

Methylnaltrexone: Peripherally Acting μ -Opioid Receptor Antagonist

TANYA J. URITSKY, PharmD, BCPS, CPE

From Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

Author's disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Tanya J. Uritsky, PharmD, BCPS, CPE, Hospital of the University of Pennsylvania, 3400 Spruce Street, Ground Floor Rhoads Building, Philadelphia, PA 19104.

E-mail: tanya.uritsky@uphs.upenn.edu

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Abstract

Opioid-induced constipation (OIC) is a common adverse effect associated with opioid therapy, with many patients never developing tolerance to this effect. There are many traditional laxatives available to help patients combat this symptom, yet OIC may not reliably respond to conventional treatment. Peripherally acting μ -opioid receptor antagonists (PAMORAs) have a place in the treatment of refractory OIC, when traditional laxatives have not resulted in effective laxation. There are a number of PAMORAs now available, and methylnaltrexone is the only PAMORA indicated for the treatment of OIC in adults with advanced illness, as well as for patients with chronic noncancer pain, including patients with chronic pain related to prior cancer treatment who do not require frequent opioid escalation. Advanced practitioners need to have an understanding of how and when to best use these medications for the different indications in patients with advanced illness or chronic noncancer-related pain.

The backbone of treatment for moderate to severe cancer pain is opioids. Opioid-induced constipation (OIC) is a common adverse effect of opioid therapy, affecting 40% to 90% of patients on long-term opioid therapy and can occur even with short-term use (Pergolizzi, 2017). Opioid-induced constipation is defined by the Rome IV criteria as an abnormal change from baseline in bowel habits or defecation patterns after initiating opioid therapy, characterized by any of the following: reduced frequency of spontaneous bowel movements (fewer than three bowel movements per week), devel-

opment or worsening of straining to pass bowel movement, a sense of incomplete evacuation, harder stool consistency, or a patient's perception of distress related to bowel habits (Nee et al., 2018). One study reported that gastrointestinal (GI) transit time increased from 22.2 hours to 43.9 hours after 5 days of oxycodone therapy ($p < .001$; Poulsen et al., 2016). Although patients will develop tolerance to other adverse effects of opioids like sedation and respiratory depression, constipation is predictable and most people do not develop tolerance despite the extended duration of opioid therapy. Constipation can have a significant impact

on quality of life, impacting mood, appetite, and pain. Opioid-induced constipation is also associated with increased physician visits, absences from work, and reduced productivity, as well as leading patients to stop their opioids or reduce their dose, thereby sacrificing pain control in favor of moving their bowels (Bell, Annunziata, & Leslie, 2009).

Lifestyle modifications, nonpharmacologic interventions, and traditional laxatives are the mainstay of OIC prophylaxis and treatment, but OIC does not reliably respond to treatment with conventional laxatives (Wald, 2016). Such agents include medications from different classes such as stimulants (senna, bisacodyl), osmotics (lactulose, magnesium hydroxide, polyethylene glycol), and pro-motility agents (metoclopramide). When standard approaches have failed, medications targeting the peripheral opioid receptor have been developed. There are currently three different medications in this class of peripherally acting μ -opioid receptor antagonists (PAMORAs). This article will focus on methylnaltrexone (Relistor), given that it has an indication for the treatment of OIC in adults with advanced illness, as well as for OIC in adults with chronic noncancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent opioid escalation.

PHARMACOLOGY AND MECHANISM OF ACTION

There are opioid receptors throughout the GI tract. These receptors play a role in peristalsis, promoting motility under normal conditions. Activation of the μ and κ receptors in the gastroduodenum leads to inhibition of gastric emptying, enhanced gastric acid secretions, and increased pyloric sphincter tone (Pergolizzi et al., 2017). When exogenous opioids are administered, this binding leads to a decrease in movement throughout the GI tract, leading to stool that is hard and difficult to move. Traditional laxatives aim to increase the water content of stool as well as promote motility to produce a bowel movement, but they do not specifically address the mechanism of OIC.

