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AGA SECTION

American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation

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This document presents the official recommendations of the American Gastroenterological Association (AGA) on the medical management of opioid-induced constipation. The guideline was developed by the AGA Institute's Clinical Guidelines Committee and approved by the AGA Governing Board. It is accompanied by a technical review that is a compilation of clinical evidence from which these recommendations were formulated.[1] Development of this guideline and its accompanying technical review was fully funded by the AGA Institute with no additional outside funding.

Approximately 9–12 million Americans suffer from chronic pain annually and most of these persons are prescribed opioid pain medications to control their symptoms.[2] It is estimated that 4%–5% of the US population use prescription opioids regularly,[3] and opioid prescribing has increased over the past several decades, particularly for non-cancer pain.[4] However, the true number of those affected by opioid dependence and opioid-induced side effects is larger due to nonmedical or illicit use, which is also on the rise.[5,6]

Three different classes of opioid receptors mediate the gastrointestinal effects of opioid medications: μ, δ, and κ. Opioids exert their gastrointestinal effects via κ-receptors in the stomach and small intestine and μ-receptors located in the small intestine and proximal colon.[7] Opioid-induced constipation (OIC) occurs primarily via activation of enteric μ-receptors, which results in increased tonic non-propulsive contractions in the small and large intestine, increased colonic fluid absorption, and stool desiccation. Opioids are also thought to increase the minimum sensory threshold of the rectum and increase anal sphincter tone. The sum of these effects results in harder stool and less frequent and less effective defecation.[7–9] Because OIC results from the specific effects of opioids, it differs mechanistically from other forms of constipation, and therefore, medical management of this disorder deserves dedicated attention.[8]

Opioid-induced bowel dysfunction refers to the set of gastrointestinal adverse effects associated with opioid therapy, including constipation, gastroesophageal reflux disease, nausea and vomiting, bloating, and abdominal pain.[9,10] Constipation is by far the most common and debilitating gastrointestinal effect of opioids, and some degree of constipation is near universal in patients taking opioid medications.[11,12] The term *opioid-induced constipation* refers simply to constipation that is a result of opioid therapy. The Rome IV definition for OIC[13] is the following: new or worsening symptoms of constipation when initiating, changing, or increasing opioid therapy that must include 2 or more of the following: (1) straining during more than one-fourth (25%) of defecations; (2) lumpy or hard stools more than one-fourth (25%) of defecations; (3) sensation of incomplete evacuation more than one-fourth (25%) of defecations; (4) sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations; (5) manual maneuvers to facilitate more than one-fourth (25%) of defecations (eg, digital evacuation, support of the pelvic floor); or (6) fewer than 3 spontaneous bowel movements per week. Similarly, a consensus definition of OIC 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 frequency."[8,14] Importantly, these definitions include not only a change in stool frequency, but also changes in stool consistency and/or difficulty with defecation. It should be noted that OIC is defined variably in the literature and some studies do not include an explicit definition.[14] OIC is estimated to affect 40%–80% of patients taking chronic opioid therapy.[11,15,16]

OIC by definition is a condition associated with opioid use. These guidelines presume that patients have been appropriately diagnosed and that they have either a

Abbreviations used in this paper: **AGA, American Gastroenterological Association; OIC, opioid-induced constipation; PAMORA, peripherally acting μ-opioid receptor antagonist; PEG, polyethylene glycol; RCT, randomized controlled trial; RR, risk ratio; SBM, spontaneous bowel movement.**

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prolonged requirement or dependence on opioids. Therefore, one of the first steps to managing patients with OIC is to ensure that the indication for opioid therapy is appropriate, that patients are participating in a pain management program (ideally in conjunction with a pain specialist), and that they are taking the minimum necessary opioid dose. A suggested approach to opioid prescribing practices and monitoring during treatment is outlined in a recent guideline from the US Centers for Disease Control and Prevention.[17] Patients on chronic opioid therapy must have a clear understanding of the risks of long-term opioid treatment, which include death due to drug misuse and abuse.[18] Vigilance of all involved providers in confirming indication for therapy, management of potential drug interactions, opioid-induced side effects, and offering evidence-based treatment resources for patients with opioid use disorders is of critical importance, given the high mortality rate of the current opioid epidemic.[17,19,20]

