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Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation

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Abstract

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CONFLICTS OF INTEREST

MC has served as an advisory board member and a consultant for AstraZeneca and Theravance, and as an adjudication committee member for AstraZeneca. MC's institution has received fees for his participation as an editorial board member for AstraZeneca and as a consultant for Theravance.

DAD has served as an advisory board member for Ironwood Pharmaceuticals, Lexicon Pharmaceuticals, and Synergy Pharmaceuticals; a consultant for AstraZeneca, Ironwood Pharmaceuticals, Ono Pharmaceuticals, and Takeda; has received grant support from AstraZeneca and Ironwood Pharmaceuticals; and currently is President of the Rome Foundation.

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LRW has served as an advisory board member for AcelRx Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Collegium Pharmaceuticals, Inspirin Therapeutics, Insys Therapeutics, Iroko Pharmaceuticals, Mallinckrodt Pharmaceuticals, Nektar Therapeutics, Orexo Pharmaceuticals, Pfizer (formerly King), Salix Pharmaceuticals, and Teva; as a consultant for Acura Pharmaceuticals, AstraZeneca, Biodelivery Sciences International, Boston Scientific, CVS Caremark, Jazz Pharmaceuticals, Mallinckrodt Pharmaceuticals, Medtronic, Nektar Therapeutics, Neura Therapeutik, Nevro Corporation, Pharmacofore, Quintiles, Shionogi, and Theravance; and has received travel support from AcelRx Pharmaceuticals, Acura Pharmaceuticals, AstraZeneca, Biodelivery Sciences International, Boehringer Ingelheim, Boston Scientific, Collegium Pharmaceuticals, Inspirin Therapeutics, Insys Therapeutics, Iroko Pharmaceuticals, Mallinckrodt Pharmaceuticals, Medtronic, Nektar Therapeutics, Nevro Corporation, Orexo Pharmaceuticals, QRx Pharma, Teva, and Theravance.

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Background—Opioids are effective for acute and chronic pain conditions, but their use is associated with often difficult-to-manage constipation and other gastrointestinal (GI) effects due to effects on peripheral μ -opioid receptors in the gut. The mechanism of opioid-induced constipation (OIC) differs from that of functional constipation (FC), and OIC may not respond as well to most first-line treatments for FC. The impact of OIC on quality of life (QoL) induces some patients to decrease or stop their opioid therapy to relieve or avoid constipation.

Purpose—At a roundtable meeting on OIC, a working group developed a consensus definition for OIC diagnosis across disciplines and reviewed current OIC treatments and the potential of treatments in development. By consensus, OIC is defined as follows: ‘A change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency’. The working group noted the prior validation of a patient response outcome and end point for clinical trials and recommended future efforts to create treatment guidelines and QoL measures specific for OIC. Details from the working group’s discussion and consensus recommendations for patient care and research are presented in this article.

Keywords

μ -opioid receptor; opioid-induced constipation; pain; palliative care; quality of life

Approximately 90% of patients who experience moderate to severe chronic pain are treated with opioids.¹ This large population, which is estimated at about 5% of adults in the United States,² includes patients with a wide variety of pain conditions, such as pain from degenerative joint diseases (including back and knee pain), other musculoskeletal pain, and neuropathic pain, collectively referred to as chronic non-cancer pain. Patients with chronic cancer pain are also treated with opioids, which are an essential component of palliative care. Moreover, opioids are also commonly used to treat acute pain syndromes that result from sprains and strains, fractures, dental procedures, and surgery, and they are sometimes used to treat migraine headaches.³

