CME CREDIT ***LEARNING OBJECTIVE:*** Readers will differentiate the types of chronic constipation and apply traditional and newer treatments to best advantage

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Chronic constipation: Update on management

ABSTRACT

Managing chronic constipation involves identifying and treating secondary causes, instituting lifestyle changes, prescribing pharmacologic and nonpharmacologic therapies, and, occasionally, referring for surgery. Several new drugs have been approved, and others are in the pipeline.

KEY POINTS

Although newer drugs are available, lifestyle modifications and laxatives continue to be the treatments of choice for chronic constipation, as they have high response rates and few adverse effects and are relatively affordable.

Chronic constipation requires different management approaches depending on whether colonic transit time is normal or prolonged and whether outlet function is abnormal.

Surgical treatments for constipation are reserved for patients whose symptoms persist despite maximal medical therapy.

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Chronic constipation has a variety of possible causes and mechanisms. Although traditional conservative treatments are still valid and first-line, if these fail, clinicians can choose from a growing list of new treatments, tailored to the cause in the individual patient.

This article discusses how defecation works (or doesn't), the types of chronic constipation, the available diagnostic tools, and traditional and newer treatments, including some still in development.

THE EPIDEMIOLOGY OF CONSTIPATION

Chronic constipation is one of the most common gastrointestinal disorders, affecting about 15% of all adults and 30% of those over the age of 60.[1] It can be a primary disorder or secondary to other factors.

Constipation is more prevalent in women and in institutionalized elderly people.[2] It is associated with lower socioeconomic status, depression, less self-reported physical activity, certain medications, and stressful life events.[3] Given its high prevalence and its impact on quality of life, it is also associated with significant utilization of healthcare resources.[4]

Constipation defined by Rome IV criteria

Physicians and patients may disagree about what constitutes constipation. Physicians primarily regard it as infrequent bowel movements, while patients tend to have a broader definition. According to the Rome IV criteria,[5] chronic constipation is defined by the presence of the following for at least 3 months (with symptom onset at least 6 months prior to diagnosis):

(1) Two or more of the following for more than 25% of defecations:

- Straining
- Lumpy or hard stools
- Sensation of incomplete evacuation
- Sensation of anorectal obstruction or blockage
- Manual maneuvers to facilitate evacuation
- Fewer than 3 spontaneous bowel movements per week.

(2) Loose stools are rarely present without the use of laxatives.

(3) The patient does not meet the criteria for diagnosis of irritable bowel syndrome.

DEFECATION IS COMPLEX

Defecation begins when the rectum fills with stool, causing relaxation of the internal anal sphincter and the urge to defecate. The external anal sphincter, which is under voluntary control, can then either contract to delay defecation or relax to allow the stool to be expelled.[6]

Colonic muscles propel stool toward the rectum in repetitive localized contractions that help mix and promote absorption of the content, and larger coordinated (high-amplitude propagating) contractions that, in healthy individuals, move the stool forward from the proximal to the distal colon multiple times daily. These contractions usually occur in the morning and are accentuated by gastric distention from food and the resulting gastrocolic reflex.

Serotonin (5-HT) is released by enterochromaffin cells in response to distention of the gut wall. It mediates peristaltic movements of the gastrointestinal tract by binding to receptors (especially 5-HT4), stimulating release of neurotransmitters such as acetylcholine, causing smooth-muscle contraction behind the luminal contents and propelling them forward.

Chronic constipation is linked to lower socioeconomic status, depression, lack of physical activity, certain medications, and stressful life events

PRIMARY CONSTIPATION DISORDERS

The American Gastroenterological Association[7] classifies constipation into 3 groups on the basis of colonic transit time and anorectal function:

Normal-transit constipation

Stool normally takes 20 to 72 hours to pass through the colon, with transit time affected by diet, drugs, level of physical activity, and emotional status.[8]

Normal-transit constipation is the most common type of constipation. The term is sometimes used interchangeably with constipation-predominant irritable bowel syndrome, but the latter is a distinct entity characterized by abdominal pain relieved by defecation as the primary symptom, as well as having occasional loose stools. These 2 conditions can be hard to tell apart, especially if the patient cannot describe the symptoms precisely.

