CME

Opioid-Induced Constipation: Challenges and Therapeutic Opportunities

REVIEW

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There has been an alarming increase in the prescription of opiates and opioids for chronic non-cancer pain in the past 15 years. It is estimated that opiate-induced constipation (OIC) is experienced by ~40% of these patients, and that constipation and other gastrointestinal symptoms may dissuade patients from using the required analgesic dose to achieve effective pain relief. Opiates have several effects on gastrointestinal functions, and the inhibition of colonic transit and intestinal and colonic secretion results in constipation. Several different pharmacological approaches are being developed to prevent or treat OIC: prolonged release formulations that contain naloxone (a less specific opiate antagonist that is widely distributed) and a new class of peripherally restricted μ-opiate receptor antagonists, including methylnaltrexone, alvimopan, tapentadol, NKTR-118, and TD-1211. Novel patient response outcomes have been developed to facilitate demonstration of efficacy and safety of drugs in development for OIC.

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INTRODUCTION

There has been an alarming increase in the prescription and chronic use of opiates and opioids for chronic non-cancer pain in the past 15 years. The objectives of this narrative review are to summarize essential aspects of the epidemiology of opiate-induced constipation (OIC), summarize the effects of opiates on gastrointestinal functions that lead to constipation, evaluate pharmacological approaches to treat or prevent OIC (**Table 1**), and describe patient response outcome instruments being developed for use in drug trials to relieve OIC. The main consideration was to provide practical information for clinicians managing OIC, and to introduce them to novel agents that are in development for this condition.

A search was conducted using the PUBMED electronic database (1966 to November 2010) using the following keywords and different combinations: epidemiology, prevalence, opioids, opiates, opioid receptors, morphine, motility, secretion, gut, bowel, bowel dysfunction, constipation, and in addition hand searching the references of the individual papers retrieved. For NKTR-118 and TD-1211, a search was conducted in the public domain (using Google) for those specific drugs; data presented in abstracts at national meetings were appraised.

OPIOID USE AND EPIDEMIOLOGY OF CHRONIC OIC

The prevalence of chronic pain in the adult population ranges from 2 to 40%, with a median point prevalence of 15% (1–3). Chronic use of opioids for months or years for non-cancer pain is commonly encountered in clinical practice. Opioid analgesia treatment for severe pain is predictably efficacious and improves level of function (4,5). Prescription opiate use has increased sharply in many parts of the United States in the last decade (6–8), as it is a clinical imperative to inquire about and manage pain reported by patients. Increase in therapeutic opioid use in the United States is well documented (9), based on data from US Drug Enforcement Administration ((10) **Figure 1**). The American Society of the Interventional Pain Physicians has issued guidelines for appropriate use of opioids (11). However, there is a "rising tide of deaths" from the "flood of opioid" use (12), with ~3% of adults in the United States currently receiving long-term opioid therapy for chronic non-cancer pain (13).

With the increased use of opioids, there are more patients presenting with OIC or opiate bowel dysfunction (OBD) (14,15). Constipation may be debilitating among those who require chronic analgesia (16); OIC or OBD affected an average of 41% patients taking an oral opioid for up to 8 weeks in a meta-analysis of 11 placebo-controlled, randomized studies in non-malignant pain (14). Patients may discontinue treatment due to constipation, despite their established need for long-term pain relief.

In a survey of patients taking opioid therapy for pain of non-cancer origin, who required laxative therapy, only 46% of opioid-treated patients reported achieving the desired treatment results >50% of the time, in contrast to the reported satisfaction in 84% of control subjects (17).

