Clinical Overview and Considerations for the Management of Opioid-induced Constipation in Patients With Chronic Noncancer Pain

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Objectives: Opioid analgesics may be associated with chronic adverse effects, such as opioid-induced constipation (OIC). Available and emerging prescription medications for OIC in patients with chronic noncancer pain are described, including concerns and challenges associated with OIC management.

Methods: Narrative review.

Results: OIC is characterized by a change in bowel habits and defecation patterns that occurs when initiating opioid therapy and is associated with reduced bowel frequency, straining, sensation of incomplete evacuation, and/or patient distress related to bowel habits. Prescription medications are indicated when OIC persists despite conservative approaches (eg, increased fiber and fluid intake, exercise, over-the-counter laxatives and stool softeners). Phase 3 studies have demonstrated the efficacy of peripherally acting μ-opioid receptor antagonists (PAMORA; methyl-naltrexone, naloxegol, naloxol) and α-cholinergic channel activator (lubiprostone) for improving OIC in patients with chronic noncancer pain. Although head-to-head studies are lacking, a meta-analysis demonstrated that μ-opioid receptor antagonists were more effective than placebo for the treatment of OIC. The most common adverse effects associated with prescription medications for OIC are gastrointestinal related (eg, nausea, diarrhea, abdominal pain, or distention), with most being mild or moderate in severity. Therapy currently in development for OIC includes the PAMORA axelopran.

Discussion: Healthcare providers should be aware of this complication in patients receiving opioids and should monitor and address constipation-related symptoms to optimize pain management and improve patient quality of life.

Key Words: chronic pain, constipation, μ-opioid receptor, opioid receptor antagonists

( Clin J Pain 2019;35:174–188)

Received for publication November 3, 2017; accepted September 15, 2018.

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Technical editorial and medical writing assistance, under the direction of the author, was provided by Mary Beth Moncrief, PhD, and Jill Gee, PhD, Synchrony Medical Communications, LLC, West Chester, PA. Technical editorial assistance was also provided by Echelon Brand Communications, Parsippany, NJ. Funding for this support was provided by Salix Pharmaceuticals, Bridgewater, NJ, USA.

Dr. Viscusi has served as a consultant to Salix, Cara, Trevena, AcelRx, Mallinckrodt, Pfizer, Egalet, Fresenius, and Merck, and has received payment for lectures for Salix. His institution has received research funding on his behalf from Pacira and Durect.

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DOI: 10.1097/AJP.0000000000000662

The use of opioids to treat the pain of cancer and other advanced diseases is broadly accepted.1 Their use to treat moderate to severe chronic noncancer pain may be considered in patients whose pain is not relieved by nonopioid multimodal drugs (eg, nonsteroidal anti-inflammatory drugs, acetaminophen, antineuropathic), physical therapy, or other interventional techniques.2 When opioid therapy is introduced, it is essential to establish treatment goals with regard to pain relief and, especially when used for the pain of non-life-threatening diseases, functional improvement, with minimal or no side effects associated with the chosen therapy.2 Initiation of opioid therapy should be entered with a clear exit strategy in the event that treatment is unsuccessful.3 Further, the lowest possible dose should be used to achieve the desired effects and tapered or terminated if clear benefit cannot be documented.2,3

The most common side effects associated with the administration of opioid therapy are gastrointestinal (GI) and include nausea, vomiting, and constipation.4–7 Opioid-induced constipation (OIC) is one of the most common and bothersome side effects associated with chronic opioid use;8–10 occurring in 262 of 322 patients (81%) taking daily oral opioids and laxatives in a patient survey conducted in the United States and Europe.10 In an analysis of The Oxford Pain Relief Database (1950 to 1994) and Medline, EMBASE, and the Cochrane Library (until September 2003), 15 randomized placebo-controlled trials of the World Health Organization step 3 opioids used for efficacy and safety in chronic noncancer pain were identified.11 In 8 of the randomized trials, constipation was reported as a specific adverse event in 41% of opioid-treated patients compared with 11% of placebo-treated patients, averaged over the 8 studies.11 In another survey of almost 500 patients from the United States with chronic noncancer pain, the most commonly reported OIC symptoms were a sense of incomplete bowel movements, either moderate to severe straining or abdominal discomfort/pain, and changes in stool consistency.12 Further, side effects associated with the chronic administration of opioids have the potential to limit the dose of opioid medication and result in patient discontinuation or deviation from the prescribed opioid regimen, which may lead to inadequate pain relief.7,13,14

Among patients with chronic noncancer pain, OIC has been found to substantially impair work productivity and health-related quality of life.9,12 Health care providers often underestimate the daily impact of OIC on quality of life and the ability of patients to manage their underlying pain condition.13 Successful treatment of OIC may both improve patient quality of life and provide a benefit in terms of reduced pain-related surgery and hospitalizations compared with a “do-nothing” strategy, in which patients reduce their analgesia to prevent OIC.14

The enteric neurons that lie within the alimentary canal provide neural regulatory input to the entire digestive tract through the production of a variety of neuroactive molecules, including acetylcholine, 5-hydroxytryptamine (5-HT), and opioid peptides (eg, met-enkephalin, β-endorphin), as
all neuronal action requires some synaptic release. These molecules control the contraction and relaxation of the longitudinal and circular muscle layer within the GI tract. In addition, these molecules regulate the secretion and retention of water within the GI tract through interactions with µ-, δ-, and κ-opioid receptors, particularly the µ-opioid receptors. Exogenously administered opioids disrupt a number of activities within the GI tract, which leads to impairment of motility and water resorption (Fig. 1). Opioids block the release of excitatory neurotransmitters (eg, acetylcholine) resulting in the inhibition of distention-induced peristalsis while also blocking the inhibitory neurons resulting in the increased activity of GI motor neurons, elevated muscle tone, and nonpropulsive motility. Once activated by µ-opioid receptor agonists, the interstitial cell-muscle network works to inhibit gastric emptying, increases pyloric muscle tone, and delays transit through the small and large intestine. The inhibition of acetylcholine release from secretomotor neurons prevents the movement of chloride (Cl\(^{-}\)) and water from epithelial cells into the GI tract. The inhibition of propulsive motility and the reduction of water moving into the colon account for the constipation caused by opioids.