A suggested general approach to patients with suspected OIC involves first taking a careful history to evaluate defecation patterns; dietary patterns; stool consistency; symptoms of dyssynergic defecation (eg, a sensation of incomplete evacuation); or alarm symptoms, such as blood in stool or accompanying weight loss. A medical history should also be taken to assess comorbid illnesses and regular medication use. Other potential causes or contributors to constipation should be explored and excluded, such as pelvic outlet dysfunction, mechanical obstruction, metabolic abnormalities, and contributions of other diseases or medications. Lifestyle modifications are an appropriate first step for all those with constipation, and include increasing one's fluid intake,[21] regular moderate exercise as tolerated,[22] and toileting as soon as possible in response to the urge to defecate. There may also be benefit in "opioid switching" or changing to an equianalgesic dose of an alternative, less-constipating opioid.[23] For example, oral or parenteral morphine preparations may induce more constipation than transdermal opioids, such as fentanyl.[24] Combination opioid agonist/antagonist agents (eg, oxycodone + naloxone) are also associated with lower risk of constipation.[25] This approach is highlighted in the accompanying clinical decision support tool (Figure 1), and is also analogous to the approach suggested in a previously published AGA guideline on constipation.[26] Once a diagnosis of OIC has been confirmed and other potential causes of constipation are excluded, the recommendations here can help guide appropriate evidence-based management.

This guideline focuses on the medical management of OIC. Therefore, it does not address the role of psychological therapy, alternative medicine approaches, surgery, or devices. The guideline and technical review also do not directly address questions regarding the diagnostic evaluation of OIC. Additionally, combination opioid agonists/antagonists are not specifically addressed by the technical review or guideline recommendation statements, though these agents may result in less constipation than pure opioid agonists when used for management of chronic pain.[25]

This guideline was developed utilizing a process outlined elsewhere.[27] Briefly, the AGA process for developing clinical practice guidelines incorporates GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology[28] and best practices as outlined by the Institute of Medicine.[29] GRADE methodology was utilized to prepare the background information for the guideline and the technical review that accompanies it.[1] Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review. The guideline panel and the authors of the technical review met face to face on October 27, 2017, to discuss the findings from the technical review. The guideline authors subsequently formulated the recommendations. Although the quality of the evidence (Table 1) was a key factor in determining the strength of the recommendations (Table 2), the panel also considered the balance between benefit and harm of interventions, patients' values and preferences, and resource utilization. The recommendations are summarized in Table 3.

Recommendations

Laxatives

Laxatives are a broad category of agents that induce laxation in various ways. While in the broadest sense, any agent that stimulates or facilitates the evacuation of the bowels can be considered a "laxative," in this document we distinguish traditional laxatives from more recently developed agents, including peripherally acting μ-opioid receptor antagonists (PAMORAs), intestinal secretagogues, and selective 5-HT agonists. It should also be noted that the laxative class includes agents that are generally very safe, widely available over the counter, and inexpensive.

Table 1. GRADE Definitions of Quality and Certainty of the Evidence

Quality grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.
Evidence gap	Available evidence insufficient to determine true effect.

Table 2. GRADE Definitions on Strength of Recommendation and Guide to Interpretation

Strength of recommendation	Wording in the guideline	For the patient	For the clinician
Strong	"The AGA recommends…"	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	"The AGA suggests…"	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
No recommendation	"The AGA makes no recommendation…"		The confidence in the effect estimate is so low that any recommendation is speculative at this time.

