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# Dyspepsia and Opioid–Induced Bowel Dysfunction: The Role of Opioid Receptor Antagonists

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Additional information is available at the end of the chapter

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## 1. Introduction

Opioid analgesics are commonly and in most cases effectively used to manage chronic pain of moderate to severe intensity. Apart from analgesia, opioids exert numerous adverse effects, several of which impact the gastrointestinal (GI) tract. The chronic use of opioid analgesics in fact is commonly associated with adverse effects on the gastrointestinal tract. [1] Opioid–induced bowel dysfunction (OIBD) comprises gastrointestinal symptoms such as dry mouth, anorexia, gastroesophageal reflux (GERD), delayed digestion, abdominal pain, flatulence, bloating, nausea, vomiting, and constipation with hard stool and incomplete evacuation. Further, side effects from long–term opioid therapy may result in more serious intestinal complications such as faecal impaction with overflow diarrhea and incontinence, pseudo–obstruction (causing anorexia, nausea and vomiting), disturbance of drug absorption, and urinary retention and incontinence. OIBD may also lead to inappropriate opioid dosing and in consequence, insufficient analgesia. As a result, OIBD significantly deteriorate patients' quality of life and compliance with their treatment. Approximately one-third of patients treated with opioid analgesics do not adhere to the prescribed opioid regimen or simply quit the treatment due to OIBD symptoms [2].

Several strategies have been advocated to prevent or treat OIBD. Use of traditional laxatives is limited by their effectiveness, yet conveys their own adverse effects. Other possibilities comprise an opioid switch or changing the opioid administration route. New therapies now target opioid receptors in the gut as they represent a main source of OIBD symptoms. A combination of an opioid and opioid antagonist (oxycodone/naloxone) in prolonged release tablets and purely peripherally acting opioid receptor antagonist (methylnaltrexone) available in subcutaneous injections are currently available treatment options. This chapter reviews the pathophysiological basis and possible treatment strategies for OIBD.

## 2. Pathophysiological mechanism of opioid-induced bowel dysfunction

Opioids produce widespread effects throughout the gastrointestinal tract through several central and peripheral mechanisms. Such effects are a mixture of inhibitory and excitatory actions. Opioid peptides and their receptors are found throughout the gastrointestinal tract, especially in the gastric antrum and proximal duodenum. The basis for OIBD is therefore complex. The peripheral opioid effect on  $\mu$ -opioid receptors in the gut wall likely plays a major role, but central effects may also be important [3].  $\mu$ -opioid receptors at a high density reside in neurons of myenteric and submucosal plexus and immune cells in the lamina propria [4]. Opioid receptors (predominantly  $\mu$ , also  $\kappa$  and  $\delta$ ) are located in the gut wall in the myenteric plexus and in the submucosal plexus. The former are responsible for gut motility and the latter for secretion. These  $\mu$ -opioid receptors are activated in the wall of the stomach, small and large intestine by both endogenous (e.g. enkephalins, endorphins and dynorphins) and exogenous (e.g. morphine, oxycodone, methadone) opioids and modify gastrointestinal function. Activation of  $\mu$ -opioid receptors inhibits excitatory and inhibitory neural pathways within the enteric nervous system that coordinates motility. Inhibition of excitatory neural pathways depresses peristaltic contractions. On the other hand, the blockade of inhibitory neural pathways increases gut muscle activity, elevates resting muscle tone, and results in spasm and non-propulsive motility patterns. These mechanisms give rise to delayed gastric emptying and slowed intestinal transit [5].

Activation of opioid receptors in the submucosa inhibits water and electrolyte secretion into the gut lumen and increases fluid absorption from the intestine and accelerates blood flow in the gut wall [6]. Opioids increase activity in the sympathetic nervous system and thereby decrease secretion. Endocrine cells located in the epithelium also may play a role in regulating motor activity and secretion in the gut. Interms of motility, peripheral  $\mu$ -opioid receptors inhibit intestinal transit independent of central  $\mu$ -opioid receptors [7]. Moreover, opioids increase ileocaecal and anal sphincter tones and impair defecation reflex through reduced sensitivity to distension and increased internal anal sphincter tone [8]. Morphine administration leads to sphincter contraction and to a decreased emptying of pancreatic juice and bile [9], which may impair digestion. The anal sphincter dysfunction is an important factor in the sensation of anal blockage [10,11].

