

## Development of Peripheral Opioid Antagonists: New Insights Into Opioid Effects

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The recent approval by the US Food and Drug Administration of 2 medications—methylnaltrexone and alvimopan—introduces a new class of therapeutic entities to clinicians. These peripherally acting  $\mu$ -opioid receptor antagonists selectively reverse opioid actions mediated by receptors outside the central nervous system, while preserving centrally mediated analgesia. Methylnaltrexone, administered subcutaneously, has been approved in the United States, Europe, and Canada. In the United States, it is indicated for the treatment of opioid-induced constipation in patients with advanced illness (eg, cancer, AIDS) who are receiving palliative care, when response to laxative therapy has not been sufficient. Alvimopan, an orally administered medication, has been approved in the United States to facilitate recovery of gastrointestinal function after bowel resection and primary anastomosis. Clinical and laboratory studies performed during the development of these drugs have indicated that peripheral receptors mediate other opioid effects, including decreased gastric emptying, nausea and vomiting, pruritus, and urinary retention. Laboratory investigations with these compounds suggest that opioids affect fundamental cellular processes through mechanisms that were previously unknown. These mechanisms include modifications of human immunodeficiency virus penetration, tumor angiogenesis, vascular permeability, and bacterial virulence.

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CCR5 = chemokine receptor 5; CNS = central nervous system; CTZ = chemoreceptor trigger zone; FDA = Food and Drug Administration; HIV = human immunodeficiency virus; ICU = intensive care unit; MNTX = methylnaltrexone; OBD = opioid-induced bowel dysfunction; OCTT = orocecal transit time; PAMORA = peripherally acting  $\mu$ -opioid receptor antagonist; POI = postoperative ileus; VEGF = vascular endothelial growth factor

People have used opioids for more than 4000 years. These substances have been intensely studied since the crystallization of morphine by Friedrich Wilhelm Sertürner in 1805.<sup>1</sup> Opioids remain the most widely accepted medications for the treatment of patients with moderate to severe acute and chronic pain, but their analgesic effects are accompanied by numerous generally undesirable additional effects (Table 1). Although dangerous toxicity, including respiratory depression, occurs infrequently with opioid use, large numbers of patients experience such debilitating opioid adverse effects as constipation, urinary retention, and nausea and vomiting.

Ironically, the clinical management of pain with opioids has not benefited meaningfully from the explosion in knowledge of opioid receptor pharmacology. In 2008, some of our oldest opioids—including morphine and meperidine, which are selective for  $\mu$ -opioid receptors—continue to be the mainstays of therapy. No analgesic that is

selective for any of the other opioid receptors has proven to be an advance in safety or efficacy.

Opioid effects may be *central* (ie, activating receptors in the central nervous system [CNS]) or *peripheral* (ie, activating receptors outside the CNS). Analgesia, respiratory depression, and miosis are examples of central effects. Depression of gastrointestinal motility—a peripheral effect—depends largely on receptors in the gut wall. Methylnaltrexone (MNTX, sold under the brand name RELISTOR [Progenics Pharmaceuticals, Tarrytown, NY; Wyeth Pharmaceuticals, Collegeville, PA]) and alvimopan (sold under the brand name Entereg; Adolor Corp, Exton, PA; GlaxoSmithKline, London, England) constitute a new class of therapeutic agents developed specifically for the management and prevention of peripheral opioid effects, primarily those affecting the gastrointestinal tract.<sup>2-4</sup> Drugs of this class, called peripherally acting  $\mu$ -opioid receptor antagonists (PAMORAs), selectively block opioid effects that are mediated by  $\mu$  receptors outside the CNS. Methylnaltrexone and alvimopan are compared in Table 2.

The ability of PAMORAs, when given with opioids, to block such gastrointestinal effects as constipation, while preserving analgesia, was the basis for their initial clinical use. Methylnaltrexone, administered subcutaneously, has recently been approved by the US Food and Drug Administration (FDA),<sup>5</sup> as well as by Health Canada and the European Medicines Agency. In the United States, it is indicated for the treatment of opioid-induced constipation in patients with advanced illness (eg, cancer, AIDS) who are receiving palliative care, when response to laxative therapy

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Dr Moss has patent interests in methylnaltrexone and serves as a consultant to Progenics Pharmaceuticals, which has the license for methylnaltrexone's development. Wyeth Pharmaceuticals entered into an agreement with Progenics in December 2005 to develop and commercialize methylnaltrexone for the treatment of patients with opioid-induced adverse effects. Dr Rosow has received research support from Progenics Pharmaceuticals.

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TABLE 1. **Undesirable Effects of Opioids**

Depression of ventilation	Nausea and vomiting
Sedation	Itching
Dysphoria	Constipation
Hypotension, bradycardia	Delayed gastric emptying
Increased skeletal muscle tone	Urinary retention
Suppression of cough	Biliary spasm
Suppression of immune function	Addiction

has not been sufficient. Alvimopan has recently been approved by the FDA to accelerate recovery from postoperative gastrointestinal dysfunction after bowel resection and primary anastomosis.<sup>6</sup>

Beyond their role in therapeutics, PAMORAs may also prove useful in characterizing (and possibly managing) other adverse effects of opioids, such as urinary retention, nausea, and pruritus. Our review of the literature on the use of PAMORAs identifies which adverse effects are central and which are peripheral. Recent laboratory studies using PAMORAs suggest that opioids acting through  $\mu$  receptors outside of the CNS may have previously unknown and intriguing roles in fundamental aspects of cellular pathophysiologic mechanisms. We briefly review how opioid receptors in nonneuronal tissue may affect a surprising and diverse group of cellular processes, including angiogenesis, viral and bacterial infection, and vascular permeability.

## GASTROINTESTINAL EFFECTS OF OPIOIDS

Although respiratory depression is the most dangerous adverse effect of opioids, constipation is a far more common problem for most patients who use opioids. Opioid-induced constipation is a symptom of a more general syndrome called opioid-induced bowel dysfunction (OBD), which includes inhibition of gastric emptying, peristalsis, and secretions, as well as increased tone of intestinal sphincters.<sup>7</sup> Slowed gastrointestinal transit, increased fluid absorption,

and desiccation of stool lead to constipation. Over time, patients who become opioid tolerant require larger doses for pain relief, but they develop little tolerance to OBD.<sup>8</sup> As a result, OBD is a clinical problem for as many as 60% to 90% of patients who receive opioids for chronic metastatic malignancy<sup>9-11</sup> or chronic noncancer pain.<sup>12</sup> Constipation is often refractory to stool softeners and laxatives, and it may limit effective pain control.<sup>13-16</sup> Patients may actually prefer pain to severe constipation.<sup>17</sup>

A second related clinical problem is postoperative ileus (POI), the inhibition of bowel function after surgery.<sup>18,19</sup> Postoperative ileus results in bloating, distention, pain, nausea, and inability to resume oral feeding. In severe cases, paralytic POI can persist for many days after surgery and is often a primary reason for delay of hospital discharge. The etiology of POI is multifactorial and may include opioid administration, direct trauma, manipulation of the bowel during surgery, inflammatory mediators, electrolyte disturbances, and other metabolic effects of anesthesia and surgery. A portion of the inhibitory effect in POI is thought to involve sympathetic reflexes mediated by the release of endogenous opioid peptides in the enteric nervous system.<sup>20-23</sup> It is well accepted that the  $\mu$ -opioid receptors modulate gut effects<sup>24</sup> and that endogenous opioid peptides directly influence gut motility.<sup>23,25</sup>

At least three lines of evidence support a direct role for both endogenous and exogenous opioids in the etiology of POI. First, endogenous opioid peptides have been implicated in the pathophysiologic mechanisms of an animal syndrome, equine colic, which is the second leading cause of mortality in horses. The symptoms of equine colic mimic those of POI, and marked elevations in levels of serum endorphins have been observed in horses with this syndrome.<sup>26</sup> In the second line of evidence, the role of exogenous opioids in POI has been demonstrated by comparing different analgesic regimens. Kehlet and Holte<sup>18</sup> conducted a remarkable

TABLE 2. **Comparison Between Methylnaltrexone and Alvimopan**

Characteristic	Methylnaltrexone	Alvimopan
Approved indication	Opioid-induced constipation in patients with advanced illness receiving palliative care, when response to laxatives has not been sufficient	Facilitation of gut function after bowel resection and primary anastomosis
Dosage	8 mg every other day (body weight, 38-62 kg) 12 mg every other day (body weight, 63-114 kg)	12 mg twice daily, starting preoperatively (limit, 15 doses total)
Administration	Subcutaneous	Oral
Adverse effects	Flatulence Abdominal cramping Nausea Vomiting	Anemia Dyspepsia Hypokalemia Back pain Urinary retention
Contraindications	Mechanical bowel obstruction	Opiate use >1 wk Restricted to hospitals
Wholesale cost/dose <sup>a</sup>	\$38.54	\$61.88

<sup>a</sup> Information on cost per dose was obtained from Massachusetts General Hospital, Pharmacy Department.