Naloxone antagonizes opioid receptors and has been given by mouth in the treatment of OIC for many years (Liu & Wittbrodt, 2002). This practice can be effective in the relief of constipation, but comes with the risk of potentially revers-

ing the central effect of opioids on pain control. In an effort to achieve the same efficacy in the treatment of OIC but with a decreased risk of inducing a withdrawal state, PAMORAs were developed. These drugs are methylated or polarized, which decreases their ability to cross the blood brain barrier, so they target the peripheral opioid receptor that lines the entire GI tract. The presence of the opioid receptor throughout the GI tract led some to start using the term “opioid-induced bowel dysfunction” in favor of “constipation” (Müller-Lissner et al., 2017). Effectively, PAMORAs reverse the constipating effect of opioids but are minimally associated with a reversal of analgesia or induction of a withdrawal state (Pergolizzi et al., 2017).

Naloxegol (Movantik) and naldemedine (Symproic) are also PAMORAs with the indication for OIC in patients with chronic noncancer pain, like methylnaltrexone. These two agents are only available in the oral formulation and are not indicated for OIC in patients with advanced illness. For a comparison of PAMORAs, please refer to Table 1.

CLINICAL TRIALS

A systematic review and meta-analysis showed that certain PAMORAs were more effective than placebo in treating OIC. In a 2013 meta-analysis, methylnaltrexone resulted in an improvement in symptoms, defined as three or more spontaneous bowel movements weekly, with a number needed to treat (NNT) of three (four for naloxegol; Ford, Brenner, & Schoenfeld, 2013; Nee et al., 2018). A more current analysis demonstrated an NNT of five for all of the PAMORAs (Ford et al., 2013; Nee et al., 2018). There were no more adverse reactions associated with the PAMORAs than with placebo.

A randomized, double-blind, phase III trial with open-label extension was conducted by Thomas and colleagues (2008) on 133 patients with terminal disease receiving opioids for at least 2 weeks and laxatives for at least 3 days. Patients were administered methylnaltrexone injection at 0.15 mg/kg subcutaneously every other day. Methylnaltrexone was significantly more effective than placebo in achieving laxation, with 48% of patients having a bowel movement in the methylnaltrexone group vs. 15% in the placebo group after a single dose ($p < .001$). A second dose resulted in 52% overall success in laxation vs. 8% in placebo

Table 1. Peripherally Acting μ -Opioid Receptor Antagonists

Drug	Indication	Dosing/route	Administration considerations	Drug interactions	Cost
Methylnaltrexone	<ul style="list-style-type: none"> SQ: OIC in the setting of advanced illness po/SQ: OIC in CNCP^a 	<ul style="list-style-type: none"> Advanced illness (SQ) <ul style="list-style-type: none"> » 8 mg (38–62 kg) » 12 mg (62–114 kg) » 0.15 mg/kg (< 38 kg or > 114 kg) CrCl < 60 mL/min <ul style="list-style-type: none"> » SQ: 50% of standard dosing recommendations » po: 150 mg daily CNCP <ul style="list-style-type: none"> » SQ: 12 mg once daily » po: 450 mg once daily 	<ul style="list-style-type: none"> SQ: administer into upper arm, abdomen, or thigh; rotate injection sites; not studied when used for more than 4 months po: administer on an empty stomach at least 30 minutes before the first meal of the day 	None	<ul style="list-style-type: none"> SQ: \$130.80 (8-mg or 12-mg syringe) po: \$1,962.00 (450 mg; 90 tablets)
Naloxegol	OIC in CNCP ^a	<ul style="list-style-type: none"> 25 mg po once daily; decrease to 12.5 mg if not tolerated CrCl < 60 mL/min: 12.5 mg po once daily; increase to 25 mg as needed/tolerated Avoid use in severe liver impairment (Child-Pugh Class C) 	<ul style="list-style-type: none"> Administer on an empty stomach at least 1–2 hours before the first meal of the day May be crushed and dissolved 	<ul style="list-style-type: none"> Moderate to strong CYP3A4 inhibitors/inducers Avoid ingestion of grapefruit juice 	\$414.04 (12.5 mg or 25 mg; 30 tablets)
Naldemedine	OIC in CNCP ^a	<ul style="list-style-type: none"> 0.2 mg po once daily Avoid use in severe liver impairment (Child-Pugh Class C) 	Administer without regard to meals	<ul style="list-style-type: none"> Moderate to strong CYP3A4 inhibitors/inducers Avoid ingestion of grapefruit juice 	\$376.74