The central mechanism of opioid effects on the gastrointestinal tract is supported by the results of animal studies in which intracerebroventricular administration of morphine inhibited GI propulsion [12]. This effect was reversed by intracerebroventricular administration of naloxone [13] and vagotomy [14]. Intrathecal administration of morphine reduced gastroduodenal motility while intramuscular morphine gave additional effects. Thus, it seems that both central and peripheral opioid effects play a role in opioid GI effects [15]. The indirect evidence of both central and peripheral components of opioid effects on bowel function may be the observed 50–60% response rate to the treatment of OIBD with methylnaltrexone (MNTX), which displays only peripheral  $\mu$ -opioid receptor antagonist effect in the treatment of patients with OIBD [16,17]. The stool remains in the gut lumen for a longer time, allowing greater absorption of fluid. Enhanced absorption combined with opioid inhibition

of secretomotor neurons in the epithelium of the gut [18] leads to the stool becomes hard and dry. In summary, OIBD is the consequence of reduced gastrointestinal motility, increased absorption of fluids from the gut and decreased epithelial secretion.

### 3. Dyspepsia

Dysfunction of the upper gastrointestinal tract (esophagus, stomach and duodenum) often manifests as dyspepsia. Dyspepsia represents a constellation of symptoms rather than a single disease entity. Its diverse symptoms may be expressed as epigastric pain, anorexia, belching, heartburn, bloating, nausea and vomiting, post-prandial fullness, early satiety, and/or regurgitation [19].

Two types of dyspepsia may be diagnosed:

- *Structural (organic) dyspepsia* for which a structural change can be demonstrated, often due to acid-related disease such as a gastric ulcer. In advanced cancer patients, symptoms may arise from NSAID, corticosteroid and bisphosphonate administration.
- *Functional dysmotility (non-ulcer dyspepsia)* due to dysmotility and/or altered sensitivity of the upper GI tract affecting the esophagus, stomach and duodenum. Esophageal and gastroduodenal dysmotility can be differentiated.

In cancer patients, it may be iatrogenic (e.g.; opioid-induced delayed gastric emptying) and associated with disease-related complications like hepatomegaly or massive ascites. Furthermore, paraneoplastic visceral autonomic neuropathy seems to play an important role. Opioids and other drugs such as anticholinergics, tricyclic antidepressants, benzodiazepines, nitrates and calcium channel blockers may decrease lower esophageal sphincter tone and lead to reflux (GERD) that would be aggravated secondarily by delayed gastric emptying. Gastric secretory and motor activity may be also affected by chronic alcoholism, diabetes, uremia, anxiety and depression. Gastroparesis is a symptomatic chronic disorder characterized by impaired gastric emptying in the absence of a structural cause. This occurs as a component of paraneoplastic syndromes, most commonly in the course of small cell lung, breast, ovarian cancer, Hodgkin disease or multiple myeloma. In addition to opioid adversely affecting gastric emptying, other drugs such as anticholinergics, neuroleptics or tricyclic antidepressants can aggravate gastroparesis. Meanwhile, concurrent conditions such as diabetes, prior gastric surgery, and neuromuscular disorders may further impair gastric emptying. Lastly, gastric or pancreatic tumors can inflict a mechanical outlet obstruction.

Another component that might co-exist is gastroesophageal reflux disease (GERD) due to reflux of gastric contents into the esophagus, causing mucosal damage and heartburn.

