Chronic opioid induced constipation in patients with nonmalignant pain: challenges and opportunities

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Abstract: With the recent introduction and approval of medications directed at the treatment of opioid induced constipation (OIC) in patients with nonmalignant pain, there is increased interest and understanding of the unmet need and opportunities to enhance patient management. The high incidence of OIC is associated with rapid increase of narcotic analgesic prescriptions for nonmalignant chronic pain. This review addresses briefly the mechanisms of action of opioids that lead to OIC, the differential tolerance of gastrointestinal organs to the effects of opioids, the size and scope of the problem, the definition and outcome measures for OIC, current differential diagnosis and management algorithms, and the pharmacology and efficacy of treatments for OIC in patients with nonmalignant pain.

Keywords: constipation, opioids, pain

Introduction

Opioid analgesics are one of the most commonly prescribed classes of medication for chronic nonmalignant pain. Apart from other adverse effects of chronic opioid use, gastrointestinal adverse effects are among the most frequently encountered. Opioid induced bowel dysfunction (OBD) refers to the constellation of gastrointestinal adverse effects of opioids: nausea, vomiting, opioid induced constipation (OIC), abdominal cramping, bloating and abdominal pain [Chou *et al.* 2009]. OIC is the most common adverse effect; since tolerance does not develop over the long term, in contrast to symptoms such as nausea, vomiting and sedation, OIC can be experienced at any point of time after initiation of opioid analgesics.

Among the indications for chronic noncancer pain, opioids are used for conditions such as pain following orthopedic and other surgeries, back pain, osteoarthritis, peripheral neuropathy, chronic back pain, refractory headache and fibromyalgia [Camilleri *et al.* 2014]. The prevalence of constipation in patients receiving opioids for chronic noncancer pain ranges from 41 to 81% [Kalso *et al.* 2004; Bell *et al.* 2009].

Size and scope of the problem of opioid use and abuse

Opioids are the major pain relieving medications prescribed for malignant and nonmalignant pain in the US. Healthcare providers in the US wrote more than 259 million prescriptions for opioid analgesics in 2012 (see <http://www.cdc.gov/vitalsigns/opioid-prescribing/>); prescription rates per capita were highest in southern US states (Figure 1). The dispensing of opioid analgesics has grown exponentially in the last 10 years from nearly 149 million prescriptions in early 2003 to 207 million in 2013 (see <http://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2014/prescription-opioid-heroin-abuse>). In fact, 4% of US adults are taking chronic opioid therapy, chiefly for noncancer pain. The US Centers for Disease Control and Prevention (CDC) estimated that providers prescribe almost 2–3 times more opioid analgesics than are required for the entire duration of therapy, and the providers that prescribe most of these opioids are physicians. The increase in prescriptions of opioid analgesics for pain relief has also led to an increase in the number of deaths due to opioid overdose. Some of the increased demand for prescription opioid analgesics for chronic pain is

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Figure 1. Rates of opioid sales and opioid substance abuse treatment admissions in the United States, 1999–2010. Reproduced from 'Addressing Prescription Drug Abuse in the United States: Current Activities and Future Opportunities', http://www.cdc.gov/HomeandRecreationalSafety/pdf/HHS_Prescription_Drug_Abuse_Report_09.2013.pdf.

from people who use them nonmedically (without a prescription or for recreational purposes), or sell them, or get the opioids from multiple prescribers at the same time. There is concern that large quantities of opioids are prescribed to people who do not require them for medical indications (see <http://www.cdc.gov/primarycare/materials/opioid-abuse/docs/pda-pherspective-508.pdf>).

The increase in prescriptions for opioid analgesics has been fueled, in part, by the focus on pain as the fifth vital sign. To improve pain management, the Veterans Health Administration launched the 'Pain As the 5th Vital Sign' initiative in 1999, requiring a pain intensity rating (0 to 10) at all clinical encounters (see <http://www.va.gov/painmanagement/docs/TOOLKIT.pdf>). The Joint Commission on Accreditation of Health Care Organization (JCAHO) proclaimed that pain assessment be recorded as the 'fifth vital sign', despite the fact that pain is a symptom and not really a measurable sign.

The World Health Organization (WHO) developed a three-step 'ladder' for cancer pain relief in adults (see <http://www.who.int/cancer/palliative/painladder/en/>) [Jadad and Browman, 1995]. According to WHO, if pain occurs, there should be prompt oral administration of drugs in the following order: STEP 1 – non-opioids [aspirin, paracetamol (acetaminophen), diclofenac, ibuprofen]; then, as necessary, STEP 2 – mild opioids (codeine, tramadol); and finally STEP 3 – strong opioids such as morphine, buprenorphine, fentanyl, hydromorphone, methadone and oxycodone, administered until the patient is free of pain. In addition, in order to calm

fears and anxiety accompanying the pain, additional drugs ('adjuvants') are recommended. To maintain freedom from pain, WHO recommends that drugs be given in scheduled intervals, that is, every 3–6 hours, rather than 'on demand'.