The use of opioid analgesics requires careful selection and monitoring of patients to achieve an optimal balance between the benefits and risks of these agents.^{4–8} Apart from the well-known inhibitory effects of opioids on gastrointestinal (GI) function (see below), a variety of other physiologic alterations are associated with their use. These effects include sedation,⁴ hormonal^{4,6} and cognitive^{4,5} changes, pruritus,⁴ sweating,⁶ bladder dysfunction,⁶ respiratory depression,⁶ opioid-induced hyperalgesia,⁹ narcotic bowel syndrome (NBS),⁹ and myoclonus.⁴ The potential also exists for opioid dependence, abuse, addiction, and overdose.^{4–6} Despite these limitations, opioid analgesics remain a viable treatment option for patients with chronic pain,⁴ where efficacy has been established^{7,8} and therapy can be individualized for each patient from the variety of medications and formulations that are available.^{7,8}

Opioids are effective for alleviating pain via their actions at opioid receptors in the central nervous system (CNS) and the peripheral nervous system¹⁰; however, a small proportion (about 5%) of patients treated with high or prolonged doses may paradoxically develop

central hyperalgesia called NBS.^{9,11} In addition, opioid actions on μ -receptors throughout the GI tract often lead to impairment of motility and secretion and a variety of symptoms, including nausea, gastroparesis, secondary pseudo-obstruction, and constipation, which are called opioid bowel dysfunction (OBD). The focus of this article addresses the most prevalent of these conditions: opioid-induced constipation (OIC).

In January 2013, a working group of US and international basic science and clinical experts in pain medicine, palliative care, gastroenterology, and gut neurobiology conducted a roundtable meeting to discuss the definition, diagnosis, prophylaxis, and treatment of OIC as a first step toward addressing the current unmet needs in chronic OIC. This article summarizes the discussion and consensus reached at that meeting. The objectives of this article are to propose a consensus definition of OIC that can be used across disciplines for diagnosis, to raise awareness regarding the frequency and impact of OIC, to briefly review current treatments and drugs in development for OIC, and to outline the need for future efforts, including the creation of treatment guidelines and quality-of-life (QoL) measures specific for patients with OIC.

OPIOID RECEPTORS AND THE MECHANISM OF GASTROINTESTINAL DYSFUNCTION

There are three classes of opioid receptors involved in GI function: μ , κ , and δ . These receptors are also widely distributed in the CNS. The κ - and δ -receptors are expressed primarily in the stomach and proximal colon, whereas the μ -receptors are expressed widely throughout the GI tract. OIC develops predominantly as a result of activation of enteric μ -opioid receptors, which leads to a decrease in neurotransmitter release from enteric nerves. In contrast to opioid-associated nausea and vomiting, tolerance to OIC rarely develops¹²; for example, in a mouse motility model, tolerance to morphine was shown to develop in the ileum but not in the colon.¹³ Because of their ubiquitous distribution in the GI tract, μ -opioid receptors mediate numerous effects on gut functions when activated by exogenous opioids, and these effects can produce a variety of symptoms known as OBD.¹⁴ For example, activation of μ -opioid receptors causes esophageal non-peristaltic contractions,¹⁵ decreases gastric motility and emptying and increases pyloric sphincter tone; decreases GI, biliary, and pancreatic secretions; inhibits propulsion in the small and large intestines; increases the amplitude of non-propulsive segmental contractions in the small intestine; increases water absorption from bowel contents; increases anal sphincter tone; and constricts the sphincter of Oddi.¹⁴ Thus, activation of μ -opioid receptors in the targeted area can induce dysphagia, gastroparesis, ileus or secondary intestinal pseudo-obstruction, and OIC. This defined mechanism causes the constipation of OIC, in contrast to functional constipation, which involves multiple contributing factors.¹⁶ This article focuses specifically on OIC, as discussed below.

