Opioid-Related Constipation

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KEYWORDS

• Constipation • Opioid • PAMORA • Pharmacotherapy

KEY POINTS

- Opioid-related constipation (ORC) refers to constipation that is caused or exacerbated by opioid therapy and should be differentiated from other forms of chronic constipation.
- Opioids affect not only intestinal transit but also pelvic floor function, which may be reflected by abnormal pelvic floor dynamic testing.
- Over-the-counter laxatives may be efficacious for opioid-induced constipation (OIC) and should be considered first-line agents. When these fail, peripherally acting μ-opioid receptor antagonists (PAMORAs) are suitable alternatives.
- More research is needed to determine the impact of secretagogues and prokinetics, which may be more efficacious for treating opioid-exacerbated constipation (OEC).

INTRODUCTION: THE SPECTRUM OF OPIOID-RELATED CONSTIPATION

Chronic idiopathic constipation (CIC), a term that frequently overlaps with functional constipation (FC), has been reported in approximately 12% and 7% of the international and US populations. In the United States, constipation accounts for almost 1 million physician visits per annum.[1,2] Multiple pathogenic mechanisms are responsible for constipation, with opioids a common precipitant. Opioids are currently prescribed to more than 1 in 5 adults with chronic noncancer pain (CNCP), and opioid-induced constipation (OIC) is considered a secondary and direct consequence of their use.[3]

Although not considered a distinct functional gastrointestinal disorder, OIC shares the same symptom profile as FC, including both subjective and objective symptoms such as straining, incomplete evacuation, reduced defecatory frequency, and hard stools.[4,5] OIC is thought to affect more than 40% of individuals prescribed opioids for CNCP with a number needed to harm (number of individuals who must be treated with an opioid before developing constipation) of approximately 3.3.[6–8] Many patients are willing to reduce, skip, or completely discontinue opioids, which in most instances results in inadequate pain relief.[9] This limitation indicates that improved treatment algorithms, based on new terminology that reflects nuances in clinical progression and likelihood of response to specific therapies, are needed to combat OIC without minimizing analgesia (**Table 1**).

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Table 1
Current definitions for OIC

Rome IV diagnostic criteria for OIC include new or worsening of *2* or more of the following after initiation of, changes, or increases in opioid therapy.[4] Loose stools rarely present without laxatives and:	Diagnostic criteria for OIC: Consensus Working Group Definition[5] "A change when initiating opioid therapy from baseline bowel habits that is, characterized by any of the following:"
<3 SBM per week	Reduction in BM frequency
Lumpy or hard stools (BSFS 1–2) >25% BM	Harder stool consistency (BSFS 1–2)
Straining >25% of BM	Worsening of straining
Sensation of incomplete evacuation >25% BM	Sensation of incomplete rectal evacuation
Sensation of blockage >25% BM	
Manual maneuvers (digital manipulation/ pelvic floor support) to assist >25% BM	

Abbreviations: BM, bowel movement; BSFS, bristol stool form scale; IBS, irritable bowel syndrome; SBM, spontaneous bowel movement.

Use of the term opioid-related constipation (ORC) provides the framework for a novel classification schema, which differentiates two subtypes of constipation associated with opioid use: OIC, constipation that specifically develops after the initiation of opioid therapy, and opioid-exacerbated constipation (OEC), worsening of pre-existing constipation symptoms due to opioids. In most instances, the two can be differentiated by an accurate history[6,7] (**Fig. 1**). This distinction may appear semantic but is important as up to 50% of patients taking opioids suffer from pre-existing constipation and may be more responsive to medications with proven efficacy against both the constipating effects of the opioids and other underlying pathogenic mechanisms.[10]