Guidelines from the American Society of Interven- tional Pain Physicians on the responsible use of opioids for chronic noncancer pain recommend monitoring for side effects, such as OIC, and initiating a regimen to manage these side effects (eg, use of laxatives) if necessary. A consensus statement from the American Academy of Pain Medicine (AAPM), which has been endorsed by the American Gastroenterological Association, has recommended that first-line treatment strategies for OIC include increased fiber and fluid intake, exercise, consideration of opioid switching, over-the-counter stool softeners, natural dietary supplements, and laxatives. As opioids can impact multiple regulatory systems within the GI tract, therapies that improve only some aspects of constipation (eg, osmotic laxatives that decrease water absorption from stool) may not be sufficient to alleviate OIC. The AAPM consensus statement recommends that the failure of first-line options to provide adequate constipation relief must be quickly determined to minimize patient distress and discomfort and expedite the consideration of prescription medications for the treatment of OIC in these patients and in those patients who score at least 30 points on the Bowel Function Index, a clinically validated tool for assessing OIC.

Prescription medication for use in patients with OIC are summarized in Table 1. The first once daily oral peripherally acting µ-opioid receptor antagonist (PAMORA) approved by the Food and Drug Administration (FDA) in September 2014 for the treatment of OIC in adult patients with noncancer pain was naloxegol. Of the therapies listed in Table 1, methylnaltrexone is the only prescription medication available in 2 delivery formulations and for 2 indications: OIC resulting from the treatment of chronic noncancer pain (a subcutaneous injection and an oral tablet [the tablet was approved by the FDA in July 2016]) and for OIC in patients receiving opioids for active cancer (subcutaneous injection) and other advanced illnesses. Naldemedine, which is available as an oral tablet, is the most recently approved therapy (March 2017 approval). Originally a schedule II-controlled substance because it can be derived from opium alkaloids, the Drug Enforcement Administration descheduled naldemedine in September 2017, citing limited availability of effective therapies for OIC, its good safety profile, and nonapplicability of criteria for scheduling, due to its distinction from opioid analgesics. This article provides a narrative overview of current OIC therapies and therapies in development and discusses a variety of clinical concerns and challenges associated with OIC management.

**Prescription Medications for the Treatment of OIC**

**Overall Efficacy**

Several phase 3 studies have evaluated the efficacy of methylnaltrexone, naloxegol, and nalmedine (PAMORAs) and lubiprostone (a chloride channel activator [CIC-2]) for the treatment of OIC in patients with chronic noncancer pain (Table 2). In addition, methylnaltrexone has been evaluated in patients with advanced medical illnesses. These therapies have either limited or no effect on central analgesia, as evidenced by patients in clinical trials reporting similar pain levels at baseline and throughout treatment. Further, few patients using these therapies reported the need for rescue analgesic medication or an associated increase in opioid dose.

Because no head-to-head comparative trials between prescription medications for OIC have been conducted and outcome measures of published trials vary considerably, direct comparisons among these therapies remain difficult. A meta-analysis was conducted of placebo-controlled trials from 1947 to 2012 that evaluated the efficacy of µ-opioid receptor antagonists in adults with OIC. Overall, the meta-analysis demonstrated that µ-opioid receptor antagonists were more effective than placebo for the treatment of OIC with the relative risk (RR) of the failure to respond to therapy similar for patients treated with naloxone (RR, 0.64; 95% confidence interval, 0.56-0.72) and methylnal- trexone (RR, 0.67, 95% confidence interval, 0.54-0.84).

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**FIGURE 1.** Overview of mechanisms underlying opioid-induced constipation. Reprinted from Holzer. Copyright Elsevier, Oxford, United Kingdom. All permission requests for this image should be made to the copyright holder.
| Product                        | Mechanism of Action                | OIC Approval Year | Available Doses                                           | Recommended Dosing                                                                 | Cost*                                                                 |
|-------------------------------|-----------------------------------|-------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Methylnaltrexone              | Advanced illness (SC): 2008       | CNCP (SC): 2014   | Oral: 150-mg tablet                                      | Oral: 450 mg QD in the morning                                                   | Oral: 150-mg tablet: Average drug acquisition cost data not available $21-$22 per tablet (estimated pharmacy price) |
|                              | Subcutaneous: (SC): 2016          | CNCP (oral): 2016 | Subcutaneous: single-use vial or prefilled syringe       | Subcutaneous: 12 mg QD                                                          | Subcutaneous: 12 mg/0.6 mL syringe or vial: $100 per mL (average drug acquisition cost); $116-$125 per syringe (estimated pharmacy price) |
|                              |                                   |                   | (12 mg/0.6 mL)                                           | Moderate or severe renal impairment (CrCl <60 mL/min): oral 150 mg QD or SC 6 mg QD | 8 mg/0.4 mL syringe: $242 per mL (average drug acquisition cost); $116-$123 per syringe (estimated pharmacy price) |
|                              |                                   |                   | Single-use prefilled syringe (8 mg/0.4 mL and 12 mg/0.6 mL) | Moderate or severe hepatic impairment (Child-Pugh class B or C): oral 150 mg QD | $8 24-$32 per mL (average drug acquisition cost); $116-$123 per syringe (estimated pharmacy price) |
| Lubiprostone                  | Chloride channel activator        | 2013              | 8-µg capsule                                            | 24 µg BID                                                                        | 24-µg and 8-µg capsules: $5 per capsule (average drug acquisition cost); $7 (estimated pharmacy price) |
|                              |                                   |                   | 24-µg capsule                                           | Moderate hepatic impairment: 16 µg BID                                           |                                                                                                                                  |
|                              |                                   |                   |                                                        | Severe hepatic impairment: 8 µg BID                                              |                                                                                                                                  |
| Naloxegol                     | PAMORA                            | 2014              | 12.5-mg tablet                                          | 25 mg QD                                                                         | 12.5-mg and 25-mg tablets: $9 per tablet (average drug acquisition cost); $14-$15 (estimated pharmacy price) |
|                              |                                   |                   | 25-mg tablet                                            | 12.5 mg QD (if 25 mg QD not well tolerated)                                      |                                                                                                                                  |
|                              |                                   |                   |                                                        | Renal impairment: 12.5 mg QD; increase to 25 mg QD if tolerated and monitor for AEs |                                                                                                                                  |
|                              |                                   |                   |                                                        | Hepatic impairment: mild to moderate impairment does not require dose adjustment; do not use in patients with severe impairment |                                                                                                                                  |
| Naldemedine                   | PAMORA                            | 2017              | 0.2-mg tablet                                           | 0.2 mg QD                                                                         | 0.2-mg tablet: Average drug acquisition cost data not available; $13-$14 (estimated pharmacy price) |
|                              |                                   |                   |                                                        | Hepatic impairment: mild to moderate impairment does not require dose adjustment; do not use in patients with severe impairment |                                                                                                                                  |