PREVALENCE AND IMPACT OF OIC IN CHRONIC OPIOID USERS

In a systematic review of eight placebo-controlled studies in patients with chronic non-cancer pain, 41% of patients receiving World Health Organization (WHO) step 3 opioids (fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone) reported

constipation compared to 11% of patients receiving placebo.¹⁷ Among the patients receiving opioids, constipation was the most commonly reported adverse effect.¹⁷ In patients with cancer pain, the prevalence of OIC, as indicated by the use of laxatives (a commonly used surrogate parameter), was reported to be ~94%.¹⁸ In a population-based survey, 57% of individuals with chronic non-cancer pain using opioids experienced constipation that those individuals associated with opioid treatment; moreover, 33% reported constipation as their most bothersome symptom.¹⁹

The occurrence of OIC may vary according to the opioid used. Results of a survey of ~1000 adults in the United States treated with a single opioid (codeine, hydrocodone, propoxyphene, morphine, oxycodone, or tramadol) indicated that morphine was most commonly associated with constipation (67%).¹⁹ A systematic review of the literature found that transdermal preparations were associated with less OIC than modified-release oral morphine and that transdermal fentanyl was preferred by patients.²⁰

Opioid-induced constipation compromises patient satisfaction with analgesic treatment. Pain symptoms increase when patients decrease or eliminate their opioid medication to relieve or avoid constipation, which also affects QoL. Thus, there was a significant difference in QoL between patients, depending on the degree of the 'problem with OIC'.²¹ In the Patient Reports of Opioid-related Bothersome Effects (PROBE) 1 survey conducted in patients with chronic pain in the United States and Europe, 33% of the 322 patients responded that they missed doses, decreased the dose, or stopped using their opioid medication to relieve bowel-related side effects; 92% of those patients subsequently experienced increased pain, and 86% of those experiencing increased pain reported that it moderately to greatly reduced their QoL and activities of daily living.^{22,23} Patients reported abdominal discomfort, nausea, gas, loss of appetite, heartburn and reflux, bloating, straining, hard bowel movements, and incomplete evacuation.²² Other consequences include fecal impaction with overflow diarrhea and stool incontinence.²³ These adverse effects limit opioid use.²² Despite such findings, QoL has not been studied extensively in patients with OIC, being limited to evaluations of constipation distress on a 5-point scale²⁴ and to use of the Patient Assessment of Constipation-Quality of Life (PAC-QOL) questionnaire,²⁵ which was not developed for OIC; no OIC-specific QoL assessment tools are available.

DIAGNOSIS OF OIC

Current methods for diagnosing OIC include both objective and subjective criteria. The methods of OIC diagnosis vary among disciplines and demonstrate the need for a consensus definition. A summary of assessment tools and outcome measures identified in a systematic review of 47 clinical trials assessing OIC published in the past 20 years is presented in Table 1.²⁶ Of the 47 trials included, only 16 (34%) provided a definition. Those publications that provided a definition most frequently relied on (1) history of present or recent opioid therapy, (2) defecation frequency (most often: fewer than three spontaneous bowel movements per week), and (3) at least two of the following symptoms at least 25% of the time: straining, hard or lumpy stool, incomplete evacuation, and infrequent stools.²⁷

Unfortunately, criteria used in clinical trials exclude many individuals who are constipated,²⁸ and definitions used do not necessarily identify all patients who are experiencing constipation in a palliative care setting.²⁹ Patients who develop OIC often have subjective definitions of constipation based on their own experiences, emphasizing the need for a consensus definition for OIC based on frequency, difficulty with evacuation, consistency of bowel movements, and change from previous bowel habits (functions). Ultimately, formal psychometric validation of any consensus definition will also be necessary.

