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Opioids and the Gastrointestinal Tract: The Role of Peripherally Active μ-Opioid Receptor Antagonists in Modulating Intestinal Permeability

Brian E. Lacy, MD, PhD, FACG[1] and David J. Cangemi, MD[1]

Opioid receptors are found throughout the gastrointestinal tract, including the large intestine. Many patients treated with opioids experience opioid-induced constipation (OIC). Laxatives are not effective in most patients, and in those who do initially respond, the efficacy of laxatives generally diminishes over time. In addition, OIC does not spontaneously resolve for most patients. However, complications of opioids extend far beyond simply slowing gastrointestinal transit. Opioid use can affect intestinal permeability through a variety of mechanisms. Toll-like receptors are a crucial component of innate immunity and are tightly regulated within the gut epithelium. Pathologic μ-opioid receptor (MOR) and toll-like receptor signaling, resulting from chronic opioid exposure, disrupts intestinal permeability leading to potentially harmful bacterial translocation, elevated levels of bacterial toxins, immune activation, and increased cytokine production. Peripherally active MOR antagonists, including methylnaltrexone, are effective at treating OIC. Benefits extend beyond simply blocking the MOR; these agents also act to ameliorate opioid-induced disrupted intestinal permeability. In this review, we briefly describe the physiology of the gastrointestinal epithelial border and discuss the impact of opioids on gastrointestinal function. Finally, we consider the use of peripherally active MOR antagonists to treat disrupted intestinal permeability resulting from opioid use and discuss the potential for improved morbidity and mortality in patients treated with methylnaltrexone for opioid-induced bowel disorders.

KEYWORDS: methylnaltrexone; μ-opioid receptor; intestinal permeability; peripherally active μ-opioid receptor antagonists

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INTRODUCTION

In the United States, approximately 22% of adults use prescription opioids to treat chronic pain (1). Between 41% and 81% of patients using opioids experience opioid-induced constipation (OIC) (2,3). This term encompasses those patients with new onset constipation after initiation of opioids, as well as those with an exacerbation of underlying constipation after the initiation of opioids. For some patients, OIC is temporary; for others, it becomes chronic in nature. OIC is defined as a change from baseline in bowel habits and patterns of defecation after initiation of opioid therapy (4). Over the counter laxatives are not effective for most patients with OIC; for those who do initially respond, these treatments generally become less effective over time (5). Opioid use, whether intermittent or chronic, carries a significant risk of other adverse events, including dizziness, drowsiness, fatigue, hot flashes, increased sweating, pruritus, nausea, vomiting (6), and respiratory depression (7).

The impact of opioids on gastrointestinal function is more than simply acting on opioid receptors to slow gastrointestinal transit (Table 1) (8). Importantly, although less well recognized, opioids disrupt intestinal permeability and immune signaling in the intestine, resulting in heightened inflammation and susceptibility to infections (9,10). The mucosal layer of the intestine is a critical mediator of gut homeostasis through its multiple roles in regulating the transport and absorption of nutrients, metabolites, and electrolytes; modulating blood flow; and regulating gut immune function (11–13).

This review will summarize the effects of opioid use on intestinal permeability and homeostasis and will discuss findings which suggest that peripherally active μ-opioid receptor antagonists (PAMORAs) improve clinical outcomes in patients receiving opioids beyond that of simply improving constipation symptoms (14).

PHYSIOLOGY OF GASTROINTESTINAL FUNCTION

Transport in and out of the gastrointestinal lumen is regulated by the mucosa, which consists of two primary components. The first component is a monolayer of epithelial cells consisting primarily of villi-containing enterocytes and small populations of specialized epithelial cells. The second component is a secreted mucinous layer overlying the epithelial cell layer (Figure 1) (15,16). The submucosal layer lies beneath the epithelial cell layer and consists of a loose matrix of extracellular material (e.g., glycosaminoglycans) (17) with embedded neurons and other

[1]Mayo Clinic, Jacksonville, Florida, USA. **Correspondence:** Brian E. Lacy, MD, PhD, FACG. E-mail: Lacy.Brian@mayo.edu.
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Table 1. The effects of opioids on the gastrointestinal tract (8)

Pharmacological effects	Clinical effects
• Decrease gastric emptying	• Constipation
• Pyloric tone stimulation	• Nausea
• Inhibit propulsion	• Vomiting
• Increase nonpropulsive segmental contractions	• Gastroesophageal reflux
• Increase intestinal fluid absorption	• Gastroparesis
• Increase anal sphincter tone	• Abdominal pain
• Impair anal sphincter reflex relaxation in response to rectal distention	

supporting cells, such as glia (11). The neurons of the submucosal plexus are intimately involved in regulating permeability of tight junctions (TJs), blood flow, secretion, and gut immune function. Enteric glia cells regulate adhesion, differentiation, and proliferation of intestinal epithelial cells (11). Enteric glial cells express toll-like receptors (TLRs) which play a critical role in normal gastrointestinal function; these can be adversely affected with opioid use (9,10,18,19).