The prevalence of functional dyspepsia is high in the normal population (24–34%) and even higher in cancer patients (70%) [20]. Opioids adversely affect the esophagus. This class of drugs impairs esophageal inhibitory innervation and so induces spastic esophageal dysfunction.

tion while impairing lower esophageal relaxation, leading to swallowing difficulties (dysphagia). Opioids also reduce the lower esophageal sphincter (LES) pressure, thereby decreasing the barrier pressure between the stomach and the esophagus, producing acid-reflux symptoms. This effect is reversed by naloxone. Opioids inhibit gastric emptying, a product of enhanced gastric relaxation and heightened pyloric tone. This decrease in gastric emptying results from both central and peripheral effects, although a peripheral  $\mu$ -opioid receptor mechanism is dominant. Opioid administration increases duodenal motility by generating patterns of contractions resembling migrating motor complex (MMC) phase III patterns. Endorphins in humans decrease antral phasic pressure activity and increase pyloric phasic pressure activity and induce MMC III-like bursts of contractile activity in the proximal gut followed by motor quiescence. Exogenous and endogenous opioids impair gastric emptying [21, 22].

The evaluation of patients with functional dyspepsia and gastroparesis is based on a careful history taking and physical examination that allow differentiating between functional and structural dyspepsia and GERD. The symptoms of gastroparesis, as quantified by the Gastroparesis Cardinal Symptom Index (GCSI), consists of 9 symptoms, each graded from 0 (none) to 5 (very severe), divided into 3 subscales: postprandial fullness/early satiety, nausea/vomiting, and bloating [23]. Upper endoscopy is usually needed to exclude mechanical obstruction and to assess for mucosal lesions. It is recommended in patients with alarming symptoms e.g.; those suspected for gastrointestinal bleeding. Endoscopy may be also conducted when symptoms develop with NSAIDs administration and when treatment with antisecretory drugs or antacids is unsuccessful. Blood tests assessing complete blood count and biochemistry might be useful. An ultrasound or CT abdominal scan is helpful to assess for cancer spread. In some patients, solid phase gastric scintigraphic emptying studies or breath tests may be needed to confirm gastroparesis. Other investigations such as electro-gastrography, antroduodenal manometry are infrequently used in cancer patients.

## 4. Management of opioid-induced bowel dysfunction

### 4.1. The management of dyspepsia

#### a. Non-pharmacological measures

Treatment should be directed at cause of symptoms. Functional dyspepsia may be treated with non-pharmacological measures and drugs. The former comprise explanation and education of patients and families. Advice on the diet may play an important role. Fatty foods should be avoided as lipids impair gastric emptying, while lipids entering the duodenum may aggravate impaired gastric accommodation and gastric hypersensitivity. Medications that may cause dyspepsia (e.g. NSAIDs) should be discontinued when possible [24].

#### b. Pharmacological approach

Pharmacological treatment is usually needed. First-line therapy for dyspepsia is usually acid suppression. Proton pump inhibitors (PPIs) such as omeprazole, esomeprazole or pantopra-

zole are used once daily in doses 20–40 mg, best given 30 minutes before breakfast. In cancer patients, prokinetic agents are commonly administered, aiming to counteract opioid-induced motility disorders.

Typically, metoclopramide is prescribed (commonly as 10 mg t.i.d.) for patients with functional dyspepsia, especially when symptoms arise from gastroparesis. Metoclopramide works mostly in the upper GI tract through blocking dopaminergic receptors. As metoclopramide also acts centrally, its use is associated with the added risk of extra-pyramidal effects, particularly in younger patients and children. Metoclopramide also inhibits the cytochrome, CYP2D6 enzyme [25]. The most common adverse effects of metoclopramide are restlessness, drowsiness and fatigue. Concomitant use of antidepressants, such as tricyclics, selective serotonin reuptake inhibitors (SSRIs) and newer serotonin–noradrenalin reuptake inhibitors (venlafaxine, duloxetine), may aggravate the adverse effects of metoclopramide [26]. Extrapyrarnidal effects are unlikely to occur when using domperidone, which does not cross blood–brain barrier [27]. Cisapride is a 5HT<sub>4</sub> receptor agonist, affecting the entire GI tract; however, its cardiotoxicity has limited use [28].

