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PERIPHERALLY ACTING MU-OPIOID RECEPTOR ANTAGONISTS

Stephanie Martinez-Cox, PharmD Candidate
Karla Espinosa, PharmD Candidate
Chad Friece, PharmD, BCPS
Anita Rahman, PharmD, BCPS

Opioid agonists are widely used therapeutically for the relief of acute or chronic pain and are the main class of analgesics in the treatment and palliation of cancer. More recently, the rates of opioids prescribed for noncancer pain have greatly increased (Dowell, Haegerich, & Chou, 2016). The term "opioids" includes natural derivatives of opium (opiates; from the poppy *Papaver somniferum*), as well as semisynthetic and synthetic drugs that act as agonists at the opiate receptors. Most opioids used clinically for pain relief act as agonists at the μ (mu)-opioid receptors. Other types of opioid receptors include δ (delta) and κ (kappa) receptors. These receptors are widely distributed and penetrate into the central nervous system, producing analgesia, euphoria, and antitussive action. Mu-opioid receptors are also located throughout the body, leading to a group of well-recognized side effects including respiratory depression, depression of mental status, and miosis. Because of the large number of mu-opioid receptors located in the enteric system, reduced gastrointestinal motility is also common. When activated, the enteric receptors can slow gastrointestinal tone and contractility, leading to increased fluid absorption and ultimately constipation. With repeated use, patients will develop tolerance to most of these side effects, with the exception of reduced gastrointestinal motility causing severe constipation and miosis, which is often valuable in the diagnosis of an opioid overdose (Trescot,

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About the authors: *Stephanie Martinez-Cox, is PharmD Candidate, School of Pharmacy and Health Professions, Creighton University, Omaha, NE.*

Karla Espinosa, is PharmD Candidate, Texas Tech University Health Sciences Center, Lubbock.

Chad Friece, PharmD, BCPS, is Director of Pharmacy Services, Medical City Plano, Plano, TX.

Anita Rahman, PharmD, BCPS, is Clinical Manager of Pharmacy Services, Medical City Plano, Plano, TX.

The authors declare no conflicts of interest.

Correspondence to: *Anita Rahman, PharmD, BCPS, Clinical Manager of Pharmacy Services, Medical City Plano, 3901 West 15th Street, Plano, TX 75075 (Anita.Rahman@MedicalCityHealth.com).*

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Datta, Lee, & Hansen, 2008; Vallejo, Barkin, & Wang, 2011).

Peripheral effects such as opioid-induced constipation (OIC) are an effect that will not diminish with frequent use. Naloxone (Narcan) and related tertiary opioid receptor antagonists such as nalmefene (Revex) have been found to reduce constipation, but because they can easily cross the blood–brain barrier, they reverse centrally produced analgesia and respiratory depression and are therefore used in the treatment of opioid overdoses. Exercise, laxatives, dietary changes, and/or cathartics are often prescribed with the opioid therapy so that prevention and treatment of constipation begin immediately. These strategies, however, are often ineffective, decreasing the patient's quality of life. New approaches to the treatment of OIC are peripherally acting mu-opioid receptor (PAM-OR) antagonists. These peripheral opioid receptor antagonists offer the potential to relieve or reverse this undesired effect without compromising analgesia (Holzer, 2015).

Currently, there are four PAM-OR antagonists: methylnaltrexone, naloxegol, naldemedine, and alvimopan. Table 1 provides a comparison for all Food and Drug Administration (FDA)-approved medications.

Methylnaltrexone (Relistor) is a quaternary derivative of naltrexone with restricted ability to cross the blood–brain barrier, inhibiting OIC while preserving analgesic effects. Naloxegol (Movantik) is composed of naloxone conjugated with a polyethylene glycol polymer, which inhibits its ability to cross the blood–brain barrier and is a substrate of p-glycoprotein transporter increasing efflux across the blood–brain barrier. Naldemedine (Symproic) is structurally similar to naltrexone and is currently a Schedule II controlled substance. Alvimopan (Entereg) also has limited ability to cross the blood–brain barrier and selectively and competitively binds to the gastrointestinal mu-opioid receptors, antagonizing peripheral effects ("Lexi-Comp Online," n.d.).