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Table 1. Summary of pharmacological approaches to treat opiate-induced constipation

Drug name	Drug class	Pharmacodynamic efficacy in humans	Clinical trial optimal efficacy and safety
Naloxone	Non-selective opioid antagonist	Reverses opiate-induced delay in orocecal and colonic transit	Naloxone PR formulation prevents OIC in patients receiving PR oxycodone
Methylnaltrexone	μ-Opioid antagonist	Reverses effects of opiate in health and of chronic methadone treatment on orocecal transit; no effect on small intestinal or colonic transit delayed by codeine 30 mg q.i.d. in opiate-naive healthy subjects	s.c. methylnaltrexone 0.15 mg/kg on alternate days effective in inducing laxation in patients with advanced illness
Alvimopan	PAMORA	8 mg Oral dose accelerates colonic transit and reverse effects of codeine in opiate-naïve healthy volunteers receiving codeine 30 mg q.i.d.	0.5 mg Alvimopan dose efficacious in treating OIC; rare instances of ischemic heart disease
Tapentadol	Narcotic analgesic plus norepinephrine reuptake inhibitor	ND	Tapentadol ER 100-250 mg b.i.d. equally effective for moderate to severe chronic osteoarthritis-related knee pain compared to oxycodone HCl (CR) 20–50 mg b.i.d. daily with less bowel dysfunction symptoms
NKTR-118	PAMORA; PEGylated naloxol conjugate	Normalized morphine-induced delay in orocecal transit	25 and 50 mg NKTR-118 had increased number of SBM during the first week and overall 4 weeks of treatment of OIC patients
TD-1211	PAMORA	ND	5 and 10 mg/day TD-1211 increased average SBM/week over 2 weeks in OIC patients

CR, controlled release; ER, extended release; ND, not done; OIC, opiate-induced constipation; PAMORA, peripherally-restricted μ-opioid receptor antagonist; PEG, polyethylene glycol; PR, prolonged release; SBM, spontaneous bowel movement; s.c., subcutaneous administration.

Among 100 ambulatory patients with moderate-to-severe chronic non-cancer pain, who returned a bowel disease survey and had taken opioids for a median of 1 year at a median daily dose of 127.5 mg morphine-equivalent units, prevalence of constipation was 46.9% and chronic abdominal pain 58.2%. Prevalence of constipation increased with duration of treatment. Health-related quality of life was low in patients with chronic abdominal pain (18).

In the United States and European survey of 322 patients taking daily oral opioids and laxatives, 45% of patients reported <3 bowel movements per week, 81% reported constipation, and 58% straining, symptoms were most often reported as severe, had at least a moderate negative impact on overall quality of life and activities of daily living, and a third of patients had missed, decreased, or stopped using opioids in order to make it easier to have a bowel movement (19).

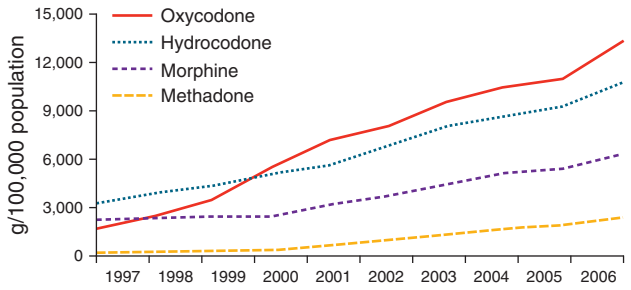

Figure 1. The increase in therapeutic opioid use in the United States (g/100,000 population) from 1997 to 2006. Reproduced from Manchikanti and Singh (9). On the basis of the data from US Drug Enforcement Administration (10).

μ-OPIATE RECEPTORS AND GASTROINTESTINAL FUNCTIONS

Three types of receptors for opioid peptides have been identified as having effects on human gastrointestinal function: δ-, κ-, and μ-receptors. They all belong to the family of G-protein-coupled receptors, and inhibit adenylate cyclase. At the membrane level, they reduce neuronal excitability and neurotransmitter (acetylcholine) release (20) with an overall inhibitory effect on the neuron.

Opioid receptors are widely distributed in the central and peripheral nervous system, the intestinal musculature, and other tissues. The high concentrations of opioid receptors in the dorsal horn of the spinal cord relay afferent nociceptive signals to the central nervous system (21), and those different areas of the brain are involved in pain transmission (22). In the gastrointestinal tract, μ-receptors are widely distributed in the submucosa (23), as well as in the ileal mucosa where they influence ion transport changes (24). Stomach and proximal colon have the most dense μ- and κ-opiate receptors (25).

