JAMA Clinical Guidelines Synopsis

Medical Management of Opioid-Induced Constipation

Vijaya L. Rao, MD; Dejan Micic, MD; Andrew M. Davis, MD

GUIDELINE TITLE Medical Management of Opioid-Induced Constipation

DEVELOPER American Gastroenterological Association (AGA)

RELEASE DATES October 30, 2018 (online); January 2019 (print)

FUNDING SOURCE AGA Institute

TARGET POPULATION Patients with a prolonged requirement of or dependence on opioids with constipation

MAJOR RECOMMENDATIONS

- Traditional laxatives such as stool softeners and osmotic, stimulant, and lubricant agents are recommended as initial treatment of opioid-induced constipation (OIC) (strong recommendation; moderate-quality evidence).
- In laxative-refractory OIC (ongoing moderate or severe constipation despite use of ≥2 traditional laxatives), peripherally acting μ-opioid receptor antagonists (PAMORAs) should be considered as next-line therapies (strong recommendation), such as naldemedine (high-quality evidence) or naloxegol (moderate-quality evidence).
- No recommendation is made for use of lubiprostone (intestinal secretagogue) or prucalopride (selective 5-hydroxytryptamine agonist) for treatment of OIC (evidence gap).

Summary of the Clinical Problem

Opioid pain medications are frequently used to treat acute and chronic pain and have had a major increase in use over the last 2 decades, particularly for noncancer pain. In 2017, there were 58 opioid prescriptions written for every 100 people in the United States. An estimated 17% of the US population has had at least 1 opioid prescription filled, although there is some uncertainty about this estimate because of illicit and nonprescription use.[1]

A wide variety of gastrointestinal effects are associated with opiate use. Opioid-induced constipation is attributed to activation of enteric μ-opioid receptors, which decrease bowel tone and contractility and increase colonic fluid absorption and anal sphincter tone while reducing rectal sensation. This leads to harder stools, which can be difficult to pass. The development of OIC is quite common, affecting 41% to 94% of opioid users.[2]

The Rome IV work group defined OIC as new or worsening symptoms of constipation when initiating, changing, or up-titrating opioid therapy. To meet criteria, 2 or more of the following symptoms should be associated with at least 25% of a patient's bowel movements: straining, lumpy or hard stools, sensation of incomplete evacuation or anorectal obstruction/blockage, need for manual maneuvers to facilitate the passage of stool (eg, digital evacuation or support of the pelvic floor), or having 3 or fewer spontaneous bowel movements per week.[3]

Characteristics of the Guideline Source

The guideline was based on results of a systematic technical review of 9 current pharmacologic treatments in management of OIC, conducted using GRADE methodology and published by the AGA (**Table**).[4] The members of the guideline panel and the authors of the technical review included experts in gastroenterology and methodologists with experience in evidence appraisal and guideline development. All members completed a disclosure statement on financial, professional, or intellectual conflicts of interest, with pertinent disclosures published within the guideline report.

Related article

Evidence Base

There were 20 eligible trials of patients using opioids for noncancer pain, the majority of which were randomized clinical trials (RCTs). The pharmacologic interventions assessed included traditional laxatives, PAMORAs (naldemedine, naloxegol, and methylnaltrexone), lubiprostone, and prucalopride compared with placebo.

Treatment outcomes in these studies varied but often included increase in bowel movement frequency (goal of >3 spontaneous bowel movements per week or >1 spontaneous bowel movement per week over a patient's prior baseline), improvement in stool consistency, and reduction in painful defecation and straining.

The recommendation for laxatives as first-line therapy for OIC remained strong given that these medications are relatively inexpensive, safe, and widely accessible. Osmotic laxatives such as polyethylene glycol, magnesium hydroxide or magnesium citrate, and lactulose act by drawing water into the gastrointestinal lumen. Agents like mineral oil lubricate the gut lining. Stimulant laxatives such as bisacodyl, sodium picosulfate, and senna stimulate colonic motility and reduce colonic water absorption; there is little evidence of harm, even with routine use.[5] Soluble and insoluble fiber may have some value for OIC in persons with fiber deficiency, even though these are bulking agents that do not affect colonic motility.

The strong recommendation for use of naldemedine as a therapy in laxative-refractory OIC is supported by 4 RCTs demonstrating increased ability of treated patients to have 3 spontaneous bowel

Table. Guideline Rating

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Good
Guideline development group composition	Fair
Clinical practice guideline–systematic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
Articulation of recommendations	Good
External review	Good
Updating	Fair
Implementation issues	Fair

movements vs patients receiving placebo (52% vs 35%; relative risk, 1.51; 95% CI, 1.32-1.72) and statistically significant changes in straining, stool consistency, and quality of life.[4] In a study of 446 patients, naloxegol was also associated with a higher rate of response to therapy (42% vs 29%; relative risk, 1.43; 95% CI, 1.19-1.71), although the overall evidence was thought to be only moderate.[4]

Five RCTs were reviewed regarding use of methylnaltrexone, and while these demonstrated an improvement in bowel movement frequency compared with placebo, the evidence was considered low quality because of inconsistency in several outcomes.[5] Therefore, use of methylnaltrexone was given only a conditional recommendation. There was insufficient evidence supporting use of either lubiprostone or prucalopride in OIC, and no recommendation was made.[5]

Benefits and Harms

Each intervention was systematically reviewed for benefits and harms associated with treatment. Adverse events were an important outcome in establishing the quality of evidence for each recommendation. Notably, naldemedine was the only prescription agent in the guideline that had 1-year safety data available, which likely strengthened the recommendation of its use in laxative-refractory OIC. The guideline found no statistically significant increase in adverse effects leading to discontinuation of methylnaltrexone.