Slow-transit constipation

Slow-transit constipation—also called delayed-transit constipation, colonoparesis, colonic inertia, and pseudo-obstruction—is defined as prolonged stool transit in the colon, ie, for more than 5 days.[9] It can be the result of colonic smooth muscle dysfunction, compromised colonic neural pathways, or both, leading to slow colon peristalsis.

Factors that can affect colonic motility such as opioid use and hypothyroidism should be carefully considered in these patients. Opioids are notorious for causing constipation by decreasing bowel tone and contractility and thereby increasing colonic transit time. They also tighten up the anal sphincters, resulting in decreased rectal evacuation.[10]

Outlet dysfunction

Outlet dysfunction, also called pelvic floor dysfunction or defecatory disorder, is associated with incomplete rectal evacuation. It can be a consequence of weak rectal expulsion forces (slow colonic transit, rectal hyposensitivity), functional resistance to rectal evacuation (high anal resting pressure, anismus, incomplete relaxation of the anal sphincter, dyssynergic defecation), or structural outlet obstruction (excessive perineal descent, rectoceles, rectal intussusception). About 50% of patients with outlet dysfunction have concurrent slow-transit constipation.

Dyssynergic defecation is the most common outlet dysfunction disorder, accounting for about half of the cases referred to tertiary centers. It is defined as a paradoxical elevation in anal sphincter tone or less than 20% relaxation of the resting anal sphincter pressure with weak abdominal and pelvic propulsive forces.[11] Anorectal biofeedback is a therapeutic option for dyssynergic defecation, as we discuss later in this article.

SECONDARY CONSTIPATION

Constipation can be secondary to several conditions and factors (**Table 1**), including:

- Neurologic disorders that affect gastrointestinal motility (eg, Hirschsprung disease, Parkinson disease, multiple sclerosis, spinal cord injury, stroke, spinal or ganglionic tumor, hypothyroidism, amyloidosis, diabetes mellitus, hypercalcemia)
- Drugs used to treat neurologic disorders
- Mechanical obstruction
- Diet (eg, low fiber, decreased fluid intake).

TABLE 1

Causes of secondary constipation

Neurologic and motility disorders
Amyloidosis
Diabetes
Hirschsprung disease
Hypothyroidism
Multiple sclerosis
Parkinson disease
Spinal cord injury
Spinal or ganglionic tumors
Stroke

Diseases in which treatment can cause constipation
Bipolar disorder
Chronic pain
Depression
Parkinson disease
Schizophrenia

Medications
Anticholinergics
Anticonvulsants
Antidepressants
Antipsychotics
Antispasmodics
Calcium channel blockers
Opioids

Other causes
Chagas disease
Conversion disorder
Decreased fluid intake
Hypercalcemia
Hyperparathyroidism
Low-fiber diet
Mechanical obstruction

EVALUATION OF CONSTIPATION

It is crucial for physicians to efficiently use the available diagnostic tools for constipation to tailor the treatment to the patient.

Evaluation of chronic constipation begins with a thorough history and physical examination to rule out secondary constipation (**Figure 1**). Red flags such as unintentional weight loss, blood in the stool, rectal pain, fever, and iron-deficiency anemia should prompt referral for colonoscopy to evaluate for malignancy, colitis, or other potential colonic abnormalities.[12]

A detailed perineal and rectal examination can help diagnose defecatory disorders and should include evaluation of the resting anal tone and the sphincter during simulated evacuation.

Laboratory tests of thyroid function, electrolytes, and a complete blood cell count should be ordered if clinically indicated.[13]

Red flags: unintentional weight loss, blood in the stool, rectal pain, fever, iron-deficiency anemia

Further tests

Further diagnostic tests can be considered if symptoms persist despite conservative treatment or if a defecatory disorder is suspected. These include anorectal manometry, colonic transit studies, defecography, and colonic manometry.