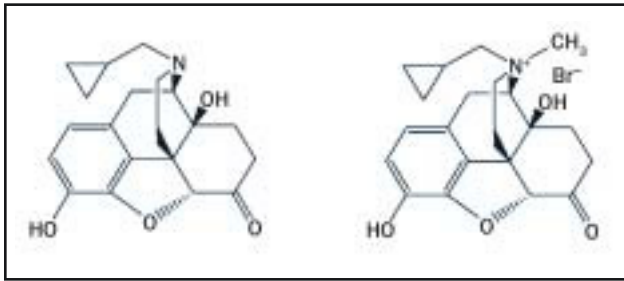


FIGURE 1. Chemical structures of naltrexone (left) and methylnaltrexone (right).

series of clinical studies on the management of postoperative pain with multiple analgesic therapies in combination with thoracic epidural anesthesia (ie, multimodal therapy). Studies of multimodal analgesia after laparotomy show that analgesic combinations that omit opioids reliably improve bowel function and shorten recovery time for patients.<sup>18</sup> The third line of evidence involves the prevention of POI with alvimopan (data reviewed in “Management of Postoperative Ileus”). This evidence is consistent with a role for both endogenous and exogenous opioids in POI.

### PHARMACOTHERAPY FOR OPIOID GASTROINTESTINAL EFFECTS

The gastrointestinal effects of morphine and similar substances involve both central and peripheral mechanisms; however, the actions at  $\mu$  receptors in the gut wall appear to be the most important mechanisms.<sup>23-25</sup> Thus, a logical goal of treatment is to block these gut receptors while sparing those receptors mediating analgesia.

The first attempts to accomplish this goal involved low doses of orally administered naloxone. Naloxone, a tertiary amine that is lipid soluble and easily crosses membranes, undergoes extensive first-pass metabolism, with only 2% systemic bioavailability. In theory, relatively large amounts of naloxone must reach the gut before enough is absorbed to reverse central effects of opioids. In several small trials, naloxone and similar tertiary opioid antagonists successfully reversed the constipating effects of opioids.<sup>27-30</sup> Unfortunately, precise titration of these antagonists has proved difficult. Because these compounds act both centrally and peripherally, they can reverse analgesia or precipitate withdrawal.<sup>27-30</sup>

In the United States, 2 PAMORAs have been approved by the FDA—MNTX, as a subcutaneous injection for opioid-induced constipation in patients receiving palliative care, and oral alvimopan, for gastrointestinal recovery after bowel surgery with primary anastomosis. Clinical studies of these medications have greatly increased our understanding of the effects of opioids in the gut and in other organs.

### METHYLNALTREXONE

**Preclinical Pharmacology.** Methylnaltrexone, a quaternary amine and a derivative of the opioid antagonist naltrexone, was developed by the late Leon Goldberg, a pharmacologist at the University of Chicago, with the specific goal of treating patients with opioid-induced constipation. The chemical structures of MNTX and naltrexone are compared in Figure 1. Goldberg reasoned that this permanently charged, polar molecule would function at opioid receptors in the gastrointestinal tract but would not penetrate the blood-brain barrier.<sup>31,32</sup>

Methylnaltrexone is produced as a water-soluble powder for its injectable formulation. It is a competitive antagonist that is relatively selective for  $\mu$  receptors and has no intrinsic opioid-agonist properties.<sup>33</sup> In vitro studies of human and guinea pig gut tissue show that MNTX has one third the potency of naloxone in reversing morphine-induced inhibition of contraction.<sup>33,34</sup> In these studies, 97% of morphine's effect on intestinal motility could be reversed by MNTX administered on gut tissue.

**Pharmacokinetics.** Interestingly, administration of MNTX alone in a human small intestine preparation increased smooth muscle contraction by 30%, suggesting the reversal of endogenous opioid activity.<sup>34</sup> When injected subcutaneously, MNTX neither reversed analgesia in rats<sup>33</sup> nor precipitated withdrawal in animals that were physically dependent on morphine.<sup>32</sup>

Peak plasma concentration and area under the concentration-time curve for MNTX are proportional to dose after intravenous or subcutaneous administration in human volunteers.<sup>35</sup> Time to peak is approximately 30 minutes after subcutaneous dosing.<sup>36</sup> After oral administration, extremely low plasma concentrations of MNTX are observed; enteric coating reduces the concentrations further, suggesting that a small amount of the drug may be absorbed in the upper gastrointestinal tract. No correlation exists between drug effects and plasma concentrations after doses of 3.2 mg/kg or 6.4 mg/kg of enteric-coated MNTX.<sup>36</sup>

Methylnaltrexone undergoes a moderate distribution (volume of distribution = 1.1 L/kg), and its terminal elimination half-life is 8 hours. Administration of MNTX at a dose of 0.3 mg/kg every 6 hours, for a total of 12 doses, did not result in accumulation or toxicity in healthy human volunteers.<sup>37</sup> Approximately 85% of a dose is eliminated in the urine as unchanged drug. Unlike rats and mice, humans do not demethylate MNTX to the centrally active antagonist, naltrexone.<sup>38</sup>

**Intestinal Motility.** In studies with morphine-treated volunteers, intravenous MNTX shortened oral-cecal transit time (OCTT) with no effect on analgesia. These effects of MNTX were initially assessed in a crossover experiment involving 12 volunteers who were given intravenous placebo, morphine (0.05 mg/kg), or MNTX (0.45 mg/kg) plus

morphine (0.05 mg/kg).<sup>39</sup> Mean OCTTs (measured by the lactulose hydrogen breath test) were 105, 163, and 106 minutes for placebo, morphine, and MNTX/morphine, respectively (Figure 2). These results demonstrate a nearly complete reversal of the opiate effect on OCTT. Pain was also measured in these patients using the cold pressor test.<sup>39</sup> Like naloxone, intravenously administered MNTX almost completely reversed gastrointestinal effects; however, unlike naloxone, it did not alter the analgesic effect of morphine. This study was the first demonstration in humans that opioid effects on the gastrointestinal tract are mainly peripherally mediated.<sup>39</sup> Another study with volunteer subjects confirmed that MNTX does not reverse opioid-mediated ventilatory depression, a centrally mediated opioid effect.<sup>40</sup> These results are important because they show that MNTX cannot be used, like naloxone, to treat patients with opioid overdose.

**Subcutaneous and Oral Administration.** Many patients who have advanced illness, such as the late stages of cancer or AIDS, are given large doses of opioids in home or hospice settings. For this reason, both subcutaneous and oral dosage forms of MNTX that would be practical to use outside of a hospital were needed. Subcutaneous administration of MNTX at doses of 0.1 mg/kg or 0.3 mg/kg was reported to reverse completely the delay in intestinal transit caused by morphine (0.05 mg/kg).<sup>41</sup>

When the efficacy of orally administered MNTX was tested, doses as high as 19.2 mg/kg were required to produce complete reversal of intestinal transit delay.<sup>42</sup> An enteric-coated oral preparation was subsequently developed to reduce gastric absorption and release MNTX only in the small and large intestine. Using this formulation, Yuan et al<sup>36</sup> achieved a complete reversal of intestinal transit delay with an MNTX dose of only 3.2 mg/kg. Because the enteric-coated preparation had greater potency but lower systemic bioavailability than the non-enteric-coated formulation, these results are consistent with a site of action in the colonic lumen.<sup>36</sup>

**Opioid Bowel Dysfunction in Methadone Maintenance.** Therapy using MNTX in opioid-tolerant volunteers represents a complex problem of dose titration. Opioid abusers who receive long-term methadone maintenance treatment for addiction are prone to having severe OBD. These volunteers typically defecate infrequently—perhaps only once or twice a week—and OCTT is markedly prolonged.

