

Guidelines add latest evidence for managing opioid-induced constipation

The American Gastroenterological Association (AGA) updated its guidelines on medical management of opioid-induced constipation (OIC), which were published last October in AGA's journal *Gastroenterology*.¹ Considering the climbing rate of opioid use in the United States and the rate at which OIC accompanies opioid therapy, clinicians may find that reviewing this latest evidence will confer benefits to many of their patients with chronic pain.

Approximately 9 to 12 million Americans suffer from chronic pain annually, and 4% to 5% of the U.S. population uses prescription opioids regularly. OIC is estimated to affect 40% to 80% of patients on chronic opioid therapy. While rates of opioid prescribing have risen throughout several decades, a true representation of those affected by opioid-induced adverse effects and dependence is greater because of increased nonmedical or illicit use.¹

As a condition specifically associated with the effects of opioids, OIC differs mechanically from other forms of constipation. For this reason, it deserves dedicated attention and an approach to treatment individualized for specific patients' needs.

"In my palliative care practice, I have found that untreated constipation—or suboptimal treatment of constipation—can significantly impact a patient's quality of life," noted Leah Sera, PharmD, MA, BCPS, assistant professor of pharmacy practice and science at the University of Maryland School of Pharmacy. "We know that constipation is a predictable opioid-related adverse effect, and that patients don't become tolerant to it. Several new drugs have been approved to treat OIC in the last few years. Guidelines help clinicians translate medical evidence into clinical practice and provide optimal care to patients."

Recommendation review

This guideline was developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology and best practices determined by the Institute of Medicine. Strong recom-

mendations indicated that most individuals should receive the recommended courses of action, while conditional recommendations suggested that different choices would be appropriate for different patients and that clinicians should spend more time on these decisions. See the table for a graded summary of AGA recommendations for medical management of OIC.

Traditional laxatives were recommended as first-line agents for treatment of OIC because of their low cost,



few safety concerns, and wide accessibility in generic or OTC formulations. To avoid potentially undertreating laxative-refractory OIC, the panel suggested treatment combining use of at least two types of laxatives from different classes before escalating therapy. These should also be administered in a scheduled fashion, versus "as needed" use, before considering alternative OIC therapy.

Four peripherally acting μ -opioid receptor antagonists (PAMORAs) were reviewed, with naldemedine and nalox-

egol receiving strong recommendations. "Because PAMORAs all have similar mechanisms of action," said Sera, "the authors of this guideline based their recommendation primarily on the quality of available evidence for each agent."

Naldemedine was the only prescription drug evaluated by AGA with available long-term safety data available. The overall quality of evidence for use of naldemedine in OIC refractory to laxatives was considered high, but cost may pose limitations. Naloxegol was the first PAMORA approved by FDA, but its moderate-quality evidence for OIC management and high cost denote judicious use. Evidence supporting the use of methylnaltrexone was marked low, receiving downgrades for indirectness, inconsistency, and imprecision across outcomes. The availability of a S.C. formulation, however, may convey advantages in some clinical situations.

Limited consistent evidence exists to support a recommendation for use of lubiprostone or prucalopride for OIC

treatment. In the literature, 6.4% of patients who received lubiprostone experienced adverse effects leading to treatment discontinuation, compared with 3.0% in the placebo arm. The quality of evidence for OIC treatment with prucalopride was inconsistent and marked down for suspected publication bias and imprecision.

Distinguishing OIC

OIC has variable descriptions throughout the literature. The most widely used

definitions include not only a change in stool frequency, but also changes in stool consistency with or without difficulty upon defecation. On the other hand, opioid-induced bowel dysfunction more generally refers to a group of GI adverse effects associated with opioid therapy, including constipation, gastroesophageal reflux disease, nausea and vomiting, bloating, and abdominal pain.