Itopride works through peripheral blocking dopaminergic receptors. It inhibits acetylcholinesterase and so increases acetylcholine levels. Itopride works through the whole GI tract. It is devoid of activity at 5-HT<sub>4</sub> and 5-HT<sub>3</sub> receptors. Itopride is metabolized through monooxidase system. Thus, it has no significant risk of pharmacokinetic interactions with other drugs. Itopride does not cross blood–brain barrier and in consequence does not induce extrapyramidal effects. The dose usually equals 50 mg t. i. d. [29]

Prucalopride, a new prokinetic agent, is a highly selective 5HT<sub>4</sub> receptor agonist that stimulates gut motility *in vitro* and *in vivo*. Prucalopride at 2–4 mg daily accelerates whole gut, gastric, small bowel and colonic transit in constipated patients [30]. The recommended dose is 1–2 mg once daily. Prucalopride is used in managing chronic constipation predominantly in women, but has not been evaluated in gastroparesis as yet [31]. Treatment is usually well-tolerated; typical adverse effects are headaches (present in 25–30% of treated patients), nausea (12–24%), abdominal pain or cramps (16–23%) and diarrhea (12–19%) [32]. Both itopride and prucalopride appear safe relative to cardiac function.

Linaclotide is a minimally absorbed peptide guanylate cyclase-C agonist that appears quite effective for chronic constipation and the irritable bowel syndrome [33,34]. It looks promising in the treatment of gastroparesis and so may have a role in OBID.

Lubiprostone, a bicyclic fatty acid derived from prostaglandin E1, acts by specifically activating chloride channels on the apical aspect of gastrointestinal epithelial cells, producing a chloride-rich fluid secretion. These secretions soften the stool, increase intestinal motility, and so promote spontaneous bowel movements. Lubiprostone thus has value in treating functional constipation.

#### 4.2. Oral and rectal laxatives for Opioid-induced Bowel Dysfunction

General measures to be taken in patients with OIBD and OIC include the assessment and applying prophylactic measures matched to the patient's general condition [35]. Change of

diet (increased food and fluid intake), more physical activity, assuming a sitting position during bowel movement and obtaining privacy during defecation process are recommended [36]. Patients treated with opioids should be considered for prokinetic administration [37]. Any reversible causes such as hypercalcaemia should also be treated. Discontinuing or decreasing doses of drugs that may aggravate constipation (e.g. tricyclics, neuroleptics, anticholinergics) should also be considered. Patients and families should be educated about the means to prevent and treat OIBD [9].

In most patients with OIBD, laxatives are necessary. The general recommendation is to combine orally administered osmotic agents – usually lactulose or macrogol (PEG – polyethylene glycol) which have an osmotic effect in the colon [10] with stimulants activating on neurons in the myenteric and submucosal plexus in colon and reducing absorption of water and electrolytes from the intraluminal contents: anthracenes (senna), polyphenolics (bisacodyl) or sodium picosulphate. Unfortunately, these drugs exhibit limited efficacy in patients suffering from OIBD. Moreover, they may cause several adverse effects and must be administered on a regular basis [38]. Other classes of laxatives are faecal lubricants (liquid paraffin), stool softeners (surfactants: sodium docusate); however, they are usually ineffective when administered alone [39]. The use of bulk-forming agents such as fibre, bran, methylcellulose and psyllium seeds has limited role in patients with advanced constipation and warrant ingesting adequate fluids (at least 2 liters per day) [40–42]. Castor oil is not recommended due to its sudden stimulating effect on bowel motility and the risk of developing severe abdominal cramps [43]. If oral laxatives are found to be ineffective, rectal treatment should be considered.