Anorectal manometry and the rectal balloon expulsion test are usually done first because of their high sensitivity (88%) and specificity (89%) for defecatory disorders.[14] These tests measure the function of the internal and external anal sphincters at rest and with straining and assess rectal sensitivity and compliance. Anorectal manometry is also used in biofeedback therapy in patients with dyssynergic defecation.[15]

Colonic transit time can be measured if anorectal manometry and the balloon expulsion test are normal. The study uses radiopaque markers, radioisotopes, or wireless motility capsules to confirm slow-transit constipation and to identify areas of delayed transit in the colon.[16]

Defecography is usually the next step in diagnosis if anorectal manometry and balloon expulsion tests are inconclusive or if an anatomic abnormality of the pelvic floor is suspected. It can be done with a variety of techniques. Barium defecography can identify anatomic defects, scintigraphy can quantify evacuation of artificial stools, and magnetic resonance defecography visualizes anatomic landmarks to assess pelvic floor motion without exposing the patient to radiation.[17,18]

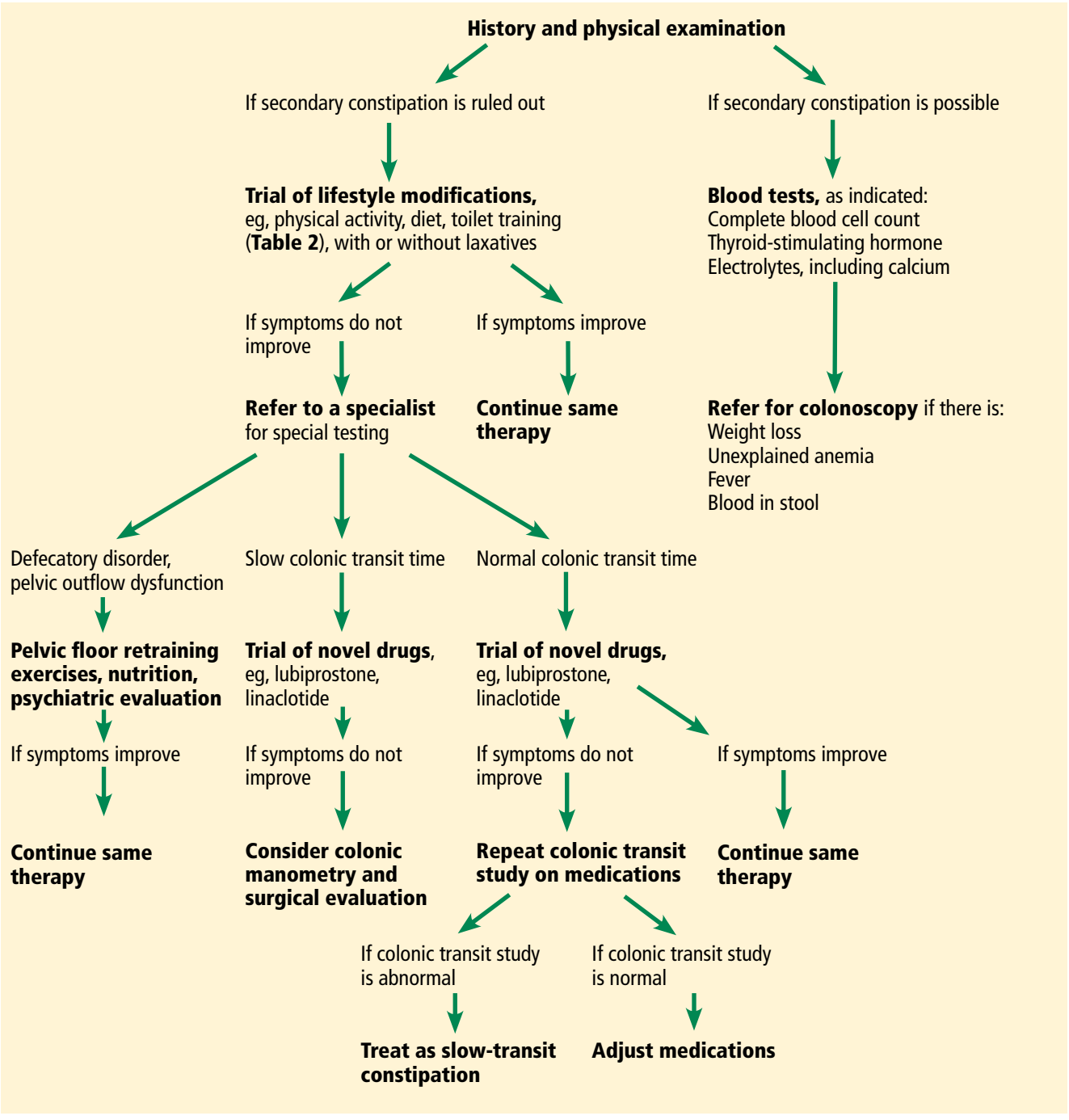

FIGURE 1. Diagnosis and management of chronic constipation.

Colonic manometry is most useful in patients with refractory slow-transit constipation and can identify patients with isolated colonic motor dysfunction with no pelvic floor dysfunction who may benefit from subtotal colectomy and end-ileostomy.[7]

TRADITIONAL TREATMENTS STILL THE MAINSTAY

Nonpharmacologic treatments are the first-line options for patients with normal-transit and slow-transit constipation and should precede diagnostic testing. Lifestyle modifications

and dietary changes (**Table 2**) aim to augment the known factors that stimulate the gastrocolic reflex and increase intestinal motility by high-amplitude propagated contractions.

Increasing physical activity increases intestinal gas clearance, decreases bloating, and lessens constipation.[19,20]

Toilet training is an integral part of lifestyle modifications.[21]

