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Opioids in Gastroenterology: Treating Adverse Effects and Creating Therapeutic Benefits

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Abstract

The use of opioid medications on both an acute and chronic basis is ubiquitous in the U.S. As opioid receptors densely populate the gastrointestinal tract, symptoms and side effects can be expected in these patients. In the esophagus, dysmotility may result manifesting with dysphagia and a syndrome indistinguishable from primary achalasia. In the stomach, a marked delay in gastric emptying may ensue with postprandial nausea and early satiety. Postoperatively, particularly with abdominal surgery, opioid induced ileus may ensue. In the colon, opioid induced constipation (OIC) is common. A unique syndrome termed narcotic bowel syndrome is characterized by chronic abdominal pain often accompanied by nausea and vomiting in the absence of other identifiable causes. With the recognition of the important role of opioids on gastrointestinal function, novel drugs have been developed which utilize this physiology. These medications include peripheral acting opioid agonists to treat OIC and combination agonist and antagonists used for diarrhea predominant irritable bowel syndrome. This review summarizes the most recent data in these areas.

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Dr. Katzka: clinical and pharmacological effects of opioids

Introduction

Pain as the Fifth Vital Sign and the WHO Ladder of Analgesics Use for Chronic Non-Cancer Pain

The concept of pain as the fifth vital sign was introduced to draw attention to the need to provide adequate pain relief to patients.[1] The World Health Organization (WHO) recommended the use of opioids for management of moderate to severe chronic cancer pain; this strategy has been adopted for patients with chronic non-cancer pain in recent years.[2]

The following order of analgesic use was recommended in the WHO three-step ladder for treatment of cancer pain:[3]

STEP 1: non-opioids (aspirin, acetaminophen, diclofenac, ibuprofen); then, as necessary,

STEP 2: mild opioids (codeine, tramadol);

STEP 3: strong opioids such as morphine, buprenorphine, fentanyl, hydromorphone, methadone and oxycodone, administered until the patient is free of pain.

Non-opioids can be added to opioids for moderate to severe pain.

Opioid Use in Chronic Non-Cancer Pain

Chronic pain, defined as persistent pain for more than 3 months[4] affects 10%–15% of the general population.[5] In patients with chronic non-cancer pain, 80% of patients experience at least one adverse event, with constipation (41%), nausea (32%) and somnolence (29%) being most common[6]. Overall, the prevalence of OIC varies from 41 to 81%.[6,7] In the United States, 4% of adults are taking chronic opioid therapy, chiefly for non-cancer pain, including 4.1% in population studies in Olmsted County, Minnesota.[8] This study demonstrated a weak association with age, but not with gender, and the most common indications for opioid use in non-cancer pain were musculoskeletal (e.g. back, degenerative joint disease, fibromyalgia), post-surgery, and vascular pain.[8] Opioids are more effective than non-opioid analgesics in controlling moderate to severe pain. Thus, ~90% of patients with moderate to severe pain are treated with opioids.[9] An estimated 20% of patients presenting to physicians' offices with pain symptoms in the United States were prescribed opioids.[10] The Center for Disease Control (CDC) estimates that the reason for opioid-related overdosing is over-prescription of opioids by healthcare providers.[11]

Given that ~4% of adults in the United States are on opioids for at least 3 months for chronic non-cancer indications, there are several public health initiatives[12] aimed at reversing the epidemic of opioid use for different pain indications and the rising tide of deaths from opiates.[13]

Types of Opioid Receptors: μ, δ, κ

Opioid receptors are G(i/o) G-protein coupled receptors that regulate several functions, including pain, reward, mood, stress, gastrointestinal functions and respiration. The three main opioid receptors (μ, δ, κ)[14] show a high degree of sequence homology, and a common

opioid receptor binding pocket within a helical transmembrane core.[15,16] The main differences in sequence between the receptors occur in the extracellular domains which contributes to ligand selectivity.[17] The opioid peptides reduce intracellular cAMP by inhibiting adenylate cyclase. At the membrane level, they reduce neuronal excitability (by hyperpolarization resulting from increased potassium permeability of the membrane) and neurotransmitter release (by inhibition of voltage-gated calcium channels).[18] The overall effect at the cellular level is thus inhibitory, resulting in a reduction in acetylcholine release, with overall inhibitory effect on the neuron.

Opioid receptors are widely distributed in the central and peripheral nervous system, the intestinal musculature and other tissues including the dorsal horn of the spinal cord where they process and relay afferent nociceptive signals to the central nervous system.[19] In the brain, opioid receptors are mainly in areas involved in pain transmission: the thalamolimbic system, the periaqueductal grey matter, the rostral ventral medulla, the nucleus paragigantocellularis lateralis and the locus ceruleus.[20]

The pharmacologic and potential clinical effects of organ specific opioid stimulation are summarized in Table 1.