Barriers to the diagnosis and treatment of OIC

The working group identified barriers in clinical practice that hinder the diagnosis and treatment of OIC. First, there is a lack of awareness among clinicians of the adverse consequences of OIC. With the recommendation from authoritative bodies such as the Joint Commission and the Veterans Health Administration that pain assessment should be considered the fifth vital sign and the need for ‘around-the-clock’ pain relief, as well as adjunctive approaches to calm fears and anxiety, clinicians generally focus on the efficacy of pain relief provided by the opioid and/or the disease causing the pain.² Second, even though clinicians may be aware of the adverse effects of opioid use, they may not ask their patients whether they have developed constipation. Third, despite the negative impact of constipation, many patients may feel ashamed or uncomfortable initiating a discussion about their bowel habits with their healthcare provider. Fourth, there are no universal diagnostic criteria for OIC, and the symptoms are similar to other types of primary or secondary constipation. Furthermore, efforts to use standard criteria for functional constipation (e.g., Rome III) in clinical care or research may not capture the full spectrum of OIC, which occurs in a variety of clinical settings and is diagnosed by a variety of specialists in patients with or without a history of constipation. Fifth, because the mechanism of OIC is specifically due to opioid administration and differs from that of slow colonic transit constipation,^{16,30–32} there are specific treatments for OIC that may be more effective than standard treatments for chronic idiopathic constipation.²³ Finally, most of the currently available treatments specifically addressing the pharmacologic mechanisms inducing OIC, particularly naloxone, have limited efficacy, and agents that cross the blood-brain barrier interfere with opioid analgesia. Hence, the working group considered that the ultimate goal of OIC treatment is to alleviate the constipation while maintaining analgesia, which would require restriction of the μ -opioid receptor antagonist to the peripheral compartment without central action.

PROPOSED CONSENSUS ON SYMPTOMS OF OIC

Factors considered by the working group as content for developing a consensus definition of chronic OIC included the following: opioid treatment for more than 1 week, reduced bowel frequency to fewer than three spontaneous bowel movements per week, straining, sense of incomplete evacuation, and harder stool. However, patients may also experience acute OIC even after taking one dose of an opioid. In specialty practice, the definition of harder stool may be aided by use of a standard visual scale such as the Bristol Stool Form scale.³³

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Because OIC is defined by symptoms rather than by pathophysiologic features or biomarkers, it mimics many other medical conditions. Therefore, it is first important to exclude comorbid conditions that may be responsible for or that may exacerbate the constipation. Commonly encountered medical conditions include chronic idiopathic constipation (functional constipation), obstructing colon cancer, Parkinson's disease, diabetes, and constipating medications, such as antidepressants or iron supplements. Furthermore, it is also important to evaluate the patient for an underlying rectal evacuation disorder (e.g., dyssynergic defecation or large rectocele) that is aggravating the constipation. This is because ~15% of the general population without symptoms suggestive of colonic pain more than six times per year experience symptoms of excessive straining to evacuate or a sense of incomplete rectal evacuation.³⁴ In addition, the highly prevalent dyssynergic defecation among patients with chronic constipation³⁵ may be confused by patients and doctors as functional constipation. These comorbid disorders or underlying borderline disturbances of rectal emptying may be brought to clinical attention as a result of opioid use. Thus, the challenge to the clinician is to determine the degree to which 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 as above, or is due to causes other than OIC. It should be kept in mind that, on average, half of the patients given opioids will not develop OIC.³⁶

The working group definition of OIC considers the change in bowel habits from baseline (before opioid initiation), recorded over 7 days, as opposed to a specific number of bowel movements per week. Based on variations in bowel habits and defecation patterns and what individuals would consider abnormal, the following definition of OIC was proposed by the working group as a starting point, acknowledging the need for future psychometric validation:

A change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following:

- reduced bowel movement frequency
- development or worsening of straining to pass bowel movements
- a sense of incomplete rectal evacuation
- harder stool consistency

There are several operating factors that led to this definition:

1. the concept of a subjective change in bowel habit obviates the need for any quantitative standard (e.g., fewer than three bowel movements/week) because it reflects a true clinical situation
2. change from baseline takes into consideration that patients may have had pre-existing constipation or a prior normal bowel habit made worse by opioids and that patients have known variability in response to opioids based on genetic factors

3. it is applicable to patients seen in a variety of clinical settings: primary care, pain centers, or gastroenterology clinics
4. the absence of a required time frame allows for utilization of the definition even in patients who develop OIC after only one or a few doses of opioid
5. the simplicity of the items permits clinicians to use the definition as a screening measure in clinical practice.

