Assessing the Burden of Opioid-Induced Constipation:

In Pursuit of Fast Relief and Minimal Pharmacokinetic Drug–Drug Interactions

Overview of OIC

OIC is classified as secondary constipation. It is a common and relatively predictable adverse event (off-target pharmacodynamic event) associated with opioid analgesic (on-target) therapy. In a survey of 322 patients taking oral opioids daily, 45% of patients reported less than 3 bowel movements per week, 81% reported constipation, and 58% reported straining. A meta-analysis of 11 randomized, placebo-controlled studies of patients with CNCP showed that 41% of patients (275/673) who received opioid analgesics experienced constipation compared with 11% (50/441) who received placebo. OIC may occur with frequent or infrequent use of opioids, and changes to dosing do not appear to affect OIC.

The consequences of OIC are diverse and significant. For example, in an American and European survey of patients taking daily oral opioids and laxatives, OIC was most often reported as severe and had at least a moderate negative impact on overall quality of life and activities of daily living. Additionally, non-adherence was reported: One-third of patients had missed, decreased, or stopped using opioids to make it easier to have a bowel movement, thereby resulting in decreased pain control.

Other complications of OIC may include hemorrhoidal bleeding, nausea/vomiting, poor absorption of oral drugs, bowel obstruction, and abdominal pain.
In contrast to physiologic constipation (ie, reduced frequency of bowel movements due to decreased physical activity, and inadequate dietary fiber and fluid intake) or constipation resulting from underlying diseases of the gastrointestinal (GI) tract, nervous system, or metabolic disorders, OIC is mediated by a distinct pathophysiologic process. Specifically, OIC is mediated by the effect of opioids on μ-opioid receptors that are located throughout the GI tract and enteric nervous system. These effects include inhibition of gastric emptying, reduction of mucosal secretions, increased absorption of fluids from stool, sphincter dysfunction, and a decrease in peristalsis (motility) throughout the GI tract, thereby delaying transit.

As a result, dietary or behavioral changes and the over-the-counter (OTC) medications that are usually used for the treatment of more routine constipation may not be effective for the management of OIC, as those measures do not address the particular causative pathophysiologic mechanism.

Insights From the US Pain Foundation Survey

To better characterize the patient population with OIC and identify unmet needs, a national, 1-week online survey sponsored by Salix Pharmaceuticals, in partnership with the US Pain Foundation and conducted by Wakefield Research, evaluated 441 US adults, aged 18 years or older, who were living with chronic pain, on opioid therapy, and suffering from OIC.

A notable finding was the duration of unrelieved OIC was reported as being relatively long. The duration of OIC was greater than 1 year in 77% of respondents and greater than 3 years in 43%, suggesting this condition may have been underrecognized and/or undertreated. Furthermore, 29% of patients reported self-reducing their dose of opioid medication in an attempt to obtain relief from OIC.

Patients reported waiting an average of 18 hours to have a bowel movement after taking their constipation medication, which may have included OTC laxatives and prescription medications (Table 1). Furthermore, 53% of patients stated they prefer OIC relief in under 4 hours.

Patients on chronic opioid therapy often have comorbid conditions that require them to take multiple other medications. This is consistent with results from the same survey of patients with OIC, which reported that 47% of patients were taking a total of 6 to 10 prescription medications on a regular basis and 20% were taking more than 10 prescription medications. Consequently, the rationale of using polypharmacy in these patients leaves them vulnerable to potential pharmacokinetic drug–drug interactions caused by the addition of any other medications.

Of the survey population, 32% of patients reported that their doctor did not speak with them specifically about potential adverse drug–drug interactions of current prescription and/or OTC medications.

Another area of concern identified by the survey is that there may have been insufficient communication between patients and their doctors with regard to OIC. Only 50% of patients stated they were advised regarding the potential to develop OIC when they were first prescribed opioid medications. (Table 2). Also, only 38% of responders had reported being given prescription medications to specifically address OIC, while the majority was given traditional laxatives or advice regarding lifestyle changes.