The μ-receptors are the principal mediators of analgesic action of endogenous and exogenous opioids, as well as the major side effects of sedation, bowel dysfunction, respiratory depression and dependence.[21] The κ-receptors also mediate analgesia; other effects include bowel dysfunction, increased diuresis and sedation,[22] κ agonists may relieve hyperalgesia produced by chronic use of μ opioid receptor therapies.[23] However, the central activation of κ opioid receptors produces dose-dependent dysphoria and some agonists, such as salvinorin A, produce hallucinations.[24] The δ-receptors are predominantly in the CNS where they produce analgesia, but they are also found in myenteric and submucosal neurons of the gut; their action results in inhibition of motility and secretion.[19] μ and δ receptors are the principal opioid receptors in the gastrointestinal tract, and they are expressed predominantly in the submucosal and myenteric plexuses, respectively.[25]

Table 2 summarizes endogenous and exogenous mediators (focused on currently available medications) of the three major opioid receptor types, and their general effects on gastrointestinal motor and sensory functions.

Since the clinically relevant opioids are μ opioids, this update focuses on μ-opioid receptors.

Gastrointestinal Effects of μ Opioids

Opioids have pharmacological effects throughout the gastrointestinal tract. They decrease gastric emptying and stimulate pyloric tone,[26] inhibit propulsion, increase amplitude of nonpropulsive segmental contractions, increase fluid absorption in the small and large intestine, increase anal sphincter tone,[27] and impair reflex relaxation of the anal sphincter in response to rectal distention. The acute effects of opioids on esophageal function are not as clear. Two studies have demonstrated an acute decrease in lower esophageal sphincter pressure by μ opioid receptor stimulation.[28,29] Nevertheless, the sum of these motor and secretory effects result in anorexia, nausea, emesis, impaired ability to evacuate the bowel,

as well as abdominal spasm, cramps, and pain.[19,30] Decreased gastric, biliary, pancreatic and intestinal secretions interfere with digestion.

Differences in Acute vs. Chronic μ Opioid Effects in the GI Tract

One of the characteristics of μ opioid effects is the development of tolerance, which results in the need for increasing doses of opioids to achieve the same effects, such as on analgesia or euphoria. This tolerance develops from a desensitization in which opioid receptor stimulation by an agonist leads to lower signal transduction and effector response.[31] The effects of chronic opioids on the gut similarly derive from the effects of generalized tolerance, but also differ due to the differential tolerance of gut regions to μ-opioids. For example, tolerance to the effects of μ opioids[32,33] occurs in all gastrointestinal organs, except in the colon.[34] Therefore, effects such as constipation do not abate over time. These differences may also reflect varying densities of opiate receptors that are organ specific in the gut.[35] The exact mechanism of tolerance in humans is unclear, although the prevailing hypotheses are either de-phosphorylation which leads to activation of the receptor to bind an agonist,[36] or binding of β-arrestin-2 which causes receptor internalization in the endosome, prolonging the desensitization of the receptor.[37]

Internalization of the opioid receptors may also occur. The down regulation of β-arrestin-2 does not occur in the ileum, thus causing tolerance to morphine, but this is not observed in the colon, which leads to receptor recycling to the plasma membrane and, hence, lack of tolerance in the colon and development of opiate-induced constipation as discussed.[17] Finally, the different downstream effects of stimulating an opioid receptor may follow different time courses of dependence, also leading to a variation of gut effects.[31]

μ Opioids, GI Symptoms and Syndromes

Esophageal Motility Disorders

μ opioids may be associated with dysphagia or heartburn that may reflect intrinsic neural or sphincter dysfunction.

In patients with gastroesophageal reflux disease (GERD),[38] acute morphine administration significantly decreases the rate of transient LES relaxations in patients vs controls, resulting in less reflux episodes and a decrease of the time at pH <4. Resting LES pressure is decreased both in health and in achalasia; swallow-induced LES relaxation is also significantly decreased by morphine in the healthy subjects.[39] A range of manometric abnormalities have been reported in patients with dysphagia using chronic opioids, such as impaired LES relaxation, high amplitude/velocity and simultaneous esophageal waves,[40] as well as esophagogastric junction outflow obstruction, higher integrated relaxation pressure, and lower distal latency on esophageal pressure topography.[41] Some of these findings are in contrast to the acute opioid effects cited previously. This suggests a different esophageal physiology with acute and chronic usage. There may also be clinical and manometric features that mimic type 3 more commonly, or type 2 achalasia, as many of these patients cannot stop and/or require chronic opioid treatment, similar to primary achalasia, though

there is some evidence that treatment outcome is worse in those with opioid-induced achalasia.[42]