EFFECTS OF OPIATES THAT RESULT IN CONSTIPATION

The cause of constipation in opiate users is multi-factorial (26). Opioids interfere with normal gastrointestinal motility by delaying transit, stimulating non-propulsive motility, segmentation and tone, and stimulation of sphincters such as the pylorus and ileocecal sphincter (26) through their effects on enteric neurons (27). Opioids stimulate the absorption of fluids, mainly by delayed transit increasing contact time for absorption, and by stimulating mucosal

sensory receptors that activate a reflex arc that facilitates further fluid absorption (28,29). These multiple effects lead to OIC.

THERAPEUTIC APPROACHES TO TREAT OIC

Avoid the OIC while relieving the pain with a novel opioid agent: tapentadol

Tapentadol HCI is a μ-opioid agonist that also inhibits norepinephrine reuptake (30). The latter function adds to the analgesic potential of the μ-opioid agonism, predominantly through stimulation of α2-adrenergic receptors (31); in human pharmacodynamic and clinical trials, norepinephrine reuptake inhibition (e.g., with venlafaxine (32)) and the α2-adrenergic agonist clonidine (33,34) are associated with reduced colonic or rectal sensation in response to distension, and provided satisfactory relief of symptoms in patients with irritable bowel syndrome with predominant diarrhea (35). It seems, therefore, that the combined mechanistic effects of tapentadol on pain sensation can be achieved with a relatively lower level of μ-opioid agonism, which therefore reduces the gastrointestinal adverse effects such as constipation. As an analgesic, tapentadol has a more favorable gastrointestinal side-effect profile than the classic micro-opioid receptor agonist oxycodone (36). Although tapentadol's analgesic efficacy in acute postsurgical dental pain is inferior to ibuprofen, 400 mg (37), treatment with tapentadol extended release, 100–250 mg twice daily (b.i.d.), or oxycodone HCl controlled release, 20–50 mg b.i.d., were both effective for the management of moderate-to-severe chronic osteoarthritis-related knee pain. However, there were substantially lower incidences of gastrointestinal-related adverse effects with tapentadol extended release than with oxycodone controlled release (38). Similarly, tapentadol extended release, 100–250 mg b.i.d., effectively relieved moderate-to-severe chronic low back pain over 15 weeks with a better gastrointestinal tolerability than oxycodone HCl controlled release, 20–50 mg b.i.d. (39). Studies of the pharmacodynamic effects of tapentadol on gastric emptying and colonic transit would be of significant interest.

Reversing OIC with μ-opioid receptor antagonists

The main challenge in reversing the gastrointestinal adverse effects of opioid with a μ-opiate receptor antagonist is that the dose efficaciousness in reversing OIC may inhibit central actions of opioids, causing either opiate withdrawal symptoms or reversal of desirable analgesia. The following is a summary of μ-opiate receptor antagonist approaches being developed.

Naloxone. Naloxone is a competitive antagonist at opioid receptors with much greater affinity for μ- than for κ- or δ-receptors. Naloxone blocks opioid intestinal receptors and has low systemic bioavailability (2%) due to a marked hepatic first-pass effect. Naloxone reversed the delays in orocecal transit induced by loperamide and in colonic transit caused by morphine (40,41). In patients with chronic pain, oral naloxone improved symptoms of laxation (42). However, despite the low systemic bioavailability, naloxone in its original formulation is widely distributed throughout the body. Thus, naloxone therapy is started at a low dose to minimize the risk of inducing opioid withdrawal symptoms, such as yawning, sweating, and shivering, as the drug crosses the blood–brain barrier.

The therapeutic index of naloxone is very narrow, and doses that reverse gut symptoms can often cause reversal of analgesia (43). However, there has been a resurgence of interest in naloxone in a prolonged-release preparation, which shows evidence of analgesic efficacy and safety when used in combination with oxycodone (prolonged release) for moderate-to-severe chronic pain (44) and improved bowel function when compared with oral oxycodone (prolonged release) alone (45). This efficacy continues for up to 52 weeks in patients with non-cancer chronic pain (46).

