Combating Opioid-Induced Constipation: New and Emerging Therapies

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Opioid use is a significant and prevalent public health problem that costs society approximately $560 to $635 billion annually, an amount equal to about $2,000.00 for every person living in the US. As a result of the number of individuals experiencing persistent pain, the National Institute of Health reported that approximately 200 million prescriptions for opioids were dispensed in 2013, a trend that has grown by more than 50% over the last 10 years, and by nearly 100% since 2000.

Almost all patients requiring chronic opioid therapy develop side effects, the most common of which affect the gastrointestinal (GI) and central nervous systems (CNS). Although tolerance develops to many of the CNS side effects over time (ie, sedation), resolution of opioid-induced bowel dysfunction (OIBD), and more specifically opioid-induced constipation (OIC), does not occur with continued use.

How prevalent is OIC? The numbers vary widely based on study design and patient populations. Based on an analysis of 16 clinical trials and observational studies, OIC...
has been reported to occur in 15% to 90% of patients.\(^5\) When these studies are qualified according to type of chronic pain, estimates from observational studies in the United States suggested that the prevalence of OIC in patients with non-cancer pain ranged between 40% and 50%.\(^6\)

In addition to being a common side effect, OIC significantly affects a patient’s quality of life.\(^7\) A study of work productivity in patients on chronic opioid therapy found that OIC impacted productivity and activity levels. Specifically, the study found that patients reported 9% work time missed, 32% impairment while working (equivalent of 14 hours of lost productivity per week), and 38% activity impairment.\(^8\) Additionally, participants in a recent OIC study commonly reported that their constipation interfered with the ability of their opioid medication to control pain, with 49% reporting moderate or complete interference, and 8% reporting that they changed how they used their opioid in order to have a bowel movement.\(^9\)

**Effect of Opioids on GI Tract**

Multiple mechanisms influence the occurrence of OIC. In fact, the very mechanisms that allow opioids to be effective pain medications are also involved in causing OIC. Opioid agonists mitigate pain by binding to opioid receptors that are located in the central and peripheral nervous systems. Mu-opioid receptors, and to a lesser extent kappa- and delta-opioid receptors, are located throughout the GI tract. Here opioids reduce contractility and tone leading to increased transit time.\(^3\) Specifically, they exert their effects in the neuronal plexi, located between the longitudinal and circular muscle layers (myenteric plexus) and within the submucosa (submucosal plexus),\(^9\) and indirectly through the central nervous system via intrathecal administration of opioids, decreasing GI motility and intestinal secretion.\(^50\)

Passive absorption of fluids is increased and intestinal secretions are reduced in the GI tract with opioids due to increased frequency and strength of circular muscle contractions that cause non-propulsive contractions.\(^3\) Within the myenteric plexus, opioids stimulate relaxation of the longitudinal smooth-muscle layer, thus increasing tonicity in the circular smooth-muscle layer. The mechanism of this action is believed to occur through inhibition of acetylcholine release and inhibition of vasoactive

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**Table 1. Commonly Used Definition of Opioid-Induced Constipation**

<table>
<thead>
<tr>
<th>Diagnosis of Opioid-Induced Constipation</th>
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<tbody>
<tr>
<td>1. Fewer than 3 bowel movements per week</td>
</tr>
<tr>
<td>2. Hard or lumpy stools</td>
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<tr>
<td>3. Sensation of incomplete evacuation</td>
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<tr>
<td>4. Sensation of anorectal obstruction</td>
</tr>
<tr>
<td>5. Straining with defecation</td>
</tr>
<tr>
<td>6. Bloating and abdominal pain relieved with bowel movements</td>
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<tr>
<td>7. Small stools</td>
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<tr>
<td>8. GERD (potentially)</td>
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</tbody>
</table>