Nausea and Emesis

Opioid administration can induce nausea or vomiting, and this is commonly seen in the postoperative period, with opioids being one factor in the multifactorial etiology.[43] The pathophysiology involves, in part, peripheral inhibitory effects of opioids on gastrointestinal transit or the stimulation of the pyloric sphincter, which delays gastric emptying or causes gastroparesis. However, the primary mechanism of opioid-induced nausea and emesis is central, with direct stimulation of the chemoreceptor trigger zone in the area postrema in the floor of the fourth ventricle.[44] NK-1 receptors in the area postrema are involved in the mechanism of emesis induced by morphine in ferrets,[45] but there are no reports of efficacy of aprepitant on nausea, even though it reverses other effects of oxycodone.[46] The clinical efficacy of 5-HT_3 antagonists for opioid-induced emesis supports the hypothesis that stimulation of the area postrema may also be relevant in morphine-induced emesis in humans.[47] Adding a prokinetic (e.g. metoclopramide), prochlorperazine, or a 5-HT_3 antagonist to the opiate regimen is beneficial, especially in a postoperative pain control setting.[48-50]

Gastroparesis

Peripheral inhibitory effects of opioids on antral motility or the stimulation of the pyloric sphincter[25] result in delayed gastric emptying or cause gastroparesis. Among patients evaluated for gastroparesis by the NIH Gastroparesis Consortium, 42% overall[51] and 48% of those with abdominal discomfort score ≥3 and 33% of those with score <3 were on opiates/narcotics.[52] It is important to note that even novel opioid agents that appear to induce less constipation when used chronically may retard gastric emptying. Thus, tapentadol (a mu-opioid receptor agonist and norepinephrine reuptake inhibitor) was associated with delayed gastric emptying comparable to the effect of oxycodone.[53] Although tramadol was reported not to retard gastric emptying of solids or liquids in a crossover study of 12 healthy participants; however the same study showed 40% slower orocecal transit and significant delay in colonic transit,[54] and tramadol induced dose-related inhibition of gastrointestinal transit in mice.[55]

Sphincter of Oddi

Opiates may have important effects on sphincter of Oddi function. The effects of opioids on the sphincter are predominantly myogenic, as evidenced by preservation of their effect on sphincter pressure in the presence of the neurotoxin tetrodotoxin.[56] Furthermore, different opioid receptors may modulate sphincter of Oddi function. This is suggested by a specific increase in tonic pressure by morphine, but an increase in phasic sphincter pressure by naloxone.[57] Nevertheless, the predominant effect of clinically used opioids appears to be an increase in sphincter of Oddi phasic pressure.[58] In a retrospective study of post-cholecystectomy patients with suspected sphincter of Oddi dysfunction (SOD), 30% had taken opiate-containing drugs 15 to 120 minutes before the onset of pain, suggesting that opiates may have been the cause of the SOD.[59] Likewise, eluxadoline, a mixed μ-opioid receptor agonist–δ-opioid receptor antagonist and δ-opioid receptor agonist recently

approved for the treatment of IBS-D, has been associated with SOD in a small percentage (~0.5%) of patients without a gallbladder.[60] This was confirmed in a more recent study of nearly 2000 patients with IBS-D with 10 patients developing sphincter of Oddi spasm, most at the higher eluxadoline dose of 100mg.[61] In a recent communication (https://www.fda.gov/Drugs/DrugSafety/ucm546154.htm), the U.S. Food and Drug Administration (FDA) issued a warning that eluxadoline should not be used in patients who do not have a gallbladder. An FDA review found these patients have an increased risk of developing serious pancreatitis that could result in hospitalization or death. In the communication dated March 15, 2017, the review showed that as of February 2017, two deaths in patients who did not have a gallbladder were considered to be associated with eluxadoline had been reported to FDA. One death was associated with pancreatitis with symptom onset within 1 hour of taking a single dose of eluxadoline, and the other death being associated with sphincter of Oddi spasm, manifested as severe abdominal pain and vomiting shortly after taking the first dose of the drug.

Post-Operative Ileus and Opioids

Opioids are a mainstay of pain relief following abdominal surgery and they inhibit gastrointestinal and colonic motility. Post-operative ileus is a complex disorder, and major intrinsic contributing factors include surgical stress (i.e., from handling the bowel), secretion of inflammatory mediators and endogenous opioids in the GI tract, and changes in hormone levels and electrolyte and fluid balance.[19,62]

Opioid-Induced Constipation

The μ opioids increase fluid absorption and inhibit motility in the colon. Opioid-induced constipation (OIC) is generally defined as a change from baseline in bowel habits and change in defecation patterns after initiating opioid therapy, which is characterized by any of the following: reduced frequency of spontaneous BM (SBM, <3 bowel movements /week); worsening of straining to pass BM; sense of incomplete evacuation; and harder stool consistency.[63] These features have been recently adopted in Rome IV criteria (Table 3).[64] OIC can occur even at low dosages of opioids[65] and at any time after initiation of opioid therapy.[66] Nausea, vomiting and gastroesophageal reflux are commonly associated with OIC.[67]