Naltrexone extended release. An open-label study assessed 12-month safety of a combination of extended-release pellets of morphine sulfate with a sequestered naltrexone core (administered once or twice daily) in patients with chronic, moderate-to-severe pain. The pain-relieving objectives of treatment were achieved using dosages of the combination that could be adjusted in accordance with the investigator's best medical judgment. The median average daily dose of morphine over the course of study in the safety population was 58.6 mg (interquartile range 39.2, 98.0 mg), and the median duration of exposure was 135 days.

Of 465 patients receiving one or more doses, 160 completed the 12-month study: 30% of the discontinuations occurred in the first month, most often because of adverse events (23.7%), with nausea the reason for withdrawal in 5.4%, constipation in 3.4%, and vomiting in 2.6%. Most of the 465 patients (81.3%) experienced one or more adverse events, most commonly constipation (31.8%) or nausea (25.2%). Opiate withdrawal symptoms were mild and affected < 5% of patients during each week of the study (47). Thus, the combination does not resolve OBD.

Peripherally restricted μ-opiate receptor antagonists.

Methylnaltrexone Methylnaltrexone is a quaternary ammonium derivative of naltrexone, an opioid antagonist similar to naloxone. It is less lipid soluble than naloxone and, thus, less likely to cross the blood–brain barrier (48). Methylnaltrexone blocks acute morphine-induced delay in orocecal transit time without affecting analgesia or causing central opiate withdrawal symptoms. Intravenous methylnaltrexone infusion reversed methadone-induced constipation, increasing stool frequency and decreasing orocecal transit times (49,50). Orally administered methylnaltrexone showed the same results (51); plasma drug levels were very low, suggesting a local site of action in the gut.

Methylnaltrexone, 0.45 mg/kg intravenously (i.v.), reversed the effects of 0.05 and 0.1 mg/kg morphine on orocecal transit in healthy volunteers (52). The effects of chronic methadone treatment were reversed in four participants receiving doses from 0.05 to 0.45 mg/kg i.v. (53). In a larger, dose-escalation study of chronic methadone users, methylnaltrexone accelerated orocecal transit time and induced laxation on 2 successive days at mean doses of 0.09 and 0.1 mg/kg, i.v. (50). A dose of 3.2 mg/kg of enteric-coated methylnaltrexone prevented the morphine-induced change in oral-cecal transit time in healthy volunteers (54).

Methylnaltrexone (at a dose of 0.15 mg/kg subcutaneously (s.c.), every other day for 2 weeks) was tested for OIC in advanced illness in 133 patients who had received opioids for 2 or more weeks and had received stable doses of opioids and laxatives for 3 or more days without relief of OIC (55). Methylnaltrexone was superior to placebo on the primary outcomes of laxation (defecation) within 4 h after the first dose and laxation within 4 h after two or more of the first 4 doses. There was continued benefit over a 3-month open-label extension trial. These effects were achieved with no reduction in analgesic effect. Methylnaltrexone s.c. has been approved by the US Food and Drug Administration, Health Canada and the European Medicines Agency (56). The approved indication is OIC in patients with advanced illness receiving palliative care after failing laxative therapy, and the usual dosing schedule is 1 dose every other day, as needed, but no more frequently than 1 dose in a 24-h period. The recommended dose of methylnaltrexone is 8 mg for patients weighing 38–62 kg or 12 mg for patients weighing 62–114 kg. Patients whose weight falls outside of these ranges should be dosed at 0.15 mg/kg (57).

In opiate-naive healthy volunteers who were exposed to short-term treatment with codeine, methylnaltrexone (s.c. 0.30 mg/kg) did not reverse the effects of codeine on small intestinal or colonic transit (58). Further studies are needed to identify the optimal dosage of methylnaltrexone in treating OIC associated with acute opioid use in opioid-naive patients, as in primary care or in patients following trauma or surgery.

Alvimopan Alvimopan is an orally administered, peripherally acting μ-opioid receptor antagonist that does not cross the blood–brain barrier at clinically relevant dosages (59) and does not reverse analgesia or cause opioid withdrawal symptoms. The pharmacology of alvimopan is reviewed elsewhere (60). Alvimopan is indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis; it is available only for short-term (15 doses) use in hospitalized patients, and it can only be prescribed in hospitals that have registered in and met all of the requirements for the ENTEREG Access Support and Education program (61). The approved dosage is 12 mg administered 30 min to 5 h before surgery, followed by 12 mg b.i.d. for up to 7 days for a maximum of 15 doses. Thus, it is not approved for treatment of OIC. However, there is already significant literature about its potential in OIC associated with chronic opioid therapy.

