

Opioid-induced bowel dysfunction (OIBD) comprises gastrointestinal symptoms such as constipation, anorexia, nausea, vomiting, gastro-oesophageal reflux, delayed digestion, abdominal pain, bloating, hard stool and incomplete evacuation that significantly deteriorate patients' quality of life and compliance. Approximately one third of patients treated with opioids do not adhere to the opioid regimen or simply quit the treatment due to OIBD. Several strategies are undertaken to prevent or treat OIBD. Traditional oral laxatives are used but their effectiveness is limited and they display adverse effects. Other possibilities comprise opioid switch or changing the administration route. New therapies target opioid receptors in the gut that seem to be the main source of OIBD. One is a combination of an opioid and opioid antagonist (oxycodone/naloxone) in prolonged-release tablets, and another is a purely peripherally acting opioid receptor antagonist (methylnaltrexone) available in subcutaneous injections. The aim of this article is to review the pathomechanism and possible treatment strategies of OIBD.

Key words: constipation, opioid analgesics, opioid-induced bowel dysfunction, opioid receptor antagonists, treatment.

The impact of opioid analgesics on the gastrointestinal tract function and the current management possibilities

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Introduction

Opioid analgesics are commonly and in most cases effectively used in chronic pain management of moderate to severe intensity. However, apart from analgesia opioids exert numerous adverse effects which may limit their effectiveness and patients' compliance. These effects also appear in the gastrointestinal (GI) tract. Opioid-induced bowel dysfunction (OIBD) is a common adverse effects syndrome associated with the chronic use of opioid analgesics [1]. The OIBD comprises several symptoms including constipation, anorexia, nausea and vomiting, gastro-oesophageal reflux, delayed digestion, abdominal pain, flatulence, bloating, hard stool, straining during bowel movement and incomplete evacuation. In the case of long-term opioid therapy these symptoms may lead to the development of more serious complications such as bowel faecal impaction with overflow diarrhoea and faecal incontinence, pseudo-obstruction (which may cause anorexia, nausea and vomiting), disturbance of drug absorption, urine retention and urine incontinence. Opioid-induced bowel dysfunction may lead to inappropriate opioid dosing and in consequence insufficient analgesia. Opioid-induced bowel dysfunction also significantly deteriorates patients' quality of life and compliance. Approximately one third of patients treated with opioid analgesics does not adhere to the prescribed opioid regimen or simply quit the treatment due to OIBD symptoms [2].

Outline of pathomechanism of opioid-induced bowel dysfunction

The pathomechanism of OIBD is complex. It seems that the peripheral opioid effect on μ -opioid receptors in the gut wall plays the main role here, but the central effects are also important [3]. High density of μ -opioid receptors was found in neurons of the myenteric and submucosal plexus and immune cells in the lamina propria [4]. Opioid receptors (predominantly μ , also κ and δ) are located in the gut wall in the myenteric plexus and in the submucosal plexus. The former are responsible for GI motility and the latter for secretion. The μ -opioid receptors are activated in the wall of the stomach and the small and large intestine by both endogenous (e.g. enkephalins, endorphins and dynorphins) and exogenous (e.g. morphine, oxycodone, methadone) opioids and modify GI function. Activation of μ -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 GI muscle activity, and elevates resting muscle tone, spasm and non-propulsive motility patterns. These mechanisms are responsible for delayed gastric emptying and slowing the 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 blood flow in the gut wall [6]. Opioids increase activity in the sympathetic nervous system and thereby decrease the secretion. Endocrine cells located in the epithelium might play a role in regulating motor activity and secretion in the gut. Studies performed in mice indicate that peripheral μ -opioid receptors inhibit the transit independently of central μ -receptors [7]. Moreover, opioids increase ileocaecal and anal sphincter tone and impair the defecation reflex through reduced sensitivity to distension and increased internal anal sphincter tone [8]. Morphine administration leads to sphincter contraction and to decreased emptying of pancreatic juice and bile [9], which may cause delayed digestion. Anal sphincter dysfunction is an important factor in the sensation of anal blockage [10, 11].