Movement of solutes out of the lumen occurs through transcellular and paracellular transport (20). Transcellular transport is accomplished through endocytosis of large (>600 Da) macromolecules (20). Paracellular transport through the epithelial monolayer is limited by a network of TJs (16). Protein components of TJs include the claudins, occludin, tricellulin, and junctional adhesion molecules (Figure 1) (16).

Extensive communication between the microbiota, immune cells, cells of the mucosa, and the submucosa plexus influences the health and function of the gastrointestinal system (21,22). For example, several species of pathogenic bacteria affect the expression or function of TJ proteins (23). Mice depleted of intestinal microbiota through antibiotic treatment have reduced myenteric ganglia as a consequence of decreased numbers of enteric neurons and glia, as well as reduced glial-derived neurotrophic factor expression, all of which are similar to the defects observed in TLR2 KO mice. These defects were partially reversed by administering a

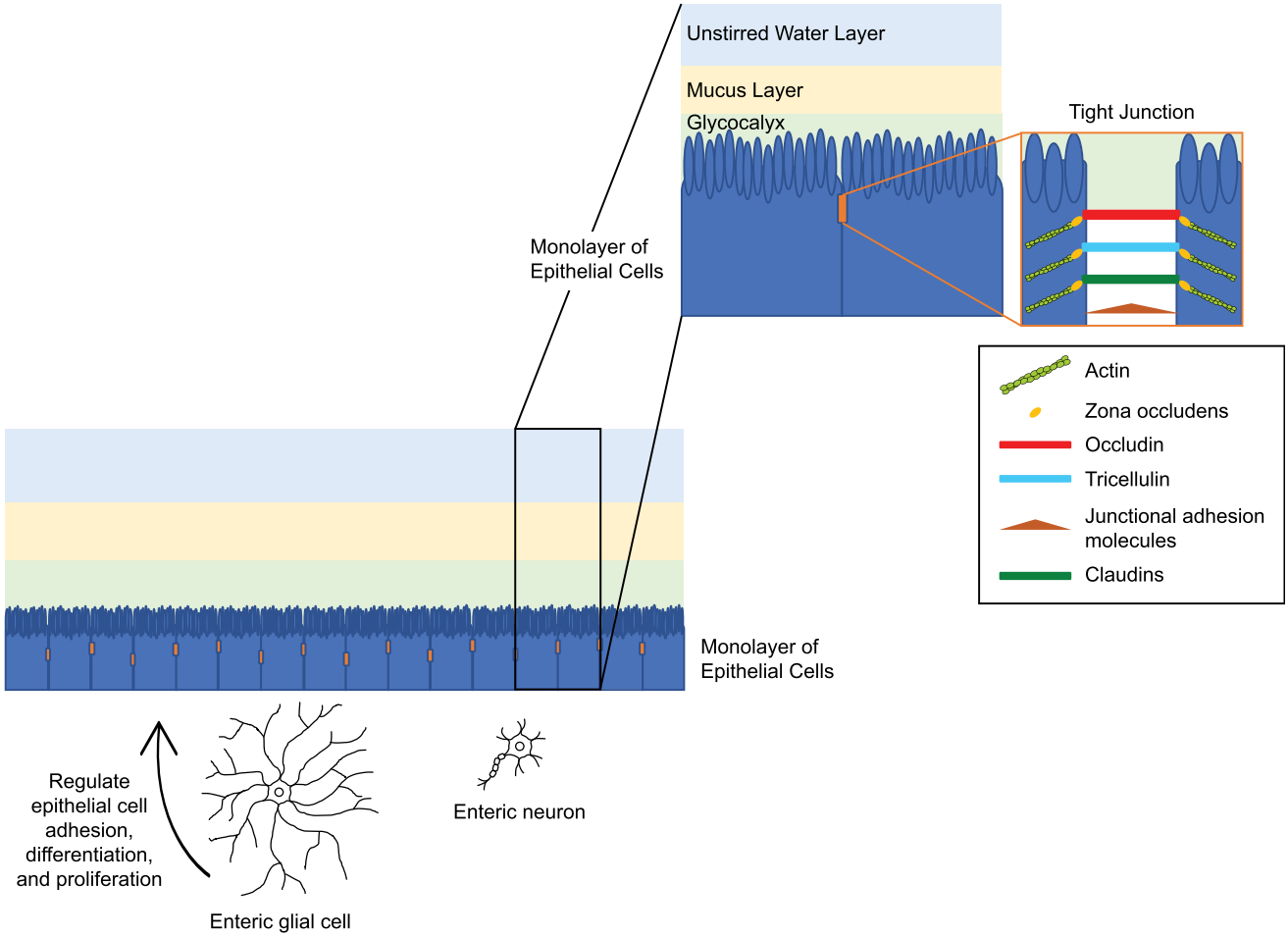

Figure 1. Layers of the gastrointestinal lumen (15,16). Transport in and out of the gastrointestinal lumen is regulated by the mucosa, which consists of a monolayer of epithelial cells and a secreted mucinous layer overlying the epithelial cell layer (15,16). The submucosal layer lies beneath the epithelial cell layer and consists of a loose matrix of extracellular material (e.g., glycosaminoglycans) (17) with embedded neurons and other supporting cells, such as glia (11). Movement of solutes out of the lumen occurs through transcellular and paracellular transport (20). Paracellular transport through the epithelial monolayer is limited by a network of TJs (16). Protein components of TJs include the claudins, occludin, tricellulin, and junctional adhesion molecules. TJ, tight junction.

