Review

Constipation
Advances in Diagnosis and Treatment

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IMPORTANCE Chronic constipation accounts for at least 8 million annual visits to health care providers in the United States and is associated with large expenditures for diagnostic testing and prescription and nonprescription laxatives.

OBSERVATIONS Strong evidence for efficacy has been established for stimulant and osmotic laxatives, new intestinal secretogogues, and peripherally restricted μ-opiate receptor antagonists, the latter a major advance in the treatment of opioid-induced constipation (OIC). An algorithm provided to evaluate chronic idiopathic constipation (CIC) that is refractory to available laxatives focuses on the importance of defecation disorders and biofeedback therapies. When used appropriately, available stimulant laxatives such as senna and bisacodyl are both safe and effective when used long-term. There is a paucity of (and a strong desire for) studies that compare inexpensive laxatives with newer agents that work by other mechanisms.

CONCLUSIONS AND RELEVANCE The choice of treatment for CIC and OIC should be based on cost as well as efficacy. The small subgroup of patients who do not respond to currently available laxatives requires further evaluation at experienced centers that are capable of performing studies of defecation and colonic transit.

JAMA. 2016;315(2):185-191. doi:10.1001/jama.2015.16994

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Section Editors: Edward Livingston, MD, Deputy Editor, and Mary McGrae McDermott, MD, Senior Editor.

Chronic constipation is a common symptom, and it is presumed (but not proven in all cases) that functional disorders of colonic or anorectal function underlie the disorder. Although a minority of those with constipation seek medical attention, it still accounts for 8 million annual visits to physicians in the United States, most of whom are seen by primary care clinicians, and who receive a prescription for laxatives and undergo diagnostic testing.[1] In addition, there are large expenditures for nonprescription laxatives and other bowel aids (such as enemas and suppositories) at all ages.

Although the diagnostic approach to patients with chronic idiopathic constipation (CIC) has changed little in recent years, there have been a number of important developments in the treatment of this disorder in the last 5 years. This article reviews recent developments in the management of constipation. These include (1) updates of newer and established laxatives and promotility agents for CIC, (2) new approaches to the treatment of opioid-induced constipation (OIC), and (3) identification of functional defecation disorders in patients whose conditions are unresponsive to standard laxatives.

Take-Home Points

- The development of peripherally restricted μ-opiate receptor antagonists represents a major advance in the treatment of OIC.
- The demonstration of noninferiority of polyethylene glycol 3350–electrolyte (PEG 3350) vs a high-affinity serotonin agonist emphasizes the desirability of studies to compare new laxatives with established and inexpensive laxatives, such as bisacodyl and PEG 3350, to help guide laxative use in CIC.
- Novel secretory drugs and high-affinity serotonin agonists remain a second-tier choice for CIC but may have a more primary role in irritable bowel syndrome with constipation.
- Patients with CIC refractory to available laxatives should be tested for a defecation disorder using both balloon expulsion testing and anorectal manometry before measuring colonic transit times. This is important because functional defecatory disorders can often be treated effectively with biofeedback techniques.

Methods

MEDLINE (January 2005-October 2015), EMBASE (January 2005-October 2015), and Cochrane Reviews were searched. Also consulted were the American Gastroenterological Association (AGA) Technical Review on Constipation and the American College of Gastroenterology (ACG) Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation for their assessment of the strength of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. A total of 21 peer-reviewed studies and 12 reviews or meta-analyses were selected to support the conclusions of the article.

Pathophysiology

Constipation may occur because of a primary motor disorder involving the colon, a defecation disorder, in association with a large number of diseases, or as an adverse effect of many drugs (**Box**). Among the primary motor disorders are slow transit through the colon (thought to involve elements of the enteric nervous system) and functional disorders of defecation (such as weak or inadequate propulsion or failure of relaxation of the external anal sphincter and puborectalis muscles, known as dyssynergic defecation). Most patients with CIC respond to conservative treatment, and it is only when they do not respond that evaluation for primary motor disorders is necessary.[1,2]

Similar to CIC, irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder that is subtyped by a predominant stool pattern; this includes constipation-predominant IBS (IBS-C). The major distinction is the presence of abdominal pain that is not necessarily relieved by improving bowel habits in IBS-C. Although the widely accepted Rome III diagnostic criteria maintain a mutually exclusive distinction between IBS-C and CIC and pharmaceutical studies have focused on them separately, most studies have identified substantial overlap between the 2 conditions.[3-5] From a clinical standpoint, drugs that have shown efficacy in both disorders simply reinforce this perspective; indeed, every agent that has demonstrated efficacy for IBS-C has shown efficacy in CIC, whereas some drugs that are efficacious in CIC have not been tested in IBS-C.