The central mechanism of opioid effects on the GI tract is supported by the results of experimental studies in which intracerebroventricular administration of morphine in rats inhibited gastrointestinal propulsion [12]. This effect was reversed by intracerebroventricular administration of naloxone [13] and vagotomy [14]. Intrathecal administration of morphine reduced gastroduodenal motility and intramuscular morphine gave additional effects. It seems that both central and peripheral opioid effects play a role in opioid GI effects [15]. 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 a peripheral μ -opioid receptor antagonist effect in the treatment of patients with OIBD [16, 17]. Opioid-induced bowel dysfunction is the consequence of reduced GI motility, increased absorption of fluids from the gut and decreased epithelial secretion. The stool remains in the gut lumen for a longer time; therefore, more fluid is reabsorbed and the stool becomes hard and dry. The above effects are also associated with opioids' inhibition of secretomotor neurons in the epithelium of the gut [18].

Possible interventions in opioid-induced bowel dysfunction

Oral and rectal laxatives

General measures to be taken in patients with OIBD and constipation include the assessment and application of prophylactic measures matched to the patient's general condition [19]. Change of diet (increased food and fluid intake), more physical activity, sitting position during bowel movement and privacy during the defecation process are recommended [20]. Patients treated with opioids should be considered for prokinetic administration (metoclopramide, domperidone, itopride, prucalopride) [21, 22]. Any reversible causes such as hypercalcaemia should also be treated. Discontinuing or decreasing doses of drugs that may be responsible for development of constipation (e.g. tricyclics, neuroleptics, anticholinergics) should also be considered. Patients and families should be educated about the ways of prevention and treatment of OIBD [9].

In the majority of patients with OIBD, laxatives need to be administered. The general recommendation is to combine oral administration of osmotic agents (usually lactulose or macrogol) which have an osmotic effect in the colon [10] with stimulants activating neurons in the myenteric and sub-

mucosal plexus in the colon and reducing absorption of water and electrolytes from the intraluminal contents: anthracenes (senna), polyphenolics (bisacodyl) or sodium picosulphate [20]. However, these drugs display limited efficacy in patients suffering from OIBD; moreover, they may cause several adverse effects and must be administered on a regular basis [23]. Other groups of laxatives are faecal lubricants (liquid paraffin), and stool softeners (surfactants: sodium docusate); however, they are usually ineffective when administered alone [24]. The use of bulk-forming agents such as fibre, bran, methylcellulose and psyllium seeds has a limited role in patients with advanced disease as enough fluids (at least 2 l per day) should be co-administered to avoid intestinal obstruction through viscous mass development in the bowel [25-27]. Castor oil is not recommended due to its sudden stimulating effect on bowel motility and the risk of developing strong abdominal cramps [28]. If the oral laxatives are found to be ineffective, rectal treatment is considered. The dose of oral laxatives should be titrated to achieve bowel movement unless adverse effects appear. If there is more than 3 days since last bowel action rectal measures (suppositories e.g. bisacodyl 10 mg and glycerine 4 g or a micro-enema) may be added to the oral regimen. Rectal measures may be administered alone in those patients who are unable to swallow oral laxatives and suffer from nausea and vomiting; they might be useful in patients with neurological deficits e.g. spinal cord compression [29].

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) that act by irritation of the mucosa in the rectum, which also enhances the motility of the colon and subsequently triggers the defecation reflex. The next step to be taken after these agents are found to be ineffective is rectal enema with normal saline (100-200 ml) or phosphates (120-150 ml).