TLR2 agonist (12). μ-Opioid receptors (MORs) are expressed within the intestine and localized to several areas and cell types, including the submucosal plexus and the epithelial cells of the intestinal villi and crypts (24,25). MORs are also found in immune cells of the gastrointestinal system (24,26,27). In a healthy individual, MOR signaling regulates intestinal secretion and peristalsis by binding to the endogenous opioids met-enkephalin, dynorphin, beta-endorphin, and endomorphins, which are released by several cell types, including enteric neurons, endocrine cells, and immune cells (Figure 2) (26,27).

PATHOPHYSIOLOGY OF OPIOIDS ON INTESTINAL FUNCTION

Morphine-mediated signaling through MORs compromises the intestinal barrier. Morphine alters the function and organization of TJs between gut epithelial cells of the small intestine by disrupting localized expression of the occludin and zona occludens 1 proteins (9) (Figure 3), thus resulting in increased intestinal permeability. The effects of morphine on TJs are TLR-dependent and interleukin (IL)-17A-dependent, and morphine exposure increases expression of both TLR and IL-17A in the small intestine (9,10). One study demonstrated that treatment with a TLR4 antagonist did not alter the morphine-induced inhibition of peristalsis in the small intestine, but it did attenuate the morphine-induced decrease in transit time in colonic segments isolated from guinea pigs; the interaction between TLR4 signaling and morphine was observed at high but not low doses (28). In addition, morphine slowed colonic transit time in wild-type mice, but this effect was attenuated in the colons of TLR4 and TLR2/4 KO mice (19), highlighting the importance of TLRs as it relates to the effects of opioids on intestinal function (18).

In patients treated with opioids, activation of MORs in the gastrointestinal tract can lead to bowel dysfunction and symptoms of constipation (Figure 4) (26,27). μ-opioid, but not δ-opioid, receptors primarily mediate the effect of morphine (29). Activation of MORs reduces electrolyte secretion and passive water movement into the colonic lumen (24). In animal models, morphine inhibits passage of water and electrolytes, thereby increasing both permeability and transit time, in a dose-dependent manner (19,25,30,31). Inflammation can also disrupt normal physiology of the intestines in several ways. Inflammation increases intestinal permeability, resulting in increased fluid accumulation in the small intestine (25,29). Inflammation increases intestinal secretion (25), thereby further raising level of fluid and mucus in the lumen (32). Intestinal transit time may be delayed in the setting of inflammation; this results in slower movement through the small intestine (29). Some studies suggest that inflammation alters the activity of opioid receptors thereby increasing the potency of opioid agonists and exacerbating the negative impact on intestinal permeability (25,30). Mechanistically, this may occur due to opioid receptors becoming sensitized or upregulated during chronic inflammation (30).

Release of tryptase from activated mast cells, which play a key role in the inflammatory response, increases intestinal permeability through apoptosis and activation of myosin light chain kinase, ultimately resulting in TJ protein alterations (33). Apoptosis, or programmed cell death, increases in the setting of inflammation; this has been shown to be important in patients with inflammatory bowel disease (34). Inflammation may be further enhanced by changes to the microflora, resulting in a state dysbiosis. Importantly, breakdown of the mucosal barrier allows bacterial translocation and leads to a localized immune response, heightened inflammation, and the potential for systemic infection (35,36). TLRs, which can be adversely affected by opioids, mediate several aspects of inflammation in the intestine. For example, in models of postoperative ileus and colitis, TLR4 signaling has a protective function (37). In addition, signaling through TLR2 reduces or prevents inflammation by supporting normal TJ function (38,39).

In addition, inflammation may alter gene expression of opioid receptors (40) as biopsy samples from patients with inflammatory bowel disease demonstrate increased levels of MORs messenger ribonucleic acid in the ileum and colon (41). Increased MOR expression in the ileum and colon may increase the potential for side effects resulting from treatment with opioid agonists.

Opioid signaling can induce changes in the gut microbiome. Endogenous opioid signaling regulates the microbiome in mice,