ARM *anorectal manometry*
BET *balloon expulsion testing*
CIC *chronic idiopathic constipation*
IBS *irritable bowel syndrome*
IBS-C *constipation-predominant IBS*
OIC *opioid-induced constipation*
PEG 3350 *polyethylene glycol 3350–electrolyte*
SBM *spontaneous bowel movement*

Box. Some Secondary Causes of Constipation

Mechanical
Colorectal cancer
Colon, rectal, or anal stricture
Rectocele (some)
Intestinal pseudo-obstruction
Megacolon

Neurologic Disease
Spinal cord lesion
Stroke
Parkinson disease
Multiple sclerosis

Metabolic Disturbances
Hypercalcemia
Hypokalemia (severe)
Hypomagnesemia
Hypothyroidism (severe)
Uremia

Medications (Partial List)
Opiates
Anticholinergics
Calcium-channel blockers
Anticonvulsants
Antidepressants
Antispasmodics
Antihistamines
Antiemetics (ondansetron)

Miscellaneous
Amyloidosis
Scleroderma
Heavy metal poisoning

Clinical Presentation and Assessment

Most patients with constipation do not have infrequent stools only but complain of defecatory difficulties as well. Although such patients may complain of bloating and some have abdominal discomfort, these are often relieved by a "satisfactory" defecation. This is in contrast to IBS with constipation in which those symptoms are more prominent and are not significantly relieved by establishing normal bowel habits. However, there is some overlap between the 2 groups, and patients in the latter group may require more attention to bloating and pain. The clinical evaluation should include the duration of symptoms, frequency and consistency of stools, presence of excessive straining, feeling of incomplete evacuation, or use of manual maneuvers during defecation. Clinical evaluation should also focus on excluding organic causes and medications (Box) and identifying the presence of "alarm" symptoms that suggest further workup is required for colon cancer (such as sudden change in bowel habits, blood mixed in the stool, unexpected weight loss, or a strong family history of colon cancer). Medication-associated constipation is probably not uncommon, but constipation due to structural abnormalities, such as tumors or strictures, is rare in clinical practice; therefore, tests should not be performed unless there are strong reasons (such as alarm symptoms) to do so. This may avoid unnecessary testing. Diagnostic colonoscopy should be performed only in patients with alarm symptoms or in patients who require colorectal cancer screening. Thyroid-stimulating hormone, calcium, and glucose should be obtained selectively, but most major gastrointestinal societies recommend a complete blood cell count as a screening test because the finding of iron deficiency with anemia would prompt further testing.

Pharmacologic Agents for Constipation

The currently available laxatives in the United States consist of 4 major groups (**Table 1**). The goal of all such agents is to increase stool water content, either directly via osmotic or intestinal secretory means or by accelerating bowel transit, thereby decreasing fluid absorption. Many laxatives are available without prescription and are relatively inexpensive (bulking agents, stimulants, and osmotic agents), whereas the newer secretory agents are by prescription only

Table 1. Available Laxatives and Strength of Recommendations to Treat Chronic Idiopathic Constipation According to GRADE Criteria[a]

	Recommendation[b]	Quality of Evidence[c]
Bulk agents	Strong	Low
Psyllium, methylcelluose, calcium polycarbophil, wheat dextrin		
Nonabsorbed substances		
PEG 3350	Strong	High
Lactulose[d]	Strong	Low
Magnesium salts	NA	NA
Stimulants		
Bisacodyl	Strong	Moderate
Senna	NA	NA
Secretory drugs[d]		
Lubiprostone	Strong	High
Linaclotide	Strong	High

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NA, not assessed; PEG 3350, polyethylene glycol 3350–electrolyte.

[a] From American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Constipation.[3]

[b] Strong recommendation indicates the committee felt that most individuals should receive the treatment and recommendation would apply to most clinical situations.

[c] Low quality of evidence suggests that future research is very likely to affect future assessments and recommendations.

[d] Prescription only.

Table 2. Cost Comparison of Constipation Treatments[a]

Treatments	Cost per Month, 2015 $
Bulk agents	
Psyllium (10 g daily), range[b]	14.22
Nonabsorbed substances	
Lactulose (20 g daily)	144.00
PEG 3350 (17 g daily)[b]	18.25
Stimulants	
Senna (2 tabs daily)	0.34
Bisacodyl (2 tabs daily)	0.75
Secretory drugs	
Lubiprostone (24 µg twice daily)	293.02
Linaclotide (145 µg daily)	283.70

Abbreviation: PEG 3350, polyethylene glycol 3350–electrolyte.