**Table 2. Categories of Anti-constipatory Agents**

<table>
<thead>
<tr>
<th>Category</th>
<th>Mechanisms of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk-producing Agents</td>
<td>Bulking agents work in both the small and large bowel, with an onset of action of 12 to 72 hours. They bulk up the stool so that it retains more water, making peristalsis easier. Examples include psyllium, methylcellulose, and dietary fiber.</td>
</tr>
<tr>
<td>Stool Softeners</td>
<td>Stool softeners soften stool and make it “slippery,” making the stool easier to pass. These work in the colon and take from 6 to 8 hours to take effect.</td>
</tr>
<tr>
<td>Lubricants or Emollients</td>
<td>Lubricants/emollients, such as mineral oil, soften and coat the stool, thus preventing colonic water absorption. Vegetable-oil enemas act as lubricants.</td>
</tr>
<tr>
<td>Hydrating Agents</td>
<td>Hydrating agents increase the water content in the stool, which makes the stool softer and easier to pass. Some of these work by increasing the bowel lumen osmolality. Examples include Fleet phospho-soda and Miralax.</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Stimulants stimulate colonic contractions that propel stools forward. These agents irritate the lining of the intestines. Examples include cascara sagrada, bisacodyl, and senna.</td>
</tr>
<tr>
<td>Others</td>
<td>Prostaglandins, prokinetic drugs, and other agents change the way the intestine absorbs water and electrolytes, and increase the weight and frequency of stools while reducing transit time.</td>
</tr>
</tbody>
</table>
intestinal peptide and nitric oxide release. Ultimately, this results in an increase in segmental contraction, while peristaltic activity is decreased, inducing constipation. Reduced propulsive contractions of longitudinal muscles also contributes to hard and dry stools. Rectal stool evacuation is decreased by an increased threshold for triggering of the anorectal reflex.

**Diagnosis of OIC**

Opioids affect the entire gut, from the mouth to the anus, and OIBD refers to the constellation of GI effects. This includes gastroparesis, gastroesophageal reflux disease (GERD), and other GI-related disorders. Although no delineation for constipation has been universally accepted, various definitions of constipation exist. According to the American College of Gastroenterology definition, constipation is defined as unsatisfactory defecation with infrequent bowel movements, difficult stool passage, and having less than 3 bowel movements per week.

Even though this definition is not restricted to opioid-induced constipation, the Rome III criteria is often used to describe this condition. Functional constipation, as outlined by the Rome III criteria, requires 2 or more of the following symptoms to occur no less than 25% of the time in the past 12 weeks: straining with bowel movements, passing lumpy or hard stools; feeling of incomplete evacuation; feeling of anorectal obstruction; using manual maneuvers for facilitation of defecation; and having less than 3 bowel movements per week. Even though this definition is not restricted to opioid-induced constipation, the Rome III criteria is often used to describe this condition (Table 1).

**Treatment Options**

Over-the-counter options for management of constipation include increasing dietary fiber intake, increasing fluid intake, and increasing physical activity. However, there is inadequate evidence to support the use of these interventions for OIC, and they often are ineffective, which necessitates use of laxatives. Stimulant laxatives are often used first-line due to their low cost and efficacy despite not correcting the underlying mechanism. Table 2 describes categories of anti-constipating agents.

Stimulant laxatives, including senna and bisacodyl, work by increasing muscle contractions. Patients, however, may develop tolerance and dependence to stimulant laxatives. Docusate, a surfactant stool softener, does not assist with muscle contractility but is non-habit forming. Bulk-forming laxatives, for example psyllium, may lead to increased abdominal pain and bowel obstruction. Lactulose and polyethylene glycol are osmotic laxatives that pull water into the GI tract and have evidence for use in OIC, but they do not target the actual OIC cause, and they may provoke electrolyte abnormalities. Unfortunately, patients may have inadequate symptom relief from OIC with these laxatives alone or combined.