The bowel function index (BFI) is a clinician assessment tool to appraise severity and responsiveness to current treatment. It includes ease of defecation, feeling of incomplete bowel evacuation, and personal judgment of constipation (Figure 1). Each variable is rated by the patient from 0 to 100, based on the experience in 7 days.[68] The reference range of BFI scores for non-constipated patients from 0 to 28.8 provides a simple discrimination between constipated and non-constipated patients on opioid therapy.[69] A BFI ≥30 is recommended as a criterion to identify patients on laxatives for whom prescriptions of FDA-approved therapies for OIC are justified.[70]

Narcotic Bowel Syndrome

Narcotic bowel syndrome (NBS) is described as persistent moderate to severe daily abdominal pain of more than 3 months duration occurring in patients requiring more than

100 mg of morphine equivalent per day; the abdominal pain does not respond and may actually increase in response to escalating doses of narcotics.[71] It is to be differentiated from the general causes of pain in patients on opiates as it is a disease of nociception independent of the opioid effects on gut motility and secretion (for review, see ref. 72). It is likely a more common syndrome than realized, but a 2009 epidemiologic study in Olmsted County estimated the prevalence at 4%.[8]

There are at least five postulated mechanisms or hypotheses to explain this paradoxical increase in pain.[73] First, the normal pain control function of descending inhibition from the medulla of pain signals rising up the spinal cord becomes a facilitator of those pain signals through neuroplastic change. Second, chronic narcotic use causes inflammation of spinal glial cells through activation of toll-like receptors, and the inflammation leads to increased neuropathic pain. Third, chronic opiate exposure results in abnormal function of the N-methyl-D aspartate receptor (NMDAR) at the level of the spinal cord. Fourth, activation of G-protein coupled receptors by opioids may excite dorsal root ganglia leading to increased pain signals. Fifth, abnormalities of central processing of pain potentiate NBS. For example, in a study of 39 patients with NBS, Drossman et al. demonstrated a high prevalence of psychologic traits and traumatic exposures which have been linked to altered brain processing of painful signals.[74]

The precise interaction of these diverse mechanisms in production of pain in NBS is unclear. The diagnosis of NBS is suggested by the presentation of a patient on chronic opiates with chronic generalized, colicky abdominal pain, despite escalating doses of opiates, and worsening of pain with tapering of the dose. The pain may be associated with nausea and vomiting, and patients may present to emergency departments. An extensive negative evaluation usually ensues. Emergency evaluation is commonly sought for pain control and to evaluate for causes of abdominal pain that may be found in these patients, such as kidney stones and bowel obstruction.[75]

Treatment of NBS is difficult, requiring detoxification with substitution of opioids with non-opiate medications to control pain, anxiety and opiate withdrawal symptoms, including the use of clonidine. This is best handled through specialists and/or centers with expertise in opiate dependence.[71] Although there is a high recidivism rate (approximately 50%), those who remain off of narcotics report improvement in pain.[74]

Acute Abdominal Pain in Patients on Chronic μ Opioid Treatment

Recent data show that, among the non-cancer patients attending the Mayo Clinic Emergency Department with acute abdominal pain, ~19% (442/2354) were on μ opioid agonists for over 3 months for chronic pain. The indication for the opioids was abdominal pain in 21% (93/442) of these patients, suggesting that, despite the lack of evidence of efficacy or safety, μ opioid agonists are being prescribed for patients with non-cancer-related abdominal pain, which likely includes IBS.[75]

Therapeutic Uses of Opioid Receptor Agonists and Antagonists in Gastroenterology

Opioid Agents in Treatment of Functional GI Diseases

μ opioid agonists—Loperamide, a synthetic peripheral mu-opioid receptor agonist, is efficacious in the treatment of diarrhea in IBS patients, delaying intestinal transit,[76] significantly decreasing stool frequency, increasing water and ion absorption, and improving stool consistency and urgency.[77] Its advantage over other μ opioids, such as codeine or diphenoxylate, is that it does not cross the blood-brain barrier. Loperamide may also result in improvement in anal sphincter tone.[78] Generally, loperamide compared with placebo does not have a significant effect on the perception of pain in IBS patients although pain associated with attacks of diarrhea may be reduced.[79,80] The typical doses of loperamide are 2 mg after each loose bowel movement (usually <8 mg per day) or preprandial 2–4 mg in IBS patients with a prominent diarrhea after feeding.

As a group, the μ-opioid agonists are used for pain relief during acute exacerbations of pain in patients with IBS in a combined European and U.S. study, which documented use of opioids in 35% of attacks either alone or in combination with other drugs.[81] In this retrospective study, IBS-D patients were more likely to use opioids during pain attacks (32% of attacks) than patients with IBS-C (20% of attacks) or IBS-M (19% of attacks). There are no randomized, controlled trials of the use of μopioid agonists in the treatment of chronic pain in patients with IBS. It is important to reiterate that there is no evidence for use of μ-opioid agonists for the pain of IBS.