[a] Data from the University of Wisconsin.[6] Retail costs are higher.

[b] Data from Super Target, Madison, Wisconsin, December 2015.

and are relatively expensive (**Table 2**). According to most population surveys, the medical management of CIC continues to be suboptimal, with many patients expressing dissatisfaction with conventional therapies.[7] As CIC is a symptom-based disorder, it is unclear whether this dissatisfaction is based on psychosocial factors or biologic factors or both. Nevertheless, there continues to be intense interest in developing drugs that stimulate gastrointestinal motility via the serotonin$_4$ receptor (prokinetics) as well as agents that directly stimulate intestinal secretion to increase stool water content (intestinal secretogogues).

In assessing new and established laxatives and other therapeutic interventions such as biofeedback for defecation disorders, the AGA technical review on constipation[2] and the ACG monograph on the management of IBS and CIC were constructed for the assessment of the strength of evidence using the GRADE system.[8] In the GRADE system, therapies are classified into 4 strength of evidence categories: high, moderate, low, and very low; whereas recommendations are classified as strong, moderate, and weak. The classification of established laxatives using the GRADE system and as determined in the ACG monograph[2] are demonstrated in Table 2.

Prokinetics

There is a lengthy published record on the efficacy of prucalopride for CIC, as summarized in a meta-analysis published in 2014.[9] Prucalopride is a high-affinity serotonin$_4$ receptor agonist that has been demonstrated to stimulate gastrointestinal motility. The drug has yet to be approved for use in the United States, although it is widely used in Europe. A recent publication demonstrated the efficacy of prucalopride (2 mg daily) in a randomized clinical study involving 358 men over a 12-week treatment period (achieved the primary end point: 38% for prucalopride vs 18% for placebo).[10] This extends and confirms previous studies of prucalopride among women with CIC.[9]

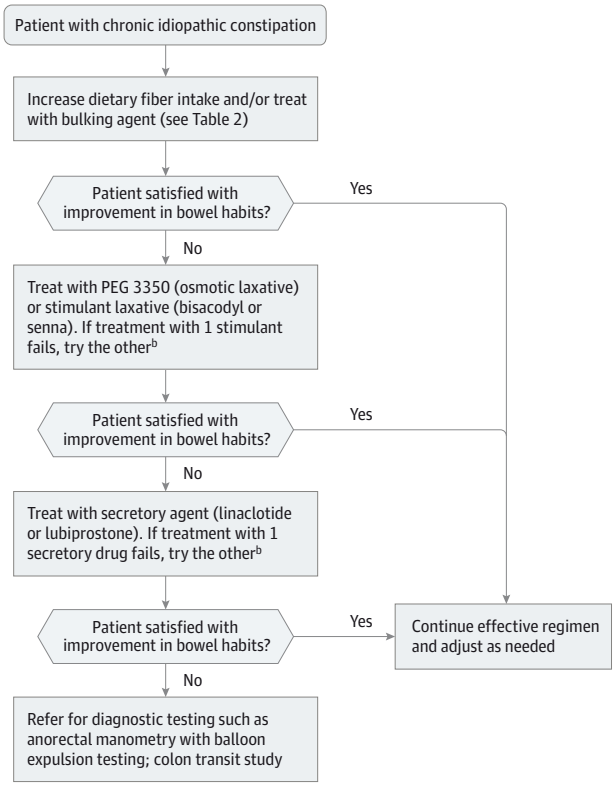
A recent single-center study compared prucalopride (1-2 mg/d) with polyethylene glycol 3350–electrolyte (PEG 3350; 26 g) administered as a split dose for 4 weeks in a noninferiority analysis.[11] The proportion of patients achieving the primary end point of more than 3 complete and spontaneous bowel movements (SBMs) that were not preceded by use of laxatives or rectal agents in the last week of therapy with prucalopride was comparable with PEG 3350(67% for PEG 3350 vs 57% for prucalopride), as were the proportion of patients achieving predefined secondary end points. A commentary of this study[12] raised the provocative issue of whether future studies of treatments for CIC should include a comparator group consisting of one of the effective but inexpensive laxatives such as PEG 3350 or bisacodyl. Comparator studies may become increasingly important in deciding which new drugs should be available as first-line agents for most patients with CIC.