<table>
<thead>
<tr>
<th>Table 1. US Pain Foundation Survey Data</th>
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<tbody>
<tr>
<td><strong>A. Time until laxation after doctor-recommended intervention</strong></td>
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<tr>
<td>Response, h</td>
</tr>
<tr>
<td>≤6</td>
</tr>
<tr>
<td>7-12</td>
</tr>
<tr>
<td>13-24</td>
</tr>
<tr>
<td>&gt;24</td>
</tr>
<tr>
<td>I have never taken medication to relieve my OIC</td>
</tr>
<tr>
<td>Average</td>
</tr>
</tbody>
</table>

| **B. Patient-indicated preferred time until laxation after doctor-recommended intervention** |
| Response, h | Total, % |
| <4 | 53 |
| 4-6 | 22 |
| 7-12 | 17 |
| 13-24 | 8 |

**OIC,** opioid-induced constipation

Based on reference 18.

<table>
<thead>
<tr>
<th>Table 2. Patient-Reported Gaps in Treatment of OIC</th>
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<tbody>
<tr>
<td>Communication</td>
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<tr>
<td>Diagnosis of OIC</td>
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<tr>
<td>Proactive approach to treatment</td>
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<tr>
<td>Consideration for drug–drug interactions</td>
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</tbody>
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**OIC,** opioid-induced constipation

Based on reference 18.
Management of OIC: Utility of PAMORAs

Because of the unique pathophysiology of OIC, a regimen of conventional laxatives (OTC laxatives, polyethylene glycol, lactulose, magnesium citrate) may not be effective for OIC. In a survey of patients on opioid therapy for pain who required laxative therapy, only 46% of opioid-treated patients reported achieving the desired treatment results more than 50% of the time. In a longitudinal study consisting of a patient survey, physician survey, and chart review focusing on the burden of OIC, the rate of inadequate response to at least 1 laxative agent within the past 2 weeks was 94%. The rate of inadequate response to use of at least 2 laxative agents from 2 or more different classes at least 4 times each within the past 2 weeks was 27%.

As a result, investigators have strived to develop pharmacologic treatments that are more suited for OIC in adult patients with CNCP and advanced disease. One class of drugs, peripherally acting μ-opioid receptor antagonists (PAMORAs), functions by blocking enteric μ-opioid receptors and therefore directly addresses the pathophysiologic mechanism of OIC. The 2015 American Academy of Pain Medicine (AAPM) consensus recommendation on OIC states that initial consideration of first-line OTC interventions for OIC is essential; however, failure of these treatments to provide adequate relief should be determined quickly to facilitate consideration of further intervention with PAMORAs or other prescription medications.

The findings of these surveys may be interpreted to suggest that the ideal agent for the treatment of OIC, would among other characteristics, be one that 1) blocks the action of opioids on GI μ-opioid receptors without interfering with the actions of opioids on the central opioid receptors that mediate analgesia (ie, a drug that does not cross the blood–brain barrier), 2) acts rapidly to promote laxation, and 3) has minimal potential for interactions with the cytochrome P450 (CYP) system and minimal potential for other drug–drug interactions. In selecting a prescription medication that targets the underlying cause of OIC, the AAPM recommends an evaluation of the severity of OIC and the response to current treatment using the Bowel Function Index (BFI): A score of at least 30 is recommended for consideration of a prescription medication. In addition to using the BFI, the AAPM consensus panel has identified the Bristol Stool Form Scale (BSFS) as a supplemental tool that provides patients more descriptive parameters.

Relistor for the Use of OIC

Several PAMORA agents have been developed and are FDA approved for the treatment of OIC in patients with CNCP, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation: methylnaltrexone bromide (Relistor, Salix), naldemedine, and naloxegol. Methylnaltrexone bromide is a PAMORA with 2 dosage forms: an oral tablet and a subcutaneous injection. While both methylnaltrexone bromide formulations share the same indication as the other 2 PAMORAs, the subcutaneous injection is the only PAMORA formulation indicated for the treatment of OIC in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care.