A mixed opioid agent, eluxadoline—Eluxadoline is a μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist with minimal oral bioavailability. Eluxadoline, at 100 mg and 200 mg, resulted in greater improvements in bowel movement frequency and urgency, global symptoms, IBS Symptom Severity Score, IBS quality of life, and adequate relief.[82] Results on the primary efficacy endpoint (combined bowel function and pain) were generally confirmed in pivotal trials with a NNT of ~8[60], though abdominal pain scores were not significant for the 75 or l00mg doses. The adverse events of pancreatitis and sphincter of Oddi spasm (SOS), each in 0.3% of patients in the controlled trials, led to exclusions from treatment of patients with a history of bile duct obstruction, pancreatitis, severe liver impairment, or severe constipation, and intake of more than three alcoholic beverages per day. An updated analysis of safety of eluxadoline in the phase 2 and 3 trials shows that clinically apparent SOS events were observed in eluxadoline-treated patients without a gallbladder and the majority were observed in with the higher (l00mg) dose of eluxadoline.[61] The FDA Adverse Event Reporting System received information of 99 cases of pancreatitis, and 39 cases of SOS within 10 months of the availability of eluxadoline in the U.S.[83]

Treatment of Opioid-Associated Postoperative Ileus: Alvimopan

Alvimopan is a peripherally acting mu-opioid receptor antagonist (PAMORA) approved in the United States for management of postoperative ileus in patients after bowel resection. Alvimopan can accelerate recovery of GI function (especially for the lower GI tract), shorten

the length of hospital stay, and reduce postoperative ileus-related morbidity without compromising opioid analgesia in an enhanced recovery setting.[81] A recent meta-analysis of nine randomized controlled trials involving 4075 patients demonstrated that alvimopan significantly decreased the time to first passage of stool post operatively and lowered the chance of serious side effects.[84]

Prevention and Treatment of OIC

Choice of medication to prevent QIC

Oxycodone and naloxone: Naloxone is a relatively nonselective opioid antagonist used intravenously to treat opioid overdosing. When administered orally, standard formulation naloxone acts locally on μ opioid receptors in the gastrointestinal tract.[85] Naloxone improved symptoms of OIC and reduced laxative use with only mild opioid withdrawal symptoms such as yawning, sweating and shivering.[86]

Prolonged release (PR) naloxone has extensive first pass metabolism (hepatic glucuronidation) which reduces its bioavailability for systematic action to <2%. Naloxone PR reduced mean colonic transit time by 2.1 hours when used in combination with oxycodone PR (20mg oxycodone/1 Omg naloxone) compared to oxycodone PR alone (20mg).[87]

Oxycodone PR and naloxone PR in combination (fixed ratio 2:1, approved at maximum dose of 40 and 20mg respectively) is superior to prolonged release oral oxycodone alone to treat OIC. Naloxone displaces oxycodone from the gastrointestinal μ opioid receptors with negligible action in the systemic circulation due to high first pass metabolism. In contrast, the bioavailability of oxycodone is 80%, and therefore its analgesic action mediated in the CNS is preserved. The combination of oxycodone PR and naloxone PR decreased BFI scores by 48.5 units (on 0-100 scale), increased the median number of complete SBM (CSBM)/week three-fold when compared to oxycodone alone and improved constipation-related quality of life.[90-92] The most common adverse effects were nausea, vomiting, headache, constipation, and diarrhea,[93] with 13% incidence of severe adverse events.

Tapentadol: Tapentadol is a μ opioid agonist and norepinephrine reuptake inhibitor;[94] the latter function adds to the analgesic potential of the μ opioid agonism, predominantly through stimulation of α2 adrenergic receptors.[95] The combined effects of tapentadol on pain sensation can be achieved with a relatively lower level of μ-opioid agonist to achieve analgesia equal to that of oxycodone with reduced gastrointestinal adverse effects such as constipation in chronic painful conditions such as moderate-to-severe chronic osteoarthritis-related knee pain[96] or moderate-to-severe chronic low back pain.[97] However, acutely administered tapentadol slows gastric emptying similarly to oxycodone, though it does not retard colonic transit.[53]

OTC laxatives and when to move to specific prescription treatments—Since laxatives were proven to be effective in some patients,[98] they should be the first line treatment in patients with diagnosis of OIC. Guidelines from the European Association for Palliative Care (EAPC) recommend laxatives for the prophylaxis or management of OIC in

patients with cancer.[99] Unfortunately, prophylactic treatment to prevent constipation is seldom prescribed to outpatients who receive prescription opioids.[100,101] A prospective, open-label study suggests that polyethylene glycol (13.81 grams daily) and sodium picosulphate (10 mg daily) are more efficacious than lactulose[102] for outpatients with cancer on opioid therapy.

Recent studies have documented inadequate response of OIC to laxative treatment.