Intestinal Secretogogues

These agents stimulate the net movement of ions and water into the intestinal lumen to accelerate intestinal transit and facilitate ease of defecation. Lubiprostone, a bicyclic fatty acid derived from prostaglandin E, was the first of these agents, working primarily, but not exclusively, through the apical chloride-2 channel in the small intestine; this drug also accelerates transit through the small and large intestines. In 1 randomized, double-blinded, placebo-controlled study, patients treated with lubiprostone (24 µg twice daily) had higher mean numbers of SBM than those given placebo ($P > .001$) and significantly higher patient assessments of effectiveness.[13] Based on multiple studies,[14] lubiprostone has been approved for the treatment of CIC at a dose of 24 µg twice daily and also for IBS-C at a dose of 8 µg twice daily. Clinical experience suggests that single doses are effective in many patients and are associated with fewer adverse effects such as nausea, headache, and diarrhea.

Another recently developed intestinal secretagogue is linaclotide, a first-in-class agent that acts on guanylyl cyclase C to open the cystic fibrosis transmembrane regulator chloride channel to secrete ions and water into the intestinal lumen. This is the pathway

Figure. Suggested Algorithm for Treating Patients With Chronic Idiopathic Constipation[a]



PEG 3350 indicates polyethylene glycol 3350–electrolyte.

[a] Laxatives are listed from least expensive and available without prescription to more expensive and available by prescription only.

[b] Laxatives of different classes may be used together (eg, an osmotic laxative plus a stimulant laxative).

identified as moderating secretory diarrheas caused by heat-stable enterotoxins produced by certain strains of *Escherichia coli*. The US Food and Drug Administration (FDA) has approved linaclotide to treat chronic constipation in adults at doses of 145 µg daily and for IBS-C with doses of 290 µg daily.

The basis for the approval of linaclotide for CIC was 2 randomized, placebo-controlled trials involving 1276 patients over 12 weeks.[15] As both doses (145 µg and 290 µg) showed efficacy, a dose of 145 µg daily was chosen in an effort to minimize diarrhea, which led to discontinuation of the drug in 4.2% of patients.

A recent systematic review identified 3 randomized, placebo-controlled studies of linaclotide in IBS-C involving 1773 patients.[16] Their conclusion was that there was "moderate confidence that linaclotide [in a dose of 290 µg] is moderately effective compared with placebo for improving typical symptoms of IBS-C." In this review, linaclotide was estimated to reduce the number of failures to achieve symptom relief by 165 patients per 1000 patients compared with placebo (FDA end point risk ratio [RR], 0.80 [95% CI, 0.76-0.85]), although this gain was offset by the need to discontinue therapy due to diarrhea in 31 patients per 1000 patients (RR, 14.75 [95% CI, 4.04-53.81]). As with lubiprostone and unlike prucalopride, there have been no comparator studies with less expensive laxatives.

Plecanatide is another secretory agent similar to linaclotide and also works as an agonist of the guanylyl cyclase C receptors, uroguanylin and guanylin, to activate guanylyl cyclase C. This increases intestinal secretion of chloride via the cystic fibrosis transmembrane regulator channel. Early studies suggest that plecanatide, similar to linaclotide, may be effective for both CIC and also IBS-C and may improve abdominal pain independent of stool frequency. The first human study to be published used 9 different doses in healthy controls; there was minimal, if any, drug absorption; the incidence of diarrhea was not different from that of placebo and increased adverse effects occurred only at high doses.[17] A preliminary phase 2a study showed "impressive and beneficial improvement of time to first bowel movement, change from baseline in spontaneous and complete spontaneous bowel movements, and Bristol stool form score" with benefit plateauing at the 1-mg dose.[18] It is likely that intestinal secretogogues will remain a second-tier option for CIC but may have a more prominent role in IBS-C, for which there are fewer alternatives to treatment.

Stimulant Laxatives

Stimulant laxatives such as senna and bisacodyl have long been available without prescription for episodic and chronic constipation. Both induce propagated colonic contractions to accelerate colonic transit; an agent similar to bisacodyl (sodium picosulfate) is available in Europe but not in the United States.[19] Stimulant laxatives continue to be underused by physicians and patients because of 2 outdated and non–evidence-based concerns. The first is that they can damage the colon when used long-term and that patients can become dependent on them. The second has been the absence of convincing studies that they are effective, using modern research study designs—an argument used to support newer laxatives and by writers of guidelines emphasizing evidence-based medicine. Both of these concerns have been allayed; there is now convincing evidence for efficacy of both bisacodyl and picosulfate in well-designed randomized clinical trials published within the past 5 years.[19,20] Moreover, there is no evidence to support the belief that stimulant laxatives are harmful to the colon in animals or man.[21,22] The take-home message for practitioners is that when used appropriately, stimulant laxatives appear to be safe and effective, with no potential for addiction. This statement is more evidence based for diphenylmethane laxatives such as bisacodyl, whereas comparable evidence to support the use of senna is lacking.