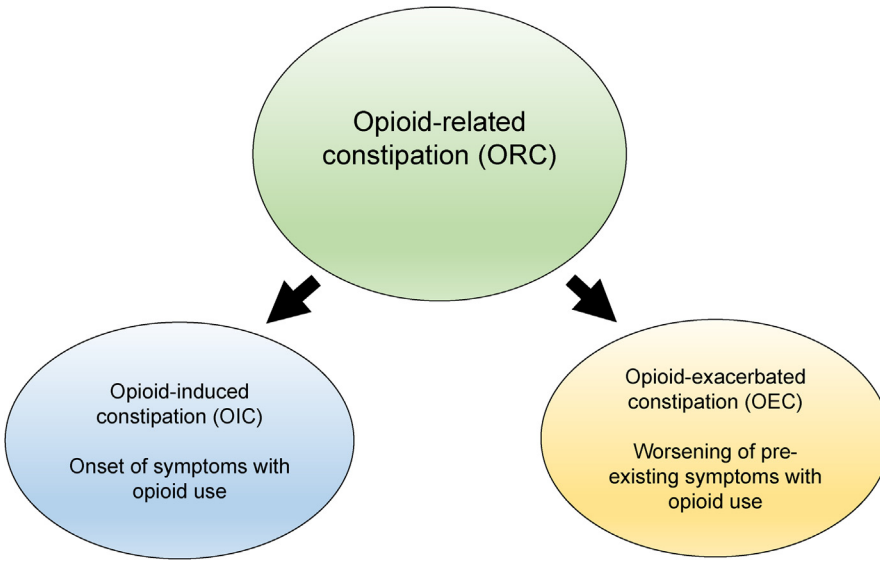


Fig. 1. Relationship between opioid-related constipation and onset of symptoms.

PATHOPHYSIOLOGY OF ORC

Opioids provide analgesia by binding to μ-opioid receptors in the central nervous system (CNS). However, these same receptors are also dispersed across the gastrointestinal mucosa with the highest concentrations identified in the stomach and colon. As opioids express no selective preference for μ-receptors in the CNS, they bind throughout the gastrointestinal tract, resulting in delayed gut transit, increased intestinal fluid reabsorption, and decreased fluid secretion.[11] Furthermore, in a retrospective study of 3452 laxative-refractory patients meeting Rome III criteria for FC undergoing pelvic floor physiologic testing at a tertiary center, patients receiving opioids had significantly higher resting anal sphincter tone, were more likely to have abnormal balloon expulsion tests (>1 minute), and met criteria for dyssynergic defecation more often than laxative-refractory individuals not consuming opioids. Rectal sensation was also significantly reduced in the cohort receiving opioids.[12] Opioids may mediate intestinal motility via alteration of the gut microbiome, although specific mechanisms have yet to be elucidated.[13] Thus, the pathogenesis of constipation in individuals consuming opioids is complex and likely multifactorial, and maximally effective treatment of ORC may require therapies directed at multiple targets.

TREATMENT OF ORC

ORC is frequently underidentified, leading to delays in treatment.[14] In a recent analysis of patient-opioid prescriber interactions, 64.4% of patients endorsed experiencing OIC, but 82.4% of prescribers failed to ask about symptoms and 33.8% did not receive a specific therapeutic recommendation.[15] In another survey of over 200 hospice agencies, 75% of agency primary contacts or hospice professionals reported that they had never used peripherally acting μ-opioid receptor antagonists (PAMORAs) to treat OIC.[16] Asking specifically about symptoms of constipation and previous laxative regimens may be revealing and indicate when treating OEC is more appropriate.[17]

First-line treatment of ORC is identical to FC. Based predominately upon anecdotal data, over-the-counter (OTC) fiber supplements, osmotic, and stimulant laxatives are safe, inexpensive, and effective in approximately 50% of cases. Should these initial interventions fail, 2 key questions must be answered: (1) when to switch to prescription therapy and (2) which therapeutic is most appropriate. Argoff and colleagues identified the Bowel Function Index (BFI) as the simplest and most accurate measure for identifying patients requiring treatment escalation, even when considering other patient-reported outcome measures such as the bowel function diary and the Patient Assessment of Constipation-Symptoms (PAC-SYM) questionnaire.[18] The BFI is a 3-item questionnaire validated to assess the severity of constipation-associated symptoms in individuals with OIC. The survey measures ease of defecation, sensation of incomplete evacuation, and an overall assessment of constipation-related symptoms over the course of the previous 7 days (**Fig. 2**). A BFI score of $\geq$ 30 has been recommended as the threshold for initiating prescription treatment in individuals with ORC nonresponsive to OTC agents. A score reduction of $\geq$ 12 points has been validated as clinically meaningful and shown to correlate patient preferences to individual therapies.[5,18,19]

In terms of choosing specific prescription therapy, the answer is predicated on the cause of the ORC. If the constipation is due to OIC, a PAMORA would be an appropriate next choice of therapy. However, if the symptoms are associated with OEC, a prescription laxative with evidence supporting its use across different constipation subtypes (ie, secretagogues, prokinetics) may prove more effective.