The use of MNTX has been investigated in 3 protocols relevant to this opioid-abuser population.<sup>35,43,44</sup> In a pilot trial, intravenous MNTX produced an extremely rapid onset of laxation.<sup>43</sup> This trial confirmed that opioid abusers are sensitive to opioid antagonists, suggesting that lower doses of MNTX should be used in this population. A second study was performed with 22 volunteers who had

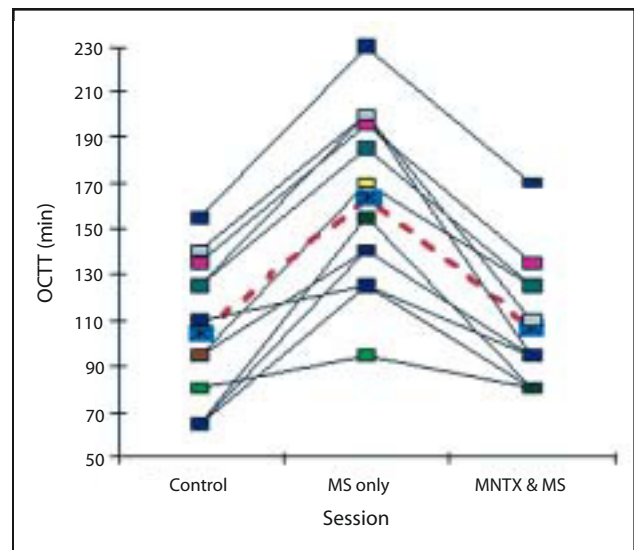


FIGURE 2. Oral-cecal transit time (OCTT) in 12 volunteers given placebo, morphine (MS), or intravenous methylnaltrexone (MNTX) plus MS. The dashed line represents the mean response. From *Clin Pharmacol Ther*,<sup>39</sup> with permission.

used methadone long term at dosages of 30 to 100 mg/d.<sup>35</sup> In this proof-of-concept trial, volunteers were given MNTX intravenously on an ascending dose schedule. Both OCTT and laxation were recorded, and signs of withdrawal were monitored. By the second day, all MNTX-treated volunteers but none of the members of the placebo group responded with laxation. Laxation typically occurred within 1 minute, and the MNTX dose required was only 0.1 mg/kg—roughly one-fifth the dose needed to reverse opioid-induced prolongation of OCTT in healthy volunteers.<sup>35</sup> These findings demonstrate that receptors in the gut, as well as in the brain, had become hypersensitive to opioid antagonists.<sup>35</sup> Oral-cecal transit time was normalized with the use of MNTX. Other than mild to moderate cramping, no volunteer showed psychological or physical signs of opioid withdrawal. A subsequent trial examined oral administration of MNTX in 12 volunteers who were treated with methadone maintenance.<sup>44</sup> Laxation occurred in 11 of the volunteers—but only after a delay that depended on the dose of MNTX. After oral MNTX doses of 0.3, 1, and 3 mg/kg, bowel movement occurred after an average delay of 18, 8.7, and 5.2 hours, respectively.

Methylnaltrexone has also been developed in a subcutaneous formulation designed to avoid the long delay associated with oral dosing, as well as to eliminate the need for vascular access with intravenous dosing. Subcutaneous administration has been shown to be effective in reversing morphine-induced changes in OCTT.<sup>41</sup> Peak plasma concentration of MNTX was achieved within only 15 minutes.

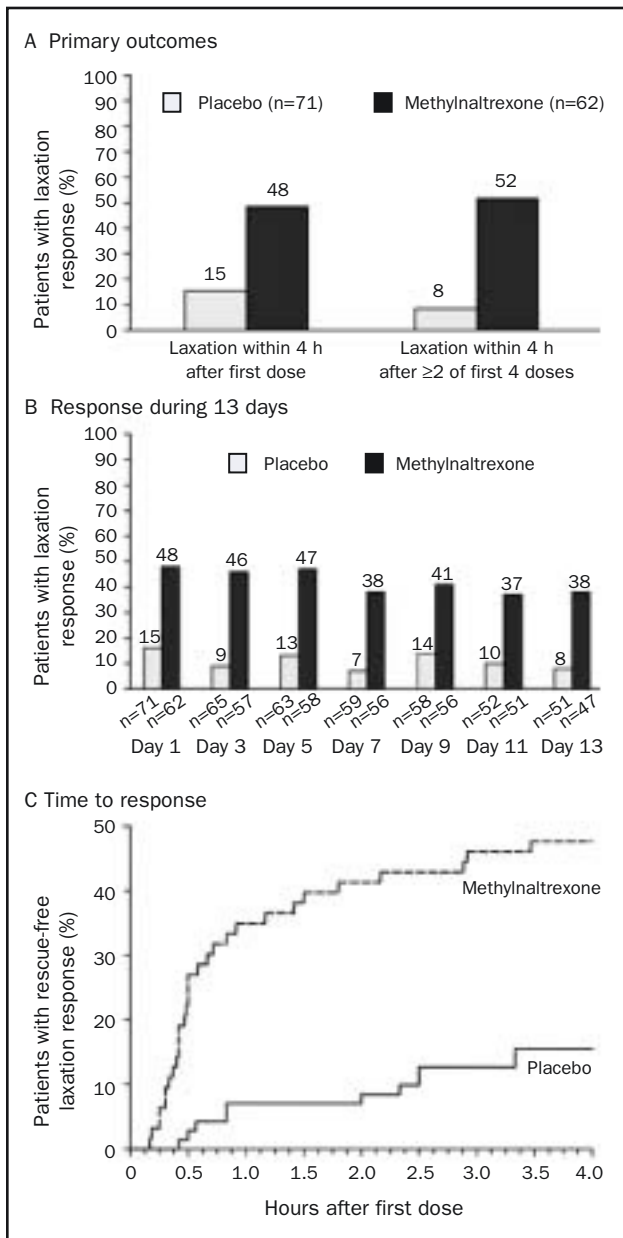


FIGURE 3. Laxation responses among patients with opioid-induced bowel dysfunction and advanced illness who were given either subcutaneous methylnaltrexone (0.15 mg/kg every other day for 1 week, with option of doubling dose in second week) or placebo. A, Primary efficacy measures: laxation within 4 hours after the first dose and laxation within 4 hours after 2 or more of the first 4 doses ( $P < .001$ ); B, Rescue-free laxation within 4 hours after each dose during a 13-day period ( $P < .005$ ). On days 9, 11, and 13, variations in doses were permitted on the basis of efficacy and adverse events; C, Kaplan-Meier curves for the time to laxation within 4 hours after the first dose ( $P < .001$ ). From *N Engl J Med*,<sup>48</sup> with permission from the Massachusetts Medical Society. © 2008. All rights reserved.

Taken together, these studies show that the route of antagonist administration can significantly affect the speed of onset.

**Opioid Bowel Dysfunction in Advanced Illness.** The clinical development program for MNTX was targeted particularly at patients with advanced illness. Such patients often have medical comorbidities, and their doses of opioids may be very high. In a phase 2b study of 33 patients with opioid-induced constipation who were receiving palliative care, subcutaneous injection of MNTX produced dose-related laxation, usually within 1 hour.<sup>45</sup> More than 70% of the treated patients responded favorably to MNTX, and there was no evidence of withdrawal.

Two pivotal phase 3 clinical trials of subcutaneous MNTX have been completed in patients with advanced illness. The first study (MNTX 301) was a multicenter trial that evaluated a single subcutaneous administration of MNTX (0.15 mg/kg or 0.3 mg/kg) in 154 patients with advanced illness.<sup>46</sup> The majority of these patients had advanced cancer, though some had severe chronic obstructive pulmonary disease, amyotrophic lateral sclerosis, or AIDS. Sixty-two percent of the patients laxated within 4 hours of their first MNTX injection, compared with 13% of the patients given placebo ( $P < .001$ ). Most patients responded within 1 hour of treatment, allowing a measure of predictability among these medically complex patients. Both doses of MNTX were effective, but the incidence of flatulence and abdominal cramping was higher in the high-dose group.