Rectal laxatives comprise suppositories increasing intestinal motility through direct stimulation of the nerve endings in the myenteric ganglia of the colon, thus inducing peristalsis (bisacodyl) or using osmotic drugs (glycerol), which act by irritating the rectal mucosa and also enhance the colonic motility that subsequently triggers the defecation reflex. The next step if these agents prove ineffective is rectal enemas, either as normal saline (100–200 ml) or phosphates (120–150 ml).

The management of faecal impaction depends on the severity of symptoms (rectal pain, abdominal colicky pain, protruding hard faeces and faecal leakage). If the symptoms are not severe in case of soft faeces, administer bisacodyl 10–20 mg once daily either rectally or orally until bowel movements are achieved. If hard faeces are present, use glycerol and bisacodyl suppositories or osmotic enemas. Enemas of arachis oil (130 ml) or of decussate sodium (100 ml) followed by a phosphate enema next day may be appropriate. Macrogol (PEG) reduces the need for digital disimpaction. Digital stool evacuation may be necessary in cases of severe symptoms, when neither oral nor rectal treatment gives a desired effect and faecal impaction is not relieved, causing significant distress to the patient. As the procedure is quite painful and distressing, it should be performed with great caution and only when necessary and sometimes necessitating intravenous sedation with midazolam combined with opioids plus topical analgesics [44].

Polyethylene glycol (PEG) and sodium picosulphate are more effective than lactulose in OIC in cancer pain patients [45]. PEG specifically appears to be more effective than lactulose in

terms of weekly bowel movement frequency, patient satisfaction, ease of defecation and reduced constipation symptoms with similar treatment tolerance and slightly higher lactulose costs [46]. For palliative care patients, different laxative regimens have no real differences. Overall, there is limited efficacy of traditional laxatives; well-done randomised controlled trials are lacking [47].

### 4.3. Opioid switch

The possibility of opioid switch for OIBD should be considered as one of the available treatment options. Opioids, which seem to be more often associated with constipation, are codeine and dihydrocodeine (opioids for mild to moderate pain), morphine, oxycodone and hydromorphone (opioids for moderate to severe pain). These opioids may be switched to other opioids belonging to the same group but having less constipating effect: codeine or dihydrocodeine may be switched to tramadol; morphine, oxycodone or hydromorphone to transdermal opioids (fentanyl, buprenorphine) or to methadone [48,49]. The most convincing evidence supporting the benefits of the opioid switch as regards constipation relief comes from the morphine to transdermal fentanyl switch [50–53]. In contrast to clinical studies, observational surveys do not provide evidence for advantages of transdermal fentanyl over other opioid analgesics with respect to bowel function. [54–55] Other studies report similar or less intense constipating effects with transdermal buprenorphine compared to CR morphine [56] and after a switch from morphine to methadone [57–59]. There may be a benefit to administering tramadol rather than small morphine doses [60–62] or dihydrocodeine [63] with respect to the constipation intensity. However, no differences were found in constipation in cancer patients with pain between transdermal opioids (buprenorphine and fentanyl) and oral controlled release hydromorphone [64].

### 4.4. Targeted treatment of opioid-induced bowel dysfunction

Few clinical studies compared the efficacy of different laxatives [65] and controlled studies are lacking [66]. Certainly traditional laxatives do not target the cause of OIBD, which is predominantly associated with opioid analgesics binding and activating  $\mu$ -opioid receptors in the GI tract [67]. Treatment directed at the cause of OIBD involves either using a combination of opioid analgesics with opioid receptor antagonists, which act both centrally and peripherally, or administering opioid receptor antagonists, which act exclusively peripherally. An important advantage of this approach is the fact that it is targeted treatment of OIBD and that it may be combined with oral laxatives, if necessary. Finally, this approach may eliminate the need for rectal measures, which patients tolerate poorly.

Apart from opioid antagonists with exclusively peripheral effects, opioid receptor antagonists with a central mode of action are naloxone, naltrexone and nalmefene. The majority of studies performed so far have used immediate release formulation of oral naloxone (IR naloxone). In spite of high IR naloxone efficacy in the treatment of OIBD, some patients experience opioid withdrawal symptoms and attenuation of analgesia, rendering IR naloxone less useful when administered alone [68–70]. Nalmefene [71] and nalmefene glucuronide [72] behave similarly.