Recently, JCAHO clarified and updated recommendations on pain relief (see http://www.jointcommission.org/assets/1/18/Clarification_of_the_Pain_Management_Standard.pdf) to affirm that the identification and management of pain are important components of patient-centered care. JCAHO stated that patients can expect their healthcare providers to involve them in their assessment and management of pain, and that both pharmacological and nonpharmacological strategies have a role in the management of pain. The clarification also noted the inclusion of the risks of dependency, addiction, and abuse of opioids when considering the use of medications to treat pain.

Whatever the societal, medical and regulatory reasons for the increased opioid consumption, OIC is increasingly encountered in clinical practice, including in gastroenterology clinics. Opioids have significant effects on neuronal mechanisms leading to constipation. A primary target for absorbed opioids is the enteric nervous system (ENS).

Anatomy of ENS and μ -opioid receptors

The ENS is composed of enteric primary sensory afferent neurons (IPAN), motor neurons (excitatory and inhibitory) and interneurons (ascending

and descending). These are synaptically interconnected to act in an integrated way in the processing of information to effector systems, such as muscles, secretory glands and blood vessels. The ENS is also controlled by the extrinsic parasympathetic nervous system through vagus and pelvic nerves, and by the sympathetic nervous system. Cell bodies of neurons form several plexi within the wall of the gastrointestinal tract. There are two prominent ganglionated plexi called the submucosal or Meissner's plexus located in the submucosa, and the myenteric or Auerbach's plexus located between circular and longitudinal muscle layers in the muscularis externa [Costa *et al.* 2000].

Intestinal peristalsis is the result of coordinated activity of the muscular and neural mechanisms in the gastrointestinal tract. IPAN respond to luminal stimuli and are primarily involved in secretomotor control. Motor and interneurons are primarily involved in smooth muscle contraction through activation of a network of pacemaker cells (interstitial cells of Cajal).

In the human gut, μ -opioid receptors are present on myenteric and submucosal neurons and on immune cells in the lamina propria [Sternini *et al.* 2004]. Opioids inhibit acetylcholine (ACh) release through μ -opioid receptors on cholinergic ascending excitatory neurons; this results in inhibition of contraction. μ -Opioid receptors in the descending neurons inhibit release of vasoactive intestinal peptide (VIP) and nitric oxide (NO); this inhibits descending relaxation during peristalsis [Sternini, 2001].

Mechanisms of action of opioids leading to chronic OIC

Organ level effects of opioids

Chronic use of opioids induces cellular adaptations that result in constipation through actions on enteric neurons [Duraffourd *et al.* 2014]. Activation of the μ -opioid receptors in the enteric system diminishes gastric, biliary, pancreatic and intestinal secretions, increases absorption of water from bowel contents, decreases gastric motility and emptying, inhibits small and large intestinal propulsion, increases amplitude of nonpropulsive segmenting contractions, increases tone at sphincteric muscles such as the sphincter of Oddi and anal sphincter, and impairs reflex relaxation of anal sphincter tone with rectal distention [Pappagallo, 2001]. It is unclear whether the increased tone

from μ -opioid receptors demonstrated in animal and human studies [Musial *et al.* 1992; Sun *et al.* 1997] actually results in impairment of defecation or only serves as a mechanism to avoid fecal incontinence.

Cellular level effects of opioids

Opioids exert their action in the gastrointestinal tract by activating three G-protein coupled receptors: μ , κ and δ [Camilleri *et al.* 2014]; μ receptors in the gastrointestinal tract are located in mesenteric and submucosal neurons, as well as in lamina propria immune cells [Kurz and Sessler, 2003]. Opioids cause bowel dysfunction through their actions on these receptors in the ENS peripherally and by altering the autonomic flow to the gut through their central effects [Shook *et al.* 1987]. Activation of μ and δ receptors by opioids results in inhibition of production of secondary intracellular messengers [cyclic AMP (cAMP) and protein kinase A (PKA)], inhibition of Ca^{++} channels which results in decreased ACh release, and activation of K^{+} channels which results in hyperpolarization of the membrane. Activation of κ -opioid receptors also decreases ACh release (Figure 2) [Galligan and Akbarali, 2014].

Recent studies in rats showed that chronic opioid administration induced activation of mitogen activated protein kinase (MAPK) and extracellular signal receptor kinase (ERK) 1 or 2 through a pathway of μ -opioid receptor internalization that causes activation of cyclic adenosine monophosphate (cAMP) response element-binding protein phosphorylation (CREB). This pathway is associated with decreased gastrointestinal transit, increasing transit time and causing constipation. Blockage of the MAPK/ERK pathway reversed the delay in gastrointestinal transit induced by chronic morphine use [Duraffourd *et al.* 2014].