In addition, it is also possible for the definition to be made more restrictive (e.g., requiring two or more items, quantifying stool frequency) for the purpose of developing inclusion criteria for subject selection in research. This definition permits the objective of appraising the ability of treatment to restore patients with OIC to what they believe is normal bowel function for them. Future studies are needed to validate these items and to develop criteria for research that reflect patient perceptions.

MECHANISMS OF ACTION AND LIMITATIONS OF CURRENT TREATMENTS FOR OIC

Laxatives

First-line treatment of OIC has involved the use of traditional stimulants and stool softeners.

Mechanisms of action—Predominant mechanisms of action are to soften the stool (detergents; e.g., docusate sodium; Colace[®], Purdue Pharma L.P., Stamford, CT, USA), retain water in the GI tract (osmotic agents; e.g., polyethylene glycol solution; MiraLAX[®], MSD Consumer Care, Inc., Memphis, TN, USA), increase GI contractility, and induce fluid secretion (stimulants; e.g., bisacodyl [Dulcolax[®], Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA], senna [Senokot[®], Purdue]).³⁷

Current application and evidence of efficacy—Guidelines from the European Association for Palliative Care (EAPC) recommend laxatives for the prophylaxis or management of OIC in patients with cancer.³⁸ There is no single laxative of choice. Laxatives have the advantage of being inexpensive; they are available in generic form or as over-the-counter preparations.

There are no randomized controlled trials to support the use of laxatives in the treatment of OIC; however, they are appropriately tried as first-line therapies in view of their safety and cost.

Thus, most have limited efficacy in OIC unless the patient was constipated before the initiation of opioid treatment.²³ In a general population survey of patients with chronic pain who were taking laxatives before initiating treatment with oral opioids, it was demonstrated that at baseline 70% reported having at least three bowel movements per week, and 20% reported having fewer than three bowel movements per week, with the remaining 10% not providing information. After initiating oral opioid therapy, 55% reported having at least three bowel movements per week, and 45% reported having less than three bowel movements per week; 81% reported constipation as an opioid-induced side effect.²²

Consequently, OIC is present even though patients are taking laxatives. Non-specific agents are effective in patients with OIC who had baseline constipation, and μ -opioid antagonists are not presently indicated for chronic constipation, even though there is evidence that a peripherally restricted μ -opioid receptor antagonist, alvimopan, is able to accelerate colonic transit in the absence of opioid treatment,³ reflecting the physiologic role of μ -opioid receptors, which may respond to endogenous ligands such as enkephalins or dynorphin. Concerns with longterm use of laxatives alone or in combination with stool softeners (e.g., Peri-Colace[®], Purdue [a mixture of senna and docusate sodium]) include electrolyte imbalances and a small risk of damage to the colonic myenteric plexus, as seen when anthraquinone laxatives (e.g., sennosides) were administered to mice,³⁹ although there were no abnormalities of GI neuropeptides in relation to mesenteric vessels or the plexuses in the cecum of rats in response to long-term senna administration.⁴⁰ A mixture of danthron and a poloxamer called Co-danthramer (a combination of a softener and a stimulant) is marketed only in the United Kingdom for patients with terminal illness because excess danthron administration is associated with liver tumors in rodents. In contrast to the lack of effects of senna, levels of neuropeptide Y in the mesenteric vessels are significantly reduced in the danthron-fed rats, with no effects on vasoactive intestinal peptide (VIP), substance P (SP), calcitonin gene-related peptide (CGRP), and catecholamine nerves.⁴⁰ When laxatives are ineffective, patients often undergo enemas, manual disimpaction, or use off-label preparations intended to cleanse the bowel before procedures such as barium enema x-ray examination and colonoscopy.