Laxatives work via a variety of mechanisms to improve the frequency of bowel movements, the consistency of stool, or to facilitate defecation (Table 4).[7,30] Stool softeners include docusate sodium, a surfactant agent that works by allowing water and lipids to penetrate the stool, thereby hydrating and softening the fecal material. Osmotic laxatives include agents such as polyethylene glycol (PEG), magnesium hydroxide or magnesium citrate, and lactulose, and work by drawing water into the gut, thereby hydrating the stool. Lubricants such as mineral oil work by softening the stool and lubricating the lining of the gut to facilitate defecation. Stimulant laxatives include agents such as bisacodyl, sodium picosulfate, and senna, and work by irritating luminal sensory nerve endings, thereby stimulating colonic motility and reducing colonic water absorption. Of note, there is little evidence that routine use of stimulant laxatives is harmful to the colon, despite despite widespread concern to the contrary.[30]

Fiber is a bulking agent that has both soluble and insoluble forms. Soluble fiber, including both dietary (eg, oats, certain fruits and vegetables) and supplemental forms (psyllium, calcium polycarbophil, and methylcellulose), is more effective for constipation compared to insoluble fiber.[31] However, because fiber is a bulking agent that does not affect colonic motility, it has a limited role in OIC, except possibly in persons with fiber-deficient diets.[32] Finally, enemas are also occasionally prescribed as a rescue therapy for constipation but are not used as regularly as other laxative agents due to convenience, patient preference, and safety concerns.[33]

1a. In patients with OIC, the AGA recommends use of laxatives as first-line agents. *Strong recommendation, moderate-quality evidence.*

The technical review identified 1 randomized controlled trial from Freedman et al[34] and 2 additional open-label

Table 3. Summary of Recommendations of the AGA Clinical Guidelines for the Medical Management of Opioid-Induced Constipation

Recommendations	Strength of recommendation	Quality of evidence
1. Traditional laxatives		
a. In patients with OIC, the AGA recommends use of laxatives as first-line agents	Strong	Moderate
2. PAMORAs		
a. In patients with laxative refractory OIC, the AGA recommends naldemedine over no treatment	Strong	High
b. In patients with laxative refractory OIC, the AGA recommends naloxegol over no treatment	Strong	Moderate
c. In patients with laxative refractory OIC, the AGA suggests methylnatrexone over no treatment	Conditional	Low
3. Intestinal secretagogues		
a. In patients with OIC, the AGA makes no recommendation for the use of lubiprostone	No recommendation	Evidence gap
4. Selective 5-HT agonists		
a. In patients with OIC, the AGA makes no recommendation for the use of prucalopride	No recommendation	Evidence gap

Table 4. Different Classes of Agents for Opioid-Induced Constipation and Mechanisms of Action

Class/type	Examples	Mechanism of action
Traditional laxatives		
Osmotic	PEG, lactulose, magnesium citrate, magnesium hydroxide	Draw water into intestine to hydrate and soften stool
Stimulant	Bisacodyl, sodium picosulfate, senna	Irritate sensory nerve endings to stimulate colonic motility and reduce colonic water absorption
Detergent/surfactant stool softeners	Docusate	Allow water and lipids to penetrate the stool to hydrate and soften fecal material
Lubricant	Mineral oil	Lubricate the lining of the gut to facilitate defecation
PAMORAs	Naldemedine Naloxegol Methylnatrexone	Block μ-opioid receptors in the gut, thereby effectively restoring the function of the enteric nervous system
Intestinal secretagogues	Lubiprostone	Act on chloride channels or guanylate cyclase receptors in enterocytes to stimulate fluid secretion into the intestinal lumen
Selective 5-HT agonists	Prucalopride	Activate 5-HT4 receptor, leading to increased colonic motility and accelerated transit