A follow-up phase 3 trial (MNTX 302) examined the effect of the lower subcutaneous MNTX dose (0.15 mg/kg) administered every other day for 1 week, with the option of doubling the dose as needed during a second week<sup>46-49</sup> (Figure 3). Of patients given MNTX, 48% had laxation responses within 4 hours of the initial dose, compared with only 16% of those given placebo ( $P < .001$ ). Overall, more than 46% of the patients responded favorably to the initial dose of subcutaneously injected MNTX, and more than 75% of the patients responded to one of the first 3 doses.<sup>47</sup> The median time to response was 30 minutes. Doses were stable during the 2-week trial and subsequent open-label extension.

Aside from the expected abdominal cramping and flatulence, few adverse effects were observed; no patient in these phase 3 trials experienced opioid withdrawal.<sup>48,49</sup> Dropout rates were similar for patients in both the treatment and control groups.

A phase 2b clinical trial of MNTX in an oral formulation was recently completed.<sup>50</sup> This study, involving 122 patients, found that a single daily dose of an oral form of MNTX effectively promoted laxation in individuals receiving opioids for chronic nonmalignant pain. Details of this trial have yet to be published.

**Postoperative Ileus.** The 3 trials of MNTX for the prevention of POI conducted to date have reported inconsistent results. The first was a phase 2 trial of intravenous MNTX in 65 patients who had colectomies. Compared

with placebo, MNTX-treated patients had a 20-hour improvement in their mean time to first laxation ( $P < .04$ ).<sup>51</sup> The mean time to become eligible for hospital discharge was 33 hours earlier for patients given MNTX than for those given placebo ( $P < .05$ ).<sup>51</sup>

However, two subsequent multinational phase 3 trials of intravenous MNTX did not show statistical significance for their primary end points. The data for these studies have not yet been published, and the reasons for the discrepancy with the phase 2 trial results are unclear.

#### ALVIMOPAN

**Preclinical Pharmacology.** Alvimopan, formerly known as ADL 8-2698, is a zwitterion (ie, molecule with both positive and negative regions of charge) that has a relatively large molecular weight (Figure 4). As would be expected for a large, polar molecule, alvimopan does not enter the CNS easily, and it produces strong peripheral opioid antagonism without affecting such central effects as analgesia.

In a study using cloned  $\mu$  receptors, alvimopan had very high binding affinity, which may account for the relatively long duration of its antagonist effect.<sup>52</sup> After oral administration to animals, alvimopan was poorly absorbed, with an absolute bioavailability of only 0.03%. Plasma pharmacokinetic data for alvimopan is derived from studies of intravenous administration to rabbits and dogs. These data indicate first-order elimination for alvimopan (ie, the amount of drug eliminated is directly proportional to the serum drug concentration), with a half-life of approximately 10 minutes.<sup>53,54</sup>

**Pharmacokinetics.** Alvimopan is available only in an oral preparation. In contrast to its minimal bioavailability in animals, systemic absorption of alvimopan in humans is approximately 6%.<sup>55</sup> Absorption is greater with fasting, after surgery, and in younger patients. Alvimopan is biotransformed to a metabolite designated as ADL-08-0011, which functions as an opioid antagonist. The fact that levels of this metabolite are decreased by administration of antibiotics indicates that gut bacteria affect biotransformation. Approximately 8% of the metabolite is absorbed; the clinical relevance of this compound is unknown.<sup>55</sup>

**Effects on Intestinal Motility.** In healthy volunteers, the use of radiolabeled markers showed that alvimopan reversed the prolongation of OCTT produced by oral loperamide. Repeated doses sustained this antagonist effect for longer than 4 days.<sup>54</sup>

Alvimopan also reversed morphine's effects on gastrointestinal motility. In a study involving 14 volunteers, the use of intravenous morphine (0.05 mg/kg) increased gastrointestinal transit time from 69 minutes to 103 minutes ( $P = .005$ ).<sup>56</sup> When alvimopan was administered orally to the volunteers at a dose of 4 mg, this effect of morphine was completely prevented ( $P = .004$ ). In a follow-up proto-

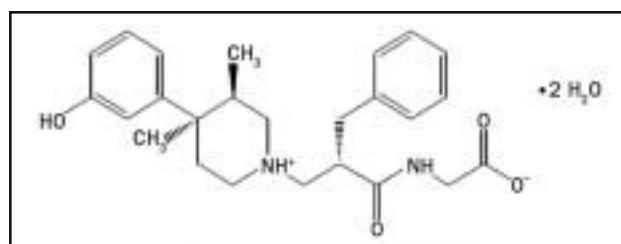


FIGURE 4. Chemical structure of alvimopan.

col, alvimopan (4 mg) or placebo was administered to 45 patients who had been given morphine for pain after dental surgery. There was no difference between the alvimopan and placebo groups in central effects, including pupil constriction and analgesia.<sup>56</sup>

In a placebo-controlled study, 36 of 72 enrolled volunteers were given codeine (30 mg 4 times daily) and 36 were given alvimopan (12 mg twice daily).<sup>57</sup> Codeine prolonged both gastric emptying and small bowel transit time. Alvimopan completely reversed codeine's effect on the small bowel, but it did not antagonize the reduction in gastric emptying.<sup>57</sup> The explanation for alvimopan's lack of effect on gastric emptying is unclear; it may be because blocking the gastric effect requires systemic absorption of the antagonist.

**Management of Postoperative Ileus.** In a pivotal phase 2/phase 3 trial, 78 patients who had abdominal or gynecologic surgery were randomized to receive alvimopan (1 mg or 6 mg) or a placebo 2 hours before surgery and then twice daily until hospital discharge, for a maximum of 7 days.<sup>58</sup> Patient-controlled analgesia with morphine or meperidine was used for postoperative analgesia. Alvimopan produced a substantial improvement in time to first flatus, time to first bowel movement, and time to be ready for hospital discharge (Figure 5).<sup>58</sup> These effects were most prominent with the higher dose. No statistical differences in opioid use or pain scores were reported among the 3 study groups. Interestingly, postoperative nausea, vomiting, and overall incidence of all gastrointestinal adverse effects were significantly reduced with use of alvimopan.<sup>58</sup>

The alvimopan phase 3 program investigated the prevention of POI with doses of 6 mg or 12 mg twice daily in 6 large trials. The results of four studies have been formally published,<sup>59-61,63</sup> but data on all studies are available from FDA online presentations.<sup>62</sup> Patients in these studies underwent either segmental bowel resection or total abdominal hysterectomy. One of the primary end points was termed GI-3, which was defined as the elapsed time until first solid food, flatus, or stool—whichever occurred last. The results for GI-3 were positive overall, although not consis-