#### 4.5. Combined opioid receptor agonist with its antagonist

One of methods to decrease the frequency of constipation in patients requiring strong opioids is using formulation composed of an opioid and opioid receptor antagonist. The formulation combining oxycodone and naloxone is available in the form of prolonged release (PR) tablets containing both drugs in the ratio of 2:1 (PR oxycodone/PR naloxone 5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg, 40 mg/20 mg) [73]. The optimal 2:1 ratio of PR oxycodone/PR naloxone tablets was demonstrated in a phase II study rendering effective analgesia and improvement in bowel function with good treatment toleration in patients with severe chronic pain [74]. PR oxycodone/PR naloxone is registered for the indication of severe pain, which may only be successfully treated with opioid analgesics. In this formulation, naloxone counteracts the development of OIBD through inhibition of oxycodone effect on opioid receptors in the gut wall [75]. The starting PR oxycodone/PR naloxone doses in opioid-naïve patients is 5 mg/2.5 mg b.i.d. Patients unsuccessfully treated with opioids for mild to moderate pain (tramadol, codeine, dihydrocodeine) may start with the dose 10 mg/5 mg b.i.d. When rotating from other opioids for moderate to severe pain to PR oxycodone/PR naloxone, the starting dose is established individually depending on the amount of previously administered opioid, analgesia and adverse effects. The maximal daily dose of PR oxycodone/PR naloxone recommended equals 40 mg/20 mg twice daily. However, in a study conducted in cancer patients with pain higher daily doses up to 120 mg/60 mg were effective and well-tolerated while symptoms of OIBD were decreased, compared to PR oxycodone administered alone [76].

Following oral administration, oxycodone displays high bioavailability (60 – 87%) and provides effective analgesia [77,78]. Naloxone exhibits low bioavailability after oral administration (<2%) and undergoes extensive first-pass metabolism in the liver with the formation of naloxone-3-glucuronide [79]. Analgesic effect is not reversed by naloxone and no symptoms of opioid withdrawal occur. This effect of orally administered naloxone depends on normal liver function. Thus, any hepatic impairment should be carefully considered. In patients suffering from decompensated liver disease, PR oxycodone/PR naloxone administration is not recommended. There is a clinically observed difference between the administration of IR and PR formulations of naloxone. IR naloxone in some patients may attenuate analgesia or induce opioid withdrawal symptoms. The PR naloxone formulation prevents saturation of hepatic enzyme system responsible for naloxone metabolism and reduces the risk of opioid antagonism in the CNS [3].

PR oxycodone/PR naloxone provides similar analgesic efficacy to oxycodone with improvement in bowel function, a lower consumption of laxatives and more frequent spontaneous bowel movements [82]. during treatment with PR oxycodone/PR naloxone in comparison to PR oxycodone therapy [80–82]. Long-term therapy (up to 52 weeks) with PR oxycodone/PR naloxone in daily doses up to 80 mg/40 mg appears effective and safe [83]. Analgesia is effective while bowel function and quality of life improved with PR oxycodone/PR naloxone (20 mg/10 mg to 40 mg/20 mg) treatment in patients with severe neuropathic non-malignant pain [84]. Even at quite high doses, PR oxycodone/PR naloxone doses exhibited a benefit compared to PR oxycodone administered alone [85]. PR oxycodone/PR naloxone in doses up