Diet. Drinking hot caffeinated beverages, eating breakfast within an hour of waking up, and consuming fiber in the morning (25–30 g of fiber daily) have traditionally been recommended as the first-line measures for chronic constipation. Dehydrated patients with constipation also benefit from increasing their fluid intake.[22]

TABLE 2

Nonpharmacologic management of chronic constipation

Increase physical activity (most beneficial in early morning)

Toilet training. Instruct patients to:
Not ignore urges to defecate
Use correct posture, ie, "brace-pump" technique: sit on the toilet and lean forward, with knees higher than hips and with feet supported on a step to straighten the anorectal angle
Do deep-relaxation techniques while defecating
Avoid straining when passing stool
Not stay on the toilet for more than 5–10 minutes

Dietary changes
Drink a hot caffeinated beverage after waking up
Eat breakfast within 1 hour of waking up
Increase fluid intake to 1.5–2 L daily
Increase dietary fiber to 25–30 g daily; do this slowly to avoid abdominal cramps and bloating

LAXATIVES

Fiber (bulk-forming laxatives) for normal-transit constipation

Fiber remains a key part of the initial management of chronic constipation, as it is cheap, available, and safe. Increasing fiber intake is effective for normal-transit constipation, but patients with slow-transit constipation or refractory outlet dysfunction are less likely to benefit.[23] Other laxatives are incorporated into the regimen if first-line nonpharmacologic interventions fail (**Table 3**).

Bulk-forming laxatives include insoluble fiber (wheat bran) and soluble fiber (psyllium, methylcellulose, inulin, calcium polycarbophil). Insoluble fiber, though often used, has little impact on symptoms of chronic constipation after 1 month of use, and up to 60% of patients report adverse effects from it.[24] On the other hand, clinical trials have shown that soluble fiber such as psyllium facilitates defecation and improves functional bowel symptoms in patients with normal-transit constipation.[25]

Patients should be instructed to increase their dietary fiber intake gradually to avoid adverse effects and should be told to expect significant symptomatic improvement only after a few weeks. They should also be informed that increasing dietary fiber intake can cause bloating but that the bloating is temporary. If it continues, a different fiber can be tried.