If there is insufficient clinical benefit with laxatives, as evidenced by a BFI score of >30 points, treatment with medications approved for OIC should be considered (PAMORA, combination of oxycodone and naloxone, lubiprostone). Reassessment of the BFI score is useful to monitor improvement in OIC.[104]

Treatment of OIC

Intestinal secretagogue: lubiprostone: *Lubiprostone* is a bicyclic fatty acid derived from PGE1 metabolite which increases fluid secretion in the gastrointestinal tract[105] by stimulating the cystic fibrosis transmembrane regulator (CFTR) and type 2 chloride channels (C1C2) in the apical membrane to secrete chloride and water into the lumen, resulting laxation and acceleration of small intestinal and colonic transit.[106]

Lubiprostone compared to placebo increased the overall frequency of SBM/week, and reduced by 50% the time to first bowel movement in patients with OIC.[107,108] In these same trials, lubiprostone significantly improved constipation symptoms such as abdominal discomfort, degree of straining, stool consistency, and constipation severity. Nausea, diarrhea, and abdominal pain were the most common side effects.

Lubiprostone-stimulated secretion of CI ions via C1C2 channels was inhibited *in vitro* in T84 cell lines by methadone. As a result of these studies, lubiprostone is contraindicated in OIC associated with methadone use. Lubiprostone, 24μg, twice daily (b.i.d.), was approved by the FDA for OIC in patients with non-cancer pain.

PAMORAs : Methyl naltrexone and naloxegol: *Methylnaltrexone* is a quarternary N-methyl derivative of naltrexone;[110] the methyl group decreases the lipid solubility and increases polarity, preventing it from crossing into the brain.[111] Peripherally administered methylnaltrexone decreased morphine-induced delay in orocecal transit time.[112] In a 4-week trial of methylnaltrexone, 12mg once daily or every other day, compared to placebo in patients with OIC, there was significantly shortened time to first rescue-free bowel movements (RFBM), increased the number of weekly RFBM, improved degree of straining, decreased sense of incomplete evacuation, and improved PAC-QOL;[113] an early response suggested excellent outcome. Another trial with same doses improved PAC-SYM scores, specifically the stool and rectal symptoms, with no effect on pain scores.[114] Abdominal pain and nausea were the most common adverse events reported; other adverse effects were diarrhea, hyperhidrosis, and vomiting. The FDA has approved 12mg subcutaneous injection of methylnaltrexone for the treatment of OIC in patients taking opioids for chronic, non-cancer pain. There have been 7 cases of gastric or intestinal perforation reported in the FDA Adverse Event Reporting System in patients association with methylnaltrexone therapy for

OIC during the first 18 months after approval.[115] The causative relationship has not been established, since patients either had coincidental gastric ulcer or severe constipation which is itself a risk factor for perforation.

Naloxegol is a PEGylated derivative of naloxone[116] that does not cross the blood brain barrier. In addition, P-glycoprotein transporter (PGP) transports naloxegol from the central nervous system.[117] Thus, only negligible amounts of naloxegol reach the central nervous system and, therefore, it does not reduce pain relief from opioids. Naloxegol antagonized morphine-induced reduced orocecal transit, but it had no effects on miosis or opioid withdrawal symptoms, suggesting exclusively peripheral action.[116,118]

Large 12-week, phase II and phase III studies all showed naloxegol improved SBM from the first week of treatment,[118,119] even in patients with inadequate response to laxatives. In these trials, naloxegol improved stool consistency, CSBM, percentage of days with straining, PAC-SYM and PAC-QOL and was well tolerated and safe.

In patients with OIC, an improvement in the frequency of SBMs by ≥3 per week was associated with consistent improvements in patient response outcomes, that is Patient Assessment of Constipation-Quality of Life (PAC-QOL) and PAC-Symptoms (PAC-SYM) at each study visit, and the Straining Scale and stool consistency or form (Bristol Stool Scale) with each bowel movement.[120] From the United Kingdom's National Health Service and Personal Social Service perspective, a recent analysis suggests that naloxegol treatment is cost-effective in patients with OIC who are not responding to laxatives.[121]

When administered for 52 weeks in OIC patients with non-cancer pain,[122] the most common side effects were abdominal pain, diarrhea, nausea, headache, and flatulence; no QT/QTc interval prolongation or serious adverse events occurred. The FDA approved naloxegol, 12.5 or 25mg, q.d., orally, for OIC in adults with chronic non-cancer pain, and requires surveillance of cardiovascular events in patients treated with naloxegol. A summary of medication trials used for OIC is given in Table 4.

Conclusion

Opioid medications are commonly used in clinical practice and have acute or chronic effects on diverse regions of the gastrointestinal tract. Given their widespread use, it is imperative to consider whether any presentation with gastrointestinal symptoms may be related to the intake of opioids. Acute administration of opioids should be accompanied by symptomatic remedies to counter the acute pharmacological effects, and these include antiemetics and laxatives. The Bowel Function Index is a useful clinical tool to identify chronic OIC that is not responding satisfactorily to first-line therapies and to select patients for treatment with prescription medications approved for the treatment of OIC.