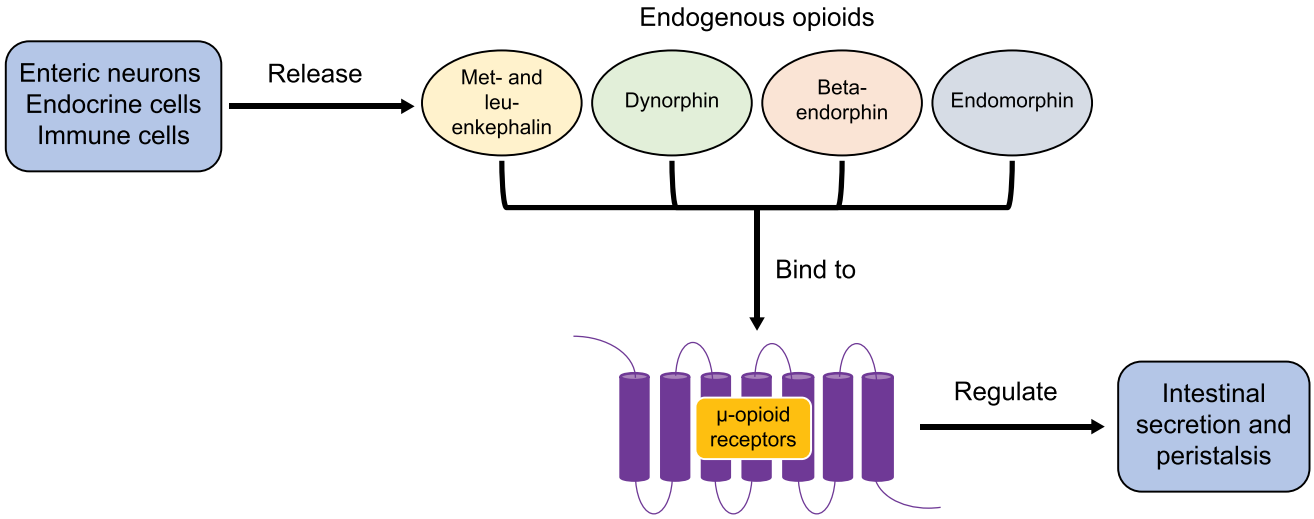

Figure 2. Regulation of intestinal secretion and peristalsis through μ-opioid receptors (26,27). μ-opioid receptor signaling regulates intestinal secretion and peristalsis by binding to the endogenous opioids met-enkephalin, dynorphin, beta-endorphin, and endomorphins, which are released by several cell types, including enteric neurons, endocrine cells, and immune cells (26,27).

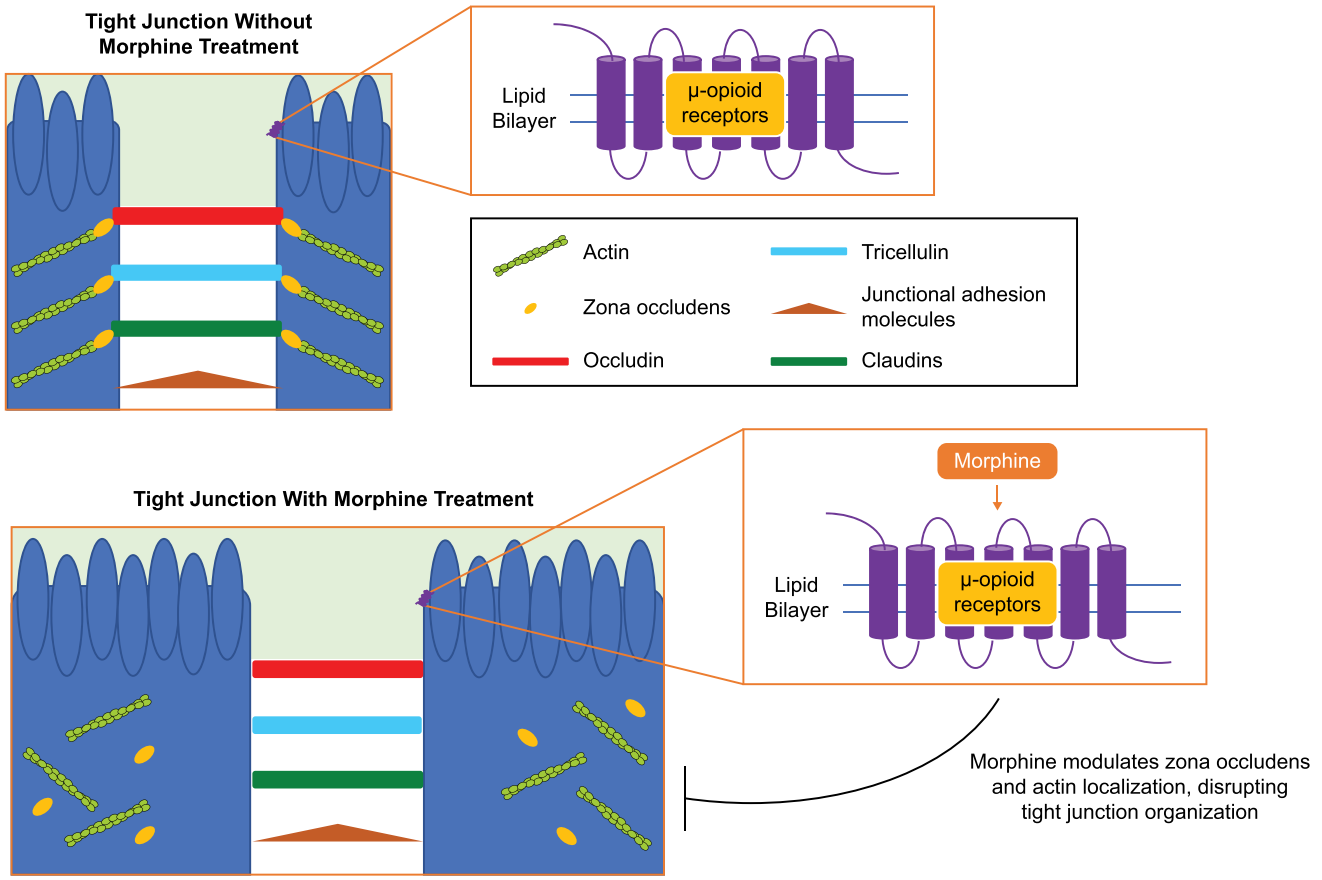

Figure 3. Effect of morphine treatment on TJs (9,16). Morphine increases intestinal permeability by altering the function and organization of TJs between gut epithelial cells of the small intestine. Morphine disturbs the TJ organization and function by disrupting the localized expression of the occludin and zona occludens 1 proteins (9). TJ, tight junction.