studies from Twycross et al[35] and Wirz et al[36] that evaluated the use of laxatives in OIC. Freedman et al compared the osmotic laxatives PEG and lactulose with placebo in patients with constipation attributed to chronic opioid therapy. This study demonstrated a significant improvement in stool consistency and frequency with both PEG and lactulose compared with placebo, though there were no significant differences between the 2 laxative regimens. Twycross et al conducted a small open-label study in cancer patients with constipation due to chronic morphine therapy, assessing the efficacy of the stimulant laxative sodium picosulfate. This study found that 75% of patients in the treatment arm experienced satisfactory bowel movement response. The Wirz et al study was a larger open-label study comparing sodium picosulfate, PEG, and lactulose, and found that although all 3 agents resulted in improvement in constipation, PEG and sodium picosulfate were more efficacious than lactulose. Additionally, the panel considered findings of 2 recent meta-analyses by Ford et al[37] and Nelson et al[38] of agents for chronic idiopathic constipation (a condition with similarities to OIC). Ford et al reported that both osmotic and stimulant laxatives were more effective than placebo for chronic idiopathic constipation, with a number needed to treat of 3 for each class. Nelson et al found specifically that the stimulant laxatives bisacodyl and sodium picosulfate were both superior to placebo for chronic idiopathic constipation. Finally, the panel considered the fact that rescue therapy (in the event that a patient did not have a BM wihin a specified time, usually 48–72 hours) was offered to patients in the majority of OIC clinical trials; patients in either the intervention or placebo arms were offered laxatives, most commonly oral bisacodyl or bisacodyl suppositories.

The panel also considered the low cost and few safety concerns associated with laxative agents, the majority of which are available in generic and/or over-the-counter forms. In sum, the technical review found moderate evidence to support a benefit of laxatives in OIC, and thus the panel issued a strong recommendation that laxatives be used as first-line agents in this disorder. This approach aligns with that suggested in a recent AGA Clinical Practice Update on the gastrointestinal effects of opioids.[39]

Laxative-refractory OIC has been defined variably in the literature. In some OIC studies, "inadequate laxative response" was defined as moderate or severe symptoms of constipation, despite the use of laxatives from 1 or more laxative classes for a minimum of 4 days within a 2-week period. Based on this, the panel favored use of a combination of at least 2 types of laxatives before escalating therapy,[40] and also that scheduled use of laxatives (vs use "as needed") is required before determining whether alternative OIC therapy is necessary. For example, daily use of an osmotic laxative in combination with a stimulant laxative at least 2–3 times per week. As noted here, the specific laxatives that have shown efficacy in OIC and chronic idiopathic constipation trials include PEG (an osmotic laxative), and bisacodyl and sodium picosulfate (stimulant laxatives). However, it should be acknowledged that strong randomized controlled trial (RCT)–level evidence supporting any particular combination or titration regimen is lacking.

If an adequate trial of laxatives results in incomplete relief of OIC symptoms, other agents might be needed. The severity of constipation symptoms can be assessed with various tools. The Bowel Function Index is a simplified 3-question tool that has been validated in the OIC patient population (Table 5).[41,42] A score of $\geq$30 on this tool is consistent with clinically significant constipation, and a consensus panel recommended using this Bowel Function Index score cutoff to determine which patients have inadequately responded to first-line laxative agents for OIC and would benefit from escalation of therapy.[43] The Patient Assessment of Constipation Symptoms is another validated symptom measure that has been used in OIC studies, though may be less practical for clinical use.[44]

Peripherally Acting μ-Opioid Receptor Antagonists

PAMORAs do not enter the central nervous system but block the μ-opioid receptors in the gut thereby effectively

Table 5. Bowel Function Index[41]

Item	Question	Scale
1	During the last 7 days, how would you rate your ease of defecation on a scale from 0 to 100?	0 = easy or no difficulty 100 = severe difficulty
2	During the last 7 days, how would you rate your feeling of incomplete bowel evacuation on a scale from 0 to 100?	0 = not at all 100 = very strong
3	During the last 7 days, how would you rate your constipation on a scale from 0 to 100?	0 = not at all 100 = very strong
Total score		**Mean of 3 scores**

restoring the function of the enteric nervous system.[8] Use of these medications should be avoided in conditions that compromise the blood–brain barrier due to potential for serious withdrawal or reversal of anesthesia.[45] Four PAMORAs are reviewed in this guideline. Naloxegol is a pegylated derivative of naloxone. Pegylation of naxolone allows for increased oral bioavailability and enhanced peripheral selectivity of the drug. Naloxegol is also a substrate for P-glycoprotein transporter, which limits entry of the medication into central nervous system. Naloxegol was approved by the US Food and Drug Administration in 2014 as the first PAMORA for management of OIC in adult patients with chronic non-cancer pain. Methylnaltrexone is a quaternary ammonium cation that cannot cross the blood–brain barrier and has opioid antagonist effects throughout the body, reversing itching as well as constipation. It is available in oral as well as subcutaneous injection forms. Naldemedine is structurally related to naltrexone, and was the latest PAMORA that was approved by the US Food and Drug Administration in March 2017 for management of OIC.