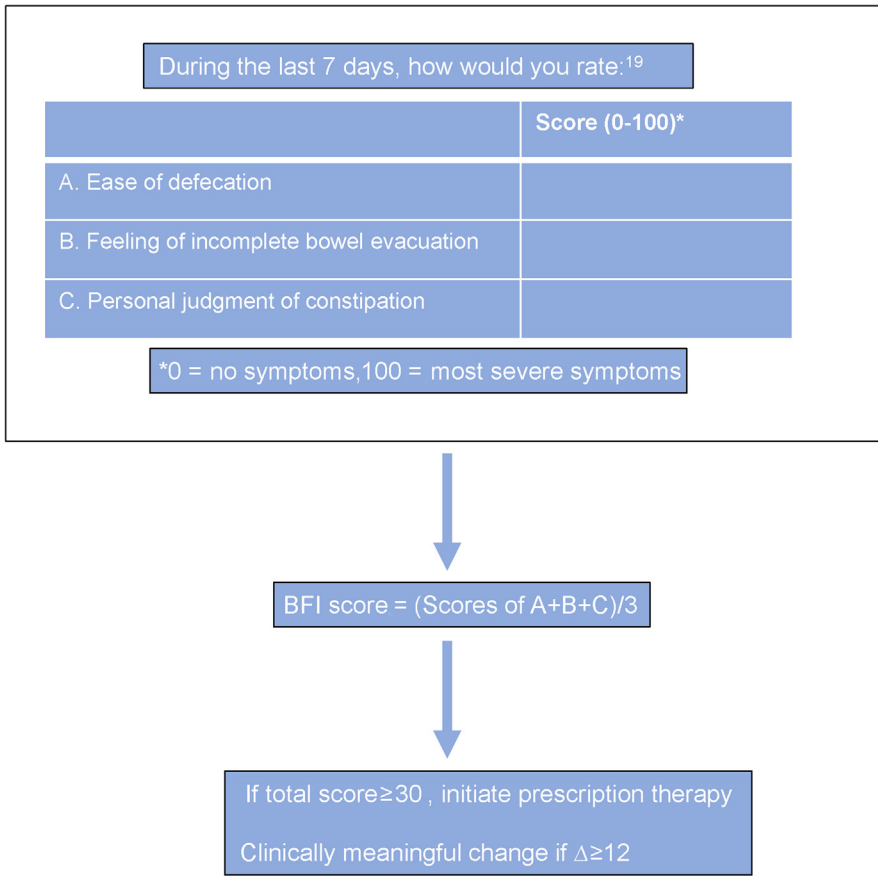


Fig. 2. The Bowel Function Index.

OTC TREATMENTS

Soluble fiber supplements (psyllium/ispaghula husk), osmotic (polyethylene glycol), and stimulant laxatives (senna, bisacodyl) are typically recommended as first-line treatments for ORC, but there is a paucity of high-quality studies supporting their use. Recently, the American Gastroenterological Association (AGA) published the first GI consensus guideline for the treatment of OIC, and strongly recommended OTC laxatives as first-line interventions, likely in part based on the fact that they are inexpensive and safe.[20–23] The most robust data supporting the use of OTCs stem from a randomized controlled crossover trial comparing the efficacy of polyethylene glycol (PEG 3350) to the PAMORA naloxegol.[24] In this study, equivalent numbers of patients endorsed subjective favorable preferences for one product over the other (P = .92) with most individuals noting a "strong" preference for their treatment of choice. This preference strongly correlated with a clinically meaningful response as identified via changes in BFI scores postintervention.

Unfortunately, for approximately 50% of individuals with OIC, OTC laxatives alone do not provide adequate relief.[25,26] For example, in a study of 322 patients taking daily opioids for cancer (4% of the study population) and non–cancer-related chronic pain, 81% reported continued constipation despite OTC laxative use and 58% reported

persistent straining with bowel movements.[9] In a multinational survey of over 400 patients over a 24-week period, 94% of individuals using one laxative agent and 27% of those using 2 or more agents reported inadequate response (<3 BMs with at least one PAC-SYM score that was at least moderate).[27] For these patients, other strategies may be required.

PERIPHERALLY ACTING μ-OPIOID RECEPTORS ANTAGONISTS

PAMORAs are an FDA-approved class of therapies developed to reverse the constipating effects of opioids with minimal likelihood of compromising central analgesia or inducing opioid withdrawal.[28] These drugs, all derivatives of naloxone and naltrexone, have biochemical properties limiting their ability to cross the blood-brain barrier. Currently, 3 PAMORAs are approved in the United States for the treatment of OIC: methylnaltrexone, naloxegol, and naldemedine[6] (**Table 2**).