It is important to note existing warnings from the US Food and Drug Administration on use of PAMORAs in patients with known or suspected lesions of the gastrointestinal tract (eg, infiltrative gastrointestinal tract malignancies or peritoneal metastases, peptic ulcer disease, diverticular disease, Ogilvie syndrome, Crohn disease) given the potential risk of bowel perforation in this subset of patients.[6]

Commonly cited adverse effects of all pharmacologic agents included abdominal pain, nausea, diarrhea, and flatulence in 10% to 30% of patients. A caveat to use of these medications is that relief of constipation can often lead to unwanted diarrhea or abdominal pain in a population already experiencing chronic pain.

Discussion

The release of this guideline is both timely and important given the wide use of opioids and attendant scrutiny of their appropriateness and potential harms. Opioid prescribing should be reconsidered for all patients receiving them to confirm the continued need for the drugs, to assess if the dosage and duration of the medications are appropriate, and to weigh the potential for reducing or stopping opioids by using other pain control modalities. Other causes of constipation should also be explored, including dyssynergic defecation, obstruction, medications, and metabolic causes. Lifestyle modifications should be discussed, including ensuring adequate fluid intake, regular exercise, and defecating as soon as possible in response to urgency. When opioids are still required, changing the type of opioid preparation may have value. For example, transdermal fentanyl may be less constipating than oral agents.[7] The guideline systematically reviews options for treatment of OIC, suggesting stepwise therapy, first with traditional laxatives, including use of a combination of at least 2 types of laxatives as well as scheduled use of laxatives, before concluding that these are insufficient. While the literature varies on this point, laxative-refractory OIC is defined here as symptoms of constipation despite use of laxatives from 2 or more laxative classes for a minimum of 4 days within a 2-week period. For patients who appear to have laxative-refractory OIC, clinicians can weigh escalation of therapy with either naldemedine or naloxegol.

Patient access is a barrier to use of these second-step pharmacologic therapies because these agents are often expensive and may not be covered by insurance.[8]

Areas in Need of Future Study or Ongoing Research

Future research is needed in several areas of medical management of OIC. There is a paucity of contemporary RCTs supporting use of traditional laxatives in management of OIC or for use of combination therapy with laxatives plus prescription agents. There is insufficient evidence supporting use of lubiprostone or prucalopride for OIC, while other intestinal secretagogues such as linaclotide and plecanatide were not addressed by the guideline. Furthermore, trials included in the technical review compared pharmacotherapy with either placebo or controls receiving no drug therapy, illustrating the need for comparative studies of various agents to guide clinicians and inform future guidelines on this topic.

Related resources

US Department of Agriculture Food Sources of Dietary Fiber

Bowel Function Index (p 222)

ARTICLE INFORMATION

Author Affiliations: Section of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, University of Chicago Medical Center, Chicago, Illinois (Rao, Micic); Section of General Internal Medicine, Department of Medicine, University of Chicago Medical Center, Chicago, Illinois (Davis).

Corresponding Author: Andrew M. Davis, MD, Section of General Internal Medicine, Department of Medicine, University of Chicago Medical Center, 5841 S Maryland Ave, Chicago, IL 60637 (amd@uchicago.edu).

Section Editor: Edward H. Livingston, MD, Deputy Editor, *JAMA*.

Published Online: November 4, 2019. doi:10.1001/jama.2019.15852

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Centers for Disease Control and Prevention. Prescription opioid data. https://www.cdc.gov/drugoverdose/data/prescribing.html. Accessed August 2, 2019.
2. Schmulson MJ, Drossman DA. What is new in Rome IV. *J Neurogastroenterol Motil*. 2017;23(2):151-163.
3. Simren M, Palsson OS, Whitehead WE. Update on Rome IV criteria for colorectal disorders. *Curr Gastroenterol Rep*. 2017;19(4):15.
4. Hanson B, Siddique SM, Scarlett Y, Sultan S. American Gastroenterological Association Institute technical review on the medical management of opioid-induced constipation. *Gastroenterology*. 2019;156(1):229-253.
5. Crockett SD, Greer KB, Heidelbaugh JJ, et al. American Gastroenterological Association Institute guideline on the medical management of opioid-induced constipation. *Gastroenterology*. 2019;156(1):218-226.
6. Food and Drug Administration. Relistor (methylnaltrexone bromide). https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021964s018,208271s002lbl.pdf. Accessed October 17, 2019.
7. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol*. 2012;13(2):e58-e68.
8. Wald A. Update on the management of constipation [published online November 1, 2019]. *JAMA*. doi:10.1001/jama.2019.16029