In case of faecal impaction the management 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 stimulating agents such as senna or bisacodyl 10-20 mg once daily orally or rectally may be administered until bowel movement is achieved. If hard faeces are present glycerol suppositories or osmotic enemas may be administered. Enema of arachis oil (130 ml) or of decussate sodium (100 ml) may be appropriate. Macrogols reduce the need for digital disimpaction. However, in cases of severe symptoms, when neither oral nor rectal treatment gives a desired effect and faecal impaction is not relieved causing significant distress, it may be necessary to perform digital stool evacuation [30]. As the procedure is painful and distressing it should be performed with caution. Patients should be sedated with midazolam; for effective pain relief systemic opioids should be given along with topical administration of local anaesthetics.

Opioid switch

The possibility of opioid switch in the treatment of 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 [31, 32]. The most evidence supporting the benefits of the opioid switch as regards constipation relief was accumulated for the morphine to transdermal fentanyl switch [33-35]. Tassinari *et al.* performed a meta-analysis comparing 3 randomized trials of transdermal opioids (fentanyl and buprenorphine) with slow-release oral morphine in the treatment of moderate-severe cancer pain in 425 patients. A significant difference in favour of transdermal opioids was observed for constipation (OR = 0.38; $p < 0.001$) and patients' preference (OR = 0.43; $p = 0.014$, in the three trials investigating transdermal fentanyl) [36].

However, in contrast to clinical studies, observational surveys that reflect a more real life conditions do not provide evidence for advantages of transdermal fentanyl over other opioid analgesics with respect to bowel function. In a large (2324 patients), multicentre, observational study, morphine (89.6%) and transdermal fentanyl (74.1%) more often induced OIBD in comparison to oxycodone and transdermal buprenorphine (59.3% each). Age over 70, cancer-related pain and transdermal fentanyl were the risk factors for the development of OIBD symptoms [37]. In another large study 4040 patients were analysed with respect to the level of constipation. A similar constipation intensity was found among patients treated with controlled-release (CR) morphine, CR oxycodone and transdermal fentanyl; no difference between cancer and non-cancer patients was found [38].

In some studies similar or less intense constipating effect was observed in patients treated with transdermal buprenorphine (1.2%) in comparison to CR morphine (6.7%) [39]. Retrospective studies highlight the benefits of less intense constipation after switch from morphine to methadone; however these studies were performed in a small number of patients [40, 41]. A prospective study demonstrated constipation relief in 80% of treated patients after the switch from morphine to methadone [42]. Some studies point to the benefits of administering tramadol rather than small morphine doses [43-45] or dihydrocodeine [46] with respect to the constipation intensity. In contrast to the above-mentioned trials stand the results of an open study performed in 174 patients with cancer pain. No differences were found in constipation that developed in patients treated with transdermal opioids (buprenorphine and fentanyl) and oral CR hydromorphone. A possible explanation of this observation could be higher doses of amitriptyline administered to patients treated with buprenorphine and fentanyl and higher activity of patients treated with hydromorphone. A possible explanation of this observation could be higher doses of amitriptyline administered to patients treated with buprenorphine and fentanyl and higher activity of patients treated with hydromorphone. No differences in the consumption of laxatives or in the intensity of nausea were found between the patient groups. The patients treated with hydromorphone experienced more intense vomiting than those treated with transdermal opioids. The cause of vomiting apart from the

opioid administered could be attributed to the primary tumour location, as patients treated with hydromorphone more often had an abdominal site diagnosed [47].

Targeted treatment of opioid-induced bowel dysfunction

Few clinical studies have compared the efficacy of different laxatives [48], with controlled studies lacking [49]. However, traditional laxatives do not target the cause of OIBD, which is predominantly associated with opioid analgesics binding and activating μ -opioid receptors in the GI tract [50]. If the oral laxatives are found to be ineffective, rectal measures are usually introduced. Another approach involves treatment directed at the cause of OIBD. This method 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 are poorly tolerated by patients.