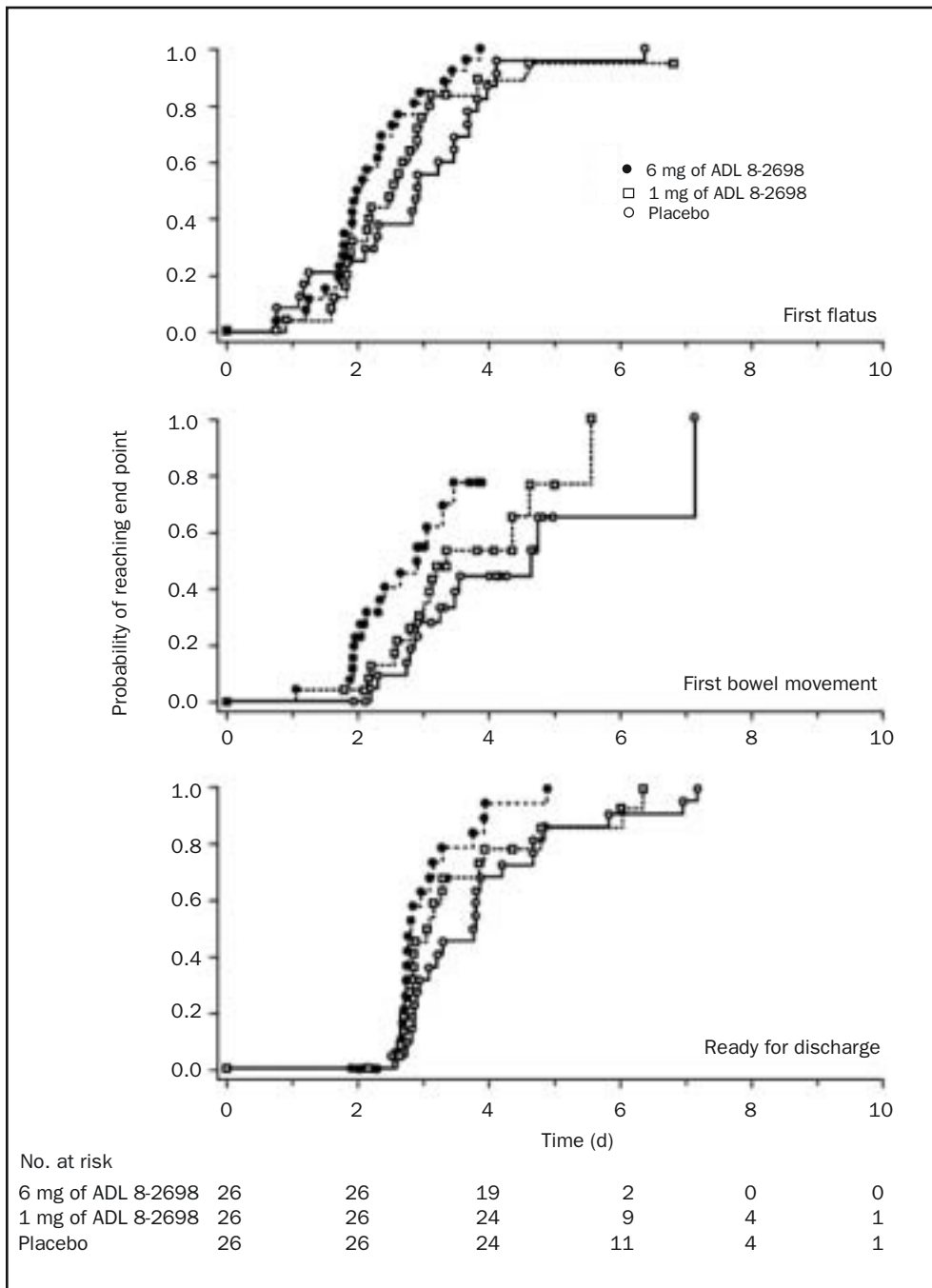


FIGURE 5. Kaplan-Meier estimates of probability of reaching end points among 78 patients with postoperative ileus who were given alvimopan (ADL 8-2698, 1 mg or 6 mg) or placebo 2 hours before surgery and then twice daily until hospital discharge, for a maximum of 7 days. Significant differences were observed among the groups in time to first passage of flatus ( $P=.03$ ), time to first bowel movement ( $P=.01$ ), and time until patient was ready for discharge ( $P=.03$ ). From *N Engl J Med*,<sup>58</sup> with permission from the Massachusetts Medical Society. © 2001. All rights reserved.

tently, and the 12-mg dose of alvimopan was not always more efficacious than the 6-mg dose of the drug.

Two explanations for the inconsistent results in the alvimopan phase 3 program are likely<sup>59-61,63</sup>: the inclusion of patients who had undergone hysterectomies (who do not usu-

ally have a problem with POI) and the use of GI-3, a composite end point (which lumped together very different phenomena). GI-2 (see Table 3 for definition) was a more consistent measurement. In one of the phase 3 trials that did not show statistical significance, many of the patients received

TABLE 3. Time to GI-2 for Patients Undergoing Bowel Resection in Phase 3 Postoperative Ileus Studies<sup>a</sup>

Study No.	Treatment <sup>b</sup>	No. of patients	Time to GI-2				HR (95% CI)	P value
			50th percentile (d)	Change from placebo (d)	75th percentile (d)	Change from placebo (d)		
302 <sup>60</sup>	Placebo	99	4.8	-0.7	5.9	-0.8	1.40 (1.04-1.89)	.029
	Alvimopan	98	4.1		5.1			
308 <sup>63</sup>	Placebo	142	4.9	-0.5	6.3	-0.9	1.37 (1.06-1.76)	.017
	Alvimopan	139	4.4		5.4			
313 <sup>59</sup>	Placebo	142	4.9	-0.9	6.3	-1.2	1.63 (1.26-2.10)	<.001
	Alvimopan	160	4.0		5.1			
001 <sup>62</sup>	Placebo	229	4.0	-0.1	5.7	-0.8	1.30 (1.07-1.58)	.008
	Alvimopan	238	3.9		4.9			
314 <sup>61</sup>	Placebo	312	4.0	-0.7	5.5	-0.9	1.53 (1.29-1.82)	<.001
	Alvimopan	317	3.3		4.6			

<sup>a</sup> CI = confidence interval; GI-2 = composite end point of first time to tolerate solid food or first bowel movement, whichever occurred last; HR = hazard ratio.

<sup>b</sup> Alvimopan dosage was 12 mg twice daily.

small or minimal amounts of opiates. Some of the GI-2 data for patients who received the 12-mg dose of alvimopan, as presented to the FDA Gastrointestinal Drugs Advisory Committee, are shown in Table 3.

Neither alvimopan nor MNTX was consistently better than placebo in the large international trials of POI, although the data from all trials suggest a greater effect from alvimopan. Do the 2 antagonists truly differ in efficacy for POI? One possible confounding factor may be the very different doses used in the trials of these 2 drugs. Alvimopan was studied at relatively high doses that were appropriate for surgical patients who did not take opioids long term. In contrast, MNTX was studied at low doses that were previously shown to be safe and effective for patients who had substantial previous exposure to opioids. Patients taking opioids long term are much more sensitive to the effects of antagonists than those who are opioid naive. In addition, results from a large international trial of alvimopan in POI<sup>61</sup> suggest that variations in surgical practice and opiate use may have contributed to statistically

nonsignificant results. In a post hoc analysis, patients who received more postoperative morphine than other patients were more likely to benefit from alvimopan.

Faster recovery of gastrointestinal function can lead to shorter hospital stays for patients, an effect that may produce economic benefit by lowering hospital costs. The times to hospital discharge for patients receiving alvimopan (12 mg) vs placebo for the 5 studies involving bowel resection, as presented to the FDA Gastrointestinal Drugs Advisory Committee, are summarized in Table 4. Taken as a whole, the alvimopan phase 3 studies support an important role for alvimopan in treating patients with POI.<sup>59-63</sup>

The adverse event profile for alvimopan in these POI trials<sup>59-63</sup> was largely unremarkable, and serious adverse events were almost always related to the surgical procedures rather than to medications. Despite the fact that alvimopan would be expected to increase bowel motility, no increase in anastomotic leakage was observed. The most common adverse reactions reported in the alvimopan phase 3 POI trials (incidence >3%) were nonspecific phenomena, including

TABLE 4. Time to Hospital Discharge for Patients Undergoing Bowel Resection in Phase 3 Postoperative Ileus Studies<sup>a</sup>

Study No.	Treatment <sup>b</sup>	No. of patients	Time to discharge		HR (95% CI)	P value
			75th percentile (d)	Change from placebo (d)		
302 <sup>60</sup>	Placebo	99	4.7		1.52 (1.11-2.09)	.010
	Alvimopan	98	4.1	-0.6		
308 <sup>63</sup>	Placebo	142	4.9		1.40 (1.09-1.78)	.008
	Alvimopan	139	4.6	-0.3		
313 <sup>59</sup>	Placebo	142	4.7		1.54 (1.20-1.96)	<.001
	Alvimopan	160	4.0	-0.7		
001 <sup>62</sup>	Placebo	229	5.7		1.11 (0.92-1.35)	.287
	Alvimopan	238	5.7	0.0		
314 <sup>61</sup>	Placebo	312	3.8		1.38 (1.17-1.63)	<.001
	Alvimopan	317	3.4	-0.4		

<sup>a</sup> CI = confidence interval; HR = hazard ratio.

<sup>b</sup> Alvimopan dosage was 12 mg twice daily.



anemia, dyspepsia, hypokalemia, back pain, and urinary retention.<sup>59-63</sup>

It is clear that patients undergoing open bowel resections who are treated with alvimopan are ready for discharge substantially earlier than patients given placebo. However, this advantage is not seen for patients who have had a simple hysterectomy (data not shown). The potential of alvimopan to reduce length of hospital stay is an important finding, but many other variables will determine whether this results in cost savings for the institution.