Bisacodyl is available in oral form as well as suppositories. Tablets are best given at bedtime, whereas suppositories are best given after breakfast to synchronize the effect to the gastrocolonic response.[2]

Which Laxatives Are Best for Constipation?

In the absence of comparator studies between older inexpensive laxatives and newer agents, physicians should be guided by cost considerations as well as potential adverse effects. There is a considerable cost difference among the available laxatives that are believed to be safe and effective (Table 2). Because there are undoubtedly discounts for laxatives, such as the intestinal secretagogues, through agreements with health care systems and insurers, actual costs will vary for patients. There remain wide differences as to costs, and there

Table 3. Available Opioid Antagonists

Drug	Receptor Antagonism[a]			Permeable to Blood-Brain Barrier
	μ	κ	δ	
Naloxone	+++	++	++	Yes
Naltrexone	+++	++	++	Yes
Methylnaltrexone	+++	++	++	No
Alvimopan	+++	None	None	No
Naloxegol	+++	None	None	No

[a] Affinity for the receptor: ++ = moderate; +++ = strong.

is no evidence of comparative efficacy. Cost-benefit ratios are very favorable to the traditional and nonprescription laxatives and therefore the more expensive laxatives should be reserved as second- to third-tier choices for CIC. A suggested algorithm for treating patients with CIC is proposed in the **Figure**. This algorithm is based on beginning with widely available and relatively inexpensive laxatives and progressing depending on response to treatment. Sometimes, effective medications have adverse effects that are unacceptable and discourage their use in some patients but are acceptable to others. Although not depicted in the algorithm, several agents may be used at once but in general, these agents should come from different categories. For example, the combination of senna and bisacodyl seems duplicative but the combination of polyethylene glycol and bisacodyl could be additive. Treatment for constipation is very much an ongoing trial and adjustment process, and no single or combined treatment works for all patients.

Opioid-Induced Constipation

An excellent review on the subject of constipation induced by opioids highlighted the substantial increase in the use of opiates and opioids for chronic pain over the past 2 decades.[23] An estimated 40% to 90% of patients who use opioids have constipation and other gastrointestinal adverse effects.[24] Opioids delay gastrointestinal transit; stimulate nonpropulsive motor activity, intestinal segmentation, and increased tone; increase fluid absorption by prolonging contract time for absorption to occur; and decrease secretion of electrolytes and water into the intestinal lumen. These effects work through 3 opiate receptors: μ, κ, and δ. By far the major activity is mediated through μ receptors located in the gut as well as the central nervous system, and the development of peripheral opioid agents has focused on blocking the μ receptors in the gut (**Table 3**). These effects may not be overcome by available laxatives in all patients and the literature on most available laxatives is scant. There is only 1 small placebo-controlled trial that suggests some efficacy of PEG 3350 and lactulose for OIC in patients taking methadone.[25]

A recent systematic review of treatment for OIC concluded that 3 different μ-opioid receptor antagonists: methylnaltrexone (6 trials, 1610 patients), naloxone (4 trials, 798 patients), and alvimopan (4 trials, 1693 patients) were all superior to placebo for OIC.[26] The use of methylnaltrexone had been restricted by the requirement for delivery by subcutaneous injection and only in patients with medically advanced illness; however, the FDA has recently approved methylnaltrexone bromide (12 mg, subcutaneous) for OIC in patients taking opioids for chronic noncancer pain.[23] Alvimopan is indicated only to shorten the duration of postoperative ileus and is not approved by the FDA due to serious cardiovascular adverse effects.[23] Long-term use of naloxone alone has not been approved for use in the United States.

Recent studies support the efficacy of 3 additional pharmacologic agents in the treatment of OIC; 2 are peripherally restricted μ-opiate receptor antagonists, whereas the third is the intestinal secretogogue lubiprostone.

A recently published study supports the efficacy of lubiprostone to treat OIC in patients with chronic pain that is not attributable to cancer.[27] In a multicenter, randomized, placebo-controlled trial, 210 patients with OIC were given lubiprostone (24 μg) twice daily and 208 patients were given a placebo over a 3-month trial period. Approximately two-thirds of the patients in each group completed the trial, and the primary end point was the change in SBM frequency at week 8 compared with baseline. Mean changes were approximately 1 SBM per week higher in patients treated with lubiprostone compared with placebo; this was statistically significant at 8 weeks but not at 12 weeks because there were fewer patients analyzed at 12 weeks. Statistically significant changes with lubiprostone were also seen in stool consistency, severity of constipation, straining, and abdominal discomfort, but not bloating or bowel regularity. Overall effectiveness was rated as slightly, but significantly, higher by patients taking the drug vs placebo (mean difference was about 0.4 higher than placebo on a 0-4 scale; 0 indicated "not effective" and 4 indicated "extremely effective"). The percentage of patients in each group who achieved the primary end point was not provided. Nausea occurred in 16.8% of patients receiving lubiprostone vs 5.8% receiving placebo; diarrhea, 9.6% for lubiprostone vs 2.9% for placebo; and abdominal distension, 8.2% for lubiprostone vs 2.4% for placebo, all statistically significant. The clinical significance of these findings is uncertain. The presumed mechanism of action is the possible reversal of the intestinal antisecretory effects of opioid agonists. Similar results were observed in patients with opioid-induced constipation and chronic noncancer pain.[28]