Note. SQ = subcutaneously; OIC = opioid-induced constipation; po = orally; CNCP = chronic noncancer pain. For all agents: Discontinue peripherally acting μ -opioid receptor antagonist (PAMORA) when discontinuing opioid therapy. Bowel movements may occur rapidly within 4 hours. Do not combine different PAMORAs (category X). Information from LexiComp, Inc. (2018).

^aDiscontinue all maintenance laxatives prior to use and reintroduce as needed after 3 days without sufficient bowel movements.

($p < .001$). The median time to laxation was 6.3 hours in the treated group vs. more than 48 hours in those receiving placebo. Among those patients who had a response within 4 hours, 50% had a response within 30 minutes of administration.

In chronic noncancer pain, both the subcutaneous and oral administration of methylnaltrexone was shown to be significantly more effective than placebo (Michna et al., 2011). A randomized, double-blind, phase III trial of 460 patients with chronic noncancer pain for more than 2 months, on opioids for over 1 month, and having fewer than three bowel movements per week, were randomized to methylnaltrexone at 12 mg daily, every other day, or placebo. Daily or every-other-day administration of subcutaneous methylnaltrexone resulted in approximately 30% of patients having rescue-free laxation within 4 hours after the first dose, vs. 9% to 10% with placebo ($p < .001$). Oral administration of methylnaltrexone at 450 mg daily resulted in approximately 27% of dosing days with rescue-free bowel movements within 4 hours, compared to 8% to 18% with placebo ($p < .0001$; Rauck, Slatkin, Stambler, Harper, & Israel, 2017). Laxatives were discontinued at screening, but rescue therapy was permitted. Abdominal pain, diarrhea, and nausea were reported more frequently with methylnaltrexone, and the rate of study withdrawal was higher in the treatment groups. No significant opioid withdrawal or change in pain scores was observed with methylnaltrexone.

DOSING AND ADMINISTRATION

Dosing and administration of methylnaltrexone is dependent on the route of administration and indication (Salix Pharmaceuticals, 2017). In the setting of advanced illness, the subcutaneous route is the only approved formulation and is dosed based on weight. The recommended dosing interval is every other day and the recommended dose is 8 mg for patients weighing 38 kg to less than 62 kg, and 12 mg for patients weighing 62 kg to 114 kg. For patients under 38 kg or over 114 kg, it is dosed as 0.15 mg/kg. It should not be given more than once daily. For patients experiencing OIC with chronic noncancer pain, all maintenance laxatives should be stopped prior to initiating methylnaltrexone and reintroduced if there is a suboptimal response after 3 days. The recommended dosing

in chronic noncancer pain is 450 mg orally or 12 mg subcutaneously once daily.

There are no recommended adjustments for older adults. In the setting of renal insufficiency with creatinine clearance less than 60 mL/minute, recommended dosing for subcutaneous administration is 50% of the standard dosing recommendations. With oral administration, the recommended dose is 150 mg daily in renal impairment. Methylnaltrexone has not been studied in patients with end-stage renal disease. For hepatic impairment, the recommendation for severe impairment (Child-Pugh Class C) is to adjust the dose in the same way as with renal impairment. There is no adjustment needed for mild to moderate impairment.

Specific considerations for administration should be given for each dosing route (Salix Pharmaceuticals, 2017). Oral methylnaltrexone should be administered on an empty stomach at least 30 minutes before the first meal of the day. The subcutaneous injection should be administered into the upper arm, abdomen, or thigh. The injection site should be rotated with each dose. Bowel movements may occur rapidly within 4 hours; patients should be advised to be close to a bathroom or commode. Subcutaneous administration for more than 4 months has not been studied. When the patient is no longer taking opioids, they should be instructed to stop taking methylnaltrexone.