**Opioid Bowel Dysfunction in Patients With Chronic Pain and Addiction.** The use of alvimopan has been evaluated in 5 clinical trials involving patients who had OBD (chiefly constipation) and who were receiving long-term opioid treatment, but the results from most of these studies remain unpublished.<sup>64,65</sup> Four of the studies enrolled patients with noncancer pain (with one of these studies including a small group of addicts who were receiving methadone maintenance therapy), and the fifth study enrolled patients with cancer-related pain. Results of one phase 2 clinical trial were promising,<sup>65</sup> but the remaining trials failed to show a consistent beneficial effect of alvimopan in the clinical setting of OBD. The trial of 233 patients with chronic cancer pain found that 0.5 mg to 1 mg twice daily did not increase the frequency of spontaneous complete bowel movements. There were two phase 3 trials of patients with chronic pain: the first (522 patients) concluded that alvimopan worked, whereas the second (485 patients) failed to reach significance.<sup>66</sup> It should be noted that a placebo rate of greater than 50% was seen in the latter study. This high placebo rate suggests a problem in trial design or implementation. Placebo rates in the phase 3 trials of MNTX for advanced illness were half of those observed in the chronic pain trials with alvimopan.

**Recent Safety Issues.** An additional large study was carried out to examine the long-term efficacy and safety of alvimopan vs placebo in treating patients with OBD.<sup>62</sup> A preliminary analysis of the safety data from this study revealed serious adverse events, which were confirmed when the study completed enrollment. Most troubling were reports of serious cardiovascular toxicity (although levels reported were not statistically significant): 7 of 538 patients in the alvimopan group had myocardial infarctions vs 0 of 267 patients in the placebo group. According to reports submitted to the FDA Gastrointestinal Drugs Advisory Committee, these cardiovascular events were seen in patients who were at high risk for cardiovascular disease or who had established cardiovascular disease, and most events occurred during the first 12 weeks of treatment.

The adverse cardiovascular effects of alvimopan use were unexpected; no comparable toxicity had ever been observed when patients were given much higher doses of

alvimopan for chronic POI. There is no reason to suspect that these adverse effects are endemic to the PAMORA drug class. No cardiovascular problems have been encountered with MNTX or with high doses of naltrexone given for long-term addiction.

Given the nature of alvimopan and the drug's extremely low systemic exposure, the observed cardiovascular problems were likely not true toxic effects of alvimopan. Although the cardiovascular effects observed in the long-term alvimopan study were not statistically significant, the FDA took a very conservative approach in its recent approval of alvimopan. Until more is known about the drug's risk/benefit profile, the FDA is qualifying its approval of alvimopan with a Risk Evaluation and Mitigation Strategy, which is historically reserved for a small number of drugs about which the FDA has special concerns. Alvimopan is the first new molecular entity included in this strategy, which was adopted by the US Congress in the Food and Drug Administration Amendments Act of 2007.<sup>6</sup>

Alvimopan is approved with the following restrictions.<sup>6</sup> It may be given to patients to restore bowel function postoperatively, but only to adults who have undergone large or small bowel resection. In order to prevent off-label use, a black box warning is included in the package insert, noting the drug's approval for short-term hospital use in institutions that have met requirements for the Entereg Access Support and Education program. Alvimopan is indicated only in hospitalized patients, for a total of no more than 15 doses per patient. In addition, alvimopan should not be used in patients who have received opiates for more than 1 week. This last restriction was included because data presented to the FDA indicated that the 12-mg dose of alvimopan can actually be painful for patients receiving long-term opioid therapy.

## EFFICACY OF PAMORAS IN ATTENUATING OTHER OPIOID-INDUCED ADVERSE EFFECTS

### DELAYED GASTRIC EMPTYING

Effects of PAMORAs on gastric emptying have not been as well studied as effects on bowel motility, and the potential clinical implications of delayed emptying are rather different from implications of POI or constipation. Opioids decrease the tone of gastric smooth muscle and increase the tone of sphincters—and gastric emptying is a function of both these effects. As mentioned previously, a trial of alvimopan did not show any effect on gastric emptying.<sup>57</sup> Two studies showed that MNTX attenuates morphine-induced delay of gastric emptying, suggesting that gastric emptying is a peripheral effect of opioids.<sup>67,68</sup> Eleven healthy volunteers were given placebo, morphine (0.09 mg/kg), or a combination of morphine and MNTX, and the rate of gastric emptying was measured by tests of

bioimpedance and acetaminophen absorption.<sup>67</sup> The time for 50% emptying was 5.5, 21.0, and 7.4 minutes after administration of placebo, morphine, and morphine/MNTX, respectively. Morphine delayed acetaminophen transfer from stomach to proximal jejunum and decreased acetaminophen peak plasma concentration.<sup>67,68</sup> These effects were also prevented by MNTX.<sup>67,68</sup>

These preliminary data indicate 3 main ways in which MNTX could be helpful for certain patient populations receiving opioids. First, by decreasing the volume of gastric contents, MNTX may decrease the risk of regurgitation and pulmonary aspiration. This effect may be of particular relevance for patients undergoing general anesthesia, because the esophageal sphincter is relaxed, and protective airway reflexes are absent. Second, by increasing the rate at which an orally administered drug (eg, acetaminophen) passes into the proximal small bowel, MNTX may increase that drug's rate of absorption and peak concentration. Third, by decreasing gastric residuals, MNTX may increase the rate at which enteral feedings can be administered to patients who are taking large doses of opioids—an effect that may be of great importance for patients in the intensive care unit (ICU). No controlled studies of the effects of MNTX on enteral nutrition have been conducted. However, one case report describes the successful use of MNTX to initiate feedings in a patient with a 30% burn.<sup>69</sup>

#### NAUSEA AND VOMITING

Nausea and vomiting are well-known adverse effects of opioids that may have both peripheral and central components. The mechanisms involved in this association are complex. Low doses of opioids stimulate vomiting by binding to receptors in the chemoreceptor trigger zone (CTZ), whereas higher doses of opioids may suppress vomiting by acting at receptor sites deeper in the medulla. The CTZ is located in the floor of the fourth ventricle. Because this part of the brain has an incomplete blood-brain barrier, it is technically “peripheral.”<sup>70</sup>

Nausea and vomiting were reduced in patients who were given PAMORAs in several trials that were not specifically designed to look at this effect. A recent meta-analysis of phase 3 clinical trials examining the use of alvimopan in patients with POI showed a significant reduction in postoperative nausea and vomiting.<sup>71</sup> In one small study, MNTX markedly attenuated the nausea associated with parenteral morphine administration.<sup>71</sup> In another small study, patients who received MNTX for reversal of opioid urinary effects had a decrease in vomiting compared with those who received placebo.<sup>71</sup> This decrease in vomiting may have resulted from an action at the CTZ receptors or a modulation of afferent impulses from the enteric nervous system to the brain.<sup>72</sup>

#### URINARY RETENTION

Opioids cause urinary retention by inhibiting bladder detrusor (ie, smooth muscle) tone, by suppressing the micturition reflex, and by decreasing awareness of bladder distention. The clinical problem of urinary retention has not been as well studied as OBD, but some reports suggest a high incidence of urinary retention during the perioperative period.<sup>73</sup> Certain patient populations are likely at greater risk of this problem. For example, one study reported an incidence of urinary retention of 18.1% in older patients who used patient-controlled analgesia with morphine after lower limb joint replacement.<sup>73</sup> Complete urinary retention can be painful and distressing for the patient, and the usual treatment is immediate insertion of a bladder catheter to relieve symptoms.

Opioid actions on the brain and spinal cord undoubtedly affect the bladder. Until recently, however, the involvement of peripheral opioid receptors had not been shown. In a recent study, the effects of placebo, naloxone, and MNTX were compared for reversal of bladder dysfunction induced by the opioid agonist remifentanyl.<sup>74</sup> Detrusor pressure was measured by using bladder and rectal catheters in 13 male volunteers, and pupil constriction was measured by using infrared pupillometry. Remifentanyl decreased detrusor pressure in 21 of 25 sessions and caused complete urinary retention in 18 of 25 sessions. Voiding was possible after administration of placebo, naloxone, and MNTX in 0%, 86%, and 42% of sessions, respectively ( $P=.0013$ ; Figure 6).<sup>74</sup>

Pupil constriction was reversed only by naloxone, indicating once again that MNTX works peripherally. To our knowledge, this MNTX study<sup>74</sup> was the first demonstration of a peripheral opioid effect on bladder function. The results suggest that MNTX should be evaluated as a potential treatment for patients with opioid-induced urinary retention.

