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Review Article

MU-OPIOID RECEPTOR ANTAGONISTS AND THEIR ROLE IN TREATMENT OF CHRONIC CONSTIPATION

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ABSTRACT

Constipation disproportionately affects older adults, with a prevalence of 50% in community-dwelling elderly and 74% in nursing-home residents. Loss of mobility, medications, underlying diseases, impaired anorectic sensation, and ignoring calls to defecate are as important as dyssynergic defecation or irritable bowel syndrome in causing constipation. Opioid antagonists not only have well-established indications in the reversal of life-threatening opioid toxicity but also hold considerable promise for other applications in palliative care practice, particularly management of opioid-induced constipation (OIC). This review summarizes the pharmacology of new peripherally acting mu (μ) opioid receptor antagonists (PAMORA).

Keywords: Constipation, Opioid-Induced Constipation (OIC), Opioid receptor antagonists, Methylnaltrexone, Alvimopan, Naloxegol

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INTRODUCTION

Constipation is when one has hard, dry bowel movements, or one goes longer than usual between bowel movements or there are fewer than three bowel movements a week. It is defined as a disorder characterized by persistent difficulty or seemingly incomplete defecation and/or infrequent bowel movements (once every 3–4 d or less) in the absence of alarm symptoms or secondary causes [1].

Inadequate fibre or fluid intake and poor bowel habits, Lack of physical activity are the most common causes of constipation. Sometimes medicines used to treat pain, depression, or high blood pressure and medical conditions, such as hemorrhoids, diabetes, or a stroke can also lead to constipation. It occurs in 10-15% of adults and is a common reason for seeking medical attention especially in women.

The other causes in adults have been summarized in table 1.

Table 1: Causes of constipation in adults [2]

Common Causes	Inadequate fiber or fluid intake Poor bowel habits
Systemic Diseases	*Endocrine:* Hypothyroidism, hyperparathyroidism, diabetes mellitus. *Metabolic:* Hypokalaemia, hypercalcemia, uremia, porphyria. *Neurological:* Parkinson's disease, multiple sclerosis, sacral, Nerve damage (prior pelvic surgery, tumor), Paraplegia, autonomic neuropathy.
Medications	
Opioids	*Calcium and iron supplements*
Diuretics	*NSAIDs*
Clonidine	*Calcium channel blockers*
Anticholinergics	*Cholestryamine*
Psychotropics	
Structural Abnormalities	*Anorectal:* rectalprolapse, rectocele, rectal intussusception, anorectal stricture, anal fissure, solitary rectal ulcer syndrome. *Perineal descent* *Colonic mass with obstruction:* adenocarcinoma *Colonic stricture:* radiation, ischemia, diverticulosis *Hirschsprung disease* *Idiopathic megarectum*
Slow Colonic Transit	*Idiopathic (isolated to colon)* *Psychogenic* *Eating disorders* *Chronic intestinal pseudo-obstruction*
Pelvic Floor dyssynergia	
Irritable Bowel Syndrome	

The main signs and symptoms of constipation include

- Difficulty pushing out your bowel movement
- Pain or bleeding during your bowel movement
- A feeling that you did not finish having your bowel movement
- Nausea
- Bloating

- Headache

Constipation can be classified based on etiology:

Primary constipation [3]

- Results from intrinsic defects of colonic or an rectal function
- Considered typically after secondary causes have been ruled out

Secondary constipation [3]

- Caused by pathologic changes such as disease or intestinal obstruction
- Caused by medications (iatrogenic) such as opioids

Constipation can either be acute or chronic. Acute constipation is sudden in onset and lasts for several days only. It is usually caused by medication, blockage, dehydration, prolonged activity, or missing a bowel movement.

Chronic constipation is infrequent bowel movements or difficult passage of stools that persists for several weeks or longer. It can interfere with the ability of a person to go about their daily tasks. Chronic constipation may also cause excessive straining to have a bowel movement and other signs and symptoms.

Signs and symptoms of chronic constipation include:

- Passing fewer than three stools a week
- Having lumpy or hard stools
- Straining to have bowel movements
- One incident of faecal incontinence each week.
- Big stools in the rectum or apparent upon examination of the abdomen.
- Feeling as though there's a blockage in your rectum that prevents bowel movements
- Feeling as though you can't completely empty the stool from your rectum
- Needing help to empty your rectum, such as using your hands to press on your abdomen and using a finger to remove stool from your rectum

Chronic constipation (CC) is a highly prevalent, heterogeneous disorder that significantly affects patient's life. Estimates on the prevalence of constipation vary depending on how the disorder is defined. A recent review estimated the overall prevalence of constipation in the US to be approximately 15% [4]. Recent studies have demonstrated that CC reduces patient's quality of life [5] and imposes a significant economic burden on the healthcare system [6].