Differential tolerance of gastrointestinal organs to the effects of opioids

OIC develops with increased duration of opioid therapy; one study showed that 79% patients on long-term opioids reported OIC [Tuteja *et al.* 2010]. Morphine-induced contraction of the circular muscle is found least in the ileum. Nonpropulsive contractions gradually increase in the colon and are maintained in the rectum. This contributes to the development of OIC [Ling *et al.* 1989; Ono *et al.* 2014]. Thus, opioids have different actions in different segments of the

Figure 2. Intracellular signaling following activation of opioid receptors involves G proteins which result in activation of K⁺ channels, inhibition of Ca²⁺ channels, and inhibition of cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA). The results are generally membrane hyperpolarization or neurotransmitter release. Reproduced with permission from Galligan and Akbarali [2014].

gastrointestinal tract [Akbarali *et al.* 2014]. The persistence of constipation may cause some patients to withdraw the opioid treatment in spite of pain relief experienced on opioids and insufficient pain relief when the medication is withdrawn or the dose is reduced [Hjalte *et al.* 2010; Camilleri *et al.* 2014].

All opioids induce gastrointestinal adverse effects, except for constipation, and improve over time. This is called 'tolerance' [Ling *et al.* 1989]. Recent evidence provides a mechanistic explanation to the question: Why does constipation persist in the long term, whereas other adverse effects subside?

Tolerance to the effects of opioids, such as morphine, occurs in mouse ileum, but not in the colon [Ross *et al.* 2008].

Opioid tolerance develops through differential β -arrestin-2 dependent opioid receptor desensitization and internalization in the enteric neurons of the colon [Galligan and Akbarali, 2014], compared with the ileum. Thus, β -arrestin-2 down-regulation occurs in the ileum, causing tolerance [Kang *et al.* 2012] whereas, in the colon, there is preserved expression of β -arrestin-2, causing intracellular signaling to the endosome for receptor recycling [Galligan and Akbarali, 2014]. This results in persistent activation, without the emergence of tolerance [Akbarali *et al.* 2014].

Further pharmacological studies utilizing naloxonazine (NLXZ), an irreversible antagonist of the μ -opioid receptor, showed differences in the distribution patterns of the two receptor populations. Pretreatment with NLXZ reduced the antinociceptive effects of morphine administered intracerebroventricularly (i.c.v), but not intrathecally (i.t). This indicates that antinociceptive effects were mediated *via* the NLXZ sensitive μ -receptors at the supraspinal level [Akbarali *et al.* 2014]. Morphine, oxycodone and fentanyl reduced colonic transit through distinct NLXZ sensitive and insensitive receptors at the peripheral and central sites [Mori *et al.* 2013]. The differential tolerance of gastrointestinal organs to opioids is likely due to the existence of different splice variants of mu receptors in the ileum, colon and central nervous system (CNS) [Akbarali *et al.* 2014].

Advances in the appraisal and diagnosis of OIC

Definition and outcome measures of OIC

There is no current consensus definition for OIC. A consensus working definition for OIC was developed by a multidisciplinary group [Gaertner *et al.* 2015] after assessing clinical trials and Cochrane reviews. OIC was defined as a change, after initiating opioid therapy, from baseline bowel habits that were characterized by any of the following: reduced

frequency of spontaneous bowel movements; development or worsening of straining to pass bowel movements; a sense of incomplete rectal evacuation; or harder stool consistency.

In addition to standardizing definitions of OIC, future clinical trials will be enhanced by the development of endpoints for study. In an analysis of the categories of outcome measures for OIC trials in the literature, three general groups of outcomes were identified: first, objective measures such as stool frequency and Bristol Stool Form Scale (BSFS); second, patient reported outcome measures (PROM) such as the Bowel Function Index (BFI) or straining, and patient assessment of constipation symptoms (PAC-SYM); and third, patient reported global burden measures of OIC by PAC-quality of life (PAC-QOL) [Gaertner *et al.* 2015].

Further psychometric validation has been reported for some of these endpoints in OIC. A three-item, clinician administered, bowel function index, specific for OIC, has been validated, based on data from three multicenter, randomized, double-blind studies in patients with cancer and noncancer pain being treated with oral opioids or usual care. With this index, patients rate the following on a scale of 0 [worst] to 100 [best rating]: perception of ease of defecation; feeling of incomplete bowel evacuation; and personal judgment of constipation based on the previous 7 days [Rentz *et al.* 2009].

A more detailed series of endpoints were based on a bowel function diary to assess OIC. This diary approach was validated for both spontaneous bowel movements (SBMs) and complete SBMs (CSBMs). The validation occurred in a multicenter observational study of patients with chronic noncancer pain and included documentation of psychometric properties, intraclass correlation coefficient ≥ 0.71 for numbers of SBMs and CSBMs and other bowel function symptoms (except stool consistency), and evidence of responsiveness. The bowel function diary included:

- a. A four-item module (#1) in the form of a questionnaire about straining, ability to empty bowels completely, pain around the rectum, and stool shape and consistency that patients completed after recording each bowel movement and time of occurrence.
- b. A five-item module (#2) based on a questionnaire addressing inability to have a bowel movement, bloating, abdominal pain,

bothered by gas and lack of appetite. Patients completed the questionnaire each evening to capture symptoms experienced in the previous 24 hours.