2a. In patients with laxative refractory OIC, the AGA recommends naldemedine over no treatment. *Strong recommendation, high-quality evidence.*

Data to support naldemedine use come from 4 randomized double-blind trials comparing naldemedine against placebo including 1 phase 2b trial (Webster et al[46]) and 3 phase 3 trials (COMPOSE 1, 2, and 3[47,48]), including >2400 patients in total. The primary end point for 3 of these studies (Webster et al. and COMPOSE 1 and 2 trials) was the ability to achieve at least 3 spontaneous bowel movements (SBM) per week. Approximately 52% of patients treated with naldemedine achieved this primary end point compared to 35% of those treated with placebo. The pooled risk ratio (RR) for SBM response rate was 1.51 (95% CI, 1.32 to 1.72) favoring naldemedine use. Naldemedine was also associated with an increase in the frequency of SBMs per week. In the COMPOSE 3 trial, which included 52 weeks of follow-up, naldemedine was associated with roughly 1 more SBM per week compared to placebo (0.95 more; 95% CI, 0.57 more to 1.33 more). Statistically significant improvements in straining, stool consistency, and quality of life were also reported in the studies, however, the magnitudes of these effects were not clearly clinically meaningful.

Adverse events leading to treatment discontinuation in the 4 trials were more common in the treatment arm (RR, 1.44; 95% CI, 1.03–2.03) and they included infection, abdominal pain, diarrhea, flatulence, nausea, and back pain. Importantly, the absolute increase in adverse events was low (2 more per 100 treated patients vs placebo), and fell below the threshold for clinically meaningful harm. Naldemedine is also the only prescription agent evaluated in this guideline, for which long-term (52-week) safety data are available.[48]

The overall quality of evidence supporting use of naldemedine for management of OIC was considered high. The AGA issued a strong recommendation for use of naldemedine vs no treatment in patients with OIC refractory to laxatives. However, patient and provider use of this medication may be limited by its cost.

2b. In patients with laxative refractory OIC, the AGA recommends naloxegol over no treatment. *Strong recommendation, moderate-quality evidence.*

The use of naloxegol is supported by 1 phase 2 trial (Webster et al[49]) and 2 phase 3 double-blind randomized controlled trials (KODIAC-04 and KODIAC-05, Chey et al[50]). The primary end points in these studies were different, so only data from the phase 3 trials could be used for estimates for treatment effect. Response was defined as 3 SBMs/week with an increase from baseline of at least 1 SBM for at least 3 out of 4 final weeks of the 12-week study period. These trials showed that 41.9% of patients treated with naloxegol had a response compared to 29.4% of those treated with placebo, thus naloxegol use would result in 13 more patients with response per 100 (95% CI, 6 to 21 more). Naloxegol was associated with higher rate of response to

therapy compared to placebo (RR, 1.43; 95% CI, 1.19 to 1.71).

The safety extension studies conducted by Webster et al[49] and Chey et al[50] showed that the most common treatment emergent side effects were generalized or upper abdominal pain, diarrhea, nausea, headache, and flatulence (RR, 2.33; 95% CI, 1.62–3.35).[51] Two deaths occurred in the safety study with 1 death in each study arm. None of these deaths were considered to be related to study medication.

The use of naloxegol for management of OIC is supported by moderate-quality evidence. The available evidence was rated down for imprecision. The AGA issued a strong recommendation for use of naloxegol over no treatment in patients with laxative refractory OIC. Use of naloxegol should be judicious, given the cost of this drug.