**Pharmaceutical Therapy**

It is not often in medicine that a pharmacological antidote exists to a drug treatment or adverse effect. Although newer select agents (ie, ion channel activators) have been approved for OIC, there is only one class of drug that targets the specific underlying cause of OIC—binding of opioids to the mu-receptors in the enteric nervous system. This new class, known as PAMORAs (Peripheral Acting Mu Opioid Receptor Antagonists), work by selectively inhibiting opioid receptors in the gut, thereby decreasing the constipating effects of opioids without affecting opioid-mediated analgesic effects within the central nervous system or precipitating withdrawal symptoms (Table 3).

### Table 3. Current and Emerging Treatments for Opioid-Induced Constipation

<table>
<thead>
<tr>
<th>Agent (Brand)</th>
<th>Company</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvimopan (Enterag)</td>
<td>GlaxoSmithKline</td>
<td>FDA approved for postoperative ileus; results in OIC were equivocal</td>
</tr>
<tr>
<td>Axelopran (formerly TD 1211)</td>
<td>Theravance, Inc.</td>
<td>In Phase 3 clinical trials</td>
</tr>
<tr>
<td>Bevenopran</td>
<td>Cubist Pharmaceuticals</td>
<td>In Phase 3 clinical trials</td>
</tr>
<tr>
<td>Methylenealtrexone (Relistor)</td>
<td>Salix Pharmaceuticals</td>
<td>FDA approved for OIC in advanced illness in palliative care and CNCP</td>
</tr>
<tr>
<td>Naldemedine (S-297995)</td>
<td>Shionogi Inc.</td>
<td>In Phase 3 clinical trials</td>
</tr>
<tr>
<td>Naloxegol (Movantik)</td>
<td>AstraZeneca</td>
<td>FDA approved for OIC in CNCP</td>
</tr>
</tbody>
</table>

CNCP, chronic non-cancer pain; OIC, opioid-induced constipation; PAMORA, peripheral acting mu opioid receptor antagonists.
**Alvimopan**

The first available medication in this class was alvimopan (Entereg), which is indicated to accelerate the time to upper and lower gastrointestinal recovery following surgeries that include partial bowel resection with primary anastomosis.\(^{19}\)

Although not specifically approved for OIC, alvimopan has been studied in 522 patients with OIC.\(^{20}\) The patients, who were all receiving 30 mg per day of morphine equivalent, were randomly assigned to receive oral alvimopan at three doses (0.5 mg twice daily, 1 mg once daily, 1 mg twice daily), or placebo for 6 weeks. When compared with placebo, alvimopan significantly increased the mean weekly frequency of spontaneous bowel movements (SBM) over the initial 3 weeks of treatment: 0.5 mg twice daily (+1.71 mean SBMs per week), 1 mg once daily (+1.64), and 1 mg twice daily (+2.52) (\(P<0.001\) for all comparisons). The increased frequency of SBMs and additional treatment effects (less straining, incomplete evacuation, abdominal bloating or discomfort; more stool consistency; and better appetite) were sustained for more than 6 weeks.\(^{20}\)

In a study employing alvimopan (0.5 mg twice daily) for patients with chronic non-cancer pain (CNCP) on opioids, almovipan was associated with an increased risk of myocardial infarction compared to placebo, leading to the issuance of a boxed warning and REMS program.\(^{19}\) The manufacturer requires hospitals to enroll in the E.A.S.E. program to be able to acquire alvimopan. A hospital in the E.A.S.E. program must acknowledge the following:

- Hospital staff who prescribe, dispense, or administer the product have been provided the educational materials on the need to limit the use to short-term, inpatient use.
- Patients will not receive more than 15 doses.
- The product will not be dispensed to patients after they have been discharged from the hospital.\(^{15}\)

**Methylnaltrexone Bromide**

The next PAMORA introduced to the market was methylnaltrexone bromide (Relistor). In 2010, methylnaltrexone subcutaneous injection was FDA approved for the treatment of OIC in patients with advanced illness receiving palliative care. More recently, the agent was also approved for the treatment of OIC in adult patients with CNCP.\(^{21}\) Methylnaltrexone bromide is a quaternary amine with limited penetration through the blood-brain barrier.