- c. Documentation of constipation treatments used in the previous 24 hours to relieve constipation [Camilleri *et al.* 2011].

A screening tool has been developed to appraise stool symptoms in patients on opioids and has proved to be useful to facilitate a discussion on the topic of OIC between provider and patient. Stool symptoms assessed for their utility to screen for OIC were: incomplete bowel movements, bowel movements too hard, straining, and feeling of a need to pass a bowel movement with inability to do so. Results of this study showed the need for greater patient awareness and education regarding OIC and laxative use [Coyne *et al.* 2014a].

Differential diagnosis of OIC

Comorbid conditions that may be responsible for or may exacerbate the constipation in patients receiving opioids should be sought when evaluating patients, as they represent opportunities to enhance patient care. These include: a prior diagnosis of chronic idiopathic (functional) constipation; the presence of obstructing colon cancer or neurological disorders (e.g. Parkinson's disease, diabetes); and use of constipating medications (e.g., tricyclic antidepressants, 5-HT₃ antagonists or iron).

In all patients, it is relevant to exclude a rectal evacuation disorder (e.g. dyssynergic defecation or large rectocele) by careful rectal examination [Lembo and Camilleri, 2003].

It remains challenging to determine whether constipation in the setting of opioid use is caused exclusively by the opioid (i.e. OIC) or reflects a combination of OIC and other constipating factors. In general, management is enhanced by addressing all possible factors contributing to the development of constipation.

Current treatment approaches to chronic OIC

Typical algorithms for the management of chronic OIC start with nonpharmacological measures such as increase in dietary fiber, fluid intake and physical activity. This is followed by pharmacological approaches with laxatives including stimulant, stool softeners, bulk forming laxatives or use of enemas (Tables 1 and 2). The final step is to

Table 1. Clinical trials of drugs approved for OIC.

Drug	Study type	Study length (weeks)	Study cohort	Study endpoints	Specific outcomes	Reference
Lubiprostone	1. RCT	12	439	>3 or more SBM/week for at least 9 weeks	26.9% versus 18.6% with $p < 0.005$	Jamal <i>et al.</i> [2012]
	2. RCT	12	418	Δ from baseline in SBM # at week 8 and overall	At 8 weeks, SBMs/week mean 3.3 versus 2.4 (placebo), $p = 0.005$; overall mean, 2.2 versus 1.6 (placebo) SBMs/week, $p = 0.004$	Cryer <i>et al.</i> [2014]
Oxycodone and naloxone (OXY PR)	1. RCT extended to open label for 52 weeks	12	278	a. Change in BFI at week 4 compared with baseline	40.9 BFI score at week 4 and 34.01 at week 12 compared with a baseline of 67.4	Lowenstein <i>et al.</i> [2009]
				b. CSBM	51% achieved CSBM in OXY PR compared with 26% in only oxycodone group at 4 weeks	
Methyl-naltrexone (MNTX)	2. RCT	12	35	Change in BFI at week 12 compared with baseline	BFI score at week 12 40.0 compared with baseline of 61.3 ($p < 0.0002$)	Koopmans <i>et al.</i> [2014]
	1. RCT	4	460	Rescue free BM (RFBM) within 4 hours of first dose	34.2% had RFBM with MNTX compared with 9.9% (placebo)	Michna <i>et al.</i> [2011]
	2. RCT	4	460	Time to BM within first 24 hours	46% had RFBM within 24 hours with MNTX compared with 25.3% (placebo)	Iyer <i>et al.</i> [2011]
				PAC-SYM: Rectal symptoms Stool symptoms	At 4 weeks, MNTX compared with placebo: -0.56 versus -0.30 ($p < 0.05$) -0.76 versus -0.43 ($p < 0.001$)	

(Continued)

Table 1. (Continued)

Drug	Study type	Study length (weeks)	Study cohort	Study endpoints	Specific outcomes	Reference
Naloxegol	1. RCT	4	207	Median Δ from baseline in SBM/week after 4 weeks	25 mg naloxegol [3.0 <i>versus</i> 0.8 (placebo); $p = 0.0022$] 50 mg naloxegol [3.5 <i>versus</i> 1.0 (placebo); $p < 0.0001$]	Webster <i>et al.</i> [2013]
	2. RCT (two studies: 04 and 05)	12	641	≥ 3 SBM/week and increase of ≥ 1 SBM compared with baseline for ≥ 9 of 12 weeks	Response rates higher with 25 mg of naloxegol: study 04: 44.4% <i>versus</i> . 29.4% (placebo), $p = 0.001$ study 05: 39.7% <i>versus</i> . 29.3% (placebo), $p = 0.02$	Chey <i>et al.</i> [2014]
			696	Δ Severity of straining Δ Stool consistency	study 04: -0.73 ± 0.05 ; study 05: -0.80 ± 0.06 study 04: 0.66 ± 0.07 ; study 05: 0.71 ± 0.07	
BFI, Bowel Function Index; BM, bowel movement; CSBM, complete spontaneous bowel movement; PAC-SYM, patient assessment of constipation symptoms; RCT, randomized controlled trial; SBM, spontaneous bowel movement.						

