) or had established cardiovascular disease, and rates of both of these traits were higher in the alvimopan group compared with placebo.[57] The clinical hold on alvimopan trials prompted by these numerical imbalances has recently been lifted.[74]

In patients who have developed tolerance resulting from chronic opioid use, low doses of a mu-opioid antagonist can precipitate a moderate to severe withdrawal syndrome within minutes, comparable with that seen after abrupt cessation of opioid use. This heightened sensitivity to a mu-opioid antagonist in an opioid-tolerant patient is not well understood; however, it is thought to be related to physiologic changes at the cellular/receptor level. Both methylnaltrexone (0.05–0.45 mg/kg) and the highest single dose of oral alvimopan used in patients receiving long-term opioid therapy (3 mg) caused abdominal cramps, diarrhea, and loose stools within hours of administration but did not cause symptoms of CNS opioid withdrawal in patients receiving chronic opioid therapy.[60,75]

Because of the imbalance in cardiovascular events reported in the OBD trial, a FDA-mandated Risk Evaluation and Mitigation Strategy was implemented to assure the safe use of alvimopan under new FDA guidelines for the management of known or potential serious risks associated with drugs or biological products. This included a boxed warning in the prescribing information stating that alvimopan is indicated for short-term hospital use only. Additionally, hospitals performing BR surgeries are required to enroll in the Entereg Access Support and Education program to allow their pharmacies to order, stock, and dispense alvimopan.[55] Alvimopan is the first drug to be approved after the passage of the FDA amendments act in 2007.

SUMMARY AND PERSPECTIVES

POI is an important health care problem that contributes to patient morbidity and is associated with prolonged hospital stays after BR.[3] Therefore, accelerated resolution of POI may provide benefits to patients and to the health care system. Because the etiology of POI is multifactorial, the most successful approach for managing POI may be multimodal and could include a variety of components, techniques, and drugs (e.g., fast-tracked surgery, thoracic epidurals, opioid-sparing techniques, and the use of PAM-OR antagonists). Anesthesiologists, as perioperative clinicians, are optimally positioned to implement peri- and postoperative approaches to help improve postoperative patient outcomes.[76,77] A complete patient history, including a review of the patient's GI function and history (e.g., opioid intolerance or pain control issues), allows the anesthesiologist to determine the most appropriate anesthesia and postoperative analgesia for a particular patient. The anesthesiologist can also begin to educate the patient about potential postoperative complications, such as POI, and the planned clinical pathways implemented to reduce complications. With this information an anesthesiologist may work with the surgical team to develop individual patient plans with the goal of reducing complications during and after surgery.

The PAM-OR antagonists were designed to address one of the main causes of POI, the negative GI-related adverse effects of opioids. The use of PAM-OR antagonists may allow anesthesiologists the option to use opioids for anesthesia and pain management without the concern for certain GI-related adverse effects associated with opioids. The PAM-OR antagonists methylnaltrexone and alvimopan have each accelerated time to various components of upper and lower GI recovery in patients undergoing BR and receiving opioid-based IV PCA. Moreover, these drugs were well tolerated and did not appear to compromise centrally mediated opioid analgesia. Because of differences in trial design and lack of head-to-head trials between alvimopan and methylnaltrexone, the two drugs cannot be directly compared. However, certain observations can be made. Time to first BM, an end point measured individually in all trials, was shorter in the placebo arms of the alvimopan trials compared with the placebo arm of the methylnaltrexone trial (Fig. 2C),*[27–31] indicating that the standardized accelerated postoperative care pathway used in the alvimopan trials alone reduces time to recovery of GI function. However, in the most recent alvimopan trial,* alvimopan accelerated time to first BM by an additional 15 h compared with use of a postoperative care pathway alone. This suggests that alvimopan can provide pathophysiologic receptor-directed benefits beyond those offered solely by accelerated postoperative care pathways alone.

PAM-OR antagonists are likely to be used as part of a multimodal pathway for GI recovery. There are many varied multimodal pathways currently in use in clinical practice. In Phase III clinical trials of alvimopan, a standard accelerated multimodal postoperative care pathway was used that included early NGT removal, ambulation, and liquid nutrition offered on postoperative day 1, and solid nutrition offered on postoperative day 2. Because opioid use is linked to adverse effects, it is generally believed that epidural analgesia and other opioid-sparing techniques will improve postoperative outcomes. Most studies suggest that epidural anesthesia can reduce the duration of POI, as summarized in a recent review.[78] Moreover, a meta-analysis reported that epidurals containing only bupivacaine reduce the duration of POI by 36 h compared with systemic opioids and by 24 h compared with opioid epidural anesthesia, although addition of an opioid to epidural local anesthetic may provide superior postoperative analgesia to local epidural anesthetics alone.[79] Concomitant use of nonsteroidal antiinflammatory drugs (ketorolac,[80]

cyclooxygenase-2 inhibitors[81]) or the calcium-channel modulator gabapentin[82,83] have been shown to reduce postoperative opioid use; however, it is not yet clear whether these drugs are effective for management of POI. Nonpharmacologic interventions, such as mechanical massage of the abdominal wall[84] and gum chewing,[85] have also been investigated for management of POI after colectomy. Although gum chewing does not appear to reduce the duration of POI or shorten hospital LOS,[86,87] a single study of massage reported shorter time to first flatus and reduced postoperative pain scores and analgesic use.[84] Other drugs that have been suggested for use in the management of POI include allmotin, a peptide analog of human motilin, and lubiprostone, a bicyclic fatty acid/chloride channel opener.[78] Clinical trials investigating the use of lubiprostone for management of POI are currently underway.[78]

It is likely that the use of PAM-OR antagonists in conjunction with other multimodal approaches to facilitate GI recovery after surgery will provide a clinically meaningful acceleration of GI recovery beyond what can be achieved with multimodal pathways alone. It is hoped that the addition of PAM-OR antagonists to physicians' armamentarium will allow for the optimal management of both acute and chronic pain without the unwanted GI adverse effects of opioids.

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