Apart from opioid antagonists with exclusively peripheral effects, opioid receptor antagonists which also have a central mode of action should be listed: naloxone, naltrexone and nalmefene. The majority of studies performed so far refer to the use of an immediate-release formulation of oral naloxone (IR naloxone). In spite of high IR naloxone efficacy in the treatment of OIBD, in some patients opioid withdrawal symptoms and attenuation of analgesia were observed, rendering IR naloxone less useful when administered alone [51-53]. Similar results were obtained in the studies on nalmefene [54] and nalmefene glucuronide [55].

Combined opioid receptor agonists with antagonists

One method to decrease the frequency of constipation in patients requiring strong opioids is to use a formulation composed of an opioid and an 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) [56]. 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 [55]. PR oxycodone/PR naloxone is registered for the indication of severe pain which may only be successfully treated with opioid analgesics; naloxone counteracts the development of OIBD through inhibition of oxycodone's effect on opioid receptors in the gut wall [58]. 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 of 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 is 40 mg/20 mg twice daily. However, in some studies higher daily doses up to 120 mg/60 mg were explored [59].

Following oral administration, oxycodone displays high bioavailability (60-87%) [60] and provides effective analgesia [61]. Naloxone exhibits low bioavailability after oral administration (< 2%) and undergoes extensive first-pass metabolism in the liver with the formation of naloxone-3-glucuronide [62]. The analgesic effect is not reversed by naloxone and no symptoms of opioid withdrawal are observed [51]. The effect of orally administered naloxone depends on normal liver function, so any hepatic impairment should be carefully considered; in patients suffering from liver failure, 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 [52]. The PR naloxone formulation prevents saturation of the hepatic enzyme system responsible for naloxone metabolism and reduces the risk of opioid antagonism in the central nervous system [3].

PR oxycodone/PR naloxone provides similar analgesic efficacy to oxycodone [56] with improvement in bowel function expressed by better results of the Bowel Function Index (BFI) [63] and the Patient Assessment of Constipation Symptoms (PAC-SYM) questionnaires and more frequent spontaneous bowel movements: 62.1% vs. 23.3% [64] and 65% vs. 39%, respectively [65]. Lower consumption of laxatives during treatment with PR oxycodone/PR naloxone in comparison to PR oxycodone therapy was also observed [63-65]. Long-term analysis (over a period of up to 52 weeks of therapy) of two phase III studies [63, 64] in patients with chronic pain demonstrated that the treatment with PR oxycodone/PR naloxone in daily doses up to 80 mg/40 mg was effective and safe [66]. In a large, observational study PR oxycodone/PR naloxone (in the daily dose range of 20 mg/10 mg to 40 mg/20 mg) was an effective analgesic and improved bowel function measured by BFI and quality of life over the period of 4 weeks of the treatment in 1488 patients with severe neuropathic non-malignant pain [67].

A randomized, double-blind study with the use of higher PR oxycodone/PR naloxone doses (converted from oxycodone 60-80 mg per day and allowed to titrate the dose up to 120 mg/day) demonstrated significant improvement in bowel function assessed by BFI ($p < 0.0001$), increase in spontaneous bowel movements per week (median 3.0 vs. 1.0) and lower laxative intake in patients treated with PR oxycodone/PR naloxone in comparison to PR oxycodone administered alone [68]. Adverse effects of PR oxycodone/PR naloxone and PR oxycodone are similar; the frequency of diarrhoea is slightly higher in PR oxycodone/PR naloxone in comparison to PR oxycodone administered alone (5.2% vs. 2.6%) [64]. However, PR oxycodone/PR naloxone less frequently 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 [65]. These differences might be explained by naloxone's antagonist effect on gastric and gut opioid receptors and in consequence naloxone's prokinetic properties [69].