METHYLNALTREXONE

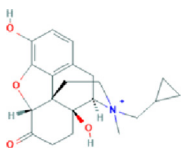
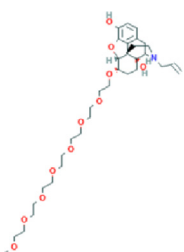
Methylnaltrexone (MNTX) was the first PAMORA to receive approval for the treatment of OIC, initially as a second-line agent for OIC in individuals with advanced illness receiving palliative care. It was subsequently approved for patients with CNCP and is the only PAMORA available in both subcutaneous (SC) and oral formulations. Its efficacy for treating OIC is supported by multiple randomized controlled trials (RCTs).

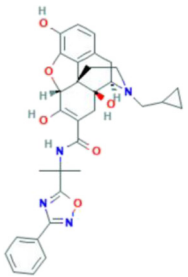
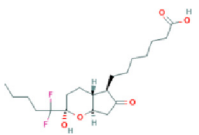
In a study enrolling 460 patients with nonmalignant pain-related OIC, individuals were randomized to receive SC injections of placebo or 12 mg of MNTX daily or every other day (alternating with placebo) for 4 weeks. Patients receiving daily and every other day injections of MNTX were significantly more likely to achieve a rescue-free bowel movement (RFBM) within 4 hours of receiving their initial injection compared with placebo (34.2% MNTX vs 9.9% placebo, $P<.001$). Furthermore, the percentage of injections resulting in RFBM in $\leq$4 hours was comparable between the MNTX groups (MNTX QOD 30.2%, MNTX QD 28.9%) but significantly greater than placebo (9%, $P<.001$ between groups).[29] A post-hoc analysis of 137 patients who initially received a 12 mg injection of MNTX daily revealed that patients who responded to at least 2 of the first 4 doses were more likely to experience a significant average increase in RFBMs (4.8 RFBM/wk) compared with those failing to achieve this endpoint (2.0 RFBM/wk; $P<.001$) Furthermore, the percentage of individuals achieving an average rate of $\geq$ 3 RFBMs was also significantly higher (81% vs 43%, $P<.001$). Thus, an initial response to treatment prognosticated better longer-term outcomes.[30]

In a later analysis, oral MTNX was also prospectively studied in 803 patients randomized to 150 mg, 300 mg, or 450 mg of MNTX QD or placebo.[31] An overall response was defined as $\geq$3 spontaneous bowel movements (SBMs) per week plus an increase of $\geq$1 SBM/wk from baseline for at least 3 of 4 weeks of the trial. A significantly higher percentage of individuals in the 300 and 450 mg cohorts achieved this endpoint compared with placebo (300 mg-49.3%, 450 mg-51.5%, placebo-38.3%; 300 mg vs placebo, $P<.03$; 450 mg vs placebo, $P = .005$). In addition, the proportion of dosing days resulting in an RFBM within 4 hours was significantly higher in patients receiving 300 mg (24.6%, $P = .002$) and 450 mg (27.4%, $P<.0001$) compared with placebo (18.2%).[31]

Both SC and oral MNTX were well-tolerated and serious adverse events were rare. In both studies, the most common treatment-emergent adverse events (TEAEs) occurring in individuals receiving MNTX included abdominal pain (19.3%), diarrhea (16.4%), and nausea (15.1%) in the SC and abdominal pain (8.0%), diarrhea (6.0%), and nausea

Table 2
FDA-approved treatments for OIC in patients with chronic noncancer pain with chemical structures

	Class (Biochemical Properties Preventing Transport Across Blood-Brain Barrier)	Class (Year of FDA Approval for OIC)	FDA-approved Dose and Route of Administration for OIC[a] CNCP	Primary Endpoint of Seminal Trials	Most Common TEAEs[c]	Clinical Considerations
Methylnaltrexone (MTNX)[54] 	PAMORA (Quaternary compound (N-methylation) derived from naltrexone, positive charge and low lipid solubility)	2014 (s.c.) 2016 (p.o.)	12 mg daily s.c. 450 mg daily p.o.	s.c: % injections resulting in RFBM in $\leq$4 h p.o.: $\geq$ 3 SBMs/wk plus an increase of $\geq$1 SBM 3/4 wk	Abdominal pain, nausea, diarrhea	Only PAMORA available in s.c. form and also approved for patients with cancer. Consider in inpatient use given studies' outcome of RFBM within 4 h[51]
Naloxegol[56] 	PAMORA (PEGylated derivative of naloxone, P-gp transporter substrate)	2014	25 mg daily p.o., on an empty stomach	12-wk response rate[b]	Diarrhea, abdominal pain, nausea	Can be crushed.[52] Weaker recommendation for patients using methadone.