Osmotic laxatives

Osmotic laxatives are often employed as a first-line laxative treatment option for patients with constipation. They draw water into the lumen by osmosis, helping to soften stool and speed intestinal transit. They include macrogols (inert polymers of ethylene glycol), nonabsorbable carbohydrates (lactulose, sorbitol), magnesium products, and sodium phosphate products.

Increasing dietary fiber is less likely to benefit patients with slow-transit constipation or refractory outlet dysfunction

Polyethylene glycol, the most studied osmotic laxative, has been shown to maintain therapeutic efficacy for up to 2 years, though it is not generally used this long.[26] A meta-analysis of 10 randomized clinical trials found it to be superior to lactulose in improving stool consistency and frequency, and rates of adverse effects were similar to those with placebo.[27]

Lactulose and sorbitol are semisynthetic disaccharides that are not absorbed from the gastrointestinal tract. Apart from the osmotic effect of the disaccharide, these sugars are metabolized by colonic bacteria to acetic acid and other short-chain fatty acids, resulting in acidification of the stool, which exerts an osmotic effect in the colonic lumen.

Lactulose and sorbitol were shown to have similar efficacy in increasing the frequency of bowel movements in a small study, though patients taking lactulose had a higher rate of nausea.[28]

TABLE 3

Agents for treating chronic constipation

Bulk-forming laxatives
Insoluble fiber (bran)
Soluble fiber (psyllium, methylcellulose, calcium polycarbophil)

Osmotic laxatives
Polyethylene glycol, lactulose, sorbitol, magnesium hydroxide, magnesium citrate, sodium phosphate enemas

Stool softeners
Docusate

Stimulant laxatives
Bisacodyl, anthraquinones, glycerin suppository

Intestinal secretagogues
Linaclotide, lubiprostone

Opioid receptor antagonists
Methylnaltrexone, neloxegol

AGENTS IN DEVELOPMENT

Selective serotonin (5-HT4) agonists
Naronapride, prucalopride, velusetrag

Ileal bile acid transporter inhibitors
Elboxibat

Intestinal secretagogues
Plecanatide

NHE3 sodium transporter inhibitors
Tenapanor

The usual recommended dose is 15 to 30 mL once or twice daily.

Adverse effects include gas, bloating, and abdominal distention (due to fermentation by colonic bacteria) and can limit long-term use.

Magnesium citrate and magnesium hydroxide are strong osmotic laxatives, but so far no clinical trial has been done to assess their efficacy in constipation. Although the risk of hypermagnesemia is low with magnesium-based products, this group of laxatives is generally avoided in patients with renal or cardiac disease.[29]

Sodium phosphate enemas (Fleet enemas) are used for bowel cleansing before certain procedures but have only limited use in constipation because of potential adverse effects such as hyperphosphatemia, hypocalcemia, and the rarer but more serious complication of acute phosphate nephropathy.[30]

Stimulant laxatives for short-term use only

Stimulant laxatives include glycerin, bisacodyl, senna, and sodium picosulfate. Sodium piosulfate and bisacodyl have been validated for treatment of chronic constipation for up to 4 weeks.[31–33]

Stimulant laxative suppositories should be used 30 minutes after meals to augment the physiologic gastrocolic reflex.

As more evidence is available for osmotic laxatives such as polyethylene glycol, they tend to be preferred over stimulant agents, especially for long-term use. Clinicians have traditionally hesitated to prescribe stimulant laxatives for long-term use, as they were thought to damage the enteric nervous system.[34] Although more recent studies have not shown this potential effect,[35] more research is warranted on the use of stimulant laxatives for longer than 4 weeks.

STOOL SOFTENERS: LITTLE EVIDENCE

Stool softeners enhance the interaction of stool and water, leading to softer stool and easier evacuation. Docusate sodium and docusate calcium are thought to facilitate the mixing of aqueous and fatty substances, thereby softening the stool.