*National Average Drug Acquisition cost data were obtained on January 24, 2018 from https://data.medicaid.gov/Drug-Pricing-and-Payment/NADAC-National-Average-Drug-Acquisition-Cost-/a4y5-998d. Estimated pharmacy prices were obtained on January 24, 2018 from https://www.goodrx.com, which is based on multiple sources, including published price lists, purchases, claims records, and data provided by pharmacies. AE indicates adverse event; BID, twice daily; CNCP, chronic noncancer pain; CrCl, creatinine clearance; OIC, opioid-induced constipation; PAMORA, peripherally acting µ-opioid receptor antagonist; q12h, once every 12 hours, QD, once daily; SC, subcutaneous.
| Study                      | Study Design | Baseline Characteristics                                      | Treatment                                      | Efficacy Results                                      |
|---------------------------|--------------|---------------------------------------------------------------|------------------------------------------------|-------------------------------------------------------|
| Methylnaltrexone injection| RCT 4 wk     | Methylnaltrexone injection 12 mg SC QD (n = 150) Methylnaltrexone injection 12 mg SC QOD (n = 148) Placebo (n = 162) | Methylnaltrexone injection 12 mg SC QD (n = 150) Methylnaltrexone injection 12 mg SC QOD (n = 148) Placebo (n = 162) | RFBM within 4 h of first dose Methylnaltrexone injection 12 mg QD: 33.3%* Methylnaltrexone injection 12 mg QOD: 33.3%* Placebo: 9.9% Active injections per patient resulting in an RFBM within 4 h Methylnaltrexone injection 12 mg QD: 29.9%* Methylnaltrexone injection 12 mg QOD: 30.2%* Placebo: 9.4% Straining (“none” or “mild”) at week 1 Methylnaltrexone injection 12 mg QD: 28.1%† Methylnaltrexone injection 12 mg QOD: 28.5%† Placebo: 14.0% Complete evacuation Methylnaltrexone injection 12 mg QD: 27.4%† Methylnaltrexone injection 12 mg QOD: NR Placebo: 19.9% |
| Viscusi et al.            | OLE 8 wk     | Methylnaltrexone oral tablet RCT 12 wk (4-wk QD, 8-wk PRN) | Methylnaltrexone oral tablet RCT 12 wk (4-wk QD, 8-wk PRN) | RFBM within 4 h of dose Methylnaltrexone injection 12 mg PRN (OLE): 45.9% Placebo (RCT): 9.7% Injections resulting in an RFBM within 4 h Methylnaltrexone injection 12 mg PRN (OLE): 34.5% Placebo (RCT): 9.0% Placebo (RCT) (range): 2.3-2.7 |

(Continued)
| Study             | Study Design | Baseline Characteristics                                                                                                                                 | Treatment                          | Efficacy Results                                                                                                                                 |
|-------------------|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| **Lubiprostone**  | RCT 12 wk    | Methylaltrexone 300 mg/d (n = 201): 87 (43.3) Methylaltrexone 450 mg/d (n = 200): 72 (36.0) Placebo (n = 201): 71 (35.3) | Lubiprostone 24 µg BID (n = 210) | Change from baseline in SBM frequency at week 8 Lubiprostone 24 µg: 2.28 Placebo: 1.6 Straining*, abdominal discomfort†, constipation severity†, and stool consistency* were significantly improved vs. placebo |
| Cryer et al 33    |              | SBMs/wk, mean (SD) Lubiprostone 24 µg BID (n = 210): 1.4 (1.1) Placebo (n = 208): 1.5 (1.0) P = 0.793 Morphine equivalent dose, mg/d, mean (SD) Lubiprostone 24 µg BID (n = 210): 265 (407) Placebo (n = 208): 237 (451) P = 0.012 | Placebo BID (n = 208)              | Percentage of SMB responders‡ at wk 12 Lubiprostone 24 µg: 27.1%† Placebo: 18.9% Mean change in SBM frequency overall Lubiprostone 24 µg: 3.2* Placebo: 2.4 Improvement from baseline in straining*, stool consistency*, and constipation severity† greater vs. placebo |
| Jamal 2015 34     | RCT 12 wk    | SBMs/wk, mg/d, mean (SD) Lubiprostone 24 µg BID (n = 212): 1.3 (0.8) Placebo (n = 212): 1.4 (0.8) P = 0.049 Morphine equivalent dose, mg/d, mean (SD) Lubiprostone 24 µg BID (n = 212): 129.9 (226.7) Placebo (n = 212): 99.0 (120.3) P = 0.148 Age, y, mean (SD) Lubiprostone 24 µg BID (n = 214): 51.9 (9.1) Placebo (n = 217): 51.5 (12.0) P = 0.662 Male, n (%) Lubiprostone 24 µg BID (n = 214): 80 (37.4) Placebo (n = 217): 79 (26.4) P = 0.842 | Placebo BID (n = 217)              | Percentage of responders** Frequency of SBMs and BMs increased throughout study* Response of ≥ 3 SBMs/wk for ≥ 50% of week in month: range from 74.0% to 79.8% of patients during 9 months |
| Sterlings et al 53 | OLF 36 wk    | SBMs/wk, mean (SD) Lubiprostone 24 µg BID (n = 439): 1.4 (0.98) Morphine equivalent dose, mg/d, median (range) Lubiprostone 24 µg BID (n = 439): 300 (5.3-15210) | Placebo (n = 439)                 | Lubiprostone 24 µg ≤ 24 µg BID (n = 439) Frequency of SBMs and BMs increased throughout study* Response of ≥ 3 SBMs/wk for ≥ 50% of week in month: range from 74.0% to 79.8% of patients during 9 months |
| Chey et al 36     | 2 RCT 12 wk (Study 04 and Study 05) | KODIAC-04 (Study 04) SBMs/wk, mean (SD) Naloxegol 12.5 mg (n = 213): 1.4 (0.85) Naloxegol 25 mg (n = 214): 1.3 (1.11) Placebo (n = 214): 1.4 (0.89) Morphine equivalent dose, mg/d, mean (SD) Naloxegol 12.5 mg (n = 213): 139.7 (167.4) Naloxegol 25 mg (n = 214): 143.2 (150.1) Placebo (n = 214): 135.6 (145.8) Age, y, mean (SD) Naloxegol 12.5 mg (n = 213): 51.9 (10.4) Naloxegol 25 mg (n = 214): 52.2 (10.3) Placebo (n = 214): 52.9 (10.0) | Naloxegol 12.5 mg (n = 445) Naloxegol 25 mg (n = 446) Placebo (n = 446) | KODIAC-04 (Study 04) Percentage of responders** Naloxegol 12.5 mg: 40.8%† Naloxegol 25 mg: 44.4%† Placebo: 29.4% Change (SE) from baseline in number of SBMs/wk Naloxegol 12.5 mg: 2.62 (0.18)† Naloxegol 25 mg: 3.02 (0.18)† Placebo: 2.02 (0.18) KODIAC-05 (Study 05) Percentage of responders** Naloxegol 12.5 mg: 34.9% Naloxegol 25 mg: 39.7%† |
Male, n (%)  
Naloxegol 12.5 mg (n = 213): 78 (36.6)  
Naloxegol 25 mg (n = 214): 96 (44.9)  
Placebo (n = 214): 74 (34.6)  
KODIAC-05 (Study 05)  
SBMs/wk, mean (SD)  
Naloxegol 12.5 mg (n = 232): 1.6 (1.05)  
Naloxegol 25 mg (n = 232): 1.3 (0.85)  
Placebo (n = 232): 1.5 (0.95)  
Morphine equivalent dose, mg/d, mean (SD)  
Naloxegol 12.5 mg (n = 232): 151.7 (153.0)  
Naloxegol 25 mg (n = 232): 136.4 (134.3)  
Placebo (n = 232): 119.9 (103.8)  
Age, y, mean (SD)  
Naloxegol 12.5 mg (n = 232): 52.0 (11.0)  
Naloxegol 25 mg (n = 232): 51.9 (12.1)  
Placebo (n = 232): 52.3 (11.6)  
Naldemedine Hale et al 37  
2 RCT 12 wk (COMPOSE-1 and COMPOSE-2)  
COMPOSE-1  
SBMs/wk, mean (SD)  
Naldemedine (n = 273): 1.3 (0.7)  
Placebo (n = 272): 1.3 (0.7)  
Morphine equivalent dose at baseline, mg/d, mean (SD)  
Naldemedine (n = 273): 108.1 (104.0)  
Placebo (n = 272): 128.4 (162.9)  
Age, y, median (range)  
Naldemedine (n = 273): 53.0 (47.0-60.0)  
Placebo (n = 272): 53.0 (46.0-60.5)  
Male, n (%)  
Naldemedine (n = 273): 112 (41)  
Placebo (n = 272): 104 (38)  
COMPOSE-2  
SBMs/wk, mean (SD)  
Naldemedine (n = 276): 1.2 (0.8)  
Placebo (n = 274): 1.2 (0.7)  
Morphine equivalent dose at baseline, mg/d, mean (SD)  
Naldemedine (n = 276): 106.9 (127.2)  
Placebo (n = 274): 115.2 (143.4)  
Age, y, median (range)  
Naldemedine (n = 276): 54.0 (47.5-61.0)  
Placebo (n = 274): 54.0 (47.0-60.0)  
Male, n (%)  
Naldemedine (n = 276): 111 (40)  
Placebo (n = 274): 106 (39)  
Naldemedine 0.2 mg/d (n = 549)  
Placebo (n = 546)  
COMPOSE-1  
Percentage of responders**  
Naldemedine vs. placebo: 47.6%† vs. 34.6%  
Change (SE) from baseline in number of SBMs/wk to last 2 wk of the treatment period  
Naldemedine vs. placebo: 3.42 (0.193) vs. 2.12 (0.192)  
Least squares mean difference  
Naldemedine vs. placebo: 1.30 (95% CI, 0.77-1.83), P < 0.0001  
COMPOSE-2  
Percentage of responders**  
Naldemedine vs. placebo: 52.5%*; placebo: 33.6%  
Change (SE) from baseline in number of SBMs/wk to last 2 wk of the treatment period  
Naldemedine vs. placebo: 3.56 (0.174) vs. 2.16 (0.174)  
Least squares mean difference  
Naldemedine vs. placebo: 1.40 (95% CI, 0.92-1.88), P < 0.0001  
* P ≤ 0.001 vs. placebo.  
† P ≤ 0.05 vs. placebo.  
‡ P = 0.004 vs. placebo.