A more biologically plausible approach to OIC is to combine a strong opiate agent with an effective opioid receptor antagonist that will not counteract the benefits of pain reduction. An example of this is oxycodone/naloxone. Naloxone is an opioid receptor antagonist that exhibits a local effect on gastrointestinal opioid receptors but is nearly completely inactivated by the liver after oral administration. A timely review that summarized the use of oxycodone/naloxone in patients with chronic pain (nonmalignant pain and cancer-related pain) was recently published.[29] An initial dose of 10 mg/5 mg twice daily or 20 mg/10 mg twice daily was often effective, and the drug can be titrated to a maximum of 40 mg/20 mg twice daily with the goal of achieving effective analgesia. Oxycodone/naloxone has been approved as an "abuse-

deterrent" agent for use in "pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."[30]

A variation on this theme is the development of naloxegol, a pegylated derivative of naloxone that limits the ability of naloxegol to cross the blood-brain barrier so that it acts only on peripheral μ-opioid receptors. On the basis of successful phase 2 randomized clinical studies,[31] 2 identical randomized, clinical phase 3 studies consisting of 1352 patients were performed with patients with OIC receiving 12.5 mg or 25 mg of naloxegol daily vs placebo over a 3-month period.[25] The primary end point was the 12-week response rate (≥3 SBMs per week plus an increase from baseline of ≥1 SBM for ≥9 of 12 weeks and for ≥3 of the final 4 weeks). Two populations were analyzed: (1) all patients in an intention-to-treat model and (2) only patients with an inadequate previous response to laxatives.

Response rates to the 25-mg dose in both studies were statistically significantly higher than placebo (44.4% for naloxegol vs 29.4% for placebo; 39.7% for naloxegol vs 29.3% for placebo) with a number needed to treat (NNT) of 6.7 and 9.7, respectively. This was also true for the subpopulation with a previously inadequate response to laxatives (48.7% for naloxegol vs 28.8% for placebo, NNT 5.0; 46.8% for naloxegol vs 31.4% for placebo, NNT, 6.5). Mean daily opioid doses remained stable during both studies and adverse effects were infrequent; the most frequent was abdominal pain in both studies (12.6% and 19.0% for naloxegol vs 3.3% and 7.8% for placebo, respectively). Similar findings were reported in a more recent European-based, multicenter, placebo-controlled trial.[32] Naloxegol was approved for use in patients with OIC with chronic noncancer pain in September 2014. Although initially listed as a controlled schedule II substance, that designation has recently been lifted.[33] Naloxogol should be considered in patients who do not respond to available laxatives, including lubiprostone; the reason, in part, is due to the difficulty in defining who has OIC vs constipated patients who are using opiates.

As is true with all FDA-sponsored studies, these results are based on monotherapy. As they work by different mechanisms, combining opioid antagonists with other available laxatives may improve outcomes, although this has not been formally studied.

Defecation Disorders

Many patients with CIC who respond poorly or not at all to conventional therapy have a defecation disorder. These are sometimes associated with an anatomic cause (ie, a large rectocele or enterocoele) but more often is caused by a functional disorder such as dyssynergic defecation or inadequate propulsive forces during attempted defecation. The traditional diagnostic approach to such patients has been to perform a colon transit study with radio-opaque markers or, more recently, a wireless capsule[2,34] to determine if the patient has slow colonic transit (a colonic problem) as well as anorectal manometry (ARM) with balloon expulsion testing (BET) to identify a functional disorder of defecation.[2,34] A recent technical review proposes an important shift in the algorithm for diagnostic testing[2]; another study confirms the validity of an office-based BET as a screening test in such patients.[35]

The new technical review on constipation released by the AGA suggests that patients with intractable constipation should initially undergo ARM and the BET without a colon transit study.[2] There were 2 reasons advanced for this position. First, up to 50% of patients with dyssynergic defecation have slow colonic transit, many of whom will normalize after successful treatment of the dyssynergic defecation. If initial testing is normal or if patients normalize the dyssynergic pattern with biofeedback but symptoms persist, a colon transit study should be performed to identify patients with slow transit. If patients with dyssynergic defecation respond clinically to biofeedback, colon transit testing is not necessary. This presumes that there are experienced laboratories that perform both studies when evaluating these patients. Unfortunately, no single test is sufficiently definitive to make a diagnosis of dyssynergic defecation.