All PAM-OR antagonists, except alvimopan, have been approved for OIC in patients with chronic noncancer pain. Alvimopan is approved to decrease the time to gastrointestinal recovery following surgical procedures that include partial bowel resection with primary anastomosis. Alvimopan requires a Risk Evaluation and Mitigation Strategy (REMS) program because of the potential for myocardial infarction risk with long-term use. Use is limited to 15 doses in a hospital setting and a maximum of 7 days of therapy. In addition, it is contraindicated for patients who have received opioid therapy for greater than 7 consecutive days before alvimopan administration (Merck, 2015). Methylnaltrexone is the oldest PAM-OR antagonist and the only agent available in injectable and tablet formulations. The methylnaltrexone injection is the only FDA-approved agent for OIC in palliative care patients (after laxative therapy has failed). Available dose adjustments for patients with hepatic impairment, advanced illness, and/or renal impairment are contained within Tables 2, 3, and 4. Methylnaltrexone has the lowest potential for drug–drug interactions among the OIC-approved agents but remains an expensive option (Salix Pharmaceuticals, 2017). Naloxegol is unique in that it can be crushed and administered via nasogastric tube or with water for patients who have trouble swallowing (AstraZeneca Pharmaceuticals, 2016). Naldemedine is the newest agent (approved March 2017) and is expected to come to market within the year as an oral tablet ("Lexi-Comp Online," n.d.). It will be the only oral formulation that can be administered without regard to meals. Naldemedine is also the only medication that is currently classified as a Schedule II medication and is currently under evaluation by the U.S. Drug Enforcement Administration for descheduling (Shionogi, 2017).

All agents approved for OIC have a risk for gastrointestinal perforation caused by peristaltic action above an intestinal blockage or reduced structural integrity of the gastrointestinal tract wall and opioid withdrawal symptoms (sweating, chills, abdominal pain, and anxiety). Patients should not take two or more PAM-OR antagonists concomitantly, as they have synergistic effects and can increase the likelihood of withdrawal symptoms. Patients should also be warned to discontinue therapy and contact their provider if they experience severe or persistent diarrhea. Use of any PAM-OR antagonist does not require adjusting analgesic doses of opioids before initiating therapy. There is little data regarding PAM-OR antagonist use in pregnant or lactating patients, but PAM-OR antagonists have the potential to cause opioid withdrawal in the fetus (AstraZeneca Pharmaceuticals, 2016; Merck, 2015; Salix Pharmaceuticals, 2017; Shionogi, 2017).

There is a lack of head-to-head data for these agents, as they are fairly new to the market. All agents are currently available as brand-only medications. When choosing therapy for a patient, cost and insurance coverage in addition to the patient's specific presentation should be taken into consideration. When a patient is prescribed an opioid for chronic pain, prevention strategies should be initiated including the options discussed earlier (exercise, increasing fiber and water intake, and laxative therapy). Continual reassessment of the patient should occur for titration, possible substitutions with nonopioid analgesics, and/or surgical intervention, if applicable (Dowell et al., 2016; Manchikanti et al., 2012). Laxative therapy should focus on agents that stimulate gastrointestinal motility (e.g., stimulant laxatives such as senna and bisacodyl) (Pharmacist's Letter, 2017). Laxative therapy should not rely on a stool softener alone (e.g., docusate) because stool softeners alone will not counteract the reduction in bowel motility seen in OIC (Twycross,

TABLE 1. Comparison of Current Peripherally Acting Mu-Opioid Receptor Antagonists