Acute and chronic therapy with opioids may cause constipation by decreasing intestinal motility, which results in prolonged transit time and increased absorption of fecal water. Thus, opioid antagonists have recently developed as a promising therapy for chronic constipation as well as for opioid-induced constipation (OIC) per se [7].

Treatment of constipation

Medicine or a fiber supplement may help make the bowel movement softer. A laxative may help relax and loosen the intestines to help one to have a bowel movement. Medicines may be taken to increase fluid in the intestines which help in moving the bowel movements through intestines. Regular non-strenuous exercise and dedicated time for passing bowel movements can be useful, but limited data is available to support all these measures [8].

The treatment of constipation, however, is customized for each individual considering the cause of constipation, patient's age, co-morbid conditions, underlying pathophysiology, and the patient's concerns and expectations. The pharmacologic management of constipation, with special emphasis on newer agents used, is given in table 2.

Table 2: Drugs used for treating constipation [9]

1.	**Fiber laxatives** *Dietary fibre:* Bran, Psyllium (Plantago), Ispaghula, Methylcellulose, Calcium polycarbophil, Guargam	
2.	**Stool softeners:**	Docusates (DOSS), Liquid paraffin etc
3.	**Stimulant purgatives** *a) Diphenylmethanes:* Phenolphthalein, Bisacodyl, Sodium picosulfate *b) Anthraquinones (Emodins):* Senna, Cascara sagrada *c) Fixed oil:* Castor oil	
4.	**Osmotic purgatives** *Magnesium salts:* sulfate, hydroxide *Sodium salts:* sulfate, phosphate Miscellaneous: Sodium Potassium tartrate; Lactulose; Poly Ethylene Glycol (PEG); Sorbitol etc.	
5.	**Serotonergic enterokinetic agents:**	*5HT$_4$ receptor agonists:* Prucalopride, Tegaserod, Velusetrag, Norcisapride [10]
6.	**Chloride channel activator:**	Lubiprostone
7.	**Guanylate cyclase C activators:**	Linaclotide, Plecanatide
8.	**Opioid receptor antagonists:**	Methylnaltrexone, Alvimopan, Naloxegol, Naldemedine, Axelopran, Relistor.
9.	**Motilin agonists:**	Mitemcinal [11]
10.	**Enantiomer of 1,5-benzothiazepine:**	Elobixibat [10]
11.	**Miscellaneous:**	Neurotrophin-3 (R-Methunt-3), Botulinum Toxin, Probiotics, Prebiotics Misoprostol (Cytotec), colchicine/probenecid (Col-Probenecid) etc. [11]

Although many drugs are available for treatment of constipation, however, constipation caused due to use of opioids especially in terminally ill cancer patients can be treated with the newly developed class of drugs i.e., Opioid receptor antagonists.

Pharmacology of opioid receptors

The term opioid describes all compounds that work at opioid receptors. Opioid receptors μ (mu), ***κ*** (kappa) and *δ* (delta), belonging to the class of G-protein coupled receptors are expressed widely on GIT with μ receptors seen over intestinal submucosa and ileal mucosa where as ***κ*** and *δ* receptors predominate in stomach and proximal colon. The predominant actions of opioids on gastrointestinal tract are mediated by μ receptors [12] located pre-junctionally and modulating the release of acetylcholine. It also act on post junctional receptors and decrease the release of neurotransmitters and inhibit calcium channels. These mechanisms delay intestinal transit leading to a decrease in peristalsis, inhibit gastric emptying and also reduce mucosal secretions [13]. The ultimate effects are complicated wherein opioids also stimulate non-propulsive motility and increase the tone of anal sphincters and segmentation in intestines, facilitating fluid absorption from intestines.

All these mechanisms ultimately lead to constipation, to which there is no development of tolerance even on chronic use [14].

Role of peripherally acting Mu opioid receptor antagonists (PAMORAs) in constipation

The quaternary opioid antagonists acting only in periphery (PAMORAs) have been found to selectively antagonize the μ-opioid receptors within the gastrointestinal (GI) tract [15] and have very limited ability to block the opioid receptors in the central nervous system and thus these drugs reverse the OIC without any effect on the analgesic actions of the opioids [16].