A recent study was designed to test the reproducibility and agreement of the BET with ARM or anal electromyography.[35] In a single center, 286 consecutive patients with chronic constipation and 40 healthy controls underwent BET on 2 occasions less than 1 month apart. Patients also underwent ARM and electromyography; 47 patients with conflicting ARM and BET underwent defecography.

All healthy controls passed a 50-mL water-filled balloon within 2 minutes (93% within 1 minute), with perfect reproducibility, thus establishing the upper limit of normal. Of 286 patients, 145 patients had a normal BET and 141 were abnormal, also with perfect reproducibility. The level of agreement between BET and ARM was 78% and between BET and anal electromyography was 83%. Thus, BET is an office-based procedure that is a reliable first test for dyssynergic defecation; if abnormal, ARM or defecography can be used to determine why expulsion is abnormal in a patient with chronic refractory constipation. BET or ARM is insufficient to evaluate a patient with suspected dyssynergic defecation. This is important to emphasize because normative data for ARM and anal electromyography during defecation are not universally agreed upon.

The importance of diagnosing dyssynergic defecation and other functional defecation disorders concerns effective treatment for these patients. Biofeedback is the preferred treatment for dyssynergic defecation in adults, based upon 3 randomized clinical trials comprising 370 patients that showed a clear-cut superiority of biofeedback against comparator groups.[36,37]

ARTICLE INFORMATION

Conflict of Interest Disclosures: Dr Wald has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and reports advising Takeda Sucampo, Ironwood, Actavis, Entera Health, and Forest Laboratories.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

REFERENCES

1. Shah ND, Chitkara DK, Locke GR, Meek PD, Talley NJ. Ambulatory care for constipation in the United States, 1993-2004. *Am J Gastroenterol*. 2008;103(7):1746-1753.

2. Bharucha AE, Pemberton JH, Locke GR III. American Gastroenterological Association technical review on constipation. *Gastroenterology*. 2013;144(1):218-238.

3. Ford AC, Moayyedi P, Lacy BE, et al; Task Force on the Management of Functional Bowel Disorders. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol*. 2014;109(suppl 1):S2-S26.

4. Wong RK, Palsson OS, Turner MJ, et al. Inability of the Rome III criteria to distinguish functional constipation from constipation-subtype irritable bowel syndrome. *Am J Gastroenterol*. 2010;105(10):2228-2234.

5. Heidelbaugh JJ, Stelwagon M, Miller SA, Shea EP, Chey WD. The spectrum of constipation-predominant IBS and CIC: US survey assessing symptoms, care seeking, and disease burden. *Am J Gastroenterol*. 2015;110:580-587.

6. Naloxegol (Movantik) for opioid-induced constipation. *Med Lett Drugs Ther*. 2015;57(1478):135-137.

7. Johanson JF, Kralstein J. Chronic constipation: a survey of the patient perspective. *Aliment Pharmacol Ther*. 2007;25(5):599-608.

8. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3: rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401-406.

9. Shin A, Camilleri M, Kolar G, Erwin P, West CP, Murad MH. Systematic review with meta-analysis: highly selective 5-HT4 agonists (prucalopride, velusetrag, or naronapride) in chronic constipation. *Aliment Pharmacol Ther*. 2014;39(3):239-253.

10. Yiannakou Y, Piessevaux H, Bouchoucha M, et al. A randomized, double blind, placebo controlled, phase 3 trial to evaluate the efficacy, safety and tolerability of prucalopride in men with chronic constipation. *Am J Gastroenterol*. 2015;110(5):741-748.

11. Cinca R, Chera D, Gruss HJ, Halphen M. Randomised clinical trial: macrogol/PEG 3350+electrolytes versus prucalopride in the treatment of chronic constipation—a comparison in a controlled environment. *Aliment Pharmacol Ther*. 2013;37(9):876-886.

12. Ford AC. Death knell for placebo-controlled trials in chronic idiopathic constipation? *Gastroenterology*. 2013;145(4):897-898.

13. Barish CF, Drossman D, Johanson JF, Ueno R. Efficacy and safety of lubiprostone in patients with chronic constipation. *Dig Dis Sci*. 2010;55(4):1090-1097.