Recently the results of a randomized, double-blind, multicentre study, which assessed PR oxycodone/PR naloxone efficacy and tolerance in comparison to PR oxycodone in patients with moderate to severe cancer pain and their impact on constipation, have been published. A total of 185 patients were randomized to receive up to 120 mg per day of PR oxycodone/PR naloxone or PR oxycodone over 4 weeks. After 4 weeks mean BFI and PAC-SYM scores were significantly lower with PR oxycodone/PR naloxone and the mean total laxative intake was 20% lower in this patient group compared to PR oxycodone. The mean BPI-SF (Brief Pain Inventory-Short Form) scores were similar for both treatments and the consumption of rescue analgesics was low and comparable between the two patient groups. Quality of life (assessed by the EORTC QLQ-C30 and the EuroQoL) results showed better scores with respect to constipation-related symptoms in the group treated with PR oxycodone/PR naloxone. Adverse effects were similar in both patient groups. Specifically, no difference in scores of the modified Subjective Opiate Withdrawal Scale was found between the two patient groups. The results suggest that PR oxycodone/PR naloxone in doses up to 120 mg/60 mg per day may provide effective analgesia and improve bowel function [59].

In an open, uncontrolled study 26 patients with advanced cancer received different opioids due to severe pain. The former opioid treatment was switched to PR oxycodone/PR naloxone at a maximum daily dose of 40 mg/20 mg, administered for a period of 14 days. Bowel function was assessed by BFI, the Bristol Stool Form Scale (BSFS) and the Patient Global Impression of Change Scale (PGIC). In 21 patients constipation improved as measured by BFI, BSFS and PGIC, while adequate analgesia was provided. The most frequent adverse effects were nausea in 9 patients and abdominal pain in 5 patients. Two patients experienced diarrhoea. Two patients experienced diarrhoea. Opioid withdrawal symptoms were not observed. In a recent study the cost-effectiveness and quality of life were compared for PR oxycodone/PR naloxone and PR oxycodone in patients with moderate-to-severe non-malignant pain and opioid-induced constipation. Although the direct treatment cost of PR oxycodone/PR naloxone compared to oxycodone PR was slightly higher, when analysing constipation treatment costs and benefits of PR oxycodone/PR naloxone in terms of improved quality-adjusted life-years, PR oxycodone/PR naloxone was a cost-effective option in the UK [70]. However, in contrast to PR oxycodone, PR oxycodone/PR naloxone tablets are not reimbursed, and thus they are of limited availability for patients with chronic cancer and non-cancer pain in Poland [71].

The contraindications for PR oxycodone/PR naloxone comprise bowel obstruction, acute abdominal conditions, diarrhoea and allergy to the drug. It should be noted that PR oxycodone/PR naloxone studies were performed mainly in patients with chronic, non-malignant pain [63-66, 68, 72]. PR oxycodone/PR naloxone is available in several European countries including Poland. 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. In a recent study a cost-effectiveness and quality of life was compared for PR oxycodone/PR naloxone and PR oxycodone in patients with moderate-to-severe non-malignant pain and opioid-induced

constipation. Although PR oxycodone/PR naloxone direct treatment cost compared to oxycodone PR was slightly higher, when analysing constipation treatment costs and benefits of PR oxycodone/PR naloxone in terms of improved quality-adjusted life-year PR oxycodone/PR naloxone was a cost-effective option in the UK [73]. However, in contrast to PR oxycodone, PR oxycodone/PR naloxone tablets are not reimbursed of and thus available to a limited extent for patients with chronic cancer and non-cancer pain in Poland.

Purely peripherally acting opioid receptor antagonists

Methylnaltrexone (MNTX) is a derivative of naltrexone, a peripheral μ -opioid receptor antagonist which does not cross the blood-brain barrier [74]. As MNTX has low oral bioavailability it is administered subcutaneously or intravenously and is rapidly absorbed [75]. However, studies in healthy volunteers demonstrated the efficacy of oral MNTX in the prevention of delay in oro-caecal transit time after intravenous morphine administration [76]. The MNTX plasma half-life equals 105 to 140 minutes, protein binding is approximately 11-15%. Methylnaltrexone is excreted unchanged in 50% to the urine. Methylnaltrexone is a weak CYP2D6 inhibitor with no significant drug interactions [77]. Methylnaltrexone is used in the treatment of opioid-induced constipation in advanced diseases in adult patients 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. A single MNTX dose equals 8 mg in patients with body weight 38-61 kg or 12 mg if the body mass is 62-114 kg [78].