Naldemedine[55] 	PAMORA (Large steric side chain on naltrexone increasing polarity and molecular weight, P-gp transporter substrate)	2017	0.2 mg daily p.o.	12-wk response rate[b]	Abdominal pain, nausea, diarrhea	Has a "Strong" recommendation with high quality of evidence from the AGA based on trial data
Lubiprostone[53] 	Chloride channel (ClC-2) agonist	2013	24 mcg twice daily p.o.	Δ Number of SBMs/wk from baseline at week 8[42] ≥3 SBM/wk for 9/12 wk + increase of 1 BM from baseline for all weeks[44]	Nausea, abdominal pain	Also approved for IBS and CIC, may be better for patients with worsening of pre-existing constipation. No risk of opioid withdrawal. Should not be given to patients using methadone.

[a] Dose adjustments recommended for hepatic and renal function, as well as patients taking CYP inhibitors.
[b] ≥ 3 SBMs/wk plus an increase of ≥ 1 SBM/wk from baseline for at least 9 of the 12 treatment weeks + 3 of last 4 weeks.
[c] No bowel perforations, serious cardiovascular events, or deaths in study drug groups.

(6.8%) in the oral MNTX cohorts, respectively.[32,33] There was no evidence of opioid withdrawal or major cardiovascular events.

NALOXEGOL

Naloxegol was the first oral PAMORA to receive FDA approval for treating OIC. This approval—for a daily dose of 25 mg—was based on 2 identical phase III studies (KODIAC-04 [N = 652], and KODIAC-05 [N = 700]) demonstrating sustained efficacy and safety over a 12-week period.[34] In these trials, durable responders were defined as having ≥3 SBMs/wk plus an increase of ≥1 SBM from baseline for ≥9 of 12 weeks inclusive of at least 3 of the final 4 weeks. Patients were randomized to receive 12.5 mg or 25 mg of naloxegol or placebo daily. In both studies, the response of patients receiving 25 mg daily was significant (KODIAC-04, 44.4% compared to 29.4% placebo [$P = .001$], KODIAC-05, 39.7% compared to 29.3% placebo [$P = .02$]). The response rates for the 12.5 mg cohorts were similar but not statistically significant for KODIAC-05. In an important subset analysis of individuals who had failed to respond to OTC laxatives before enrolling in KODIAC trials (KODIAC 04 N = 350, KODIAC 05 N = 370), data revealed that those receiving 25 mg daily in both trials were more likely to respond (48.7% vs 28.8% in placebo, $P = .002$, and 46.8% vs 31.4% in placebo, $P = .01$, respectively) and patients receiving 12.5 mg daily in KODIAC-04 had a statistically significant improvement (42.6% vs 28.8% in placebo, $P = .03$).[35]

The most common TEAEs in patients receiving naloxegol were diarrhea (5.4% in patients receiving 12.5 mg daily and 9.2% in patients receiving 25 mg daily) and abdominal pain (9.8% in the 12.5 group and 10.3% in the 25 mg group) and most were mild to moderate in severity. In KODIAC-04, 2 patients receiving naloxegol experienced myocardial infarctions, whereas in KODIAC-05, 2 events occurred in patients receiving placebo. Only one of these events was considered related to the study drug and occurred in an individual receiving placebo.[35] Eight patients reported symptoms consistent with opioid withdrawal including one in the placebo group and another in the treatment group who ran out of opioid medication. In a subsequent 52-week safety trial of 534 patients receiving 25 mg of naloxegol (KODIAC-08), TEAEs were similar with most mild to moderate in nature and occurring early in the course of therapy. Overall, naloxegol was well tolerated with only 11 patients discontinuing treatment because of diarrhea and 9 because of abdominal pain. In this long-term analysis, no cardiovascular events or episodes of opioid withdrawal were associated with naloxegol.[36]