ADVERSE EVENTS

For a review of adverse events associated with the use of methylnaltrexone, please refer to Table 2.

Table 2. Adverse Events of Methylnaltrexone

- Most common adverse events: abdominal pain (14%–29%), nausea (9%–12%), flatulence (13%)
- Patients should immediately report to their provider if they experience severe or persistent diarrhea; severe abdominal pain; severe abdominal edema; tremors; hematemesis; or black, tarry stools
- Contraindicated for patients with known or suspected GI obstruction or at increased risk of GI obstruction
- Should be used with caution in patients with advanced illness associated with impaired structural integrity of the GI wall
- Discontinue if severe abdominal pain develops

Note. GI = gastrointestinal. Information from Salix Pharmaceuticals (2017).

IMPLICATIONS FOR THE ADVANCED PRACTICE PROVIDER

Peripherally acting μ -opioid receptor antagonists, specifically methylnaltrexone, have provided a new drug class that can be considered for those suffering from OIC. The American Pain Society recommends starting a prescription medication for OIC when a patient has had inadequate response to first-line treatments and when the Bowel Function Index score is greater than or equal to 30 (Argoff et al., 2015). For resistant constipation, the American Pain Society recommends using combination drugs with different mechanisms of action and considering methylnaltrexone when traditional laxatives are not effective.

In general, there are some things to consider regarding the use of PAMORAs in advanced illness (see Table 3).

SUMMARY

New agents for OIC have come to market in the past 10 years. This is an exciting opportunity to provide relief to patients experiencing refractory constipation that is thought to be opioid induced.

Given the medication cost and the fact that constipation is often multifactorial, these agents are not recommended as first-line treatments for OIC, but rather after traditional bowel medications have not been effective. For rapid relief, subcutaneous administration is likely to be more effective and can be continued for chronic maintenance. For long-term maintenance, oral methylnaltrexone may be a more sustainable approach. ●

Disclosure

The author has no potential conflicts of interest to disclose.

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Table 3. Considerations for Treating Patients With Advanced Illness With Peripherally Acting μ -Opioid Receptor Antagonists

- The first-line treatments for OIC have not changed, including but not limited to senna, docusate, polyethylene glycol, and magnesium hydroxide, in addition to lifestyle modifications and nonpharmacologic interventions, as tolerated.
- Some patients may need two or even three different agents from three different classes to achieve efficacy.
- Patients may also need medications administered by mouth and suppositories or enemas per rectum to help ease laxation, as long as medications can be administered via these routes safely (not neutropenic or thrombocytopenic in the case of per rectum, or not npo in the case of oral administration).
- Ensure that patients are taking traditional laxatives on a schedule to allow the best chance for efficacy. When patients have not had success on traditional therapy from at least two different laxative classes, methylnaltrexone may be considered.
- Clinicians should ensure there is no bowel obstruction prior to administering any PAMORA.
- If effective, laxation will likely occur rapidly within 4 hours of administration.
- Given higher rates of withdrawal in the treatment group in studies and the more significant cost, traditional laxatives are still the backbone of constipation treatment, so the PAMORAs may require special authorization for insurance coverage and will carry a higher copay. This must be considered in the overall plan, as this may be a significant barrier for many patients.
- For patients with a history of cancer, any of the PAMORAs are indicated and can be considered treatment options for OIC in these patients.
- For patients with active disease, methylnaltrexone is the only PAMORA with an FDA indication for this population. This can be important to consider for insurance coverage with individual agents.
- When prescribing methylnaltrexone, be sure to educate on appropriate subcutaneous injection technique (in the upper arm, abdomen, or thigh) and to rotate injection sites with each use.

Note. OIC = opioid-induced constipation; npo = nothing by mouth; PAMORA = peripherally acting μ -opioid receptor antagonist; FDA = US Food and Drug Administration.

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