Patients falling outside of this range should receive a dose of 0.15 mg/kg. In patients with mild to moderate hepatic or renal impairment no dose adjustment is necessary. However, in patients with severe renal failure (creatinine clearance < 30 ml/min) the MNTX dose should be reduced by one-half [79]. 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. Methylnaltrexone is recommended for the treatment of OIBD in adults with advanced illness. In Poland MNTX is available in ampoules (12 mg) and the drug is not reimbursed. Methylnaltrexone adverse effects comprise abdominal pain (28% of patients), flatulence (13%), nausea (11%), dizziness (7%) and diarrhoea (5%) which usually have mild to moderate intensity and are associated with the defecation act [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 concomitant medications (NSAIDs, bevacizumab). The majority of GI perforation cases indicate different possible locations (duodenum, small and large bowel). A possible contributing factor might be the prokinetic effect of MNTX. It is not known if the dose and duration of the treatment with MNTX relate to this complication [80]. As MNTX does not cross the blood-brain barrier, the attenuation of analgesia or opioid withdrawal symptoms are not observed [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. Methylnaltrexone 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, 78, 79, 81-83].

In a systematic review on the use of laxatives in palliative care patients no differences were found between different regimens through analysis of 4 randomised controlled trials. The only exception was a combination of lactulose with senna that was superior to dantron combined with poloxamer. Overall limited efficacy of traditional laxatives was demonstrated, with a lack of randomised controlled trials [84]. However, in a recent controlled, open-label study polyethylene glycol and sodium picosulphate were more effective than lactulose in opioid-induced constipation in cancer pain patients [85].

Two systematic reviews assessed the efficacy and safety of peripherally active opioid receptor antagonists in the treatment of OIBD in 2352 patients [86] and in 2871 patients [87] who took part in randomized, controlled trials of μ -opioid receptor antagonists. Alvimopan (8 and 9 studies respectively), MNTX (6 trials), naloxone (7 studies) and nalbuphine (1 study) were studied. MNTX and alvimopan which is not registered for the treatment of OIBD in patients with chronic diseases [88] were better than placebo in reversing opioid-induced increased gastrointestinal time and constipation. Alvimopan was safe and effective in the treatment of postoperative ileus [89]. The incidence of adverse events was similar to placebo and of mild to moderate intensity. Effects of naloxone and nalbuphine were not demonstrated. Long-term efficacy and safety of opioid antagonists were not clearly established. A recent systematic review confirmed MNTX efficacy in opioid-induced constipation but its long-term efficacy could not be clearly established. The efficacy and differences among traditional laxatives in palliative care patients with constipation could not be established due to limited number of randomized studies [90].

In conclusion: OIBD in patients diagnosed with chronic diseases is a clinical problem that is difficult and often underestimated by medical staff. This is an important issue especially in the case of 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. Benefits were demonstrated from the use of a new prokinetic agent prucalopride in non-cancer patients suffering from OIBD. However, further clinical studies should be undertaken to develop more effective guidelines for the management of OIBD and to establish more precisely the role of opioid receptor antagonists in the treatment of OIBD. The role of opioid receptor antagonists as potential antiemetic and prokinetic agents should be further explored, as suggested by the results of experimental studies in animals. High costs of new therapies should be carefully considered, although overall resources may also be saved on traditional laxative use. The most important advantage of targeted therapies is the decrease of patients' suffering associated with OIBD and substantial reduction in the need to perform invasive rectal procedures and in consequence improvement in patients' quality of life.

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