Table 2. Approved drugs for OIC: mechanisms of action, dosage, adverse effects and caveats/precautions.

Drug	Mechanisms of action	Dosage approved	Adverse effects	Caveats/precautions in patients with
Lubiprostone	Induces secretion of Cl through CIC2 and CFTR	24 µg twice daily orally	Nausea, diarrhea, and abdominal distension	Mechanical gastrointestinal obstruction Severe diarrhea Moderate and severe hepatic impairment Nausea is reduced by concomitant administration of drug with food.
Naloxone and oxycodone	Naloxone displaces oxycodone from µ-opioid receptors in the GI tract and make oxycodone available for analgesic action	Maximum strength is oxycodone 40 mg/ naloxone 20 mg orally	Nausea, vomiting, headache and diarrhea	Moderate to severe hepatic impairment Significant respiratory depression Acute or severe bronchial asthma Known or suspected paralytic ileus and GI obstruction Interactions with CNS depressants Patients with head injury or increased intracranial pressure
Methylnaltrexone	PAMORA	0.15 mg/kg subcutaneously (dose varies with weight)	Abdominal pain, nausea, diarrhea and hyperhidrosis	Patients with known or suspected mechanical gastrointestinal obstruction Severe or persistent diarrhea occurs during treatment
Naloxegol	PAMORA	12.5 or 25 mg once per day orally	Diarrhea, abdominal pain, flatulence and vomiting	Patients at increased risk of GI perforation Caution in patients with cancer related pain

CIC2, chloride type 2 channel; CFTR, cystic fibrosis transmembrane regulator; CNS, central nervous system; GI, gastrointestinal tract; OIC, opioid induced constipation; PAMORA, peripherally active µ-opioid receptor antagonists.

introduce opioid antagonists such as methylnaltrexone or fixed dose combinations of oxycodone/naloxone, or a secretagogue such as lubiprostone which is approved in the US for pain severe enough to require long-term opioid treatment [Kumar *et al.* 2013].

Limitations of current treatments for OIC

There are no published guidelines for the prophylaxis or management of OIC in patients with non-cancer chronic pain. Laxatives are typically the first line of choice because they are inexpensive and available as over-the-counter preparations. First-line laxatives have limited efficacy in OIC unless the patient was constipated before the initiation of opioid treatment. A community-based survey of patients with chronic pain who were taking laxatives before initiating treatment with oral opioids showed that 70% reported a baseline frequency, prior to starting opioids, of ≥ 3 bowel movements per week. After initiating oral opioid

therapy, the proportion with ≥ 3 bowel movements per week fell to 55%, with 81% reporting constipation as an opioid induced side effect [Bell *et al.* 2009].

A study of laxatives used for OIC in noncancer patients revealed 64% used at least 1 laxative and 36% reported no laxative use. In addition, 94% had inadequate response to OIC when 1 laxative was used within the prior 2 weeks. Inadequate response to OIC decreased to 27% when ≥ 2 laxatives of different classes were used more than 4 times within the prior 2 weeks [Coyne *et al.* 2014b]. A commonly used regimen for OIC combines stimulant (e.g. senna alkaloid or bisacodyl) laxatives with stool softeners (e.g., docusate) or osmotic laxatives [e.g. polyethylene glycol (PEG) or magnesium salts]. The only randomized, controlled trial conducted with laxatives involved PEG, which resulted in more nonhard stools in patients with methadone-induced constipation compared with placebo [Freedman *et al.* 1997].

Table 3. Drugs in development for OIC.

Drug	Mechanism of action	Current status	Clinical/pharmacodynamic efficacy	Adverse effects (AEs)
Alvimopan	PAMORA	Ongoing phase III studies in OIC. Approved to accelerate the time to upper to lower GI recovery after partial large or small bowel resection with primary anastomosis.	0.5 mg twice daily increased ≥ 3 SBMs per week over treatment period of 12 weeks (72% versus 48%, $p < 0.001$)	Significant AEs cardiovascular events, myocardial infarction, angina, and arrhythmia. GI related AE: abdominal pain and diarrhea
Prucalopride	Full agonist of 5-HT ₄ receptors	Ongoing phase II studies. Approved for chronic constipation 1–2 mg every day but not approved for OIC.	Increased from baseline of ≥ 1 CSBM per week during the treatment period of 1–4 weeks with efficacy of 35.9% and 40.3% in 2 mg and 4 mg prucalopride groups, respectively, compared with 23.4% with placebo.	Abdominal pain, headache, diarrhea, nausea, vomiting.
TD-1211	PAMORA	Ongoing phase II studies in OIC patients	TD-1211 (5 and 10 mg/day) increased average SBMs per week over a period of 2 weeks in OIC patients	Abdominal pain, diarrhea, nausea, vomiting.