as evidenced by altered microbiota in MOR KO mice and in mice treated with the opioid antagonist, naltrexone (18,42). Exposure to morphine or other opioids substantially alters the microbiota of the intestine. Studies in rodents have found a reduced ratio of *Bacteroidetes* to *Firmicutes*, with elevated abundance of the *Staphylococcus* and *Enterococcus* genuses (18,43). Other studies have documented enrichment of the *Flavobacterium*, *Fusobacterium*, *Sutterella*, and *Clostridium* genuses (42). Studies of

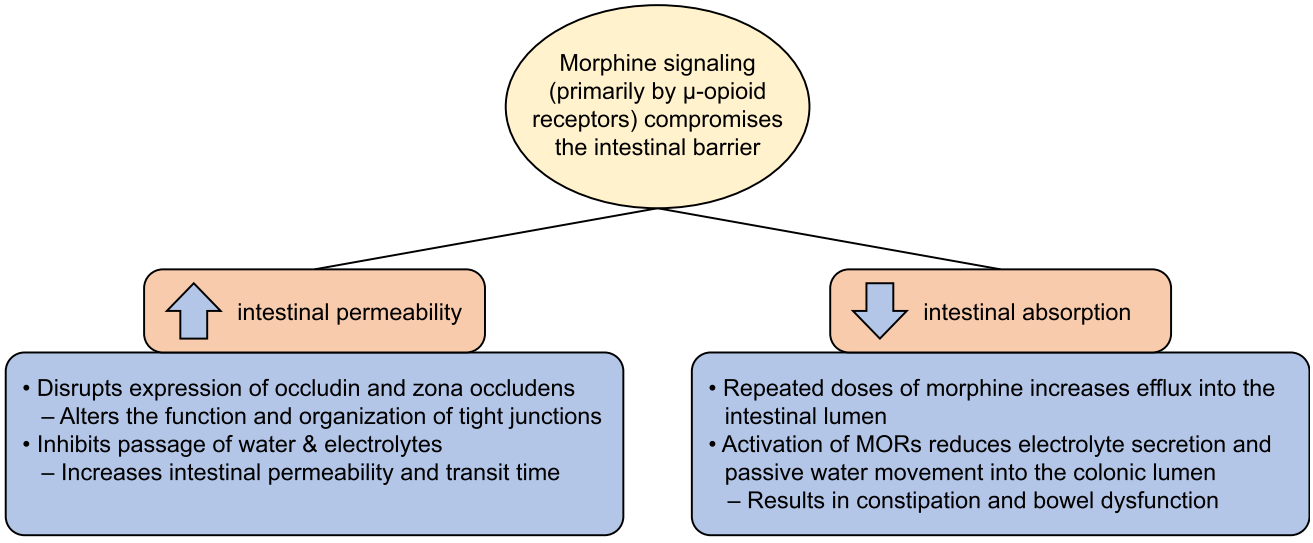

Figure 4. Effects of morphine signaling on the intestinal barrier (9,19,24–27,29–31,66,67). Activation of MORs in the gastrointestinal tract can lead to bowel dysfunction and symptoms of constipation (26,27). MOR, μ-opioid receptors.

human flora have revealed increased numbers of *Bifidobacterium* with decreased colonization by *Bacteroidacea*, *Clostridiales XIV*, and *Ruminococcaceae* (43). Changes in the bacterial profile appear as early as 1 day after exposure to morphine and persist through 6 days (Figure 5) (42,44). Opioid interactions with the microbiota are bidirectional in nature as the microbiota alters the pharmacokinetics of morphine metabolism in the gut (42,44). Morphine-induced increases in intestinal permeability may be reduced through treatment with antibiotics (45).

Treatment with morphine potentiates the development of septic conditions (45). Morphine increases the concentration of intestinal bacteria in a rat model (31). Morphine enhances the amount of bacterial translocation from the gut lumen into the peritoneal organs and the circulatory system, as well as delays the clearance of bacteria from these locations (10,31). In an animal model of sepsis, morphine treatment led to overgrowth of *Staphylococcus* and *Enterococcus* in the gut lumen and resulted in dissemination of these Gram-positive species to a greater extent than Gram-negative *Escherichia coli* (10). Morphine and tumor necrosis factor synergize to increase bacteria in the intestine and the degree of bacterial translocation through the intestinal epithelium (31). As with its effects on TJs, morphine signaling by MORs promotes bacterial dissemination through a TLR-dependent and IL-17A-dependent mechanism (9,10).