However, there is little evidence to support the use of docusate for constipation in hospitalized adults or in ambulatory care. A recent review reported that docusate was no better than placebo in diminishing symptoms of constipation.[36]

INTESTINAL SECRETAGOGUES

The secretagogues include lubiprostone, linaclotide, and plecanatide. These medications are preferred therapy for patients with normal- or slow-transit constipation once conservative therapies have failed. Even though there is no current consensus, lifestyle measures and conservative treatment options should be tried for about 8 weeks.

Lubiprostone and linaclotide are approved by the US Food and Drug Administration (FDA) for both constipation and constipation-predominant irritable bowel syndrome. They activate chloride channels on the apical surface of enterocytes, increasing intestinal secretion of chloride, which in turn increases luminal sodium efflux to maintain electroneutrality, leading to secretion of water into the intestinal

lumen. This eventually facilitates intestinal transit and increases the passage of stool.

Lubiprostone

Lubiprostone, a prostaglandin E1 derivative, is approved for treating chronic constipation, constipation-predominant irritable bowel syndrome in women, and opioid-induced constipation in patients with chronic noncancer pain.

Adverse effects in clinical trials were nausea (up to 30%) and headache.[37,38]

Linaclotide

Linaclotide, a minimally absorbed 14-amino acid peptide, increases intestinal secretion of chloride and bicarbonate, increasing intestinal fluid and promoting intestinal transit.[39] It also decreases the firing rate of the visceral afferent pain fibers and helps reduce visceral pain, especially in patients with constipation-predominant irritable bowel syndrome.[40] It is approved for chronic constipation and constipation-predominant irritable bowel syndrome.[41–43]

Dosage starts at 145 µg/day for chronic constipation, and can be titrated up to 290 µg if there is no response or if a diagnosis of constipation-predominant irritable bowel syndrome is under consideration. Linaclotide should be taken 30 to 60 minutes before breakfast to reduce the likelihood of diarrhea.[44]

Adverse effects. Diarrhea led to treatment discontinuation in 4.5% of patients in one study.[42]

Plecanatide

Plecanatide is a guanylate cyclase-c agonist with a mode of action similar to that of linaclotide. It was recently approved by the FDA for chronic idiopathic constipation in adults. The recommended dose is 3 mg once daily.

Data from phase 2 trials in chronic constipation showed improvement in straining, abdominal discomfort, and stool frequency after 14 days of treatment.[45]

A phase 3 trial showed that plecanatide was more effective than placebo when used for 12 weeks in 951 patients with chronic constipation (P = .009).[46] The most common adverse effect reported was diarrhea.

SEROTONIN RECEPTOR AGONISTS

Activation of serotonin 5-HT4 receptors in the gut leads to release of acetylcholine, which in turn induces mucosal secretion by activating submucosal neurons and increasing gut motility.[47]

Two 5-HT4 receptor agonists were withdrawn from the market (cisapride in 2000 and tegaserod in 2007) due to serious cardiovascular adverse events (fatal arrhythmias, heart attacks, and strokes) resulting from their affinity for hERG-K+ cardiac channels.

The newer agents prucalopride,[48] velusetrag, and naronapride are highly selective 5-HT4 agonists with low affinity for hERG-K+ receptors and do not have proarrhythmic properties, based on extensive assessment in clinical trials.

Prucalopride

Prucalopride has been shown to accelerate gastrointestinal and colonic transit in patients with chronic constipation, with improvement in bowel movements, symptoms of chronic constipation, and quality of life.[49–52]

Adverse effects reported with its use have been headache, nausea, abdominal pain, and cramps.

Prucalopride is approved in Europe and Canada for chronic constipation in women but is not yet approved in the United States.

Dosage is 2 mg orally once daily. Caution is advised in elderly patients, in whom the preferred maximum dose is 1 mg daily, as there are only limited data available on the safety of this medication in the elderly.