The clinical trials leading to methylnaltrexone's approval found that the agent produced reliable relief of constipation in opioid-treated pain patients—59% of patients receiving methylnaltrexone (12 mg subcutaneous injection daily for 4 weeks) had more than 3 SBMs per week compared to 38% in the placebo treatment group.\(^{22}\) The most common side effects are abdominal pain, nausea, and vomiting. Furthermore, methylnaltrexone did not appear to reverse the opioid's analgesic effect or cause opioid withdrawal symptoms.\(^{21}\)

In addition, significantly more methylnaltrexone-treated patients had a bowel movement within 4 hours than did placebo-treated patients (52% vs. 9%; \(P<0.0001\) ). In approximately 30% of treated patients, laxation was reported within 30 minutes of a dose of methylnaltrexone. Two open-label extension studies suggested the laxation response appeared to be maintained over the course of 3 to 4 months.\(^{22}\)

According to the Prescribing Information, methylnaltrexone is available in single use vials and single use pre-filled syringes. The dosage for CNCP is 12 mg, similar to those patients with OIC in advanced illness weighing 62-114 kg; patients weighing 38-62 kg should receive 8 mg. Outside of this range, dosing is recommended at 0.15 mg/kg. Administration for CNCP is daily, with the caveat to discontinue all maintenance laxative therapy prior to starting injections; laxative(s) can be used as needed if there is a suboptimal response to the agent after 3 days. Dosage reduction is recommended for patients with severe renal impairment.\(^{21}\)

**Naloxegol**

Recently, the FDA approved the first orally administered, once-daily PAMORA for OIC in patients with CNCP. Naloxegol (Movantik) is polyethylene glycol (PEG)ylated form of naloxone, and as a result of its chemical nature, it is not appreciably absorbed via the GI tract. It is expected to be available in the first half of 2015.\(^{23}\)

The efficacy of naloxegol was studied in over 1300 patients who had been on oral opioids for an average of 3.6 years. OIC was defined as less than 3 SBMs per week with hard/lumpy stools, straining, or sensation of incomplete evacuation or obstruction in 25% or more bowel movements in the last 4 weeks. Patients were randomly assigned to 3 treatment arms: naloxegol 25 mg daily, naloxegol 12.5 mg daily, or placebo daily for 12 weeks. During the study, no other bowel regimens were permitted, but bisacodyl was allowed as rescue medication if patients did not have a bowel movement in 3 days.\(^{24}\)

Two identical efficacy and safety studies were performed (Study 1 and Study 2). The primary endpoint was defined as ≥3 SBMs per week and a change from baseline of ≥1 SBM per week for at least 9 out of the 12 study weeks, and 3 out of the last 4 weeks.\(^{23}\) There was a statistically significant difference in response for the 25 mg naloxegol treatment group versus placebo.
for the primary endpoint in Study 1 and Study 2. Statistical significance for the 12.5 mg treatment group versus placebo was observed in Study 1 but not in Study 2.23

One secondary endpoint in both studies was response in laxative users with OIC symptoms. In this subgroup, 42% and 50%, respectively, reported using laxatives on a daily basis. A statistically significantly higher percentage of patients in both studies responded with naloxegol 25 mg versus placebo. This was also seen with naloxegol 12.5 mg in Study 1; but was not tested in Study 2.