The currently used PAMORAs for OIC and CC include:

a) Methylnaltrexone

b) Alvimopan

c) Naloxegol

d) Naldemedine

Other PAMORAs at various stages of development for OIC are:

Bevenopran (ADL5945), Axelopran (TD-1211), ALKS37, TD-8954, TD-147

a) Methylnaltrexone

It is a highly polar quaternary N-methyl derivative of naltrexone (17-[cycloproylmethyl]-4,5α-epoxy-3,14 dihydroxymorphinanium-6-one) [17]. Since the methyl group decreases the lipid solubility and increases polarity, preventing it from crossing into the brain thus it has a limited access across the blood-brain barrier and effectively counters OIC without affecting analgesic actions of opioids [18-19].

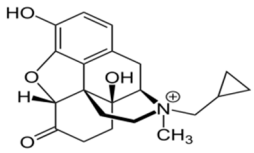

Fig. 1: Structure of Methylnaltrexone

Mechanism of action: Methylnaltrexone is a pheriphally-acting μ-opioid antagonist that acts on myenteric and submucosal neurons and on immune cells in the lamina propria of the gastrointestinal tract inhibiting an opioid-induced decrease in gastric motility and transit time. It is unable to enter the brain primarily because it carries a positive charge on its nitrogen atom and thus is unable to reverse the response of centrally acting opioid analgesics such as analgesic effect and withdrawal symptoms.

Pharmacokinetics: Methylnaltrexone is given via oral, intravenous and subcutaneous routes. It does not readily cross the blood-brain barrier because of the substitution of a polar methyl group. Subcutaneous absorption occurs rapidly, with the onset of action in 30 to 60 min. Protein binding is relatively low at approximately 11% to 15.3%. It binds to μ-opioid receptors with a K_i ranging from 26 nM to 110 nM and has a rapid dissociation rate from the μ-opioid receptor ($t_{1/2}$ = 0.46 min) [20]. When administered intravenously to patients every 6 h for 72 h consecutively, methylnaltrexone (0.3 mg/kg) has a mean plasma concentration of 14 ng/ml 6 h after the final dose. The mean steady-state volume of distribution for methylnaltrexone ranges from 1.8 L/kg to 2.6 L/kg [21].

The primary pathways of metabolism are conversion to methyl-6-naltrexol isomers (5% of total) and methylnaltrexone sulfate (1.3% of total). N-demethylation of methylnaltrexone to produce naltrexone is not significant. Data indicates that there is minor hepatic metabolism via the cytochrome P450 2D6 pathway, which is responsible for the breakdown of methylnaltrexone into methyl-6-naltrexol isomers, methylnaltrexone sulfate, and 3 other minor metabolites [21].

Approximately, 40%–60% of methylnaltrexone is excreted in the urine within 24 h of IV administration. It has an elimination half-life of approximately 8 h [21-22].

Dosage: Methyl naltrexone is usually scheduled as one dose every other day, as needed, but no more than 1 dose in 24 h in the following manner:

- 0.15 mg/kg SC every other day as needed (114 kg)
- 8 mg SC every other day as needed (38 kg)
- 12 mg SC every other day as needed (62 kg to 114 kg) [23].

Indications: The main indication of methylnaltrexone is opioid-induced constipation (OIC). It provides an option for cancer patients, as it is FDA approved for OIC in patients with advanced illness receiving palliative care after unsuccessful treatment with laxatives [24].

Adverse-Effects: The most common adverse effects experienced by patients include GI disturbances such as abdominal pain, flatulence, diarrhoea, and nausea. Additionally, dizziness has been reported [25]. Rare post-marketing adverse effects have included mild to moderate abdominal cramps prior to bowel movements, increase in body temperature, muscle spasms, and syncope.

b) Alvimopan

Alvimopan is a trans-3, 4-dimethyl-4-(3-hydroxyphenyl) piperidine [26]. It is a quaternary peripherally acting μ-opioid receptor antagonist approved in May 2008 by FDA and has a relatively higher affinity (approximately 200 times) for peripheral μ-opioid receptors compared to methyl naltrexone [27].

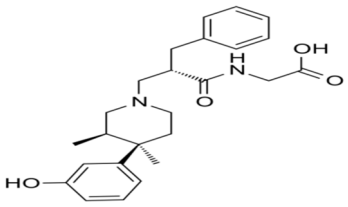

Fig. 2: Structure of Alvimopan

Mechanism of action: It shares the same mechanism of action as methylnaltrexone i.e. antagonism of peripheral μ-opioid receptors. However, the product was originally approved for the management of postoperative ileus after major abdominal surgery. Alvimopan antagonizes the peripheral effects of opioids on GI motility and secretions, thus promoting GI motility. It contains a charged quaternary structure existing in zwitterions form that lowers its lipid solubility and in turn its ability to cross the blood-brain barrier. Therefore, its oral formulation is poorly absorbed and its effects are mostly concentrated in the GI tract. Due to its limited ability to cross the blood-brain barrier, it does not compromise the analgesic effects of opioid medications [28].