	Drug				
	Methylnaltrexone (Relistor) Injection	**Methylnaltrexone (Relistor) Tablets**	**Naloxegol (Movantik)**	**Naldemedine (Symproic)**	**Alvimopan (Entereg)**
FDA approval date	2008	2016	2014	2017	2008
FDA indications	OIC in adults with chronic noncancer pain AND OIC in palliative care patients after laxative therapy has failed	OIC in adults with chronic noncancer pain	OIC in adults with chronic noncancer pain	OIC in adults with chronic noncancer pain	To accelerate time to upper and lower gastrointestinal recovery following surgical procedures that include partial bowel resection with primary anastomosis
How supplied	8 mg/0.4 ml prefilled syringe 12 mg/0.6 ml prefilled syringe or single-dose vial	150-mg tablet	12.5-mg tablet; 25-mg tablet	0.2-mg tablet	12-mg capsule
Administration	Subcutaneous injection	Orally with water on an empty stomach at least 30 min before the first meal of the day	Oral on an empty stomach 1 hr before or 2 hr after first meal of the day Can crushed and administered via an NG tube	Oral with or without food	Oral, only for hospital use
How dosed	*OIC with chronic noncancer pain*: 12-mg subcutaneous injection daily *OIC with advanced illness*: see Table 2, recommend one dose every other day, no more than one dose per 24 hr	450 mg by mouth every morning	25 mg unless not tolerated and then 12.5 mg may be used	0.2 mg once daily	12 mg given 30 min to 5 hr before surgery, followed by 12 mg twice daily beginning the day after surgery until discharge for a maximum of 7 days (maximum of 15 in-hospital doses)
Contraindications	Known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction	Known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction	Known or suspected gastrointestinal obstruction or at increased risk of recurrent obstruction, concomitant use with strong CYP3A4 inhibitors	Known or suspected gastrointestinal obstruction or at increased risk of recurrent obstruction	Patients who have taken opioids >7 consecutive days prior to administration
Adverse effects	*OIC with chronic noncancer pain*: abdominal pain, nausea, diarrhea, hyperhidrosis, hot flush, tremor, chills *OIC with advanced illness*: abdominal pain, flatulence, nausea, dizziness, diarrhea	Abdominal pain, diarrhea, headache, abdominal distention, vomiting, hyperhidrosis, anxiety, muscle spasms, rhinorrhea, chills	Opioid withdrawal, severe abdominal pain, diarrhea, gastrointestinal perforation	Opioid withdrawal, abdominal pain, diarrhea, nausea, gastrointestinal perforation	Dyspepsia

(*continues*)

TABLE 1. Comparison of Current Peripherally Acting Mu-Opioid Receptor Antagonists (*Continued*)

	Drug				
	Methylnaltrexone (Relistor) Injection	**Methylnaltrexone (Relistor) Tablets**	**Naloxegol (Movantik)**	**Naldemedine (Symproic)**	**Alvimopan (Entereg)**
Drug interactions	Weak CYP2D6 inhibitor	Weak CYP2D6 inhibitor	Avoid grapefruit juice Avoid administration with moderate CYP3A4 inhibitors (dose can be reduced to 12.5 mg with monitoring)	Avoid use with strong CYP3A4 inducers Increase monitoring with moderate/strong CYP3A4 inhibitors and p-glycoprotein inhibitors	No CYP450 interactions
Average wholesale price	$120 for each vial/prefilled syringe 1 month supply for a daily injection: $3,600	$1,800 for 90 tablets 1 month supply for 450-mg dosing: $1,800	$376.74 for 30 tablets 1 month supply for either strength: $376.74	Approved March 2017, so pricing is not available yet	$4,750.92 for 30 capsules
Absorption	Peak concentrations within 30 min	Peak concentrations within 1.5 hr	Peak concentrations at <2 hr	Peak concentrations 0.75–2.5 hr if given with food	Peak concentrations at 2 hr
Renal impairment	If CrCl < 60 ml/min: *OIC with chronic non-cancer pain*: 6 mg subcutaneous injection daily *OIC with advanced illness*: see Table 3, recommend one dose every other day, no more than one dose per 24 hr	If CrCl <60 ml/min: 150 mg every morning	Initiate at 12.5 mg daily if CrCl <60 ml/min, if tolerated can increase to 25 mg daily while monitoring for adverse reactions	No adjustment necessary	No adjustment necessary in mild to severe renal disease Use is not recommended in end-stage renal disease
Hepatic impairment	If Child–Pugh Class B or C: *OIC with chronic non-cancer pain*: see Table 4 *OIC with advanced illness*: No recommendations given	If Child–Pugh Class B or C: 150 mg every morning	No adjustment necessary in mild or moderate hepatic impairment Avoid use in severe (Child–Pugh Class C) impairment	No adjustment necessary in mild or moderate hepatic impairment Avoid use in severe (Child–Pugh Class C) impairment	No adjustment necessary in mild or moderate hepatic impairment, but use with caution Avoid use in severe (Child–Pugh Class C) impairment
Notes	>4 months of therapy has not been studied in palliative care patients Laxatives should be stopped before starting methylnaltrexone but can be continued after 3 days of therapy if response is not adequate Patient should be within close proximity of toilet facilities once administered	Laxatives should be stopped before starting methylnaltrexone but can be continued after 3 days of therapy if response is not adequate Patient should be within close proximity of toilet facilities once administered	Laxatives should be stopped before starting naloxegol but can be continued after 3 days of therapy if response is not adequate	Currently approved as a Schedule II medication	REMS program required for use with a maximum of 15 doses due to black box warning (potential risk of myocardial infarction with long-term use)