The Rome IV definition for OIC^{1,2} is new or worsening symptoms of constipation when initiating, changing, or increasing opioid therapy that must include at least two or more of the following:

- Straining during more than one-fourth (25%) of defecations
- Lumpy or hard stools with more than one-fourth (25%) of defecations
- Sensation of incomplete evacuation with more than one-fourth (25%) of defecations
- Sensation of anorectal obstruction/blockage with more than one-fourth (25%) of defecations
- Manual maneuvers to facilitate more than one-fourth (25%) of defecations
- Fewer than three spontaneous bowel movements per week

A consensus definition of OIC, determined at a roundtable meeting by a multidisciplinary working group and published in the journal *Neurogastroenterology & Motility*, is “a change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency.”^{1,3}

Treating OIC

OIC is a common and debilitating GI effect of opioids, and some degree of constipation is near universal in patients taking opioids.¹ These GI effects of opioids are mediated by κ -receptors in the stomach and small intestine and μ -receptors located in the small intestine and proximal colon. Activation of μ -receptors by opioid medications, resulting in increased tonic nonpropulsive contrac-

tion, increased colonic fluid absorption, and stool desiccation, is the primary driver of OIC. Opioids may also increase the minimum sensory threshold of the rectum and anal sphincter tone. Overall, these effects result in harder, dryer stool and less-frequent defecation.

One of the first steps to managing patients with OIC is ensuring that the indication for opioid therapy is appropriate. Patients should participate in a pain management program, ideally in conjunction with a pain specialist, and take the minimum necessary opioid dose. The guideline focuses on medical management of OIC and presumes that patients have had a prolonged requirement or dependence on opioids.

The AGA recommendations do not address the role of psychological therapy, alternative medicine approaches, surgery, or devices used to treat OIC. In addition, combination opioid agonists/antagonists are not specifically addressed, though these agents may result in less constipation than pure opioid agonists when used for management of chronic pain. “There is evidence that fixed-ratio combination prolonged-release oxycodone/naloxone may have a more favorable side effect profile with regards to constipation than other opioids,” said Sera.

Appropriate lifestyle modifications for patients with constipation include increasing fluid intake, getting regular moderate exercise as tolerated, and toileting as soon as possible in response to urges. “Opioid switching”—changing to

an equianalgesic dose of an alternative, less-constipating opioid—may also be beneficial. Oral or parenteral morphine, for example, may induce more constipation than transdermal opioids like fentanyl.

The Bowel Function Index is a three-question tool that has been validated in the OIC patient population. A score of 30 or higher is consistent with clinically significant constipation, and a consensus panel recommended using this score cutoff to determine which patients would benefit from escalation of therapy after an inadequate response to two concomitant first-line laxative agents.

“Pharmacists can play a huge role in preventing OIC by counseling patients receiving new prescriptions for opioids about this predictable side effect,” said Sera. “Most patients who are taking a long-acting opioid should also be taking a traditional laxative, as described in the guidelines. Pharmacists can also help to identify exacerbating factors by taking a thorough patient history, and can triage patients who present with red-flag symptoms such as abdominal pain, vomiting, or bloody stools.”

References

1. Crockett SD, et al. *Gastroenterology*. 2018;[Epub ahead of print]. doi: 10.1053/j.gastro.2018.07.016
2. Lacy BE, et al. *Gastroenterology*. 2016;(150)6:1393–1407
3. Camilleri M, et al. *Neurogastroenterol Motil*. 2014;26(1):1386–95

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Summary of AGA recommendations for medical management of OIC		
Recommendation	Strength of recommendation	Quality of evidence
In patients with OIC, use of laxatives as first-line agents is recommended	Strong	Moderate
In patients with laxative refractory OIC, use naldemedine over no treatment	Strong	High
In patients with laxative refractory OIC, use naloxegol over no treatment	Strong	Moderate
In patients with laxative refractory OIC, use methylnaltrexone over no treatment	Conditional	Low
In patients with OIC, AGA makes no recommendation for use of lubiprostone	No recommendation	Evidence gap
In patients with OIC, AGA makes no recommendation for use of prucalopride	No recommendation	Evidence gap

Source: Reference 1.