Time to first bowel movement was 6 to 20 hours in naloxegol-treated patients compared to 36 hours in the placebo group. The most common adverse events were abdominal pain (12%-21%), diarrhea (6%-9%), nausea, and flatulence.24

Contraindications for naloxegol include known, suspected, or at increased risk of GI obstruction; concomitant administration of strong cytochrome P (CYP) 450 3A4 inhibitors; and serious or severe hypersensitivity reaction to naloxegol or any of its ingredients.24

Prior to initiation of naloxegol, it is recommended to discontinue all maintenance laxative therapy, which can be resumed after 3 days if there is a suboptimal response to naloxegol. Standard dosing of naloxegol is 25 mg by mouth once daily 1 hour before or 2 hours following the first meal of the day. In patients unable to tolerate this dose, a 12.5 mg dose of naloxegol is recommended. Renal adjustment of the starting dose is suggested in patients with a creatinine clearance <60 mL/min.24

Serious adverse reactions that may occur include opioid withdrawal. Opioid withdrawal, considered in this trial to be at least 3 symptoms potentially related to opioid withdrawal, occurred in 1% of patients on naloxegol 12.5 mg compared to 3% on naloxegol 25 mg; less than 1% of patients on placebo experienced opioid withdrawal (see Sidebar, page 46).

**Emerging Therapies**

While the most commonly used PAMORA on the market is methyl-mu-opioid receptor.25 It successfully completed a Phase 2b study that demonstrated a sustained increase in bowel movement frequency in patients regardless of duration of OIC.26 As of September 2014, Phase 3 studies were pending.

Multiple mechanisms cause opioid-induced constipation (OIC). In fact, the very mechanisms that allow opioids to be effective are also involved in causing OIC.

**Axelopran**

Axelopran (formerly TD 1211) is an oral, once-daily peripherally selective, multivalent inhibitor of the mu-opioid receptor. It successfully completed a Phase 2b study that demonstrated a sustained increase in bowel movement frequency in patients regardless of duration of OIC.26

**Bevenopran**

Another emerging PAMORA currently in Phase 3 of development is bevenopran (CB-5945; f/k/a ADL-5945). The latest trial planned is a multicenter, double-blind, placebo-controlled, parallel-group study in subjects with OIC taking opioid therapy for CNCP. Patients will be randomized to receive either oral 0.25 mg bevenopran twice daily or placebo for the
s of press time, the Drug Enforcement Agency (DEA) has designated naloxegol (Movantik) as a scheduled II controlled substance. Naloxegol was recently approved for the treatment of opioid-induced constipation and is part of a class of medications known as PAMORAs (Peripherally Acting Mu Opioid Receptor Antagonists). Other FDA agents in this category include alvimopan (Entereg) and methylnaltrexone (Relistor).

This action was taken specifically due to naloxegol’s structural resemblance to noroxymorphone. The abuse and dependence potential of the agent have been evaluated in clinical studies, and the company has submitted a petition to decontrol this medication. According to the labeling, naloxegol has no risk of abuse or dependence.

The DEA’s decision to schedule naloxegol in any category is disillusioned at best, and in the authors’ opinion, more likely a knee-jerk reaction to the recent high scrutiny attributable to the purported “opioid epidemic.” By comparison, consider that naloxone is a legend but non-scheduled drug—both are dehydroxylated phenantherenes. Also consider that more and more states are allowing naloxone in various packaging to be dispensed without a prescription and that more and more states are allowing naloxone in various packaging to be dispensed without a prescription and that naloxone is a PEGylated form of naloxone.

Buprenorphine is a partial agonist/antagonist dehydroxylated phenantherene that is schedule III but certainly does have analgesic efficacy. But perhaps most telling is that noroxymorphone is not naloxegol, and if injected intrathecally by a substance abuser (which is incomprehensible and not studied), it would theoretically have opioid antagonist properties, not agonist activity. For all of these reasons, the authors are not convinced that there are any valid reasons to schedule naloxegol.

As noted, naloxegol is a PEGylated offshoot of naloxone, which limits its permeability across the blood brain barrier and into the central nervous system (CNS). This negligible penetration into the CNS prevents naloxegol from affecting opioid analgesia occurring centrally. High-fat meals have been shown to increase the extent and rate of absorption, explaining the administration recommendation of taking naloxegol on an empty stomach. The volume of distribution ranged from 968 to 2140 L with low plasma protein binding. Naloxegol undergoes metabolism through the CYP3A4 system and is a substrate for p-glycoprotein (pGP); it is excreted primarily as metabolites via the feces (8%). It is worth noting that the PEGylation is most probably the reason for pGP absorption as metabolites via the feces (8%).