NALDEMEDINE

Naldemedine is the most recent PAMORA approved for OIC in patients with CNCP and its efficacy is supported by 5 phase II/III trials.[37,38] Two identical 12-week phase III RCTs (COMPOSE-I and II) with a combined 1095 subjects evaluated with the same durable response endpoint utilized in the aforementioned naloxegol studies.[39] In COMPOSE-I, 47.6% of patients receiving 0.2 mg of naldemedine daily achieved this endpoint compared with 34.6% in the placebo group ($P = .002$). In COMPOSE-II, 52.5% of naldemedine-treated patients responded compared with 33.6% of those receiving placebo ($P<.0001$). COMPOSE-III, a 52-week trial, revealed that at 12, 24, 36, and 52 weeks, naldemedine-treated subjects (N = 621) experienced significantly increased rates of SBMs compared with placebo ($P<.0001$ at all timepoints).[40]

Diarrhea (8.0%) and abdominal pain (5.5%) were the two most common TEAEs reported in COMPOSE-I/II. There was no evidence of opioid withdrawal or cardiovascular events. In COMPOSE-III, TEAEs were similar between groups (68.4 vs 72.1%, respectively), with diarrhea (11%), and abdominal pain (8.2%) reported most frequently.

Notably, 11 cases of treatment-emergent opioid withdrawal were reported, with similar proportions occurring in the naldemedine (1.8%) and placebo (1.1%) cohorts.[40]

SECRETAGOGUES

Lubiprostone

Lubiprostone is a type-2 chloride channel activator that increases intestinal secretion and peristalsis.[41] Initially approved for the treatment of IBS-C in women (8 mcg twice daily) and CIC (24 mcg twice daily), it received subsequent FDA approval for OIC in individuals with nonmalignant pain syndromes in 2013. Presumably, lubiprostone reverses suppression of μ-receptor chloride secretion and improves intestinal transit time without affecting analgesia.[42] Because of its distinct mechanism of action, it has not been shown to reverse the central mediating effects of opioids.

Two identical phase III trials comparing lubiprostone to placebo yielded discordant results. In the first, patients with OIC were randomized to either lubiprostone 24 mcg twice daily (N = 209) or placebo (N = 204). The primary endpoint, the mean change from baseline in SBMs at week 8, was significantly higher in the lubiprostone cohort compared with placebo (3.3 vs 2.4, $P = .005$); however, this difference was not maintained at week 12.[42] In the second study, no significant differences in SBM frequency were detected between the cohorts at either 8 or 12 weeks.[43] Rates of adverse events were similar between groups with 63.5% of lubiprostone and 54.4% of placebo patients experiencing a TEAE. The most common TEAEs were nausea (15.4% in the lubiprostone group compared with 5.3% in the placebo group, $P<.001$), diarrhea, and abdominal distention.

In a third phase III trial, 431 patients with OIC were again randomized to either 24 mcg twice daily lubiprostone or placebo.[44] In the interim between the second trial and this subsequent study, new evidence emerged that methadone antagonizes the effects of lubiprostone at CIC-2 chloride channels, rendering it ineffective. As such, patients taking methadone were excluded.[45] Patients were considered primary responders if they experienced an increase of ≥1 SBM during all 12 weeks of the trial plus ≥3 SBM/wk for at least 9 of 12 weeks. A significantly greater percentage of lubiprostone-treated individuals (27.1%) met this endpoint compared with placebo (18.9%, $P = .003$). A greater mean change in SBM/wk frequency was also observed in the lubiprostone group (3.2 vs 2.4 placebo, $P = .001$) The most common TEAEs were diarrhea, nausea, vomiting, and abdominal pain (7.1% vs 0% in the placebo group). There was no evidence of opioid withdrawal in any of these 3 studies.[42–44]

Given the positive results of the third study, concerns emerged that the first two trial results were impacted by the enrollment of methadone patients. Subsequent post-hoc analyses excluding individuals consuming diphenylheptanes (methadone) were performed showing that patients taking nonmethadone opioids experienced significant increases in their numbers of SBMs.[46] Conversely, patients using methadone did not. Treatment (≥1 SBM increase for 12 of 12 weeks) and full response (≥3 SBMs/wk for at least 9 of 12 weeks) were also significantly greater in the nonmethadone cohorts. Given these outcomes, lubiprostone is not recommended for patients with OIC who use methadone.