to 120 mg/60 mg per day provides effective analgesia while improving bowel function [76]. Adverse effects of PR oxycodone/PR naloxone and PR oxycodone are similar; the frequency of diarrhea is slightly higher in PR oxycodone/PR naloxone compared to PR oxycodone administered alone (5.2% vs. 2.6%) [81]. However, PR oxycodone/PR naloxone less frequency induces nausea (6.3% vs. 10.5%), vomiting (1.3% vs. 4.3%), abdominal pain (1.3% vs. 4.3%) and dyspepsia (0.6% vs. 2.5%) in comparison to PR oxycodone administered alone [82]. These differences might be explained by naloxone antagonist effect on gastric and gut opioid receptors and in consequence, naloxone prokinetic properties [86]. PR oxycodone/PR naloxone studies were performed mainly in patients with chronic, non-malignant pain [80–83,85,89]. Opioid switch to PR oxycodone/PR naloxone for cancer patients generally provides adequate analgesia and improved bowel function [87], but in some requiring heightened analgesia, very high doses of PR up to 240 mg per day oxycodone administered alone may be necessary [88].

The contraindications for PR oxycodone/PR naloxone comprise bowel obstruction, acute abdominal conditions, diarrhea and an allergy to the drug. PR oxycodone/PR naloxone is available in several European countries. One pack contains 60 PR oxycodone/PR naloxone tablets of 5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg, 40 mg/20 mg strength. Direct treatment costs for PR oxycodone/PR naloxone in patients with moderate-to-severe non-malignant pain and opioid-induced constipation is slightly higher compared to oxycodone PR. When analysing constipation treatment costs and benefits of PR oxycodone/PR naloxone in terms of improved quality-adjusted life-years, PR oxycodone/PR naloxone appears to be cost-effective option in the UK [90]. Government and other insurance schemes however may not reimburse PR oxycodone/PR naloxone tablets.

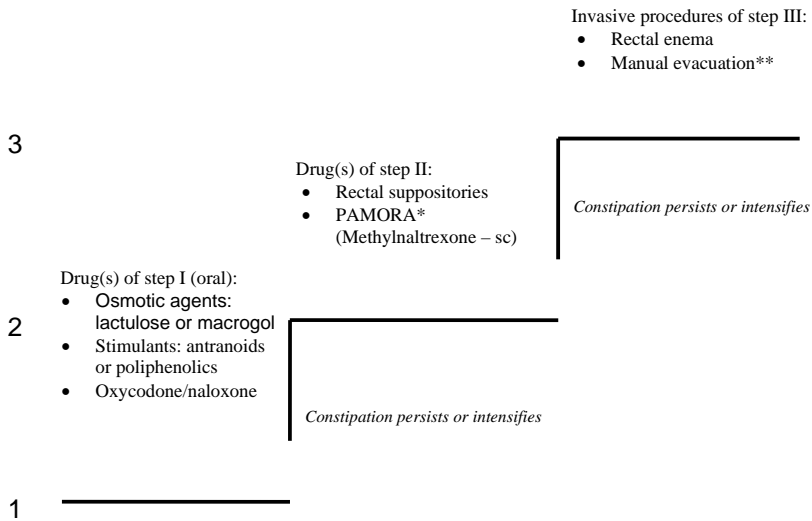
#### 4.6. Purely peripherally acting opioid receptor antagonists

Methylnaltrexone (MNTX), a derivative of naltrexone, is a peripheral  $\mu$ -opioid receptor antagonist, which does not cross blood-brain barrier [91]. Because of its low oral bioavailability, MNTX is administered subcutaneously or intravenously [92]. However, MNTX taken orally prevents the delay in oro-cecal transit time that follows intravenous morphine administration [93]. MNTX plasma half-life equals 105 to 140 minutes. 50% is excreted unchanged in the urine. MNTX is a weak CYP2D6 inhibitor with no significant drug interactions [94]. MNTX is used to treat OIC in adult patients with advanced diseases when constipation does not respond to conventional oral laxatives. The drug is available in ampoules containing 12 mg MNTX bromide in the volume of 0.6 ml and is applied via subcutaneous injections. The recommended single MNTX dose is 8 mg in patients with body weight 38–61 kg or 12 mg if the body mass is 62–114 kg [95]. Those falling outside of this range should receive a dose of 0.15 mg/kg. No dose adjustment is necessary for patients with mild to moderate hepatic or renal impairment. However, in patients with severe renal failure (creatinine clearance < 30 mL/min) the MNTX dose should be reduced by one-half [96].