2c. In patients with laxative refractory OIC, the AGA suggests methylnatrexone over no treatment. *Conditional recommendation, low-quality evidence.*

The technical review identified 5 RCTs evaluating the efficacy of methylnatrexone for patients with OIC. Only 3 of the included studies examined an outcome of ≥3 rescue-free bowel movements per week, which is similar to the US Food and Drug Administration–recommended outcome for studies of constipation agents, and only 2 of these studied non-cancer pain.[52,53] The pooled RR for the rescue-free bowel movement outcome was 1.43 (95% CI, 1.21–1.68), corresponding to a 43% improvement or an absolute improvement of 16 more patients per 100 who achieve this outcome with methylnatrexone therapy. Methylnatrexone was also associated with an improvement in "laxation response," defined generally as a bowel movement within 4 hours of taking the medication (RR, 3.16; 95% CI, 2.18–4.58). There was no statistically significant increase in adverse events leading to treatment discontinuation.

The quality of the evidence supporting the use of methylnatrexone was low. The evidence was rated down for both indirectness, inconsistency, and imprecision across several outcomes. The AGA issued a conditional recommendation due to low-quality evidence underpinning the statement. Further, the use of methylnatrexone may be limited by its high cost relative to other agents. However, the availability of a subcutaneously administered version may offer an advantage in some clinical situations.

Intestinal Secretagogues

Intestinal chloride ion secretagogues act through the guanylate cyclase C receptor with associated secretion of water into the intestinal lumen. Chloride ions secreted from enterocytes or colonocytes enter the cell through the basolateral Na-K-Cl co-transporter. Lubiprostone is a bicyclic fatty acid derived from prostaglandin E1 that activates apical membrane chloride channels to stimulate intestinal and colonic secretion of chloride-rich fluid into the intestinal lumen. It has been shown to accelerate intestinal and colonic transport without significantly impacting colonic motility or sensation.[54]

3. In patients with OIC, the AGA makes no recommendation for the use of lubiprostone. *No recommendation, evidence gap.*

Limited consistent evidence exists to support a recommendation for the use of lubiprostone for the treatment of OIC. Three large phase 3 RCTs[55–57] compared the use of lubiprostone to placebo for the treatment of OIC in adult patients with non-cancer pain on stable opiate doses for at least 30 days before enrollment. Lubiprostone 24 μg twice daily with meals and 8 ounces of fluid was administered for 12 weeks in each study. The pooled SBM response rate was RR of 1.15 (95% CI, 0.97–1.37) with 38% of patients in the lubiprostone arm achieving SBM response compared with 32.7% of patients in the placebo arm. Compared with placebo, there was some improvement in SBM frequency with an increase of 0.6 to 0.8 more SBMs. In the Spierings et al[57] study, however, no improvement in SBM frequency was reported, but there was a small reduction in straining and an improvement in stool consistency, however, it was unclear whether these small reductions correlated with clinically meaningful improvements. No meaningful changes in quality of life were noted.

Overall, 6.4% of patients who received lubiprostone had adverse effects that led to treatment discontinuation compared to 3.0% in the placebo arm. The majority of side effects were diarrhea, nausea, abdominal pain, headache, and vomiting.

The quality of the evidence for lubiprostone was low. Overall, there was concern about selective reporting bias across the studies and imprecision. Also, it was unclear if the differences reported were clinically meaningful improvements. Based on the low quality of evidence and the limitations of the evidence, the AGA made no recommendation for lubiprostone and identified this area as an evidence gap.

Selective 5-HT Agonists

5-HT is an important mucosal signaling molecule in the gut that impacts function at many levels due to the presence of multiple receptor sites present on several classes of myenteric neurons, on smooth muscle cells, and on epithelial cells. Selective 5-HT receptor agonists play an integral role in regulating gastrointestinal motility, enteric neuronal signaling, and visceral pain in the gastrointestinal tract. Over the past decade, the 5-HT_4 receptor has been identified as an important drug target for the treatment of gastrointestinal motility disorders, including irritable bowel syndrome, chronic idiopathic constipation, functional dyspepsia, and gastroparesis.

4a. In patients with OIC, the AGA makes no recommendation for the use of prucalopride. *No recommendation, evidence gap*.