#### THE COUGH REFLEX

Opioids are commonly used as cough suppressants, but cough suppression is undesirable in some clinical circumstances (eg, during the postoperative period). The receptor mechanisms of opioids in the cough reflex are different from those mediating analgesia and respiratory depression, because weak  $\mu$ -opioids (eg, codeine) and nonanalgesic stereoisomers (eg, dextromethorphan) can have high activity as antitussives. Control of the cough reflex has long been thought to be a purely central effect involving a putative cough center in the medulla.<sup>75</sup> However, no data have been published regarding whether PAMORAs prevent the antitussive effect of opiates in humans.

A study of MNTX in guinea pigs suggests that a peripheral mechanism may be involved in the cough reflex. In that study,<sup>75</sup> an intraperitoneal dose of MNTX (2 mg/kg) blocked morphine-induced cough suppression but did not

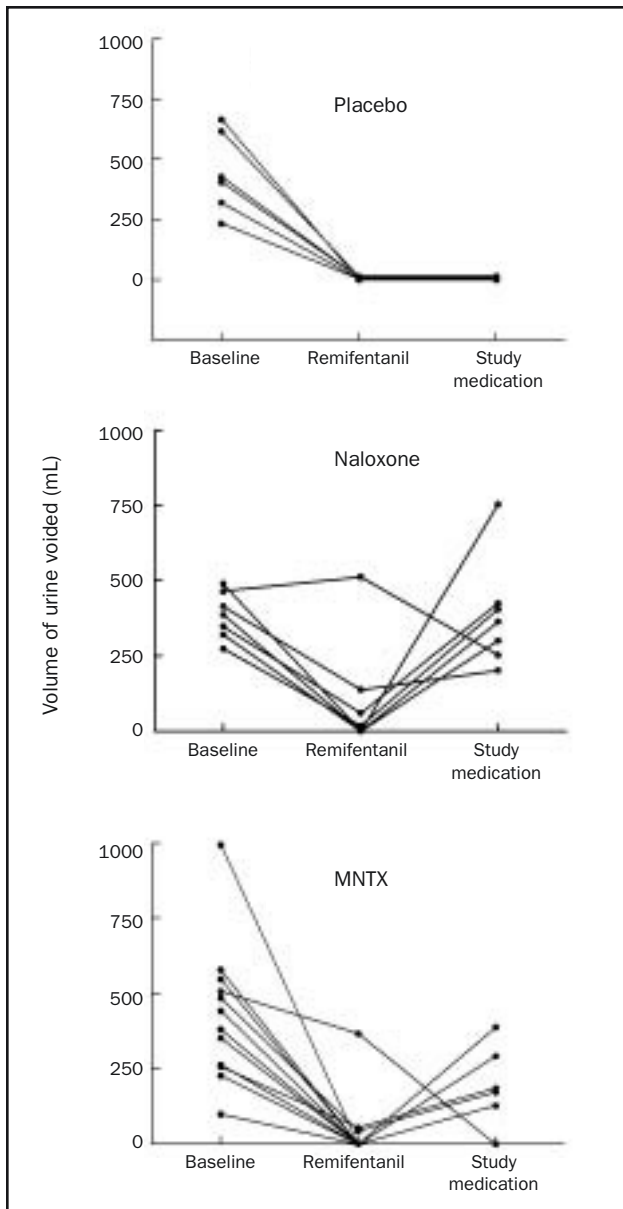


FIGURE 6. Volume of urine voided by male volunteers during urodynamic testing. Measurements were made at baseline, during infusion of remifentanyl (0.15  $\mu\text{g}/\text{kg}$  per minute), and after injection of saline placebo, naloxone (0.01 mg/kg), or methylnaltrexone (MNTX, 0.3 mg/kg). Remifentanyl greatly reduced or eliminated voiding in almost every case. The incidence of successful voiding was 0/6, 7/7, and 5/12 after saline, naloxone, and MNTX, respectively ( $P=.0013$ ). Adapted from *Clin Pharmacol Ther*,<sup>74</sup> with permission.

affect analgesia. The tertiary opioid antagonist naltrexone blocked both effects at a dose of only 0.16 mg/kg.

Further studies are needed to determine whether MNTX blocks opioid-induced suppression of other (possibly related) airway reflexes. Opioids are frequently administered to patients with chronic obstructive pulmonary disease in order to attenuate the sensation of dyspnea. This is likely a

central opioid effect, and some anecdotal reports suggest that it is not blocked by MNTX.<sup>76</sup> Understanding the effect of MNTX on dyspnea is important, because more than 10% of the patients in the phase 3 trials of MNTX for OBD had a primary diagnosis of chronic obstructive pulmonary disease or emphysema.<sup>46-49</sup>

#### PRURITUS

Opioids often cause itching, particularly around the face. Evidence suggests that itching is a dysesthesia that is mediated by opioid receptors in the CNS. Itching caused by certain opioids, particularly morphine, may also be related to the displacement of histamine from mast cells in peripheral tissues. Most itching, however, does not involve histamine release because itching can usually be reversed by naloxone and can be caused by opioids that do not release histamine (eg, fentanyl).<sup>41,77</sup> In one small trial, oral MNTX decreased itching after morphine was administered intravenously.<sup>78</sup> This result raises the intriguing possibility of a peripheral opioid receptor-mediated mechanism for itching, but such a mechanism needs to be confirmed in a larger trial.

#### CELLULAR EFFECTS

Four lines of preclinical investigation indicate that PAMORAs may prove useful in areas that are far removed from the problems of constipation and ileus. Many patients who are critically ill, including those with large tumors, are given high doses of opioids under the assumption that these drugs do little harm, provided that ventilation is adequate. However, increasing experimental evidence shows that opioids can produce undesirable effects on the growth of tumors and on the spread of infection by both bacteria and viruses, including the human immunodeficiency virus (HIV).

Many of these undesirable effects likely involve peripheral opioid receptors. In the laboratory, MNTX modulates opioid effects on the immune system, on angiogenesis, and on the production of lethality factors by bacteria. Such unexpected effects may have relevance for perioperative patients, as well as for patients with cancer or AIDS.

#### HUMAN IMMUNODEFICIENCY VIRUS

One area that is especially promising involves opioid up-regulation of chemokine receptor 5 (CCR5), the main route by which HIV enters a cell. Approximately 90% of HIV is transmitted across CCR5, and several new therapies are based on the ability to block this receptor.<sup>79,80</sup> Opioid abuse is an important risk factor for exposure to HIV. Indeed, research suggests that opioids may facilitate HIV infection of human macrophages by modulating  $\beta$  cytokines and CCR5. Methadone increases replication of the CCR5 binding site in monocyte-derived macrophages and glial