CSBM, complete spontaneous bowel movement; GI, gastrointestinal tract; OIC, opioid induced constipation; PAMORA, peripherally active μ -opioid receptor antagonists; SBM, spontaneous bowel movement.

Bulk laxatives are generally ineffective in OIC [Kumar *et al.* 2013].

Novel approaches to treatment of OIC

In this section, a brief discussion is provided on the mechanism of action, current application and evidence of efficacy of each of the classes of novel treatments.

Lubiprostone: secretagogue chloride channel activator

Mechanism of action. Lubiprostone induces Cl⁻ secretion through chloride type 2 channels (ClC2) at the intestinal apical epithelial membrane into intestinal lumen and cystic fibrosis transmembrane regulator (CFTR). This increases transport of fluid into the intestine, counteracting the antisecretory effects of opioids in the intestine [Cuppoletti *et al.* 2014].

Current application and evidence of efficacy. Lubiprostone significantly improved OIC in patients with chronic noncancer pain, with an approximate number needed to treat (NNT) of 6. Patients with OIC resulting from methadone treatment were excluded because methadone inhibits lubiprostone stimulated Cl⁻ secretion in

enterocyte preparations *in vitro* [Cuppoletti *et al.* 2013]. Efficacy was demonstrated compared with placebo among the approximately 66% of patients who completed the study for several endpoints, including time to first SBM within 24 and 48 hours of starting treatment, overall mean change in the SBM frequency from baseline [Cryer *et al.* 2014], overall constipation severity, stool consistency, abdominal discomfort and straining. Nausea, diarrhea and abdominal distension were the most common adverse effects and 4.6% discontinued lubiprostone treatment due to adverse events [Jamal *et al.* 2012]. Lubiprostone, 24 μ g twice daily (b.i.d.), recently received US Food and Drug Administration (FDA) approval for OIC in patients with noncancer pain (see http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021908s011lbl.pdf).

Opioid receptor antagonists

Mechanisms of action. Opioid receptor antagonists block, at peripheral receptors, the actions of the opioids that mediate decreased intestinal secretion and inhibit propulsive colonic motility.

Current application and evidence of efficacy. The applications, actions and adverse events differ between opioid receptor antagonists that cross the

blood–brain barrier and those that are restricted to the peripheral compartment.

Centrally active opioid receptor antagonists. Opioid receptor antagonists that cross the blood–brain barrier (e.g. naloxone and nalbuphine) may alleviate OIC; however, their CNS effects may antagonize the analgesic effects of the opioid and can cause opioid withdrawal symptoms.

Naloxone, a predominantly μ -opioid receptor antagonist. Naloxone blocks opioid receptors at the intestinal level. It has low systemic bioavailability (2%) due to marked hepatic first-pass effect. In patients with chronic pain, oral naloxone improved symptoms of laxation [Meissner *et al.* 2000]. Despite the low bioavailability, naloxone crosses the blood–brain barrier. Naloxone therapy should, therefore, be started at a low dose in order to minimize the risk of inducing opioid ‘withdrawal’ symptoms such as yawning, sweating and shivering, or decreasing the level of analgesia. These adverse effects result from central blocking of the effects of the μ -opioid receptor agonist. The therapeutic index of naloxone is very narrow and doses that reverse gut symptoms can often cause reversal of analgesia [Sykes, 1991; Yuan and Foss, 2000; Liu and Wittbrodt, 2001].

A combination of naloxone and oxycodone prolonged release is used to treat OIC. After absorption in the gastrointestinal tract, naloxone, which has high affinity (though relatively nonselectively) to the opioid receptors in the gastrointestinal tract, displaces oxycodone from binding to the opioid receptors, making it available for transport to the brain to exert the central analgesic effects. Since naloxone is extensively metabolized by the liver, only negligible amounts enter the systemic circulation [Burness, 2014]. When oxycodone and naloxone are used in combination at a ratio of 2:1, there is significantly enhanced bowel function in patients with OIC [Lowenstein *et al.* 2009; Koopmans *et al.* 2014]. The combination therapy of prolonged release oxycodone with naloxone in patients with chronic nonmalignant pain was shown to result in noninferiority compared with oxycodone alone for mean pain intensity scale [Vondrackova *et al.* 2008]. Meanwhile, bowel function index scores and laxative intake were lower for the combination therapy, and adverse effects and treatment satisfaction questionnaires were similar between the groups [Lowenstein *et al.* 2010]. The combination therapy proved to be safe and efficacious on long-term treatment

[Sandner-Kiesling *et al.* 2010]. The fixed dose ratio of 2:1 of oxycodone hydrochloride and naloxone hydrochloride extended release tablets was efficacious to treat severe pain in those who required long-term opioid treatment and who received inadequate benefit with alternative treatment options [Koopmans *et al.* 2014]. The FDA approved combination therapy at maximum strengths of oxycodone, 40 mg, and naloxone, 20 mg, orally (see http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/2057771bl.pdf).