In a 3-week study in patients with opioid bowel dysfunction and non-cancer pain, alvimopan restored bowel movements without compromising analgesia (62).

In a study of 522 subjects reporting <3 spontaneous bowel movements (SBMs) per week and requiring ≥30 mg oral morphine-equivalent unit/day, participants were randomized to alvimopan, 0.5 mg b.i.d., 1 mg once daily, 1 mg b.i.d., or placebo for 6 weeks (63). There was a significant increase in mean SBM/week over the initial 3 weeks of treatment with all 3 doses of alvimopan tested, as well as improvements in straining, stool consistency, incomplete evacuation, abdominal bloating/discomfort, and decreased appetite, which were sustained over 6 weeks. The most frequent adverse events were abdominal pain, nausea, and diarrhea, occurring more frequently in the higher dosage groups. The alvimopan 0.5 mg b.i.d. dose demonstrated the best benefit-to-risk profile for managing OBD, with a side-effect profile similar to that of placebo (63). There was no evidence of opioid analgesia antagonism.

Pharmacodynamic studies show that the efficacious dose in opiate-naive patients is probably 10-fold higher (64) than the dose effective in the treatment of OIC associated with longer-term opiate exposure.

NKTR-118 NKTR-118 is an oral PEGylated naloxol conjugate; pharmacokinetic studies in humans support once daily administration. NKTR-118 blocks peripheral μ-opioid receptors in the gut. PEGylation of naloxone alters its distribution, reducing central nervous system penetration and metabolism (reduced first-pass effect) while retaining its opioid antagonist properties peripherally (65).

NKTR-118 administered in solution or tablet formulation is rapidly absorbed in humans independent of administered dose (66). In human pharmacodynamic studies, NKTR-118 normalized morphine-induced delay in orocecal transit (67), while central effects were maintained with uninhibited pupillary onstriction.

In a phase 2, placebo-controlled clinical trial of NKTR-118 in OIC patients (<3 SBM/week, on a stable opioid dose of 30–1,000 morphine-equivalent unit/day for ≥2 weeks), 208 patients were randomized into three sequential cohorts of 5, 25, or 50 mg for 4 consecutive weeks after a 1-week placebo run-in phase. Patients receiving 25 mg or 50 mg (but not 5 mg) NKTR-118 had significantly increased (over baseline) number of SBM during the first week of treatment (primary end point) and over the 28-day treatment period, compared with placebo. There was no evidence of opioid withdrawal, reversal of analgesia, or increase in opioid use at any dose tested. Most frequent side effects were abdominal cramping, diarrhea, nausea, and vomiting, which were more frequent in the 50 mg cohort.

TD-1211 TD-1211 is an orally administered, peripherally selective, multivalent inhibitor of the μ-opioid receptor (http://files.shareholder.com/downloads/THERA/1065777793x0x411486/56fc683c-c436-4a24-85de-08622a292435/THRX_1021.pdf). It has high affinity for human μ- and δ-receptors, and guinea-pig μ-opioid receptors, with >6,000-fold selectivity for the μ-opioid receptor over non-opioid receptors, ligand-gated ion channels, enzymes, ion channels (including hERG), and transporters. It inhibits loperamide-induced reduction in gastric emptying and attenuation of castor oil-induced diarrhea following acute oral dosing to conscious rats.

In dogs, oral pretreatment with TD-1211 (3 mg/kg) reduced the loperamide (0.1 mg/kg i.v.)-induced non-productive contractile activity of the gastrointestinal tract measured by chronically implanted strain gauges. In addition, dogs dosed with TD-1211 (3 mg/kg) showed no effect on morphine (1 mg/kg i.v.)-induced sedation or anti-nociception.

Repeat doses of 20 mg of TD-1211 did not interfere with morphine's effect on pupil diameter, consistent with peripherally selectivity.