Pharmacokinetics: Alvimopan is administered orally only and is absorbed in the small intestine and peaks after approximately 2 h [29]. The steady-state volume of distribution is estimated to be 30+10 L. It is hydrolysed by gut microflora to the active metabolite, ADL 08-0011. Both alvimopan and ADL 08-0011 are bound to albumin and are substrates for p-glycoprotein. Alvimopan is neither a CYP450 substrate inhibitor nor inducer. It is unaffected by concomitant administration of acid blockers or antibiotics but high-fat meal decreases the extent and rate of absorption. Its biological half-life ($t_{1/2}$) is 10-17 h and bioavailability is 6% only. 94% of the metabolite is plasma protein bound while only 80% of the parent drug is bound. ADL 08-0011 is eliminated by glucuronidation, biliary secretion is considered the main pathway for elimination. Renal excretion accounts for 35% of the total clearance. In patients with mild to severe renal impairment, there is no need to adjust dosage. However, alvimopan is not recommended for patients with end-stage renal disease [30].

Dosage: The recommended dosage is 12 mg orally, administered 30 min to 5 h before surgery, followed by 12 mg twice daily on the day after surgery for a maximum of 7 d or until discharge, whichever

occurs first. Patients are not to receive more than 15 doses. The drug is for hospital use only [27].

Indications: Alvimopan is primarily indicated in patients with postoperative ileus following partial large or small bowel resection with primary anastomosis. It is also associated with improvements in straining, stool consistency, incomplete evaluation, decreased appetite, and abdominal bloating/discomfort [31].

Adverse-Effects: The most common side effects associated with alvimopan are nausea, vomiting, abdominal distention, [27] pruritis, post-procedural pain, pyrexia, urinary retention, hypotension, hypertension, dyspepsia, hypokalemia and back pain. However, it is well tolerated in elderly and renal-impaired patients [32].

c) Naloxegol *(*NKTR-118*)*

Naloxegol is a PEGylated (polyethylene glycol-modified) derivative of naloxone [33]. It is a peripherally-selective opioid antagonist developed by AstraZeneca and was approved by the FDA in September 2014. It is mainly indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain [34].

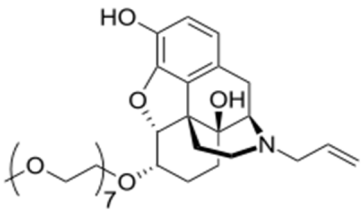

Fig. 3: Structure of Naloxegol

Mechanism of action: Naloxegol functions as a neutral antagonist at peripheral μ-opioid receptors in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids. The PEGylation of the 6-α-hydroxyl side chain of naloxone confers increased oral bioavailability and peripheral selectivity to the naloxone moiety by a reduction in passive permeability across the blood-brain barrier [35]. It is also a substrate of the P-glycoprotein (PGP) transporter, which promotes efflux of naloxegol and serves to further restrict its entry into the central nervous system, [36] thus not affecting the analgesic mechanism of opioids in the central nervous system. It shows strong selectivity (more than 6000 folds) toward peripheral μ receptors. It is administered via oral route only [37].

Pharmacokinetics: Naloxegol is absorbed orally with peak concentrations (C_{max}) achieved in less than 2 h. It is nearly 4.2% protein bound with the volume of distribution about 968 to 2140 L. The half-life ($t_{1/2}$) is 6-11 h [34]. It is metabolized primarily by the CYP450 (3A4) enzyme system and undergoes enterohepatic recycling. A total of 6 metabolites are identified in plasma, urine and feces. These metabolites are formed via N-dealkylation, O-demethylation, oxidation and partial loss of the PEG chain [31]. The activity of the metabolites at the opioid receptor has not been determined. It is eliminated via feces (68%) and urine (16%) after oral administration. A high-fat meal increases the extent and rate of naloxegol absorption. The C_{max} and AUC are increased by approximately 30% and 45%, respectively [34].

Dosage: The recommended dose of Naloxegol is 25 mg once daily in the morning. If patients are not able to tolerate Naloxegol, the dosage is reduced to 12.5 mg once daily [38].

Indications: Naloxegol is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. It works by protecting the bowel from the effects of opiate (narcotic) medications.

Contraindications: It is contraindicated in patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation. The concomitant use of Naloxegol with moderate CYP3A4 inhibitor drugs (e. g., diltiazem, clarithromycin, ketoconazole, erythromycin, verapamil) is to be avoided because these medications can significantly increase exposure to naloxegol which may precipitate opioid withdrawal symptoms such as hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning [34].