Opioids may affect the rate of infections and mortality among hospitalized patients. Both Gram-positive and Gram-negative infections are more prevalent among patients with sepsis who use opioids. Approximately 39% of septic patients who received opioids had Gram-positive infections compared with 20% of septic patients who did not receive opioids ($P < 0.0001$) (46). Of the septic patients who received opioids, 31% had Gram-negative infections compared with 27% of septic patients who did not receive opioids ($P = 0.0019$) (46). The Therapy, Resource, Evaluation, and Assessment Tool registry found that patients with Crohn's disease who received an opioid had a 2-fold increase in serious infections (47).

CLINICAL IMPLICATIONS

PAMORAs act peripherally on MOR in the gastrointestinal tract with negligible penetration across the blood-brain barrier due to their high molecular weight and polarity. Methylnaltrexone is a derivative of naltrexone with a methyl side chain added to the nitrogen group (48) with binding affinity for both μ- and κ--opioid receptors in the gastrointestinal tract (27). Naloxegol is a modified version of naloxone that has a polyethylene glycol moiety attached with binding affinity for the MOR (49). Naldemedine is derived from naltrexone and has been modified by the addition of a steric side chain with binding affinities for the μ-, δ-, and κ-opioid receptors (50). Alvimopan is zwitterionic, which

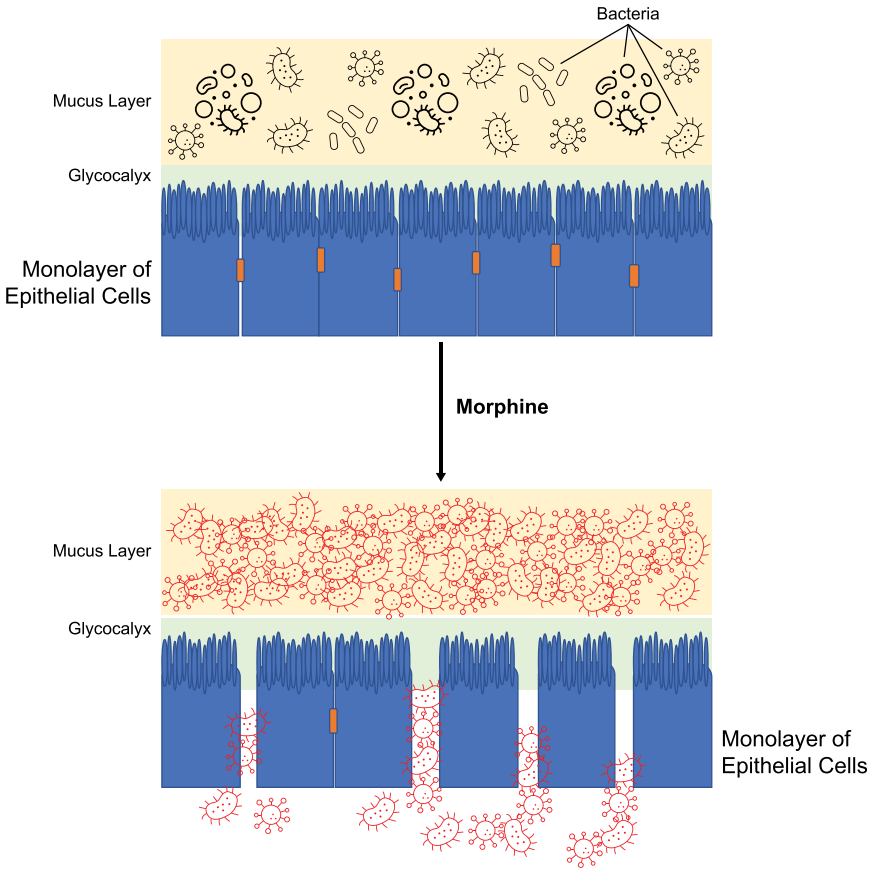

Figure 5. Morphine leads to microbial dysbiosis, disrupting gut homeostasis, and bacteria translocation (44). Exposure to morphine or other opioids substantially alters the microbiota of the intestine. Studies of human flora have revealed increased numbers of *Bifidobacterium* with decreased colonization by *Bacteroidacea*, *Clostridiales XIV*, and *Ruminococcaceae* (43). Morphine-induced increases in intestinal permeability may be reduced through the administration of antibiotics (45).