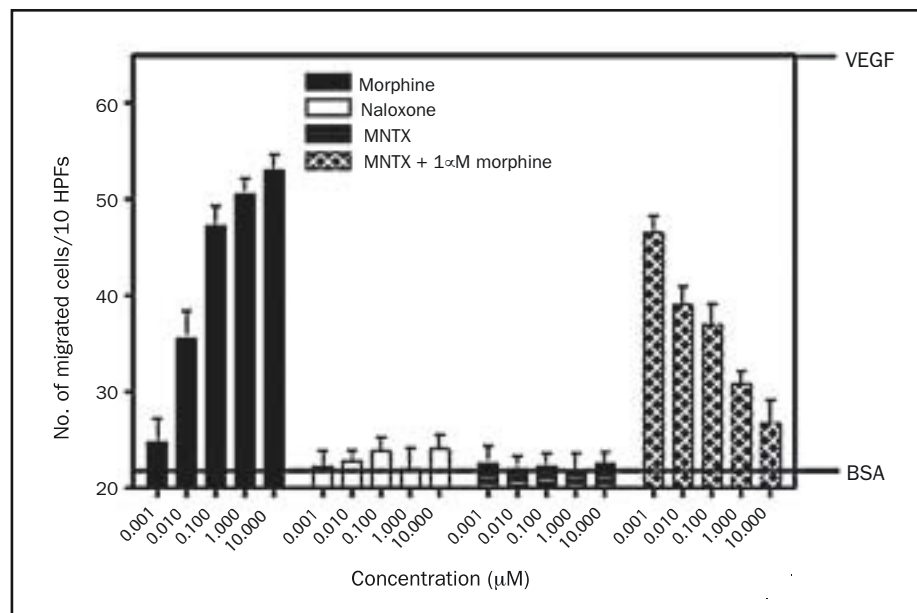


FIGURE 7. Rates of human endothelial cell migration into media containing bovine serum albumin (BSA), as a result of increasing concentrations of morphine, naloxone, methylnaltrexone (MNTX), or MNTX plus morphine. HPF = high-power field; VEGF = vascular endothelial growth factor. The line marked BSA represents background migration, and the line marked VEGF is a positive control. Increasing amounts of morphine increased cell migration, whereas naloxone and MNTX did not. Methylnaltrexone produced a concentration-dependent block of the morphine effect. From *Microvasc Res*,<sup>88</sup> with permission.

cells.<sup>81</sup> In this model system, concentrations of MNTX as low as 10 pM block the effect of methadone on viral replication and entry.<sup>82</sup> This result suggests that MNTX may possibly reduce HIV infectivity in patients who take large doses of opioids to manage pain or addiction.

Other viral infections may be modified by opioids as well. One study recently demonstrated an enhanced and sustained viral suppression in addicted patients with hepatitis C who were treated with implanted naltrexone.<sup>83</sup>

#### ANGIOGENESIS

The role of opioids and other anesthetic drugs in promoting tumor recurrence is an area of current research interest. A recent retrospective study demonstrated a 2-fold to 4-fold difference in the recurrence rate of breast cancer, depending on whether patients received general or regional anesthesia for their primary breast surgery.<sup>84</sup> In another retrospective study of patients who had undergone retropubic prostatectomy, the rate of tumor recurrence was 61% greater in patients who received general anesthesia with opioids than in those who received epidural anesthesia.<sup>85</sup> Follow-up studies are being performed to determine whether such differences in recurrence rate are caused by the primary or secondary effects of regional anesthesia or by the use of opioids.<sup>86</sup> One reason to postulate an effect of opioids on tumor growth is the ability of these drugs to promote tumor angiogenesis in

cellular models. Gupta et al<sup>87</sup> showed that clinically relevant concentrations of morphine induced new blood vessel growth in human breast tissue xenografts in mice.

We initiated laboratory studies of the effects of opioids and MNTX in angiogenesis because a few of our patients with cancer who had received MNTX under a compassionate use protocol appeared to have slower disease progression. Furthermore, we recognized that MNTX would be given to many patients with cancer after FDA approval. Our first studies showed that clinically relevant concentrations of morphine in vitro—similar to those achieved in surgery and palliative care—increased the migration and proliferation of endothelial cells from dermal and pulmonary vessels in humans (Figure 7).<sup>88</sup> These effects were antagonized by both naloxone and MNTX, showing that opioids promote angiogenesis by direct action at the  $\mu$ -opioid receptor.

This opioid effect is mediated by the angiogenic signaling pathway for vascular endothelial growth factor (VEGF). We showed that  $\mu$ -opioids enhance the efficacy of VEGF receptor binding through a process called reciprocal transactivation. Activation of the VEGF receptor is blocked by both naloxone and MNTX, thereby preventing angiogenesis.

Surprisingly, our cellular studies also showed that MNTX, even in the absence of opioids, potentiates the effects of 2 chemotherapeutic agents—5-fluorouracil and bevacizumab—on endothelial cell migration and proliferation.<sup>89</sup>

**VASCULAR PERMEABILITY**

Increased vascular permeability (ie, decreased endothelial barrier function) occurs in tumor angiogenesis, as well as in such inflammatory states as sepsis and in various types of lung injury. Singleton et al<sup>90</sup> explored the effect of MNTX in a laboratory model of pulmonary endothelial barrier disruption caused by a variety of agents, including morphine, thrombin, and lipopolysaccharide. They found that morphine and other  $\mu$ -opioid agonists disrupt barrier function at clinically relevant concentrations; this effect is blocked by MNTX and naloxone. Methylnaltrexone can block barrier disruption by both opioid-specific and non-specific mechanisms.<sup>90</sup> If confirmed clinically, these data suggest that MNTX may provide protective effects for patients with a variety of syndromes in which vascular permeability is increased.

**BACTERIAL OPIOID RECEPTORS**

*Pseudomonas* infection is a major problem in susceptible patients, including those in the ICU and those receiving palliative care. Opioids are now recognized as a cofactor in the development of sepsis in patients in the ICU.<sup>91</sup> Of the estimated 2 million nosocomial infections occurring each year in the United States, 10% are attributable to *Pseudomonas aeruginosa*—the second most common cause of pneumonia in the ICU.<sup>92</sup>

Recent in vitro studies have determined that *Pseudomonas* species have  $\mu$ -opioid receptors that mediate the production of the lethality factors procyanin and PA-I lectin.<sup>93</sup> PA-I lectin increases epithelial permeability, allowing the bacteria to penetrate the gut wall. Opioid-induced production of these lethality factors is blocked by MNTX, suggesting that the risk of bacterial sepsis might be reduced by PAMORAs in susceptible patients receiving opioids.<sup>93</sup>

**THE NEW DRUGS: FINAL THOUGHTS**

Although alvimopan and MNTX work by the same mechanism, major distinctions exist between them. One important difference is the route of administration. Methylnaltrexone has been tested in oral and parenteral forms, but FDA approval is based only on the injectable form for subcutaneous administration. Oral MNTX has been tested in small volunteer protocols, but there are no peer-reviewed publications of larger-scale trials. Alvimopan has been tested only in an oral form, and it is not clear if an injectable formulation will eventually become available.

Although orally administered antagonists are relatively slow in onset of action, they may be more convenient for outpatients to use. Injectable antagonists are not only faster in onset, but they also act on the whole gut simultaneously. Injectables may be most useful when oral administration is

problematic, as with patients in the ICU or patients who are nauseated. Parenteral formulations are most likely to be useful in hospital and hospice settings; however, many patients with advanced illness will probably inject MNTX at home. Thus, there are compelling reasons for development of both parenteral and oral peripheral opioid antagonists for clinical practice.

Not a great deal of information exists about the use of PAMORAs in particular risk groups. However, it is clear that neither MNTX nor alvimopan should be given to a patient who has mechanical bowel obstruction. Renal clearance is important for permanently charged, hydrophilic molecules, and more studies are needed to establish whether MNTX dosing should be altered for patients with renal failure. Patients with cardiovascular disease may benefit from administration of alvimopan, but caution will be required until more is known about the cardiovascular toxicity of this drug.

**CONCLUSION**

Peripherally acting  $\mu$ -opioid receptor antagonists have been proven useful for the relief of opioid-induced gastrointestinal dysfunction. The development of PAMORAs—including MNTX and alvimopan—has provided important insights into the peripheral effects of opioids. Methylnaltrexone has been approved by the FDA, Health Canada, and the European Medicines Agency. In the United States, it has been approved for subcutaneous injection in patients with advanced illness who are receiving palliative care, when response to laxative therapy has been insufficient. Alvimopan, which is orally administered, is approved for patients in the United States to accelerate gut function after bowel resection and primary anastomosis.

Methylnaltrexone has been used in clinical trials to discriminate between the central and peripheral effects of opioids. We have presented data suggesting that PAMORAs may eventually prove useful for managing cases of opioid-induced nausea and vomiting, enteral feeding, pruritus, and urinary retention. However, these data are very preliminary.

Finally, the development of PAMORAs has led to intriguing insights into the cellular effects of opioids. In laboratory studies, MNTX blocked the deleterious effects of opioids on tumor angiogenesis, vascular permeability, and bacterial virulence. If these laboratory effects prove to be clinically relevant, PAMORAs may eventually become useful therapeutic agents for physicians specializing in fields as varied as addiction, intensive care, oncology, and pain management.

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