Adverse-Effects: The most serious and important adverse effects of naloxegol are gastrointestinal perforation and opioid withdrawal [34]. Other side-effects include diarrhea, nausea, gas, stomach pain, vomiting, headache, sweating, chills, anxiety, irritability and yawning [39].

The pharmacokinetic profile of existing PAMORAs is given in table 3**.**

Table 3: Comparative pharmacokinetics of approved PAMORAs [40]

Pharmacokinetic parameter	**Methylnaltrexone**	**Alvimopan**	**Naloxegol**
Absorption: Bioavailability	-	6% (1-19%)	Not determined in humans
C_{max}	32.7 ng/ml (0.15 mg/kg dose) 35.6 ng/ml (0.30 mg/kg dose)	10.98 ng/ml	-
T_{max}	20-30 min	2 h	2 h
Distribution: V_d	1.1 L	11-98 L	160 L
Plasma Protein Binding	11-16%	70-80%	4.2%
Metabolism: Site	Hepatic: Produces 6 metabolites methyl-6-naltrexol (5%) methyl naltrexone sulphate (1.3%)	Gut microflora mediated hydrolysis producing Active amide metabolite	Hepatic: Six metabolites CYP3A4 substrate Limited glucuronidation
Half-life	8 h	14 h (4-17h) Unabsorbed excreted in feces and urine (after metabolism in gut)	10 h

d) Naldemedine

Naldemedine is a peripherally-selective μ-opioid receptor antagonist developed by Shionogi which is approved by FDA in March 2017 for the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain [41]. It is available as tosylate salt.

Mechanism of action: Naldemedine is an opioid antagonist with binding affinities for μ, *δ*, and ***κ*** opioid receptors. It functions as a peripherally-acting mu-opioid receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids [41].

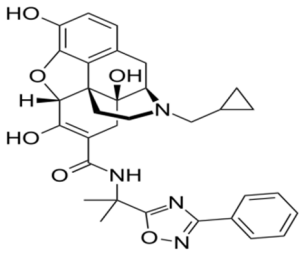

Fig. 4: Structure of naldemedine

Naldemedine is a derivative of naltrexone to which a side chain has been added that increases the molecular weight and the polar surface area, thereby reducing its ability to cross the blood-brain barrier (BBB) [42]. It is also a substrate of the P-glycoprotein (P-gp) efflux transporter. Based on these properties, the CNS penetration of naldemedine is expected to be negligible at the recommended dose levels, limiting the potential for interference with centrally-mediated opioid analgesia. Nor-naldemedine and naldemedine 3-G have been shown to have an antagonistic activity for opioid receptors, with less potent effect than naldemedine [41].

Pharmacokinetics: Naldemedine is absorbed orally with the time to achieve peak concentrations (T_{max}) of approximately 0.75 h in a fasted state. Administration with a high-fat meal reduces C_{max} by 35% and increases T_{max} to 2.5 h. Plasma protein binding of naldemedine in humans is 93% to 94%. The mean apparent volume of distribution during the terminal phase (Vz/F) is 155 L. The terminal elimination half-life of is 11 h [43].

It is primarily metabolized by CYP3A to nor-naldemedine, with a minor contribution from UGT1A3 to form naldemedine 3-G. Naldemedine also undergoes cleavage in the GI tract to form benzamidine and naldemedine carboxylic acid. 57% of naldemedine is excreted in the urine with 16-18% as the parent compound and 35% is excreted in the feces [41].

Dosage: The recommended dosage is 0.2 mg orally once daily with or without food [42].

Indications: Naldemedine is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain [42].

Contraindications: It is contraindicated in patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation [41]. It is to be cautiously used in patients with a history of a hypersensitivity reaction to naldemedine which include bronchospasm and rash [44].

Adverse-Effects: The adverse-effect profile includes gastrointestinal perforation and opioid withdrawal. Other side-effects include abdominal pain (8%), diarrhea (7%), nausea (4%), and gastroenteritis (2%) [41].

CONCLUSION

Patients who have been using opioids for a long period, usually experience constipation and this distressing side effect may compel the patient to discontinue the use of opioids. Opioid receptor antagonists especially peripherally acting mu (μ) opioid receptor antagonist (PAMORAs) can provide relief to such persons and help in improving their life style. Against this backdrop, the search for new oral PAMORA is in offing for treating opioid-induced constipation. A variety of new drugs are under different phases of clinical trials and research is on for the development of more effective and less harmful drugs in order to alleviate the sufferings of patients.

CONFLICTS OF INTERESTS

Declared none

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