†Patients who completed the RCT were eligible for the OLE.  
‡ Patients with ≥ 3 RFBMs/wk, with an increase of ≥ 1 RFBM/wk from baseline for ≥ 3 of first 4 weeks.  
‡‡ ≥ 1 SBM improvement from baseline for all treatment weeks with observed data and additional ≥ 3 SBMs/wk for ≥ 9 of 12 weeks.  
‡‡‡ Patients who experienced ≥ 3 SBMs/wk, with an increase of ≥ 1 SBM/wk from baseline for ≥ 9 of 12 weeks and for ≥ 3 of last 4 weeks of treatment.  
BID indicates twice daily; BM, bowel movement; CI, confidence interval; CNCP, chronic noncancer pain; CSBM, complete spontaneous bowel movement; NR, not reported; OIC, opioid-induced constipation; OLE, open-label extension; PRN, when necessary; QD, once daily; QOD, once every other day; RCT, randomized controlled trial; RFBM, rescue-free bowel movement; SBM, spontaneous bowel movement; SC, subcutaneous.
The calculation of RR for methylnaltrexone was based on combined data from 5 randomized, controlled trials of methylnaltrexone,30,39,44–46 for subcutaneous injection and 1 randomized, controlled trial of oral methylnaltrexone.32 Data for lubiprostone were limited, and naloxegol and naldemedine were not included in that meta-analysis.45 A review of randomized, placebo-controlled trials published in 2016 evaluated the use of methylnaltrexone subcutaneous injection, naloxegol, lubiprostone, prucalopride, or linaclootide in adults with OIC, chronic idiopathic constipation, and constipation-predominant irritable bowel syndrome (IBS) by conducting a medical literature search using MEDLINE and the Cochrane central register.47 The analysis of 6 trials of prescription medications for OIC in patients with advanced illness or chronic noncancer pain treated with methylnaltrexone subcutaneous injection or patients with chronic noncancer pain treated with naloxegol demonstrated that rates of persistent constipation (ie, nonresponse) did not differ significantly between patients using methylnaltrexone and naloxegol (P = 0.6).47 In addition, the analysis reported that most patients remained constipated with active treatment in the 2 naloxegol trials and in 2 of the 3 methylnaltrexone subcutaneous injection trials (although only 42% of patients remained constipated with active treatment in one of the methylnaltrexone trials), and 31% remained constipated with active treatment in a trial of a benzofuran derivative, prucalopride (not currently indicated for OIC). However, in studies of these 3 prescription medications, rates of persistent constipation differed among placebo groups, which suggests that participants in some studies may have been less likely to remain constipated and underscores the danger of comparing outcomes across studies with different patient populations.47