14. Schey R, Rao SS. Lubiprostone for the treatment of adults with constipation and irritable bowel syndrome. *Dig Dis Sci*. 2011;56(6):1619-1625.

15. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. *N Engl J Med*. 2011;365(6):527-536.

16. Atluri DK, Chandar AK, Bharucha AE, Falck-Ytter Y. Effect of linaclotide in irritable bowel syndrome with constipation (IBS-C): a systematic review and meta-analysis. *Neurogastroenterol Motil*. 2014;26(4):499-509.

17. Shailubhai K, Comiskey S, Foss JA, et al. Plecanatide, an oral guanylate cyclase C agonist acting locally in the gastrointestinal tract, is safe and well-tolerated in single doses. *Dig Dis Sci*. 2013;58(9):2580-2586.

18. Quigley EM. Open channels for functional bowel disorders: guanylate cyclase C agonists in IBS and CC. *Dig Dis Sci*. 2013;58(9):2446-2448.

19. Mueller-Lissner S, Kamm MA, Wald A, et al. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of sodium picosulfate in patients with chronic constipation. *Am J Gastroenterol*. 2010;105(4):897-903.

20. Kamm MA, Mueller-Lissner S, Wald A, Richter E, Swallow R, Gessner U. Oral bisacodyl is effective and well-tolerated in patients with chronic constipation. *Clin Gastroenterol Hepatol*. 2011;9(7):577-583.

21. Müller-Lissner SA, Kamm MA, Scarpignato C, Wald A. Myths and misconceptions about chronic constipation. *Am J Gastroenterol*. 2005;100(1):232-242.

22. Wald A. Is chronic use of stimulant laxatives harmful to the colon? *J Clin Gastroenterol*. 2003;36(5):386-389.

23. Nelson AD, Camilleri M. Chronic opioid-induced constipation in patients with nonmalignant pain: challenges and opportunities. *Therap Adv Gastroenterol*. 2015;8(4):206-220.

24. Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med*. 2014;370(25):2387-2396.

25. Freedman MD, Schwartz HJ, Roby R, Fleisher S. Tolerance and efficacy of polyethylene glycol 3350/electrolyte solution versus lactulose in relieving opiate-induced constipation: a double-blinded placebo-controlled trial. *J Clin Pharmacol*. 1997;37(10):904-907.

26. Ford AC, Brenner DM, Schoenfeld PS. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and meta-analysis. *Am J Gastroenterol*. 2013;108(10):1566-1574.

27. Cryer B, Katz S, Vallejo R, Popescu A, Ueno R. A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. *Pain Med*. 2014;15(11):1825-1834.

28. Jamal MM, Adams AB, Jansen JP, Webster LR. A randomized, placebo-controlled trial of lubiprostone for opioid-induced constipation in chronic noncancer pain. *Am J Gastroenterol*. 2015;110(5):725-732.

29. Leppert W. Oxycodone/naloxone in the management of patients with pain and opioid-induced bowel dysfunction. *Curr Drug Targets*. 2014;15(1):124-135. Review.

30. US Food and Drug Administration. FDA approves new extended-release oxycodone with abuse-deterrent properties. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm406407.htm. Accessed December 18, 2015.

31. Webster L, Dhar S, Eldon M, Masuoka L, Lappalainen J, Sostek M. A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation. *Pain*. 2013;154(9):1542-1550.

32. Tack J, Lappalainen J, Diva U, Tummala R, Sostek M. Efficacy and safety of naloxegol in patients with opioid-induced constipation and laxative-inadequate response. *United European Gastroenterol J*. 2015;3(5):471-480.

33. Drug Enforcement Administration, Department of Justice. Schedules of controlled substances: removal of naloxegol from control. Final rule. *Fed Regist*. 2015;80(15):3468-3470.

34. Bharucha AE, Wald AM. Anorectal disorders. *Am J Gastroenterol*. 2010;105(4):786-794.

35. Chiarioni G, Kim SM, Vantini I, Whitehead WE. Validation of the balloon evacuation test: reproducibility and agreement with findings from anorectal manometry and electromyography. *Clin Gastroenterol Hepatol*. 2014;12(12):2049-2054.

36. Rao SS, Valestin J, Brown CK, Zimmerman B, Schulze K. Long-term efficacy of biofeedback therapy for dyssynergic defecation: randomized controlled trial. *Am J Gastroenterol*. 2010;105(4):890-896.

37. Wald A, Bharucha AE, Cosman BC, Whitehead WE. ACG clinical guideline: management of benign anorectal disorders. *Am J Gastroenterol*. 2014;109(8):1141-1157, 1058.