In a placebo-controlled, double-blind, phase 2, dose-escalation study at two United States sites involving 70 patients (on chronic

opioid therapy for non-cancer pain, with 5 SBM during 2-week baseline and at least one additional symptom of constipation), the 5 and 10 mg once per day TD-1211 demonstrated significant increase in average SBM per week, and shortened median time to first SBM (mean 28.7 h for placebo, 8.6 h for 5 mg, and 3.6 h for 10 mg) of TD-1211. The most common drug adverse events, abdominal pain, nausea, vomiting, and headache, were generally mild to moderate, and the majority resolved within a few days.

Reports of systematic reviews of peripherally restricted μ-opioid receptor antagonists. The efficacy and safety of μ-opioid antagonists in the treatment of OBD have been appraised with meta-analysis (68) in 22 articles providing data on 2,352 opioid antagonist-treated patients: alvimopan (8 studies), methylnaltrexone (6 studies), naloxone (7 studies), and nalbuphine (1 study). Three studies were excluded from the meta-analysis because of insufficient data or inability to combine the outcome end point with other studies. Methylnaltrexone and alvimopan were reported to be efficacious in reversing opioid-induced increased gastrointestinal transit time (assessed in 10 studies) and constipation (assessed in 4 studies). In fact, the efficacy for gastrointestinal transit is based on five trials with methylnaltrexone and one with alvimopan in the meta-analysis that assessed the ability of the μ-opioid antagonists to reverse orocecal transit delay induced by morphine in healthy volunteers (five trials) or chronic methadone treatment in patients (one trial). Of the four studies included for assessment of efficacy in constipation, there were one each with alvimopan and methylnaltrexone and two with naloxone treatment. The duration of treatment in different trials was 2, 21, and 35 days, and end points were quite variable and included immediate laxation on day 1, laxation or bowel frequency, and bowel movement dissatisfaction. The incidence of adverse events was similar to placebo and generally reported as mild to moderate. In summary, a forest plot was provided for only orocecal transit, and the evidence of efficacy of this class of compounds was relatively weak, despite the overall assessment with the meta-analysis.

In a separate systematic review, 20 studies identified were 13 randomized controlled trials and 7 phase-2 studies assessing toxicity (predominantly in healthy volunteers or members of methadone programs and in 2 randomized controlled trials in hospice patients). After excluding five trials for small sample size (<12 participants in each) or nonrandomized, single-blind design, there were nine studies of methylnaltrexone (five in healthy participants, four in patients) and six studies with alvimopan (two in healthy participants, four in patients). There was only one study with methylnaltrexone and three or four studies with alvimopan, each involving >100 patients. A forest plot was not provided. These authors concluded that the data showed proof of concept, but not definitive effectiveness of methylnaltrexone and alvimopan in managing opiate-related constipation (69).

Treat the OIC with a colonic prokinetic 5-HT_4 receptor agonist, prucalopride

Prucalopride is a new, selective 5-HT_4 agonist with efficacy in relief of chronic constipation and safety from a cardiovascular perspective. In a phase 2, double-blind, placebo-controlled study of 196 patients with OIC randomized to placebo, prucalopride 2 or 4 mg for 4 weeks, more patients had an increase from baseline of ≥1 spontaneous complete bowel movements (SCBM) per week (weeks 1–4, primary end point) in the prucalopride groups (35.9% (2 mg) and 40.3% (4 mg)) vs. placebo (23.4%), reaching statistical significance in week 1. Prucalopride, 4 mg, significantly improved patient-rated severity of constipation and effectiveness of treatment vs. placebo, and improved Patient Assessment of Constipation–Symptom (PAC-SYM) total scores and Patient Assessment of Constipation-Quality of Life (PAC-QOL) total and satisfaction subscale scores. The most common adverse events were abdominal pain and nausea. There were no clinically relevant differences in vital signs, laboratory measures, or electrocardiogram parameters.

Treat the OIC with a secretagogue, lubiprostone

Lubiprostone is a chloride channel activator that induces intestinal secretion.