Table 2. FDA-approved medications for OIC

Medication	Class	Indication(s)	FDA approval year	Dose/dosing regimen	Most common adverse reactions
Lubiprostone	Chloride channel activator	• Chronic idiopathic constipation in adults • OIC in adults with chronic, noncancer pain • Irritable bowel syndrome with constipation in women (≥18 yr)	2006	Capsules—24 mcg twice daily[a]	Capsules (>4% of patients)[b]: • Nausea • Diarrhea
Methylnaltrexone—SC injection	PAMORA	• OIC in adults with chronic noncancer pain • OIC in adults with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient	2008	SC injection—12 mg	Injection (≥1% of patients): • Abdominal pain • Nausea • Diarrhea • Hyperhidrosis • Hot flush • Tremor • Chills
Alvimopan	PAMORA	• Indicated to accelerate the time to upper and lower gastrointestinal recovery after surgeries that include partial bowel resection with primary anastomosis	2008	Capsules—12 mg administered 0.5–5h before surgery followed by 12 mg twice daily for up to 7 d	Capsules (≥1.5% of patients) • Dyspepsia
Naloxegol	PAMORA	• OIC in adults with chronic noncancer pain	2014	Tablets—25 mg once daily. If not tolerated, reduce to 12.5 mg once daily	Tablets (≥3% of patients): • Abdominal pain • Diarrhea • Nausea • Flatulence • Vomiting • Headache
Methylnaltrexone—tablet	PAMORA	• OIC in adults with chronic noncancer pain	2016	Tablets (150 mg each)—450 mg once daily in the morning	Tablets (≥2% of patients): • Abdominal pain • Diarrhea • Headache • Abdominal distention • Vomiting • Hyperhidrosis • Anxiety • Muscle spasms • Rhinorrhea • Chills
Naldemedine	PAMORA	• OIC in adults with chronic noncancer pain	2017	Tablets—0.2 mg once daily	Tablets (≥2% of patients): • Abdominal pain • Diarrhea • Nausea

FDA, Food and Drug Administration; OIC, opioid-induced constipation; PAMORAs, peripherally active μ-opioid receptor antagonists; SC, subcutaneous.
[a]This is the recommended dosage for chronic idiopathic constipation and OIC. The recommended dosage for irritable bowel syndrome with constipation is 8 mcg twice daily.
[b]Most common adverse reactions (incidence >4%) in OIC. Most common adverse reactions (incidence >4%) in chronic idiopathic constipation are nausea, diarrhea, headache, abdominal pain, abdominal distension, and flatulence. Most common adverse reactions (incidence >4%) in irritable bowel syndrome with constipation are nausea, diarrhea, and abdominal pain.

results in low solubility and is a selective antagonist of the MOR (51).

Four PAMORAs are currently approved by the US Food and Drug Administration, of which are indicated to treat OIC (Table 2, Figure 6) (52). Methylnaltrexone tablets are indicated for the treatment of OIC in adults with chronic noncancer pain. In addition to the indication for the treatment of OIC in adults with chronic noncancer pain, the subcutaneous injection formulation is also indicated for the treatment of OIC in patients with advanced illness or active cancer (48). Naldemedine and naloxegol are indicated for the treatment of OIC in adults with chronic noncancer pain (49,50). Alvimopan is indicated to accelerate the time to upper and lower gastrointestinal recovery after surgery (51). In addition, lubiprostone, a locally acting chloride channel activator is US Food and Drug Administration approved for the treatment of chronic idiopathic constipation in adults; OIC in adults with chronic, noncancer pain; and irritable bowel syndrome with constipation in women (≥18 years of age) (53).

Although the safety and efficacy of PAMORAs have been well documented, there have been no head-to-head clinical trials, which makes it difficult to compare these agents directly (54). A meta-analysis of approximately 7,800 patients found that PAMORAs, specifically those approved for OIC, significantly improved symptoms of OIC (55). Experts agree that laxatives may not be effective in treating OIC in patients with cancer and that PAMORAs are a good therapeutic alternative (56). Experts also agree that poor OIC control in patients with cancer leads to an increase in undesired health outcomes, including a greater number of medical visits and emergency visits, and increased health care costs (56).

The effects of opioids on permeability in the small intestine can be blocked by both peripherally acting opioid antagonists and antisense oligonucleotides against opioid receptors (29,30). Epidemiologic data indicate that greater use of opioids is associated with shorter overall survival in patients with advanced cancer (57,58). Preclinical data have shown that opioids induce angiogenesis and increase migration and proliferation in human pulmonary and dermal endothelial cells; methylnaltrexone may inhibit these effects through a vascular endothelial growth factor pathway (59–61). In a post hoc analysis of 2 placebo-controlled, randomized clinical trials, methylnaltrexone was associated with increased survival among patients with OIC and advanced cancer (62). In this study, the overall survival of patients with advanced illness other than cancer was not significantly different between those treated with methylnaltrexone and those treated with placebo (62). In another post hoc analysis of 12 placebo-controlled, randomized clinical trials, patients with noncancer pain or advanced illness treated with methylnaltrexone had a 60% reduction in risk of mortality compared with patients who received placebo (14).

Opioid therapy is associated with overall higher risks of death and cardiovascular events (57,58). The TREAT registry found that patients with Crohn's disease who received an opioid had a 1.8-fold increase in mortality (47). In addition, patients hospitalized for sepsis had increased risk of mortality if they were taking opioids, compared with patients who did not take opioids (46). Use of long-acting opioids among patients with chronic noncancer pain increased their risk of death and cardiovascular mortality when compared with patients who used alternative medications (63). Methylnaltrexone is associated with survival among patients with OIC and chronic pain, including both cancer and noncancer chronic pain (14).