The number needed to treat for prescription medications varies and is typically calculated based on the primary efficacy end point (Table 3).30,32–34,36,45,48,49 Time to the first spontaneous bowel movement (SBM) is another common efficacy end point that is evaluated in some studies that appears to have varying results depending on the therapy (Table 3).30,33,34,36,39,45 Results from long-term (ie, 36 to 52 wk) safety studies of OIC treatments for improvement of bowel function in patients with chronic noncancer pain are shown in Table 4.21,23,24,35,50

### Comparison With Laxatives

As stated earlier, current guidelines recommend increased fluid and fiber intake and a laxative regimen with the initiation of opioid therapy.3 However, because laxatives do not address the underlying cause of OIC, constipation, and straining to pass a bowel movement may still be observed in patients receiving laxative therapy.10 Most clinical trials of newer prescription OIC treatments compare these agents to placebo, making it difficult to assess the advantage of a prescription OIC medication versus laxatives for laxative-naive patients. However, naloxegol has been shown to improve bowel function in patients with OIC who were unresponsive to ≥1 laxative.36,51 Similarly, studies have indicated that treatment of adult patients with advanced illness receiving opioids and constipated at baseline despite receiving laxatives had a positive laxation response to methylnaltrexone subcutaneous injection compared with placebo.38,39

In clinical trials, the use of rescue laxatives was typically lower in patients receiving methylnaltrexone subcutaneous injection or naloxegol, compared with placebo.30,36 In contrast, lubiprostone did not significantly reduce the percentage of patients who used rescue laxatives versus placebo each month during two 3-month studies.33,34

### Predictors of Response to OIC Therapy

The ability to predict a patient’s responsiveness to a specific OIC therapy would be beneficial. Although few studies have evaluated baseline or demographic factors that influence therapeutic response, those that have demonstrate no obvious impact of such factors on the overall efficacy profile for the treatment of OIC. For patients receiving opioids for both cancer and noncancer pain, the efficacy of methylnaltrexone subcutaneous injection was not substantially impacted by demographic characteristics (age, ≤65 vs. ≥65 yr; sex, primary diagnosis and thereby underlying cause of OIC), constipation-related distress score (≤3 vs. >3), or morphine equivalent dose (<150 vs. ≥150 mg/d).52 Lubiprostone provided constipation relief for patients with chronic noncancer pain with severe and very severe straining, very hard stool consistency, absent-to-normal bowel function, and severe constipation, and for those receiving phenanthrenes (eg, oxycodone, morphine, hydromorphone) but not phenylpiperidines (eg, fentanyl) or diphenylethanes (eg, methadone) at baseline.53,54 In an analysis of data from 2 studies of naloxegol for OIC in patients with chronic noncancer pain, the only demographic/clinical characteristics at baseline that impacted naloxegol treatment and provided a more therapeutic benefit for patients were fewer SBMs and treatment with more potent opioids.55

Two studies indicate that the type of opioid analgesic causing constipation may predict a patient’s responsiveness to lubiprostone54 or naloxegol55 and should therefore be taken into consideration when selecting an OIC therapy. Methadone, but not morphine, may inhibit the chloride secretion stimulated by lubiprostone and thereby interfere with lubiprostone’s mechanism of action.56 Accordingly, a pooled analysis of data from 3 phase 3 studies demonstrated that response rates (≥1 SBM/wk improvement over baseline SBM frequency) were significantly greater in patients treated with lubiprostone compared with those receiving placebo among those treated with phenanthrenes (eg, oxycodone, morphine, and hydromorphone), but not in patients taking diphenylethanes (eg, methadone).54 In addition, naloxegol administration in patients taking methadone for pain has been associated with an increased risk of GI adverse events (eg, abdominal pain and diarrhea) versus patients taking other opioid analogs with naloxegol; this difference may be related to features of opioid withdrawal that vary from drug to drug.23

The onset of action of most OIC therapies (≤1 wk for all)30,33,34,36 ensures that responsiveness should be detectable early after treatment initiation and allow for quickly switching therapies if necessary.

### Additional Efficacy Considerations for Individual Prescription OIC Therapies

Beyond nonresponse, the possibility of “over-response” (diarrhea) is another key consideration when treating patients for OIC. In an analysis of 7 randomized, controlled trials of OIC prescription medications (methylnaltrexone subcutaneous injection [n = 2], naloxegol [n = 3], lubiprostone [n = 1], and prucalopride [n = 1]), the percentage of patients with diarrhea ranged from 6% to 13% with active treatment and from 2% to 6% with placebo.47 For patients who are overresponders (eg, those who develop diarrhea or intolerable abdominal distress with OIC medications), a dose reduction
TABLE 3. Number Needed to Treat and Time to Spontaneous Bowel Movement for OIC Prescription Therapies

| Therapeutic Agent | End Point Used for NNT | NNT | Time to SBM |
|------------------|------------------------|-----|-------------|
| Methylnaltrexone (subcutaneous) | Achievement of an RFBM within 4 h of first dose | 4 | Not available (0.8-6.3 h [range for median time to RFBM in advanced illness]) |
| Methylnaltrexone (oral) | Not available | Not available | Not available |
| Lubiprostone | Responder (≥1 SBM improvement from baseline frequency during all treatment wk and complete response [additional ≥3 SBMs/wk] for ≥9 of 12 treatment weeks) | 6 | 23.5-28.5 h (range for median time to SBM) |
| Naloxegol | Achievement of ≥3 SBMs/wk | 6.7-9.7 | 5.9 h and 12.0 h in identically designed studies (KODIAC-04 [study 04] and KODIAC-05 [study 05]) |

CNCP indicates chronic noncancer pain; NNT, number needed to treat; OIC, opioid-induced constipation; RFBM, rescue-free bowel movement; SBM, spontaneous bowel movement.

may prove helpful. Because these agents are likely producing a limited opioid withdrawal response within the GI tract, it follows that doses might be titrated to mitigate the response to peripheral opioid receptor antagonism.