Velusetrag

Velusetrag has been shown to increase colonic motility and improve symptoms of chronic constipation. In a phase 2 trial,[53] the most effective dose was 15 mg once daily. Higher doses were associated with a higher incidence of adverse effects such as diarrhea, headache, nausea, and vomiting.

Naronapride

Naronapride (ATI-7505) is in phase 2 trials for chronic constipation. Reported adverse effects were headache, diarrhea, nausea, and vomiting.[54]

The newer, highly selective 5-HT4 agonists have a low affinity for hERG-K+ receptors and do not have proarrhythmic properties

BILE SALT ABSORPTION INHIBITORS

Bile acids exert prosecretory and prokinetic effects by increasing colonic secretion of water and electrolytes through the activation of adenylate cyclase. This happens as a result of their deconjugation after passage into the colon.

Elobixibat is an ileal bile acid transporter inhibitor that prevents absorption of nonconjugated bile salts in the distal ileum. It has few side effects because its systemic absorption is minimal. Phase 3 trials are under way. Dosage is 5 to 20 mg daily. Adverse effects are few because systemic absorption is minimal, but include abdominal pain and diarrhea.[55,56]

MANAGING OPIOID-INDUCED CONSTIPATION

Opioids cause constipation by binding to mu receptors in the enteric nervous system. Activation of these receptors decreases bowel tone and contractility, which increases transit time. Stimulation of these receptors also increases anal sphincter tone, resulting in decreased rectal evacuation.[57]

Though underrecognized, opioid-induced constipation affects 40% of patients who take these drugs for nonmalignant pain and 90% of those taking them for cancer pain. Patients with this condition were found to take more time off work and feel more impaired in their domestic and work-related obligations than patients who did not develop constipation with use of opioids.[58]

Initial management of opioid-induced constipation includes increasing intake of fluids and dietary fiber (fiber alone can worsen abdominal pain in this condition by increasing stool bulk without a concomitant improvement in peristalsis) and increasing physical activity. It is common clinical practice to use a stool softener along with a stimulant laxative if lifestyle modifications are inadequate.[59] If these measures are ineffective, osmotic agents can be added.

If these conventional measures fail, a peripherally acting mu-opioid receptor antagonist such as methylnaltrexone or naloxegol should be considered.

For constipation-predominant IBS, adjunctive therapies such as peppermint oil, probiotics, and acupuncture have shown promise, but more data are needed

Methylnaltrexone

Methylnaltrexone[60,61] is a peripherally acting mu receptor antagonist with a rapid onset of action. It does not cross the blood-brain barrier, as it contains a methyl group. It was approved by the FDA in 2008 to treat opioid-induced constipation in adults with advanced illnesses when other approaches are ineffective.

Adverse effects. Although the mu receptor antagonist alvimopan had been shown to be associated with cardiovascular events hypothesized to be a consequence of opioid withdrawal, methylnaltrexone has been deemed to have a safe cardiovascular profile without any potential effects on platelets, corrected QT interval, metabolism, heart rate, or blood pressure.[61] Side effects include abdominal pain, nausea, diarrhea, hot flashes, tremor, and chills.

Contraindications. Methylnaltrexone is contraindicated in patients with structural diseases of the gastrointestinal tract, ie, peptic ulcer disease, inflammatory bowel disease, diverticulitis, stomach or intestinal cancer) since it can increase the risk of perforation.

Dosing is 1 dose subcutaneously every other day, as needed, and no more than 1 dose in a 24-hour period. Dosage is based on weight: 0.15 mg/kg/dose for patients weighing less than 38 kg or more than 114 kg; 8 mg for those weighing 38 to 62 kg; and 12 mg for those weighing 62 to 114 kg.[62]

Naloxegol

Naloxegol, FDA-approved for treating opioid-induced constipation in 2014, consists of naloxone conjugated with polyethylene glycol, which prevents it from crossing the blood-brain barrier and diminishing the central effects of opioid-induced analgesia. Unlike methylnaltrexone, which is given by subcutaneous injection, naloxegol is taken orally.