Areas of uncertainty

There are several areas of uncertainty with respect to the treatment of OIC with PAMORAs. The Rome IV diagnostic criteria were reported to be approximately 82% accurate when used to differentially diagnose OIC, specifically in patients with cancer; however, in a prior study, there were a considerable number of patients with OIC that the Rome IV criteria failed to diagnose

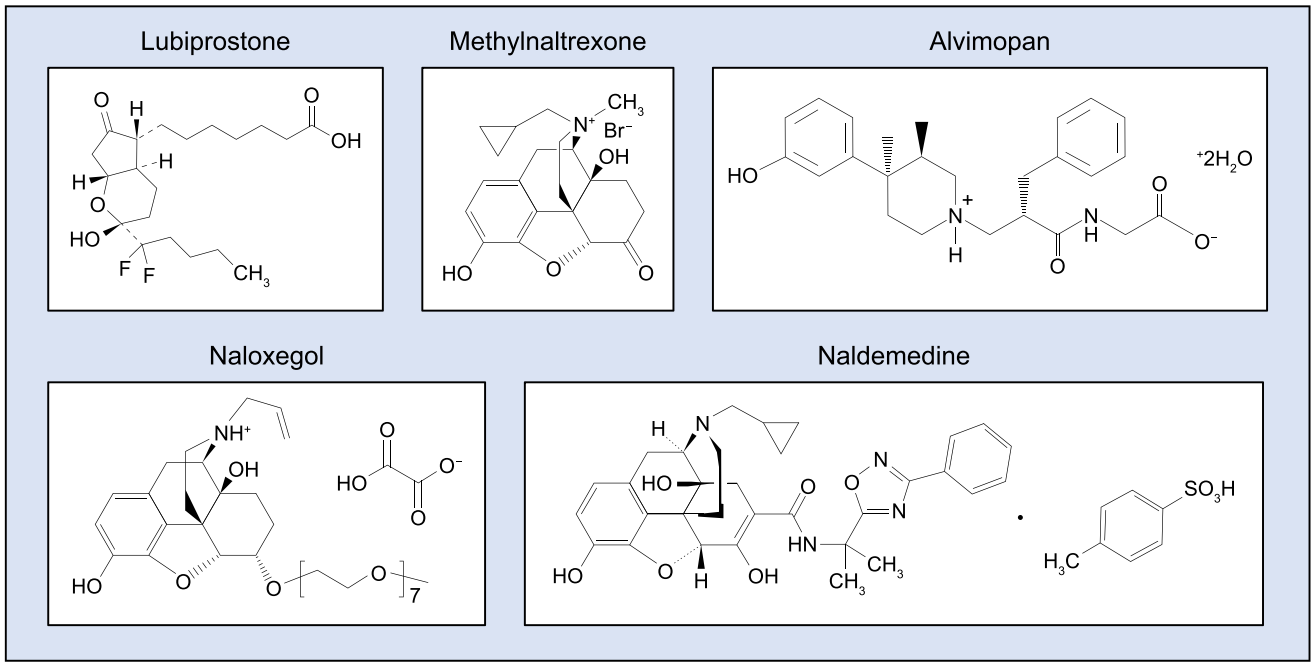

Figure 6. Chemical structures of FDA-approved medications for OIC. FDA, Food and Drug Administration; OIC, opioid-induced constipation.

(64). Although the Rome IV criteria are validated and universally recognized for OIC diagnosis, physicians still may rely on generic questions about intestinal function or patient diaries when diagnosing OIC (65).

Experts have agreed that early treatment with PAMORAs results in greater clinical benefits for patients with OIC and cancer (56). However, validated treatment algorithms and guidelines do not exist, resulting in potential uncertainty for clinicians navigating treatment of patients with OIC. It may be difficult for clinicians to decide which PAMORA or treatment should be prescribed first, which dose to use, how early to assess whether the chosen treatment strategy is working, and how long to wait when assessing whether a treatment is beneficial to the patient. Although PAMORAs are peripherally restricted, they could, in theory, alter peripheral pain perception or have other peripheral adverse effects, and these potential effects require further investigation in preclinical and clinical studies. In addition, naldemedine and naloxegol are primarily metabolized by CYP3A and drugs that are either strong CYP3A4 inducers or moderate-to-strong CYP3A4 inhibitors are not recommended to be used concomitantly (49,50). The authors are not aware of any labeling instructions for PAMORAs that recommend identifying rapid metabolizers, and physicians do not routinely assess the pharmacokinetics/pharmacodynamics before treatment for OIC.

CONCLUSIONS

Chronic exposure to opioids disrupts the neuronal, epithelial, and immune components of the mucosal barrier through MOR and TLR signaling. Consequences of disrupted intestinal permeability include increased production of cytokines and bacterial toxins, bacterial translocation, and immune activation and other hallmarks of inflammation. Use of opioids also shifts the balance between beneficial and harmful species within the gut microbiota, and this shift further promotes an inflammatory state and increased bowel permeability. PAMORAs, such as methylnaltrexone, appear to mitigate the disrupted permeability induced by opioids in the gastrointestinal tract and have been shown to improve survival in placebo-controlled trials of patients with chronic pain and OIC, although the extent to which effects on intestinal permeability affect survival requires further investigation.

CONFLICTS OF INTEREST

Guarantor of the article: Brian E. Lacy, MD, PhD, FACG.

Specific author contributions: B.E.L. and D.J.C. wrote, reviewed, and approved submission of this manuscript.

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