Chloride channel activator

Mechanisms of action—Lubiprostone (Amitiza[®], Takeda Pharmaceuticals America, Inc., Deerfield, IL, USA) is a specific activator of intestinal epithelial CIC-2 chloride channels that also induces chloride secretion through the cystic fibrosis transmembrane conductance regulator to increase the transport of fluid into the intestine. CIC-2 channel activation counteracts the antisecretory effects of opioids in the intestine.

Current application and evidence of efficacy—Originally indicated for the treatment of chronic idiopathic constipation, lubiprostone was also approved by the US Food and Drug Administration in April 2013 for the treatment of OIC in adults with chronic non-cancer pain.⁴¹ Lubiprostone significantly improved treatment response in non-methadone OIC in patients with chronic non-cancer pain, with an approximate number needed to treat of 6 and median time to first bowel movement of 24 h, which was ~12 h superior to placebo.⁴² Methadone-treated patients were excluded from the trial because methadone, but not morphine, inhibits lubiprostone-stimulated Cl⁻ secretion in enterocyte preparations *in vitro*.⁴³

Selective 5-HT₄ agonist prucalopride

Mechanisms of action—Prucalopride accelerates colonic transit and induces propagated contractions in the colon.²⁵

Current application and evidence of efficacy—One randomized controlled trial demonstrated the efficacy of prucalopride 2 mg orally in the treatment of OIC.²⁵

Prucalopride is approved in many countries (but not the United States) for the treatment of chronic idiopathic constipation but not for OIC.

By increasing the volume of luminal contents, all of the therapies described above probably work, at least in part, by stimulating GI propulsive motility and secretory functions. However, the activity of local enteric neuronal circuits is dramatically dampened downstream by the inhibitory actions of opioid therapy. Blocking the actions of opioids at peripheral opioid receptors would serve to restore the function of the enteric nervous system directly. As described below, this is the goal of the opioid receptor antagonists.

Opioid receptor antagonists

Mechanisms of action—Opioid receptor antagonists block opioid actions at peripheral opioid receptors that mediate decreased intestinal secretion and propulsive colonic motility.

Current application and evidence of efficacy

Centrally active agents: Opioid receptor antagonists that cross the blood-brain barrier act centrally and peripherally; although they may alleviate OIC, their CNS effects may antagonize the analgesic effects of the opioid.^{44,45} Examples are naloxone and nalbuphine. The CNS effects of these antagonists cause opioid withdrawal symptoms. A combination product, Targin[®]/ Targinact[®]/Targiniq[®] (Purdue; combination of an opioid antagonist [naloxone] and an opioid agonist [oxycodone]), is available in Europe and is approved for patients with severe pain. It is a fixed-dose combination, which may limit its usefulness. Its dosing is affected by the limited ability of the body to metabolize naloxone before it reaches the CNS.

Peripherally active agents: An agent that does not enter the CNS but blocks μ -opioid receptors in the gut would more specifically treat the constipation of OIC, providing a clinical advantage. By blocking μ -opioid receptors in the gut, there is restoration of the function of the enteric nervous system, and propulsive motility and secretory functions can be generated by local enteric neural circuits in response to physiologic stimuli such as meal ingestion, or sensation of a bolus to evoke normal peristalsis. Two peripherally acting μ -opioid receptor antagonists (PAMORAs) are currently available. Subcutaneous methylnaltrexone (Relistor[®], Salix Pharmaceuticals, Inc., Raleigh, NC, USA) is approved for OIC, but only for patients with advanced illness receiving palliative care who have had an inadequate response to laxative therapy.⁴⁶ The EAPC guidelines recommend subcutaneous methylnaltrexone as a secondline option for OIC in patients with chronic cancer pain when traditional laxatives are not effective.³⁸ Alvimopan (Entereg[®], Cubist Pharmaceuticals, Inc., Lexington, MA, USA), available in the United States but not in Europe, is a PAMORA indicated only for preventing or shortening the course of postoperative ileus after bowel resection and is therefore only for hospital use⁴⁷ and not approved for use in OIC.