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Based on drug interaction studies, naloxegol is not expected to alter the clearance of drugs metabolized by CYP enzymes. However, naloxegol clearance may be affected by CYP3A4 inhibitors and inducers. It is recommended to avoid the concomitant use of naloxegol with strong CYP3A4 inhibitors and inducers, as well as to avoid the consumption of grapefruit juice or other natural products/vitamin supplements that could inhibit this enzyme. If unable to avoid moderate CYP3A4 inhibitors with naloxegol, it is advised to reduce the dose of naloxegol to 12.5 mg daily.1

References

12-week treatment period, followed by a 4-week follow-up period. According to Avarex Web site, “all subjects will be followed for 16 weeks regardless of when they discontinue study medication.” The primary outcome measure is overall SBM rates over the 12-week double-blind treatment period.

Naldemedine
Another emerging PAMORA currently in Phase 3 of development is naldemedine (S-297995). The agent will be studied in a double-blind, placebo-controlled multicenter study. The study will evaluate the efficacy and safety of naldemedine (0.3 mg once-daily) compared with placebo for the treatment of OIC in CNCP patients on chronic opioid therapy. According to Shionogi’s website, naldemedine “may prove more favorable than existing treatments, given its efficacy at lower doses in alleviating not just opioid-induced constipation but also nausea and vomiting.”

Following a successful Phase 2 study completed in 2011, in which 75 subjects were randomized to 1 of 6 S-297995 cohorts (0.01 mg, 0.03 mg, 0.1 mg, 0.3 mg, 1.0 mg, or 3.0 mg), results demonstrated a statistically significant and dose-dependent increase from baseline in the number of SBMs at 24 hours post-dose, starting at doses of 0.3 mg. There was no evidence of opioid withdrawal and there was no impact on the analgesic effect of the opioids or a change in pupil size.

Cardiovascular Risk
In June 2014, a majority of FDA committee members voted that the FDA should not require cardiovascular outcomes trials for PAMORAs being developed for the treatment of OIC in patients with CNCP. Following a clarification of the vote, the majority of the committee members suggested continued post-approval data collection for cardiovascular safety.

Conclusion
OIC is the most common adverse effect of chronic opioid therapy. It occurs as a natural response to opioid binding at mu receptors throughout the GI tract. Non-pharmacological strategies and laxatives are commonly employed to combat OIC; however, these strategies often fall short in efficacy. To avoid constipation resistant to laxative treatment, patients may decrease their use of opioids, which can lead to additional pain. For those failing first-line options, PAMORAs represent a reliable treatment option that targets the underlying cause of OIC. The emergence of this new class of agents has provided an opportunity for patients to receive effective pain relief while minimizing the unwanted peripheral effects of opioids.

Clinicians need to understand the indications, limitations, and contraindications—especially in patients with suspected bowel obstruction due to the risk of perforation.

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Dr. Kominek has disclosed that he receives consultant fees from Alere, INSYS, XenoPort, Zogenix, and Necktar. He also receives speaker bureau fees from AstraZeneca, Teva, Iroka, Salix, Purdue, Depomed, XenoPort, and Mallinckrodt.

Dr. Kominek has disclosed that he receives consultant fees from Millennium Health and Zogenix. He also receives speaker bureau fees from AstraZeneca and Millennium Health.

Dr. Kominek and Dr. Laitman have no financial conflicts to disclose.

Drs. Fudin and Kominek disclosed that their involvement with this article was not prepared as part of their official government duties as Clinical Pharmacy Specialists at the VA and stated opinions/ assertions do not reflect the opinion of employers, employee affiliates, and/or pharmaceutical companies listed.

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