The cost of prescription medications for the treatment of OIC can be substantial (Table 1), but the cost burden of hospitalization resulting from OIC should also be considered when weighing the costs and benefits of prescription OIC therapies. Patients with OIC are more likely to be hospitalized than patients without OIC (33% vs. 20% in the nonelderly; 51% vs. 31% in the elderly; P < 0.001 for both), have longer mean (SD) hospital length of stay (3.0 [8.4] vs. 1.0 [3.0] d in the nonelderly; 5.2 [12.2] vs. 2.1 [4.0] d in the elderly; P < 0.001 for both), and higher total health care costs ($23,631 [$67,209] vs. $12,652 [$19,717] in the elderly; $16,923 [$38,191] vs. $11,117 [$19,525] in the nonelderly; P < 0.05 for both).57

SAFETY OF APPROVED PRESCRIPTION OIC TREATMENTS

Although laxatives are considered safe and commonly prescribed by physicians to patients who are receiving long-term opioid treatment,38,39,59 they do not treat the underlying cause of OIC10 and are associated with side effects such as flatulence, nausea, vomiting, diarrhea, and abdominal pain. In addition, laxatives may disrupt mineral metabolism (patients using these products may develop hypermagnesemia, hyperphosphatemia, hypercalcemia, or hypernatremia) and elicit enteric changes, such as neuron loss and lumen dilation in susceptible patients.39

Overall, integrated safety summaries have most commonly reported GI-related adverse events such as nausea, diarrhea, abdominal pain, or distention for prescription therapies to treat OIC (Table 5).60-63 For naloxegol, a trend for an increased incidence of adverse events was reported in patients treated with higher doses;62 therefore, at the discretion of the prescribing clinician, the lower dose formulation (12.5 µg twice daily [BID]) might be considered for patients who are unable to tolerate the 25-µg dose.22 Patients treated with lubiprostone reported nausea as the most common GI-related adverse event (14.4%);61 eating may help minimize nausea.22 The majority of the adverse events experienced with all of these OIC therapies were mild to moderate in severity.50-63

Additional clinical data analyzed after drug approval have brought to light adverse events that have prompted label changes to specific OIC therapies. The occurrence of dyspnea in patients treated with lubiprostone after drug approval and during clinical trials for chronic idiopathic constipation and constipation-predominant IBS prompted the addition of dyspnea to the Warnings and Precautions section of the label.62 The incidence of dyspnea in trials of lubiprostone for OIC was 1%, which is lower than that reported for lubiprostone 24 µg twice daily (BID) in trials for chronic idiopathic constipation (3%).22

During safety monitoring for methylnaltrexone following drug approval, perforation of the GI tract was reported in patients with OIC, advanced illness, and conditions impacting the structural integrity of the GI tract lining after they received methylnaltrexone subcutaneous injection.20 Between April 2008 and October 2009, 7 bowel perforation incidents were reported in patients with pathologic or anatomical abnormalities of the GI tract; only 1 of these cases was thought to be related to methylnaltrexone subcutaneous injection.64 Opioid withdrawal symptoms have also been documented in patients treated with methylnaltrexone subcutaneous injection following approval.20 It was suggested that the intermittent (ie, once every other day [QOD]) use of methylnaltrexone, which is the recommended regimen for adults with advanced illness,20 may have precipitated withdrawal symptoms within the GI tract and predisposed the patient to GI perforation.65 However, no such evidence of withdrawal symptoms has been observed in clinical trials of patients with chronic noncancer pain.42 Disruptions to the blood-brain barrier may also increase the risk of opioid withdrawal.20 For patients with altered GI integrity (eg, Crohn’s disease), a careful assessment of the potential risk: benefit profile of methylnaltrexone, naloxegol, and naldemedine is critical, with the label containing warnings with regard to GI perforation and opioid withdrawal and advising clinicians to consider the risk: benefit profile in patients at risk for these events, since both GI perforation and opioid withdrawal are considered class effects.20,21,25

The potential for cardiac adverse events with PAMORAs was raised after an imbalance in the number of myocardial infarctions and severe cardiovascular (CV) events was observed in patients with OIC who received alvimopan BID compared with rates of these events for patients receiving placebo.66,67 Alvimopan is a peripherally selective opioid receptor antagonist that has been approved for the
| Study | Study Design | Baseline Characteristics | Treatment | Bowel Function and Safety |
|-------|--------------|--------------------------|-----------|--------------------------|
| Methylnaltrexone injection | Webster et al\textsuperscript{21} OLE 48 wk | N = 1034 Mean BMs per week: 1.5 Mean BM Straining Score: 2.3 Mean Bristol Stool Scale score*: 2.5 Mean percentage of BMs with a sensation of complete evacuation: 27.6 Age, y, mean (SD): 51.7 (10.8) Male, n (%): 365 (35.3) | Subcutaneous methylnaltrexone 12 mg QD Dose adjustments up to a maximum of one dose per day and a minimum of one dose per week were permitted as needed | The most common AEs overall were GI-related (abdominal pain 24.0%, diarrhea 16.4%, nausea 15.1%) There were no new safety concerns BM occurring within 4 h in 34.1% of injections Improvement of OIC symptoms and the adverse event profile were consistent with other clinical trials of shorter duration in patients with chronic noncancer pain |
| Methylnaltrexone oral tablet | Long-term clinical studies have not yet been published | — | — | — |
| Lubiprostone | Spierings et al\textsuperscript{35} OLE 36 wk | N = 439 SBMs/wk, mean (SD) Lubiprostone 24 µg BID: 1.4 (0.98) Morphine equivalent dose, mg/d, median (range) Lubiprostone 24 µg BID: 300 (5.3-15210) Age, y, mean (SD) Lubiprostone 24 µg BID: 49.8 (9.99) Male, n (%): Lubiprostone 24 µg BID: 176 (40.1) | Lubiprostone ≤ 24 µg BID | The most common treatment-related AEs included nausea (5%), diarrhea (4.6%), headache (1.6%), vomiting (1.4%), abdominal pain (lower, 1.1%, flatulence (1.1%), muscle spasms (1.1%), back pain (1.1%), anemia (1.1%) Change from baseline in SBM and BM frequency (\(P<0.001\) at all months; values not available) SBM frequency was increased throughout the study (baseline: 1.4 SBM per week; range postbaseline: 4.9-5.3 SBM/wk) Response of \(\geq 3\) SBMs/wk for \(\geq 50\%\) of wk in mo: range from 74.0% to 79.8% of patients during 9 mo |
| Naloxegol | Webster et al\textsuperscript{24} Randomized, OL study: 52 wk | N = 804 Age, y, mean (SD) Naloxegol: (n = 534): 52.8 (10.1) Usual care: (n = 270): 52.7 (10.2) Male, n (%): Naloxegol: (n = 534): 181 (33.9) Usual care: (n = 270): 91 (33.7) | Naloxegol 25 mg Investigator-chosen UC laxative regimen | TEAEs that were more frequent in the naloxegol group vs. the UC group were abdominal pain (17.8% vs. 3.3%, respectively), diarrhea (12.9% vs. 5.9%), nausea (9.4% vs. 4.1%), headache (9.0% vs. 4.8%), flatulence (6.9% vs. 1.1%), arthralgia (6.2% vs. 5.9%), nasopharyngitis (6.2% vs. 5.6%), bronchitis (5.6% vs. 4.4%), upper abdominal pain (5.1% vs. 1.1%), and back pain (9.0% vs. 8.9%) There were no incidences of bowel perforation or drug-related cardiovascular events |
Diarrhea was the most common TEAE (11% naldemedine vs. 5.3% placebo). A greater proportion of patients treated with naldemedine compared with placebo reported GI-related TEAEs: abdominal pain (8.2% vs. 3.1%), nausea (7.9% vs. 5.7%), and vomiting (6.0% vs. 3.1%).