A bowel movement within 4 h after MNTX injection is observed in 50–60% patients (the median time to bowel movement after the drug administration is 30 minutes). If no therapeutic effect is observed, the injection may be repeated every other day. MNTX adverse effects

comprise abdominal pain (28% of the treated patients), flatulence (13%), nausea (11%), dizziness (7%) and diarrhoea (5%) [16]. However, the administration of MNTX may be associated with an increased risk of gastrointestinal perforation in patients with diseases that decrease gut wall integrity (cancer, peptic ulceration and Ogilvie’s syndrome) or on concomitant medications (NSAIDs, bevacizumab). GI perforation occur at different possible locations (duodenum, small and large bowel). A possible contributing factor might be the prokinetic effect of MNTX. It is not known if dose and duration of the treatment with MNTX relate to this complication [95]. As MNTX does not cross the blood–brain barrier, there is no attenuation of analgesia nor is there an opioid withdrawal syndrome [17]. The use of MNTX is contraindicated in patients with mechanical bowel obstruction, in acute abdominal conditions and in case of allergy to the drug. MNTX may be used in palliative care patients with OIBD not amenable to the treatment with oral laxatives. Several clinical studies have demonstrated the effectiveness of MNTX in patients with advanced diseases and with OIBD [16,17,95,96,98–100]. Peripherally active opioid receptor antagonists in the treatment of OIBD are effective and safe in [101-4]. Long–term efficacy and safety of opioid antagonists is not yet clearly established, in part due to a limited number of randomized studies [105-6].].

The Expert Working Group of the Polish Association for Palliative Medicine developed a three step ladder for the management of OIC (Fig. 1) [43]. This updated version of the ladder takes into account new therapies directed at the underlying mechanism of OIBD [107].



\* PAMORA–peripherally acting mu–opioid receptor antagonists (methylnaltrexone) indicated for patients who do not respond to traditional oral laxatives without bowel obstruction and acute abdominal illness; \*\* This procedure should be used only when other measures fail and the faecal impaction causes significant pain and distress for the patient. It should be preceded by a sedative and analgesics (local and systemic) administration that provide effective relief of severe pain and distress associated with manual stool evacuation; sc – subcutaneous

**Figure 1.** The three-step ladder of the management of opioid–induced constipation [43,107]

At the first step traditional oral laxatives and/or PR oxycodone/PR naloxone may be considered. PR oxycodone/PR naloxone targets the source of OIBD (prevention and treatment) as PR naloxone blocks opioid receptors in the gut and PR oxycodone provides effective analgesia. PR oxycodone/PR naloxone may be considered in cancer pain patients who are at high risk of OIBD development such as those with GI tumors, patients who require combined treatment with opioids and other drugs disturbing normal bowel function, e.g. advanced cancer patients. At the second step subcutaneous administration of MNTX may be considered when traditional oral laxatives are ineffective, which may allow avoiding invasive and often painful invasive procedures at step 3 of the ladder.

## 5. Conclusions

OIBD in patients diagnosed with chronic diseases is a challenging problem that health care providers often underestimate. This is particularly important in patients regularly receiving opioids for pain or other indications. Thanks to newly introduced drugs that target the cause of OIBD, a more effective therapy is available. The experience with MNTX and PR oxycodone/PR naloxone in patients suffering from OIBD is promising. Further clinical studies are needed to develop more effective guidelines for the management of OIBD and to establish more precisely the role of opioid receptor antagonists. The role of opioid receptor antagonists as potential antiemetic and prokinetic agents should be further explored as suggested by experimental studies in animals. The cost-benefit from new therapies must be carefully considered; overall resources may actually be saved from reduced use of traditional laxatives. The most important advantage of targeted therapies is to decrease patient suffering from OIBD, substantially reduce the need to perform invasive rectal procedures and most importantly, improve quality of life.

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