Linaclotide

Linaclotide is a guanylate cyclase-C (GC-C) receptor agonist FDA-approved to treat both CIC (72, 145 mcg daily) and IBS-C (290 mcg daily). In a recently published phase II trial, adults with OIC associated with nonmalignant chronic pain were randomized to receive a once-daily dose of linaclotide 145 mcg (N = 87), linaclotide 290 mcg (N = 88),

or placebo (N = 79) daily for 8 weeks. SBM frequency (SBMs/wk) and 6/8 week response (≥3 SBMs/wk plus an increase of ≥1 SBM/wk from baseline for 6 of 8 weeks) were measured; the response was "durable" if response was achieved for 3 of 4 weeks of treatment at the end of the trial.[47] Patients in both linaclotide cohorts experienced significantly greater mean changes in SBM rates compared with placebo (mean change 2.9 [145 mcg], 3.5 [290 mcg], 1.6 [placebo] at 8 weeks; $P<.01$ for both comparisons to placebo). Numerically, individuals receiving both doses of linaclotide had improvements in their 6/8-week responses (40.2% [145 mcg]; 47.1% [290 mcg]) compared with placebo (33.3%), with results approaching significance for the 290 mcg dose ($P = .051$). Diarrhea, the most common TEAE, occurred in 27.6%%, 36.8%, and 16.7% of patients in the linaclotide 145 mcg, linaclotide 290 mcg, and placebo groups, respectively.

Prokinetics

Prucalopride is a serotonergic 5-HT_4 receptor agonist with prokinetic effects. It was recently approved by the FDA for treating CIC at a dose of 2 mg daily. A single phase-II trial in patients with OIC compared an average increase of ≥1 complete SBM per week over 4 weeks between prucalopride 2 mg (N = 66), 4 mg (N = 64), and placebo (N = 66).[48] In the prucalopride 2 mg and 4 mg groups, 60.7% and 69% met this endpoint, respectively, versus 43% of the placebo group ($P = .01$ for the 4 mg group). The most common TEAEs were abdominal pain (12.1% in the 2 mg group, 25% in the 4 mg group compared with 9.1% in the placebo group), nausea, and diarrhea. Headaches were infrequently reported (6.1% in the 2 mg prucalopride group and 7.8% in the 4 mg prucalopride group). A subsequent phase III trial was initiated but terminated early because of nonsafety, business-related reasons.

COMPARISONS OF THERAPIES AND UTILITY IN THE TREATMENT OF OIC VERSUS OEC

Several systematic reviews comparing the efficacy of treatments for OIC in individuals with CNCP have been published; all note differing levels of evidence, enrollment populations, primary outcome definitions, and the absence of direct head-to-head studies[21,49,50] (**Table 3**). In 2019, the American Gastroenterological Association (AGA) published guidelines for the treatment of OIC.[22] Naldemedine, naloxegol, and OTC laxatives received "strong" recommendations for use but only naldemedine was considered to have high-quality evidence. Methylnaltrexone received a "conditional" recommendation presumably due to the shorter duration and reduced rigor of the endpoints used in these studies. It is important to note, however, that there was no FDA guidance for defining an OIC population or trial outcomes available when the initial MNTX studies were completed. Lubiprostone and prucalopride did not receive formal recommendations because of evidence gaps. Data for linaclotide were published subsequent to the release of the AGA guideline. However, all 3 are medications with proven efficacy for treating alternative forms of constipation.

Where does this leave the practitioner when treating individuals across the spectrum of ORC? OTC laxatives should be used as first-line therapies: they are safe, inexpensive, and effective in approximately 50% of patients. If patients are laxative-refractory (subjectively or with a BFI score ≥ 30), and have OIC, PAMORAs are a natural next choice as they have proven efficacious, safe, and tolerable with limited potential to decrease central analgesia or induce withdrawal. For OEC, lubiprostone, linaclotide, and prucalopride may exhibit superior response as each has proven effective for treating nonopioid causes of constipation (**Fig. 3**). Ultimately, the most successful outcomes are likely to occur when individuals are appropriately categorized.