The naldemedine group had a greater increase from baseline in the number of BMs per week vs. placebo over the 52-week treatment period (5.2±0.2) compared with (5.0±0.4) placebo. The difference between groups at each time point assessed exact values not reported.

**Naldemedine 0.2 mg QD**

### Placebo

- **Mean (SD)**: 1.59 (0.67) Naldemedine: 1.62 (0.62)
- **Age, y, mean (SD)**: Naldemedine: 53.4 (11.7) Placebo: 52.7 (10.6)
- **Opioid, mg/d, mean (SD)**: Naldemedine: 123.0 (146.1) Placebo: 121.2 (163.4)
- **Male, n (%)**: Naldemedine 238 (38.3) Placebo 217 (35.1)
- **BM Bristol Stool Scale score is rated from 1 (separate hard lumps) to 7 (watery with no solid pieces).** BM indicates bowel movement; GI, gastrointestinal; OIC, opioid-induced constipation; OL, open label; OLE, open-label extension (study); QD, once daily; TEAE, treatment-emergent adverse event; UC, usual care.

### Management of OIC in Chronic Noncancer Pain

Potential drug-drug interactions and restrictions with regard to use in specific patient populations are important considerations in initiating treatment with OIC therapies. Concomitant use of methylnaltrexone, naloxegol, or naldemedine with other opioid antagonists should be avoided because of the possibility of additive effects and increased risk of opioid withdrawal. Concomitant use of moderate and strong CYP3A4 inhibitors may increase plasma concentrations of naloxegol and naldemedine and increase the risk of adverse events, while strong CYP3A4 inducers may decrease concentrations of naloxegol and naldemedine and thereby negatively affect their efficacy. In vitro, methylnaltrexone does not significantly inhibit or induce the activity of cytochrome P450 isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, or CYP3A4, nor is it a substrate for these isozymes. Methadone and other diphenylethylamine opioids may interfere with the efficacy of lubiprostone. Patients treated with naldemedine and P-gp inhibitors such as
|                  | Methylnaltrexone (N = 165) | Placebo (N = 123) | Methylnaltrexone (Oral) Study† | Lubiprostone Studies‡ | Naloxegol Studies§ | Naloxegol Studies§ | Naloxegol Studies§ | Placebo (N = 444) | Naloxegol Studies§ | Naloxegol Studies§ | Placebo (N = 546) | Naloxegol Studies§ | Placebo (N = 546) |
|------------------|---------------------------|------------------|-------------------------------|-----------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Abdominal pain   | NR                        | NR               | 3 (0.5)                       | 4 (2.0)               | 26 (2.9)          | 7 (1.1)           | NR                | NR                | NR                | NR                | NR                | NR                | NR                |
| Abdominal discomfort | NR                     | NR               | 16 (2.7)                      | 6 (3.0)               | 30 (3.4)          | 14 (2.1)          | 11 (2.5)          | 11 (2.5)          | 9 (2.0)           | NR                | NR                | NR                | NR                |
| Abdominal distension | NR                     | NR               | 48 (8.0)                      | 17 (8.5)              | 62 (7.0)          | 30 (4.6)          | 71 (15.9)         | 43 (9.8)          | 25 (5.6)          | 8%                | 2%                | NR                | NR                |
| Abdominal pain   | 47 (28.5)                | 12 (9.8)         | 9 (5.5)                       | 3 (2.4)               | 36 (6.0)          | 7 (3.5)           | 105 (11.8)        | 25 (3.8)          | 41 (9.2)          | 25 (5.7)          | 19 (4.3)          | 7%                | 2%                |
| Constipation     | NR                        | NR               | NR                            | NR                    | NR                | NR                | NR                | NR                | NR                | NR                | NR                | NR                | NR                |
| Decreased appetite | NR                     | NR               | NR                            | NR                    | NR                | NR                | NR                | NR                | NR                | NR                | NR                | NR                | NR                |
| Diarrhea         | 22 (13.3)                | 7 (5.7)          | 7 (4.5)                       | 9 (4.5)               | 35 (3.9)          | 20 (3.1)          | 26 (5.8)          | 13 (2.9)          | 11 (2.5)          | NR                | NR                | NR                | NR                |
| Flatulence       | 19 (11.5)                | 6 (4.9)          | 41 (6.8)                      | 18 (9.0)              | 128 (14.4)        | 42 (6.4)          | 36 (8.1)          | 29 (6.6)          | 20 (4.5)          | 4%                | 2%                | NR                | NR                |
| Nausea           | NR                        | NR               | 16 (2.7)                      | 7 (3.5)               | NR                | NR                | 17 (3.8)          | 8 (1.8)           | 7 (1.6)           | NR                | NR                | NR                | NR                |
| Upper abdominal pain | NR                     | NR               | NR                            | NR                    | NR                | NR                | NR                | NR                | NR                | NR                | NR                | NR                | NR                |
| Vomiting         | NR                        | NR               | 16 (2.7)                      | 9 (4.5)               | 47 (5.3)          | 26 (4.0)          | 20 (4.5)          | 10 (2.3)          | 13 (2.9)          | NR                | NR                | NR                | NR                |
| Gastroenteritis  | NR                        | NR               | NR                            | NR                    | NR                | NR                | NR                | NR                | NR                | NR                | NR                | NR                | NR                |

*Data from pooled analysis of double-blind, placebo-controlled clinical studies in which patients received subcutaneous methylnaltrexone for up to 2 weeks; included all doses of methylnaltrexone (0.075, 0.15, and 0.30 mg/kg/dose).
†Data from a double-blind, placebo-controlled clinical study in which patients received oral methylnaltrexone for 12 weeks; included all doses of methylnaltrexone (150, 300, and 450 mg).
‡Data from pooled analysis of all evaluable safety patients in 3 double-blind trials and 1 open-label long-term trial of lubiprostone.
§Pooled data from two 12-week randomized, placebo-controlled trials of patients with CNCP.
|||
cyclosporine may have elevated plasma naldemedine concentrations and should be monitored for naldemedine-related adverse reactions. Treatment with methylnaltrexone is not recommended for use in women who are nursing, lubeprone stone should be used with caution in women who are nursing, and methylnaltrexone, naloxegol, and naldemedine may cause opioid withdrawal in a fetus. However, naloxegol and naldemedine may be used in nursing mothers depending on a risk: benefit assessment. Naloxegol and naldemedine should be avoided in patients with severe liver impairment.