In a randomized, double-blind trial of 401 CNCP patients with OIC, the efficacy and safety of oral methylnaltrexone bromide was compared with placebo by measuring the proportion of patients with at least 3 spontaneous bowel movements (SBMs) per week, with an increase of 1 or more SBMs per week over the baseline for 3 or more out of the first 4 weeks of the treatment period. Results showed that 52% of patients receiving 450 mg of oral methylnaltrexone bromide were considered responders compared with 38% receiving placebo (P=0.005). As the primary end point, dosing days resulting in a rescue-free bowel movement within 4 hours of dosing during weeks 1 and 4 were assessed. Results showed that 27% of patients receiving oral methylnaltrexone bromide 450 mg per day were more likely to have an SBM within

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Methylnaltrexone Bromide 450 mg Per Day, %</th>
<th>Placebo, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>4</td>
<td>2</td>
</tr>
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Based on reference 25.
4 hours of treatment compared with placebo ($P<0.0001$).\textsuperscript{22} Safety data showed the dose to be well tolerated compared with placebo (Table 3).\textsuperscript{25}

For OIC in patients with advanced disease, efficacy and safety of a single injection of subcutaneous methylnaltrexone bromide 0.15 and 0.3 mg/kg were compared with placebo in a randomized, double-blind study (Study 4) of 154 patients over a 4-week dosing period.\textsuperscript{25,28} Results showed a significantly higher rate of rescue-free laxation within 4 hours of the double-blind dose (62%) compared with placebo (14%; $P<0.0001$).\textsuperscript{25,28}

In a randomized, double-blind trial with 133 participants (Study 5), subcutaneous injections of methylnaltrexone bromide 0.15 mg/kg were compared with placebo given every other day for 2 weeks.\textsuperscript{25,29} Results showed a higher proportion of patients experiencing rescue-free laxation within 4 hours in the methylnaltrexone bromide group (48% vs 16%; $P<0.0001$) (Figure).\textsuperscript{25,28,29}

Approximately half of the patients who responded experienced relief within 30 minutes.\textsuperscript{25,28,29} These data indicate that PAMORAs, particularly methylnaltrexone bromide, can provide fast relief from OIC and are consistent with the preferences expressed by patients in the US Pain Foundation survey.

Many CNCP patients who suffer from OIC have other comorbidities that are managed medically with the use of a rational polypharmacy regimen, which can create a potential for clinically relevant pharmacokinetic drug–drug interactions, especially those metabolized through the CYP450 3A4 pathway. It would seem reasonable that the use of a drug to treat OIC that has a low potential for clinically relevant CYP3A4 drug–drug interactions would be preferred over one that has a high potential for such interactions. Clinicians should note that not all PAMORAs are similar with regard to their potential for pharmacokinetic drug–drug interactions. In fact, methylnaltrexone bromide does not significantly inhibit or induce CYP isozymes, including CYP1A2, 2A6, 2B6, 2C9, 2C19, or 3A4, nor is it a substrate for these enzymes,\textsuperscript{25} whereas other FDA-approved PAMORAs have the potential for pharmacokinetic drug–drug interactions when concomitantly used with inhibitors and inducers of the CYP3A4 pathway.\textsuperscript{26,27} These observations suggest that methylnaltrexone bromide offers a management option for OIC with a low potential for pharmacokinetic drug–drug interactions, which was a concern of chronic pain patients as identified in the US Pain Foundation survey.

**Conclusion**

OIC is a common adverse event associated with opioid therapy in patients with moderate to severe pain. As shown by the results of the US Pain Foundation survey, OIC may impose a burden on affected patients who are commonly being treated with a number of medications to manage their pain and other comorbidities. Ultimately, these patients seek rapid reliable relief.

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**Figure.** Patients who experienced an SBM within 4 hours of the initial dose of subcutaneous methylnaltrexone bromide (Relistor) for OIC.

**OIC,** opioid-induced constipation; **SBM,** spontaneous bowel movement

Based on references 25, 28, and 29.
Addressing OIC is a key consideration in optimizing opioid therapy. Thus, patients prescribed chronic opioid therapy should be educated on the potential of experiencing OIC along with the signs and symptoms of OIC, and how to mitigate and manage it through the use of lifestyle management (ie, increased water, fiber, and exercise) along with the use of OTC products. Patients and health care professionals need to adhere to a “do ask, do tell policy” that allows for an open conduit of information exchange. Attempts to quantify the impact of OIC on patients should include tools such as the BFI and BSFS. Because conventional therapies may be ineffective in restoring normal bowel function in patients with OIC, it is important to monitor for worsening of the condition and, if deemed necessary, consider the use of FDA-approved OIC-indicated products targeted to specially addressing OIC’s underlying pathophysiology. Also, it is critical to evaluate the potential for CYP3A4 isozyme–related pharmacokinetic drug–drug interactions when deciding on which targeted agent to prescribe, especially in patients receiving multiple prescription medications and/or supplements, in order to mitigate the potential for these effects.
INDICATIONS

- RELISTOR® (methylnaltrexone bromide) is an opioid antagonist. RELISTOR tablets and RELISTOR injection are indicated for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.