Peripherally active μ -opioid receptor antagonists (PAMORA). PAMORA block μ -opioid receptors in the gut. This specificity should confer a clinical advantage, with restored function of the ENS activating propulsive motility and secretory functions by local enteric neural circuits in response to physiologic stimuli such as meal ingestion or sensation of a bolus to evoke normal peristalsis. Thus, PAMORA should specifically treat the cause of constipation in OIC. Two PAMORA are currently available for the treatment of OIC in chronic nonmalignant pain: subcutaneous methylnaltrexone and oral naloxegol.

Methylnaltrexone. Methylnaltrexone is a quaternary *N*-methylated derivative of naltrexone. It acts peripherally in the μ -opioid, G protein-coupled receptors, antagonizing opioid-induced effects in the gastrointestinal tract. The *N*-methyl group in methylnaltrexone is highly ionized, thereby increasing the polarity, decreasing the lipid solubility, and preventing the compound from crossing the blood–brain barrier [Russell *et al.* 1982]. The selectively peripheral μ -opioid receptor antagonism is used for treating OIC without affecting the analgesic potential of the opioids [Yuan, 1996]. Oral methylnaltrexone delayed a morphine-induced increase in oral caecal transit time [Yuan, 1996; Michna *et al.* 2011].

A randomized, controlled trial of subcutaneous methylnaltrexone, 12 mg every day (QD) for OIC in nonmalignant pain showed an increase in the mean change in the number of rescue-free bowel movements (RFBMs) relative to baseline. Thus, 34.5% of the patients had RFBMs within 4 hours of the first dose of methylnaltrexone [Michna *et al.* 2011]. Further studies showed significant improvements in the degree of straining, complete sense of evacuation, and use of rescue laxatives [Iyer *et al.* 2011; Michna *et al.* 2011]. The NNT was 4 with methylnaltrexone QD [Michna *et al.* 2011]. Importantly, quality of life was

improved and pain intensity scores failed to increase on methylnaltrexone, despite the benefit shown by the increase in RFBMs.

Adverse effects were minimal, even after doubling the therapeutic dosage of methylnaltrexone. Using the Subjective Opioid Withdrawal Scale (SOWS) and the Objective Opioid Withdrawal Scale (OOWS), there were no withdrawal symptoms after the discontinuation of methylnaltrexone [Michna *et al.* 2011].

Methylnaltrexone (at a dose of 0.15 mg/kg subcutaneously) had been previously approved by the FDA for patients in palliative care suffering from OIC who had insufficient response to laxative therapy. Recently, the FDA approved methylnaltrexone bromide, 12 mg subcutaneous injection, for the treatment of OIC in patients taking opioids for chronic, non-cancer pain (see <http://news.salix.com/press-release/fda-approves-relistor-subcutaneous-injection-treatment-opioid-induced-constipation>).

Naloxegol. Naloxegol is an oral PEGylated derivative of naloxone. Naloxegol significantly reduced morphine-induced prolongation of oral caecal transit time by 61% relative to baseline, based on lactulose–hydrogen breath test [Neumann *et al.* 2007].

Naloxegol is a substrate of P-glycoprotein (PGP) [Faassen, 2003] transporter which enhances efflux of naloxegol and serves to decrease entry into the CNS through the blood–brain barrier [Webster *et al.* 2014; Neumann *et al.* 2007]. PEGylation alters the functional and structural functions of naloxegol, reducing immunogenicity and clearance. This leads to increased bioavailability, improved drug solubility, decreased toxicity and altered biodistribution [Roberts *et al.* 2002]. Morphine-induced miosis was used to evaluate the permeability of naloxegol across the blood–brain barrier. Results showed that 47 out of 48 participants had no change in morphine-induced pupillary constriction with naloxegol [Neumann *et al.* 2007]. In addition, most patients evaluated in the two phase III naloxegol randomized, controlled trials had no change from their baseline scores on the modified Himmelsbach opioid-withdrawal scale that appraises central withdrawal effects such as yawning, lacrimation, rhinorrhea, perspiration, tremor, piloerection, anorexia, restlessness or emesis [Webster *et al.* 2013; Cheyr *et al.* 2014]. Together, these two features are

consistent with peripheral restriction of the actions of naloxegol.

Two randomized, controlled trials of naloxegol (compared with placebo) showed overall significant differences in the numbers of SBMs per week compared with baseline, in both the intent to treat population and in those who had inadequate response to laxatives [Chey *et al.* 2014]. The number of SBMs increased throughout the treatment period with naloxegol [Chey *et al.* 2014; Webster *et al.* 2014]. Significant improvements were also observed in stool consistency, severity of straining, and increase in the number of CSBMs with naloxegol [Chey *et al.* 2014].