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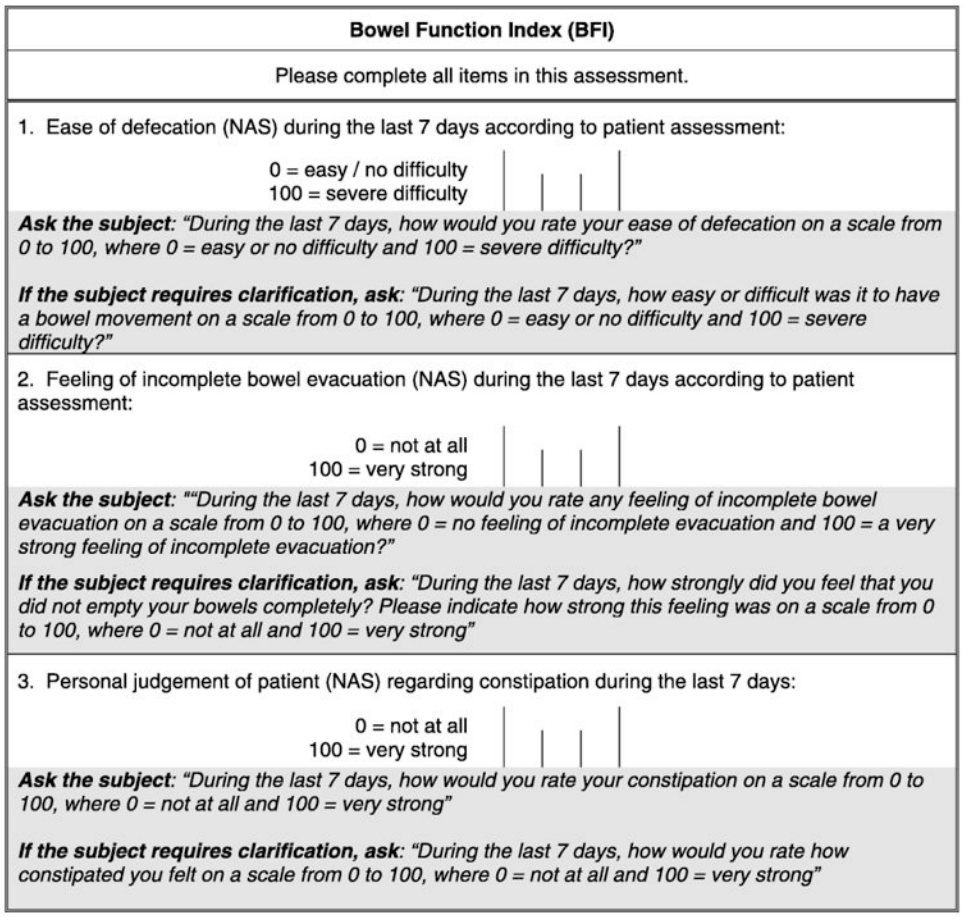

Bowel Function Index (BFI)

Please complete all items in this assessment.

1. Ease of defecation (NAS) during the last 7 days according to patient assessment:

0 = easy / no difficulty
100 = severe difficulty

Ask the subject: *"During the last 7 days, how would you rate your ease of defecation on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"*

If the subject requires clarification, ask: *"During the last 7 days, how easy or difficult was it to have a bowel movement on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"*

2. Feeling of incomplete bowel evacuation (NAS) during the last 7 days according to patient assessment:

0 = not at all
100 = very strong

Ask the subject: *""During the last 7 days, how would you rate any feeling of incomplete bowel evacuation on a scale from 0 to 100, where 0 = no feeling of incomplete evacuation and 100 = a very strong feeling of incomplete evacuation?"*

If the subject requires clarification, ask: *"During the last 7 days, how strongly did you feel that you did not empty your bowels completely? Please indicate how strong this feeling was on a scale from 0 to 100, where 0 = not at all and 100 = very strong"*

3. Personal judgement of patient (NAS) regarding constipation during the last 7 days:

0 = not at all
100 = very strong

Ask the subject: *"During the last 7 days, how would you rate your constipation on a scale from 0 to 100, where 0 = not at all and 100 = very strong"*

If the subject requires clarification, ask: *"During the last 7 days, how would you rate how constipated you felt on a scale from 0 to 100, where 0 = not at all and 100 = very strong"*

Figure 1.

The BFI assessment tool and instructions for use.

Abbreviation: BFI, Bowel Function Index. Reproduced with permission from ref. 68, Rentz AM, et al. J Med Econ 2009;12:371–83.