Note. CrCl = creatinine clearance; FDA = U.S. Food and Drug Administration; NG = nasogastric; OIC = opioid-induced constipation; REMS = Risk Evaluation and Mitigation Strategy.

TABLE 2. Methylnaltrexone Dosing in Patients With Advanced Illness

Patient Weight	Subcutaneous Dose	Injection Volume
<38 kg	0.15 mg/kg	Multiply patient weight in kilograms by 0.0075 and round to the nearest 0.1 ml
38–<62 kg	8 mg	0.4 ml
62–114 kg	12 mg	0.6 ml
>114 kg	0.15 mg/kg	Multiply patient weight in kilograms by 0.0075 and round to the nearest 0.1 ml

TABLE 3. Methylnaltrexone Dosing in Patients With Advanced Illness and Renal Impairment

Patient Weight	Subcutaneous Dose	Injection Volume
<38 kg	0.075 mg/kg	Multiply patient weight in kilograms by 0.00375 and round to the nearest 0.1 ml
38–<62 kg	4 mg	0.2 ml
62–114 kg	6 mg	0.3 ml
>114 kg	0.075 mg/kg	Multiply patient weight in kilograms by 0.00375 and round to the nearest 0.1 ml

TABLE 4. Methylnaltrexone Dosing for Chronic Noncancer Pain and Severe Hepatic Impairment

Patient Weight	Subcutaneous Dose	Injection Volume
<38 kg	0.075 mg/kg	Multiply patient weight in kilograms by 0.00375 and round to the nearest 0.1 ml
38–<62 kg	4 mg	0.2 ml
62–114 kg	6 mg	0.3 ml
>114 kg	0.075 mg/kg	Multiply patient weight in kilograms by 0.00375 and round to the nearest 0.1 ml

Sykes, Mihalyo, & Wilcock, 2012). Methylnaltrexone, naloxegol, and naldemedine are not approved to prevent OIC and are only shown effective in patients who have been taking opioids for at least 4 weeks (AstraZeneca Pharmaceuticals, 2016; Salix Pharmaceuticals, 2017; Shionogi, 2017).

Other options for patients with OIC and chronic noncancer pain include lubiprostone 24 μg (Amitiza), a chloride channel activator also approved for irritable bowel syndrome and chronic idiopathic constipation. Lubiprostone is taken twice a day and has an average wholesale price of $420.11 for a 30-day supply ("Lexi-Comp Online," n.d.). Combinations of opioids and an opioid antagonist have also been studied as an option to decrease constipation while having minimal effects on analgesia. Targiniq, for example, is a combination of oxycodone and naloxone that was approved by the FDA in 2014 but is currently unavailable in the United States ("Lexi-Comp Online," n.d.).

Opiates are an indispensable class of medications for the treatment of pain. Many treatments of OIC have been explored and failed, leaving patients with disabling side effects such as incomplete bowel evacuation, abdominal distension, bloating, and abdominal discomfort that can profoundly impair the quality of life in patients. PAM-OR antagonists offer a rational approach to these undesired effects, whereas the effects of opiates on central pain control are preserved (Holzer, 2015). The American Gastroenterological Association is expected to release guidelines for OIC in 2018 which will help lead therapy decisions in the future.

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