DRUGS IN DEVELOPMENT FOR THE TREATMENT OF OIC

Several PAMORA agents with the potential not to compromise pain relief by opioids⁴⁸ are in development for OIC. An oral formulation of methylnaltrexone (Relistor[®]) is under

investigation, and the currently available subcutaneous formulation of methylnaltrexone is under consideration for OIC in patients with chronic non-cancer pain. There are four other drugs currently in phase 2b or 3 development for OIC in patients with chronic non-cancer pain: naloxegol (AstraZeneca), which is an oral PEGylated derivative of naloxone; bevenopran (Cubist Pharmaceuticals); TD-1211 (Theravance, South San Francisco, CA, USA); and naldemedine (S-297995; Shionogi, Osaka, Japan). Thus, it is anticipated that the number of treatments available for OIC should increase in the next few years.

ACUTE OIC

Opioid-induced constipation can also occur when opioids are used to treat acute pain.³ Patients with acute OIC have special requirements for treatment of their constipation. In a recent study, more than half of almost 8000 outpatients with cancer pain starting WHO step II or III pain medications were not prescribed laxatives.⁴⁹ There are no standard international guidelines for the treatment of patients with acute OIC, and the most common medications used appear to be docusate, senna alkaloids, bisacodyl, picosulfate, enemas, and in some cases, methylnaltrexone.^{50,51} In addition, doses of PAMORA agents required by opioid-naïve patients are very different from those of chronic opioid users. For example, alvimopan 12 mg was effective in reversing the acute effects of codeine in opioid-naïve healthy volunteers,⁵² whereas the dose tested in chronic OIC is 0.5 to 1 mg twice daily.⁵³ Similarly, methylnaltrexone used at FDA-approved doses in opioid-naïve healthy volunteers was ineffective at reversing the effects of codeine on the small bowel and colonic transit.⁵⁴ Thus, there is a need for a separate regulatory path and dosing for medications required for relief of OIC in patients with acute painful conditions who use opioids. It should also be kept in mind that patients with a baseline history of chronic constipation who develop OIC may not be sufficiently treated solely with a PAMORA.

PROPOSED FUTURE EFFORTS IN OIC

Prophylaxis

The working group agreed that providing OIC prophylaxis at the initiation of opioid analgesic therapy may be desirable, analogous to providing gastroprotection at the initiation of non-steroidal anti-inflammatory drug (NSAID) therapy. Results of a recent retrospective study of patients with cancer pain given laxative prophylaxis before initiation of oral opioid analgesics suggested that laxative premedication significantly reduced the incidence of constipation compared with no premedication.⁵⁵ Although laxatives are recommended as prophylaxis in adult patients with cancer pain by the National Comprehensive Cancer Network,⁵⁶ they have been shown to be suboptimal for prophylaxis in other groups of patients.²² Use of an agent that targets the μ -opioid receptor to block the effects of the μ -agonist could provide an opportunity to change the way OIC is prevented and treated. Appropriate use of agents for prophylaxis must be defined. Elderly patients,⁵⁷ who typically have comorbidities, are less physically active, and are taking other drugs, are particularly susceptible to constipation. Risk factors or positive predictors for the presence of OBD identified in an observational study of patients receiving opioids, NSAIDs, or other chronic pain therapies were female sex, age >70 years, cancer-related pain, and the use of fentanyl.⁵⁸ Follow-up is necessary so that the laxative agent prescribed can be adjusted if not effective.