Table 1

Pharmacological effects of opiates in different regions of the gastrointestinal tract and clinical correlates

Site	Pharmacological effect	Potential Clinical effect
LES	Inhibition LOS relaxation	
Esophagus	Simultaneous contractions	“achalasia”
Gallbladder and biliary tract	Contraction	Biliary pain
	Spasm sphincter of Oddi	Delayed digestion
	Decreased secretion	
Gastroduodenum	Inhibition gastric emptying	Anorexia, nausea and vomiting, gastroparesis, postoperative ileus
	Increase duodenal motility followed by quiescence	
	Increase pyloric tone	
Small bowel	Increase tone/segmentation	Indigestion, Bloating, distension Constipation, postoperative ileus
	Increase transit time	
	Increase absorption	
	Decrease secretion	
Colon	Increase tone/segmentation	Bloating and distension
	Increase transit time	Spasm, cramps, pain
	Increase absorption	Constipation
	Decrease secretion	Hard, dry stools
Anorectum	Decrease rectal sensitivity	Incomplete evacuation
	Increase internal sphincter tone	Straining constipation

Table 2

Three major opioid receptor types in gastrointestinal tract

	δ-receptors	**κ-receptors**	**μ-receptors**
Preferred endogenous ligand	**Enkephalin**	**Dynorphin**	**β-endorphin**
Location	Myenteric plexus	Myenteric plexus	Myenteric and submucosal plexuses
	CNS	Afferent neurons	CNS and spinal cord
Pharmacological Agonists			Morphine Trimebutine Loperamide
		Eluxadoline	
Pharmacological Antagonists	Eluxadoline, Alvimopan		Naloxone, Naltrexone
- PAMORA			Alvimopan Methylnaltrexone Naloxegol
Gastrointestinal effects	Delayed transit	Delayed transit Visceral anti-nociception	

Table 3
Diagnostic Criteria for Opioid-Induced Constipation

1. New, or worsening, symptoms of constipation when initiating, changing, or increasing opioid therapy that must include 2 or more of the following:

- **a.** Straining during more than one-fourth (25%) of defecations
- **b.** Lumpy or hard stools (BSFS 1–2) more than one-fourth (25%) of defecations
- **c.** Sensation of incomplete evacuation more than one-fourth (25%) of defecations
- **d.** Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations
- **e.** Manual maneuvers to facilitate more than one-fourth (25%) of defecations (eg, digitalevacuation, support of the pelvic floor)
- **f.** Fewer than three spontaneous bowel movements per week

2. Loose stools are rarely present without the use of laxatives

Table 4

Clinical trials of drugs approved for OIC (pla=placebo; PAC-SYM= Patient assessment of constipation symptoms; # = size of study cohort; weeks refers to duration of trial in weeks; RFBM=Rescue free BM)

Updated with recent advances from ref. 123, Nelson A, Camilleri M. Ther Adv Gastroenterol 2015;8:206-20.

DRUG	DESIGN	Weeks	#	STUDY ENDPOINTS	SPECIFIC OUTCOMES	REFERENCE
LUBIPROSTONE	1. RCT	12	431	≥1 SBM improvement over baseline frequency and ≥3 SBM/week for at least 9 weeks	27.1% vs. 18.9% with p value <0.030	Jamal et al 2015
	2. RCT	12	418	Δ from baseline in SBM # at week 8 and overall	At 8 weeks, SBMs/week mean 3.3 vs. 2.4 (pla), P =0.005; Overall mean SBMs/week 2.2 vs. 1.6 (pla), P = 0.004	Cryer et al 2014
OXYCODONE AND NALOXONE (OXY PR)	1. RCT + open-label for 52 weeks	12	278	a. Change in BFI at week 4 compared to baseline b. CSBM	40.9 BFI score at week 4 and 34.01 at week 12 compared to a baseline of 67.4 51% achieved CSBM in OXY PR compared to 26% in only oxycodone group at 4 weeks	Lowestein et al 2009
	2. RCT	12	35	Δ from baseline in BFI during treatment	BFI Score change of 23.3 compared to baseline of 61.3 (P< 0.0002)	Koopmans et al 2014
METHYL NALTREXONE (MNTX)	1. RCT	4	460	Rescue free BM (RFBM) within 4 hours of first dose Time to BM within first 24 hours	34.2% had RFBM with MNTX compared to 9.9% (pla) 46% had RFBM within 24 hours with MNTX compared to 25.3% (pla)	Michna et al 2011
	2. RCT	4	460	PAC SYM: Rectal symptoms Stool symptoms	At 4 weeks, MNTX compared to placebo: -0.56 vs -0.30 (p<0.05) -0.76 vs -0.43 (p<0.001)	Iyer et al 2011
NALOXEGOL	1. RCT	4	207	Median Δ from baseline in SBM/wk after 4 weeks	25 mg naloxegol (3.0 vs 0.8 [pla]; P = 0.0022); 50 mg naloxegol (3.5 vs 1.0 [pla]; P < 0.0001); Response rates higher 25 vs. 12.5mg	Webster et al 2013
	2. RCT (two studies: 04 and 05)	12	641 696	≥3 SBM/week and increase of ≥1 SBM compared to baseline for ≥ 9 of 12 weeks Δ Severity of straining Δ Stool consistency	study 04: 44.4% vs. 29.4% [pla], P=0.001 study 05: 39.7% vs. 29.3% [pla], P=0.02 study 04: -0.73±0.05; study 05: -0.80±0.06; study 04: 0.66±0.07; study 05: 0.71+0.07	Chey et al 2014