Limited consistent evidence exists to support a recommendation for the use of prucalopride for the treatment of OIC. The panel identified one 4-week phase 2, double-blind, placebo-controlled study of 196 patients randomized to placebo, prucalopride 2 mg, or 4 mg, for 4 weeks, as well a 12-week clinical trial that was terminated early by the manufacturer (data were obtained from ClinicalTrials.gov).[58] Overall, 126 (58.3%) of 216 patients who received prucalopride had response to therapy compared with 62 (41.6%) of 149 patients who received placebo. The pooled RR was 1.36 (95% CI: 1.08–1.70). Improvement in SBM frequency was reported in a phase 2 study.[58] The mean difference from baseline was 2.2 (2 mg) and 2.5 (4 mg) in the intervention arms vs 1.5 in the placebo arm. Improvements in symptoms, such as painful defecation or straining, were not reported. The authors did report a decrease in the percentage of hard stools, although the data were not provided.

The most common adverse events reported were abdominal pain and nausea. Adverse events leading to treatment discontinuation occurred in 8 (6.2%) of 130 patients who received prucalopride compared to 7 (10.6%) of 66 patients who received placebo.

The quality of evidence for prucalopride was rated down for suspected publication bias and imprecision. Publication bias was a concern, as the trial, entitled "Prucalopride Effects on Subjects With Chronic Non-Caner Pain Suffering from Opioid Induced Constipation," was terminated by the manufacturer, in 2014 before recruitment was completed and the study results were never published. Based on the low-quality evidence, the AGA made no recommendation for prucalopride and identified this area as an evidence gap. Continued development of highly selective 5-HT4 agonists, including prucalopride, in the treatment of OIC is warranted.

Summary

These practice guideline recommendations for the management of OIC were developed using the GRADE framework and in adherence with the standards for guideline development set forth by the Institute of Medicine for the creation of trustworthy guidelines. These guidelines are intended to reduce practice variation and promote high-quality and high-value care for patients suffering from OIC. Based on a thorough assessment of the current evidence, the AGA strongly recommends traditional laxative therapy as first-line agents, given established efficacy and benefits of safety and cost. When an adequate trial of laxatives results in suboptimal symptom control, the AGA recommends escalation of therapy to PAMORA drugs with high- or moderate-quality evidence of efficacy, namely naldemedine and naloxegol. The AGA also conditionally recommends use of methylnatrexone. Due to insufficient evidence, the AGA did not issue a recommendation regarding use of either lubiprostone or prucalopride in OIC.

The recommendations are similar to those proposed by recent clinical guidelines related to OIC published by the American Academy of Pain Medicine[25] and the European Association for Palliative Care,[23] as well as a recent Clinical Practice Update published by the AGA.[39] Both guidelines and the Clinical Practice Update recommend traditional laxatives as first-line agents, and support the use of PAMORAs for cases where escalation of therapy is necessary.

We identified a number of evidence gaps and priorities for future research. As stated here, while laxative therapy is widely used, contemporary RCT-level data in OIC in particular are relatively scarce, as are data comparing the effectiveness of laxatives to newer agents, or data on the effectiveness of combining laxatives with prescription OIC medications. In addition, there are limited published data on long-term use of prescription OIC medications (most trials studied 4- to 12-week treatment durations), despite the fact that OIC is a chronic condition. Given the limited available evidence addressing the efficacy of lubiprostone and prucalopride in OIC, additional studies are needed to establish the benefit of these agents. There is a paucity of comparative effectiveness studies comparing drugs to each other, and research in this area would help guide appropriate therapy. Cost-effectiveness studies are also lacking in this field, which could inform prescribing strategy, particularly for newer, more expensive agents. The panel also acknowledged that pipeline agents for OIC are in development, and thus this topic will need to be revisited in the future as newer agents emerge.

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Conflicts of interest
All members were required to complete a disclosure statement. These statements are maintained at the American Gastroenterological Association Institute headquarters in Bethesda, Maryland and pertinent disclosures are published with the report.