In vitro, morphine inhibits chloride secretion by suppression of excitability of cholinergic secretomotor neurons in the enteric nervous system, and lubiprostone stimulates chloride secretion that was suppressed by morphine. Electrical field stimulation of submucosal neurons evokes biphasic increases in chloride secretion; morphine abolished the first phase and marginally suppressed the second phase, and lubiprostone reversed these actions of morphine.

In vivo, s.c. lubiprostone increased fecal wet weight and numbers of pellets expelled in guinea-pig and mouse (70). Morphine significantly reduced fecal wet weight and number of pellets. Injection of lubiprostone, 30 min after morphine, reversed morphine-induced suppression of fecal wet weight. The data suggest that lubiprostone, which does not directly affect enteric neurons, bypasses the neurogenic constipating effects of morphine by directly opening chloride channels in the mucosal epithelium (70).

A randomized placebo-controlled trial tested 24 μg b.i.d. lubiprostone in patients with OIC. Among the 167 patients who were able to tolerate the lubiprostone, the drug met the primary end point of increased SBM/week over baseline at week 8 of the 12-week study, as well as multiple secondary end points, including overall efficacy over 12 weeks, constipation severity, and stool consistency (71).

VALIDATED PATIENT RESPONSE OUTCOMES FOR ASSESSMENT OF TREATMENTS OF OIC

An essential element of drug development is the use of a patient response outcome that is validated in the specific context of use and in the target population. To date, the effects of classical μ-opioids and newer analgesic agents on gastrointestinal tolerability have been based on adverse event reporting and by the worse severity scores observed in the PAC-SYM among patients who experienced constipation (39,72). The performance of the PAC-SYM instrument in these patients suggests its potential use for OIC research (73), and it has been reported to parallel treatment response with prucalopride in OIC (74). There are two instruments that have been studied specifically in patients with OIC.

Bowel function index

The bowel function index is a clinician-administered, patient-reported, three-item questionnaire (ease of defecation, feeling of incomplete evacuation, and patient's personal judgment of constipation; each scored on a 0–100 scale) to evaluate OIC in cancer and non-cancer chronic pain patients (75). Unfortunately, there appeared to be no direct patient input using qualitative methods to ensure comprehensive coverage of the concept and no cognitive debriefing to ensure patient understanding; the recall period was 7 days rather than daily, and a daily diary apparently was not used. In addition, the inter-item correlations of the bowel function index items were high, suggesting that there is redundancy among the three items, so use of a total score may be misleading.

A new daily bowel function diary

The bowel function diary has been validated for use in characterizing and quantifying constipation symptoms related to opioid use, following guidance from the Food and Drugs Administration for patient response outcomes (PRO) instruments. The bowel function diary has the advantage that it supports the validity of composite PRO end points (SBM, SCBM) favored by regulatory authorities, as well as symptom severity items identified as relevant by patients. The number of SBM was shown to be a valid and stable (intraclass correlation coefficient (ICC) > 0.70) end point for differentiating patients with constipation from those without constipation during treatment with an opioid. In addition, among patients who reported constipation, the number of SBM discriminates between those who reported varying degrees of symptom severity (76).

CONCLUSIONS

Although there are recommendations for treatment (15), there continues to be unmet clinical need in the management of patients with OIC, an increasingly relevant problem with the extensive use of opioids for the relief of chronic pain, often associated with benign conditions. Several novel pharmacological approaches are being developed, including assessment of promotility and secretagogue agents that have efficacy in chronic idiopathic constipation. Other approaches are directed at the reversal of peripheral opiate effects in the gut while maintaining the desired analgesic efficacy. Although s.c. methylnaltrexone is already approved for induction of laxation in advanced illness, several new approaches are promising, including tapentadol, combination of opioids with prolonged release naloxone, NKTR-118, and TD-1211. The validation of a bowel function diary specifically in patients with OIC using Food and Drugs Administration guidance will enhance drug development in this field. An evidence-based management approach for OIC will be more feasible after the new generation of drugs is formally and thoroughly studied in large, high-quality clinical trials. Clinicians are invited to stay tuned, as the field is promising with a broad spectrum of new drugs and advances in clinical trial methods that will permit more reliable conclusions of efficacy and safety and, ultimately, effectiveness in treatment of OIC.

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CONFLICT OF INTEREST

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