Treatment guidelines and outcomes tools

Treatment guidelines that can be used across disciplines by a variety of physicians, including primary care physicians, pain specialists, palliative care specialists, and gastroenterologists, are needed. A validated outcomes tool for OIC must be used to determine whether particular treatments improve the symptoms of OIC. Thus far, there are two validated instruments:

1. A 3-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 non-cancer pain being treated with oral opioids or usual care. With this index, patients rate their perception of ease of defecation, feeling of incomplete bowel evacuation, and personal judgment of constipation based on the previous 7 days. Each item is rated on a scale of 0 to 100, with 0 being the worst rating and 100 being the best rating.⁵⁹
2. A bowel function diary to assess OIC was validated (including psychometric properties, intraclass correlation coefficient 0.71 for numbers of spontaneous bowel movements and complete spontaneous bowel movements and other bowel function symptoms except stool consistency, and evidence of responsiveness) in a multicenter observational study of patients with chronic non-cancer pain. It contained a 4-item module that patients completed after recording each bowel movement and time of occurrence, a 5-item module that patients completed each evening to capture symptoms they experienced in the previous 24 h, and a module in which the patient indicated any constipation treatments used in the previous 24 h to relieve constipation.⁶⁰

QoL measures

Assessments of QoL and clinically meaningful effect in patients with OIC are also needed. A systematic review of 47 studies revealed that most studies relied predominantly on 'objective' measures such as stool frequency to evaluate OIC therapy. Many studies aimed to capture the patients' experiences of OIC by also assessing patient-reported outcome measures. A minority of trials also assessed the global burden of OIC by measuring, for example, constipation distress (Table 1).²⁶ Validation of the QoL measures will require acquisition of firsthand patient experiences specifically with OIC. After disease-specific QoL measures are developed, their inclusion in clinical trials will be necessary to demonstrate responsiveness of QoL measures that are established to be relevant to patients with OIC.

SUMMARY/CONCLUSIONS

A large population of patients receives acute and chronic opioid treatment for moderate to severe pain. OIC is an underrecognized but common and debilitating adverse effect of opioid therapy. OIC is primarily the result of μ -opioid receptor stimulation in the GI system. Conventional treatments for functional constipation do not address the OIC-specific mechanism. To treat OIC effectively, specific blockade of μ -opioid receptor stimulation in the GI tract must be achieved without compromising CNS opioid receptor stimulation to

achieve desired analgesia. Indeed, the normalization of bowel function with a μ -opioid antagonist provides evidence that the cause of constipation was specifically OIC.

The proposed definition of OIC is intended to facilitate diagnosis, with the goal of establishing unified diagnostic criteria for this condition. Much work is needed in OIC to establish treatment guidelines and disease-specific efficacy and QoL outcome measures.

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Key Messages

- The development of a consensus definition of opioid-induced constipation (OIC) is necessary for its accurate diagnosis.
- A working group was established to evaluate the problem of OIC, assess current treatment approaches, and provide a consensus definition of OIC.
- The mechanism of action of OIC, its prevalence and symptomatology, the current treatment options, and the available assessment tools and outcome measures were examined.
- The working definition encompasses the key features of OIC in an attempt to standardize its diagnosis and provide the practitioner with guidelines for its detection.

Table 1Frequently used assessment tools and outcome measures for OIC²⁶

Category	Assessment tool/outcome measure
Objective measures *	Bowel movement frequency/change in bowel movement frequency Time to laxation Laxation within 4 h Gastrointestinal (or short bowel) transit time Bristol Stool Form scale
Patient-reported outcome measures †	Bowel Function Index Patient Assessment of Constipation – Symptoms Global Clinical Impression of Change
Patient-reported burden measures of OIC ‡	Constipation distress Patient Assessment of Constipation – Quality of Life

* Objective measures: Could theoretically be collected by an investigator as well as by the patient (eg, defecation frequency).

† Patient-reported outcome measures: ‘Reports coming directly from patients about how they feel or function in relation to a health condition and its therapy without interpretation by healthcare professionals or anyone else’.⁶¹

‡ Patient-reported burden measures of OIC: Patient-reported outcome measures that directly relate to the patient’s distress and the impact on their daily activities or QoL and are most obviously caused by OIC. OIC, opioid-induced constipation.