**Therapies in Development for Treatment of OIC**

**Axelopran**

Axelopran (TD-1211) is a peripherally selective, multi-valent μ-opioid receptor antagonist. Presentation of a 5-week, double-blind, phase 2B study conducted in patients with chronic noncancer pain treated with 3 formulations of TD-1211 for OIC demonstrated significant improvements from baseline in weekly average complete SBMs (CSBMs) during weeks 2 through 5, compared with patients receiving placebo (2.5 complete CSBMs/wk with 15 mg TD-1211, P = 0.0003; 2.6 CSBMs/wk with 10 mg TD-1211, P = 0.001; and 1.5 CSBMs/wk with 5 mg TD-1211, P = 0.04, vs. 0.8 CSBM/wk with placebo). The most common adverse events associated with TD-1211 treatment included abdominal pain (13%), nausea (9%), and diarrhea (9%). There were no indications of opioid withdrawal effects or reductions in opioid analgesia in patients treated with TD-1211.

**Prucalopride**

The benzofuran derivative prucalopride (R093877) is a highly selective serotonin 5-HT₄ receptor agonist with strong GI prokinetic activity. The efficacy and safety of prucalopride for the treatment of OIC in patients with chronic noncancer pain was demonstrated in a phase 2, randomized, double-blind, placebo-controlled study. A phase 3 study of prucalopride in patients with chronic noncancer pain and OIC was terminated early when the clinical development program for prucalopride was stopped based on a business priority decision.

**Clinical Considerations for the Treatment of OIC**

Constipation can have a variety of origins, including underlying functional disorders (eg, IBS, evacuation disorders), neurologic, endocrine, metabolic, myopathic disorders, mechanical obstruction, or malignancy. In addition, some chemotherapeutic agents (eg, vinca alkaloids) may reduce bowel motility. Constipation is often multifactorial in patients receiving opioid therapy (eg, those with malignancy). Chronic pain may lead to poor functional status and diminished activity. Hence, evaluation and treatment of constipation should include a multidimensional approach targeting all suspected causes. Clinical evaluation of a patient with suspected OIC includes a careful clinical history, physical examination, and diagnostic tests only as clinically indicated (eg, complete blood count, complete metabolic profile, thyroid-stimulating hormone, serum calcium). An etiology other than OIC should be considered if a patient has a history of constipation and the onset of or exacerbation of the symptoms of constipation are not closely associated with the initiation of opioid therapy.

Revision of the diagnostic criteria for functional bowel disorders by the gastroenterology community has resulted in the addition of OIC as a new category of GI disorder. OIC is defined as a change from baseline bowel habits and defecation patterns that occurs when initiating opioid therapy and is associated with reduced bowel frequency, the development or exacerbation of straining, a sensation of incomplete evacuation, and/or patient distress related to bowel habits. The diagnosis of OIC requires new or worsening symptoms of constipation that occur when initiating, switching, or increasing the dosage of opioid therapy and that include at least 2 of the following signs and symptoms: (1) straining during > 25% of defecations, (2) lumpy or hard stools involving > 25% of defecations, (3) sensation of incomplete evacuation involving > 25% of defecations, (4) sensation of anorectal obstruction or blockage affecting > 25% of defecations, (5) the need for manual maneuvers to facilitate > 25% of evacuations, or (6) fewer than 3 SBMs/wk. Loose stools should rarely occur unless the patient is using laxatives.

Treatments that do not influence opioid-related mechanisms (eg, laxatives, increased fiber in the diet) may provide insufficient relief for patients with OIC. However, such treatments should nonetheless be considered, both as first-line therapy and as adjunctive strategies for those taking prescription medications. Ensuring that patients are adequately hydrated and maintaining a healthy diet is also important for OIC treatment. It should additionally be considered that constipation is often multifactorial, and factors beyond opioid effects may contribute to the clinical picture. Thus, patients with OIC will often require a comprehensive treatment plan rather than a single-drug approach.

The balance of opioid-related side effects (including constipation) may vary with the specific opioid administered. Each individual patient may have a different adverse event profile response to the efficacy profile of the opioid administered, which may impact the development of opioid-related side effects, such as OIC. Consensus recommendations from the AAPM advocate for physicians to consider switching opioids before initiating prescription medication for OIC. However, in this author’s experience, the majority of patients who develop OIC do so for all opioid medications. When prophylactic laxatives and conservative therapies do not work, reduction or elimination might be the best remaining therapies. In all cases, medical professionals should implement multimodal analgesic strategies to reduce the need for opioids, and patients should be titrated to the lowest effective opioid dose. Published results, however, do not indicate that there is a dose-response relationship between OIC and opioid dose, and many patients experiencing OIC continue to experience it even following dose titration to a lower opioid dose.

To achieve an optimal effect, patients must show willingness to adhere to their prescribed OIC therapy. Therefore, patient preferences with regard to the mode of administration (subcutaneous vs. oral) and daily dosing required (QD vs. BID) should be considered. Prescription medications for OIC are available as oral formulations, and a subcutaneous formulation of methylnaltrexone is also available (Table 1). Methylnaltrexone injection and oral tablet are available as QD formulations and lubiprostone is available as BID formulations. Further, the patient experience with constipation may vary over time. It is highly recommended that patients receiving opioid therapy are assessed.
established.

stipation-related symptoms in these patients to optimize care providers should be aware of the probability of OIC in discontinuation, especially with proper dose adjustment.

mon with these medications but do not usually necessitate Most of these agents may improve constipation within days available in the United States for the management of OIC.

underlying disruption of GI motility and water retention | 186

that the risk: benefit profile of the medication can be established.

CONCLUSIONS

OIC is prevalent in patients receiving long-term administration of opioid analgesics. Laxatives are often insufficient to alleviate OIC because they do not affect the underlying disruption of GI motility and water retention produced by opioid analgesics. Several PAMORAs (eg, methylnaltrexone [injection and oral tablet], naloxegol, and naldeoxime) and a CIC-2 activator (eg, lubiprostone) are available in the United States for the management of OIC. Most of these agents may improve constipation within days of treatment initiation. GI-related adverse events are common with these medications but do not usually necessitate discontinuation, especially with proper dose adjustment. Opioid withdrawal symptoms are generally rare. Health care providers should be aware of the probability of OIC in patients receiving opioid analgesics and monitor constipation-related symptoms in these patients to optimize pain management and improve patient quality of life.

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