Table 3
Comparison of recent meta-analyses for treatments in OIC/ORC

	Nee, 2018	Hanson, 2019	Luthra 2019
	RR (95% CI) for Treatment Failure Compared to PBO	RR (95% CI) for Rate of Response Compared to PBO	RR (95% CI) for Failure to Achieve Average ≥3 BMs/wk or average ≥3 BMs/wk + ≥1 BM/wk Compared to PBO
Methylnaltrexone s.c.	0.75 (0.63–0.90) $P = .006$[a]	1.43 (1.21–1.68)[a]	0.74 (0.58–0.94), $P = .61$
Methylnaltrexone p.o.	NA	NA	0.91 (0.79–1.17), $P = .23$
Naldemedine	0.65, $P<.001$	1.51 (1.32–1.72)	0.67 (0.59–0.77), $P = .80$
Naloxegol	0.77 (0.61–0.97) $P = .026$	1.43 (1.19–1.71)	0.85 (0.71–1.01), $P = .35$
Lubiprostone	0.90 (0.83–0.97), $P = .005$	1.15 (0.97–1.37)	0.92 (0.79–1.07) $P = .22$
Linaclotide	NA	NA	NA
Prucalopride[b]	0.88 (0.68–0.98), $P = .032$	RR 1.57 (0.88–2.80)	NA

[a] Did not specify whether s.c. or p.o. or both; Hanson et al included patients with cancer.
[b] Where applicable, included incomplete trial data.

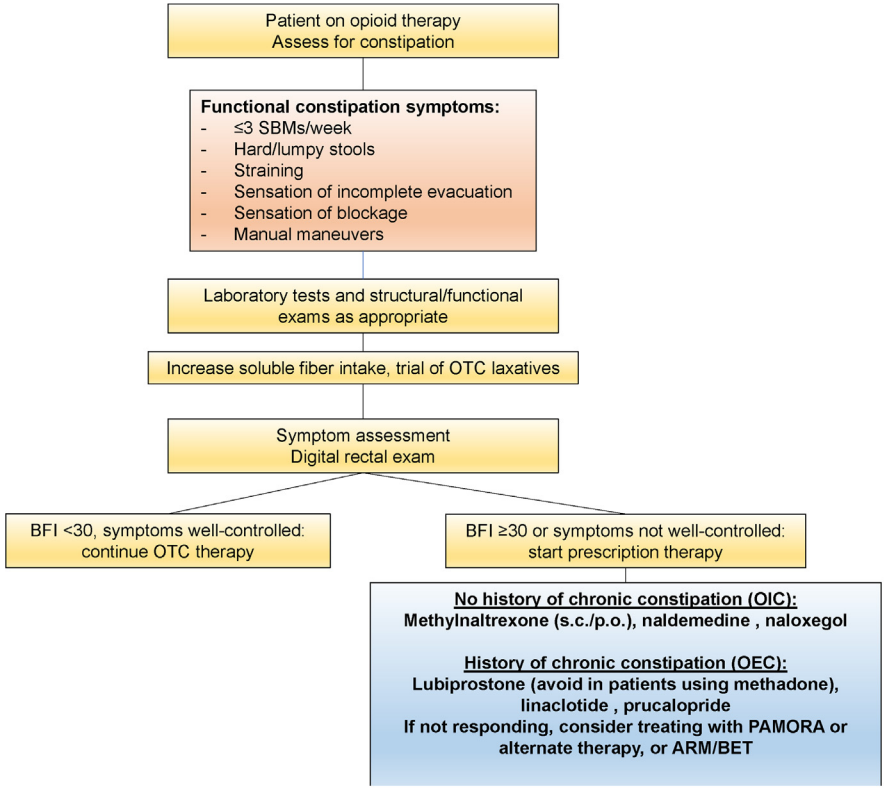


Fig. 3. Approach to diagnosing and treating ORC.

SUMMARY

Constipation is the most common adverse effect experienced by individuals taking opioids for CNCP, and it significantly impacts quality of life and optimization of analgesia. There are now multiple evidence-based therapies available to combat this disorder and which to choose is dependent upon the underlying causes of constipation. Differentiation may lead to better results, yet further studies are necessary assessing responses specifically in individuals with OEC. Future trials should also take into consideration whether outcomes are impacted by the specific opioid being consumed.

CLINICS CARE POINTS

- Opioid-induced constipation (OIC) develops in more than 40% of patients using opioids for chronic noncancer pain-related syndromes.
- Opioid-related constipation encompasses both opioid-induced and opioid-exacerbated constipation, which are differentiated by the relationship between the development of constipation and timing of opioid initiation.
- Over-the-counter laxatives are first-line treatments for opioid-induced and opioid-exacerbated constipation based on their clinical efficacy, ease of use, low cost, and safety profile.
- When over-the-counter laxatives fail, peripherally acting μ-opioid receptor antagonists (PAMORAs) are an appropriate next choice for individuals with opioid-induced constipation, whereas secretagogues or prokinetic agents may be more effective for patients with opioid-exacerbated constipation.

DISCLOSURE

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