Long-term efficacy and tolerability of naloxegol in patients with noncancer pain and OIC revealed that naloxegol, 25 mg/day up to 52 weeks, was generally safe and well tolerated [Webster *et al.* 2014]. Other beneficial effects were the absence of changes in the pain scores, opioid requirements and withdrawal scores with long-term treatment of naloxegol, as well as improvements in PAC-SYM and PAC-QOL mean scores [Webster *et al.* 2013].

Adverse effects were mainly gastrointestinal manifestations such as diarrhea, abdominal pain, and vomiting, in order of occurrence. Significant adverse events did not occur during any of the randomized, controlled trials [Chey *et al.* 2014].

Recently, the FDA approved naloxegol, 12.5 or 25 mg QD orally, for OIC in adults with chronic noncancer pain [Leonard and Baker, 2015]. The FDA is requiring postmarketing surveillance to evaluate the risk for cardiovascular adverse events in patients receiving naloxegol (see <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm414620.htm>).

Drugs in development and future targets (Table 3)

Alvimopan is a PAMORA that relieves OIC without compromising analgesia. A randomized, placebo-controlled, phase III clinical trial performed in 518 noncancer patients with OIC for 12 weeks showed an increase in CSBM per week from baseline, with efficacy of 40.3% for alvimopan compared with placebo. Alvimopan is not approved by the FDA due to serious cardiovascular adverse effects [Jansen *et al.* 2011].

Prucalopride is a 5-HT₄ agonist that causes release of 5-hydroxytryptamine (5-HT) from the enterchromaffin cells in the gastrointestinal tract. This activates intrinsic primary afferent neurons, releasing ACh and calcitonin gene related peptide (CGRP), and resulting in ascending excitation that causes contraction and descending inhibition that causes relaxation [De Maeyer *et al.* 2008]. Results of a randomized, placebo-controlled, phase II trial of prucalopride (2 mg and 4 mg) in patients with OIC with noncancer pain showed an increase of ≥ 1 CSBM per week from baseline at weeks 1–4. Patients on prucalopride had ≥ 3 SBM per week compared with placebo. Prucalopride is not yet approved for this indication [Sloots *et al.* 2010].

TD-1211 is a PAMORA which prevents OIC without any change in analgesic effects of the opioid analgesics. A phase IIb study of TD-1211 (10 mg and 15 mg) showed increased numbers of CSBMs and SBMs during the 5-week treatment period [Vickery *et al.* 2013]. TD-1211 dose dependently accelerated time to first SBM [Vickery *et al.* 2011]. Treatment related gastrointestinal adverse effects were mild and resolved within a few days of starting treatment. There were no treatment related serious adverse effects.

Naldemedine (S-297995) is a PAMORA which is currently investigated for OIC. A phase II randomized controlled trial (RCT) was studied with naldemedine for 4 weeks for the treatment of OIC in subjects with noncancer pain. Phase III studies are being conducted for the efficacy and safety of naldemedine for OIC [ClinicalTrials.gov identifier: NCT 01443403, NCT 01993940].

Linaclotide, a guanylate cyclase C (GC-C) agonist, was found to increase fluid secretion through activation of CFTR channel which causes secretion of chloride and bicarbonate into the lumen [Bryant *et al.* 2010]. It has been already approved for the treatment of chronic constipation and irritable bowel syndrome with constipation (IBS-C). Currently a phase II RCT, double-blind, placebo-controlled trial is being conducted in patients on chronic opioid treatment for noncancer pain who suffer from OIC [ClinicalTrials.gov identifier: NCT 02270983].

Conclusion

The prevailing trend of prescribing opioids long term for nonmalignant pain has increased

enormously in the US and has resulted in increased numbers of overdose deaths and side effects of opioids. Chronic OIC is becoming a commonly encountered adverse effect in clinical practice, since tolerance does not develop with long-term administration of opioids and OIC appears to be increasingly unresponsive to treatment with laxatives. Since there is no consensus treatment protocol for OIC in patients with non-malignant pain and there is lack of awareness among physicians, there is typically a treatment delay for OIC patients. The recently approved PAMORA, naloxegol and methylnaltrexone, show promising results for treatment of OIC in a nonmalignant pain setting by selectively antagonizing the opioid-induced gastrointestinal side effects without compromising the effect on analgesia. Further progress in the prevention of OIC will be achieved by efficient control of the opioids prescribed long term, by interval monitoring of patients by the prescribing physicians, and by use of laxatives or PAMORA to treat OIC.

Conflict of interest statement

M.C. has performed consulting with AstraZeneca regarding naloxegol for the treatment of opioid induced constipation. A.D. declares no conflicts of interest in preparing this article.

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