- RELISTOR injection is also indicated for the treatment of OIC in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care.

IMPORTANT SAFETY INFORMATION

- RELISTOR tablets and injection are contraindicated in patients with known or suspected mechanical gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation.

- Cases of gastrointestinal perforation have been reported in adult patients with opioid-induced constipation and advanced illness with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, Ogilvie’s syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). Take into account the overall risk-benefit profile when using RELISTOR in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn’s disease). Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue RELISTOR in patients who develop this symptom.

- If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their healthcare provider.

- Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, and yawning have occurred in patients treated with RELISTOR. Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced analgesia and should be monitored for adequacy of analgesia and symptoms of opioid withdrawal.

- Avoid concomitant use of RELISTOR with other opioid antagonists because of the potential for additive effects of opioid receptor antagonism and increased risk of opioid withdrawal.

- The use of RELISTOR during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood-brain barrier and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because of the potential for serious adverse reactions, including opioid withdrawal, in breastfed infants, advise women that breastfeeding is not recommended during treatment with RELISTOR. In nursing mothers, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

- A dosage reduction of RELISTOR tablets and RELISTOR injection is recommended in patients with moderate and severe renal impairment (creatinine clearance less than 60 mL/minute as estimated by Cockcroft-Gault). No dosage adjustment of RELISTOR tablets or RELISTOR injection is needed in patients with mild renal impairment.

- A dosage reduction of RELISTOR tablets is recommended in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. No dosage adjustment of RELISTOR tablets is needed in patients with mild hepatic impairment (Child-Pugh Class A). No dosage adjustment of RELISTOR injection is needed for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, monitor for methylnaltrexone-related adverse reactions and dose adjust per Prescribing Information as may be indicated.

In the clinical studies, the most common adverse reactions were:

**OIC in adult patients with chronic non-cancer pain**

- RELISTOR tablets (≥ 2% of RELISTOR patients and at a greater incidence than placebo): abdominal pain (14%), diarrhea (5%), headache (4%), abdominal distention (4%), vomiting (3%), hyperhidrosis (3%), anxiety (2%), muscle spasms (2%), rhinorrhea (2%), and chills (2%).

- RELISTOR injection (≥ 1% of RELISTOR patients and at a greater incidence than placebo): abdominal pain (21%), nausea (9%), diarrhea (6%), hyperhidrosis (6%), hot flush (3%), tremor (1%), and chills (1%).

**In clinical OIC in adult patients with advanced illness**

- RELISTOR injection (≥ 5% of RELISTOR patients and at a greater incidence than placebo): abdominal pain (29%) flatulence (13%), nausea (12%), dizziness (7%), and diarrhea (6%).

To report SUSPECTED ADVERSE REACTIONS, contact
Salix Pharmaceuticals at 1-800-321-4576 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Please see accompanying full Prescribing Information for RELISTOR tablets and RELISTOR injection.
References


Disclosures: Dr Pergolizzi reported that he has received grant/research support from Purdue Pharma and Salix Pharmaceuticals. He is a consultant to BioDelivery Sciences, Daiichi Sankyo, Grünenthal GmbH, Inspiron, Mallinkrodt, Neumentum, Purdue Pharma, and Salix Pharmaceuticals. Dr Pergolizzi also reported that he is a stock shareholder for Neumentum, and has received honoraria from BioDelivery Sciences, Daiichi Sankyo, Inspiron, Neumentum, and Salix Pharmaceuticals. He is on the speakers bureau for AstraZeneca, BioDelivery Sciences, Daiichi Sankyo, Inspiron, and Salix Pharmaceuticals.

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