Adverse effects reported in clinical trials[63,64] were abdominal pain, diarrhea, nausea, headache, and flatulence. No clinically relevant association with QT and corrected QT interval prolongation or cardiac repolarization was noted.[64]

Dosing is 25 mg by mouth once daily, which can be decreased to 12.5 mg if the initial dose is difficult to tolerate. It should be taken on an empty stomach at least 1 hour before the first meal of the day or 2 hours after the meal. In patients with renal impairment (creatinine clearance < 60 mL/min), the dose is 12.5 mg once daily.[65]

CONSTIPATION-PREDOMINANT IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome is the reason for 3.1 million office visits and 59 million prescriptions in the United States every year, with

patients equally distributed between diarrhea-predominant, constipation-predominant, and mixed subtypes.[66]

To be diagnosed with constipation-predominant irritable bowel syndrome, patients must meet the Rome IV criteria, more than 25% of bowel movements should have Bristol stool form types 1 or 2, and less than 25% of bowel movements should have Bristol stool form types 6 or 7. In practice, patients reporting that their bowel movements are usually constipated often suffices to make the diagnosis.[5]

Osmotic laxatives are often tried first, but despite improving stool frequency and consistency, they have little efficacy in satisfying complaints of bloating or abdominal pain in patients with constipation-predominant irritable syndrome.[67] Stimulant laxatives have not yet been tested in clinical trials. Lubiprostone and linaclotide are FDA-approved for this condition; in women, lubiprostone is approved only for those over age 18.

Antidepressant therapy

Patients often derive additional benefit from treatment with antidepressants. A meta-analysis demonstrated a number needed to treat of 4 for selective serotonin reuptake inhibitors and tricyclic antidepressants in managing abdominal pain associated with irritable bowel syndrome.[68] The major limiting factor is usually adverse effects of these drugs.

For constipation-predominant irritable bowel syndrome, selective serotonin reuptake inhibitors are preferred over tricyclics because of their additional prokinetic properties. Starting at a low dose and titrating upward slowly avoids potential adverse effects.

Cognitive behavioral therapy has also been beneficial in treating irritable bowel syndrome.[69]

Adjunctive therapies

Adjunctive therapies including peppermint oil, probiotics (eg, *Lactobacillus*, *Bifidobacterium*), and acupuncture have also shown promise in managing irritable bowel syndrome, but more data are needed on the use of these therapies for constipation-predominant irritable bowel syndrome before any definite conclusions can be drawn.[70] Other emerging pharmacologic therapies are plecanatide (discussed earlier) and tenapanor.

Peppermint oil is an antispasmodic that inhibits calcium channels, leading to relaxation of smooth muscles in the gastrointestinal tract. Different dosages and treatment durations have been studied—450 to 900 mg daily in 2 to 3 divided doses over 1 to 3 months.[71,72] The most common adverse effect reported was gastroesophageal reflux, related in part to the oil's relaxing effect on the lower esophageal sphincter. Observation of this led to the development of enteric-coated preparations that have the potential to bypass the upper gastrointestinal tract.[73]

Tenapanor inhibits the sodium-hydrogen exchanger 3 channel (a regulator of sodium and water uptake in intestinal lumen), which in turn leads to a higher sodium level in the entire gastrointestinal tract (whereas linaclotide's action is limited to the duodenum and jejunem), resulting in more fluid volume and increased luminal transit.[74] It was found effective in a phase 2 clinical trial,[75] and the most effective dose was 50 mg twice daily.

Since tenapanor is minimally absorbed, it has few side effects, the major ones being diarrhea (11.2% vs 0% with placebo) and urinary tract infection (5.6% vs 4.4% with placebo).[75] Further study is needed to confirm these findings.

Tenapanor also has the advantage of inhibiting luminal phosphorus absorption. This has led to exploration of its use as a phosphate binder in patients with end-stage renal disease.

DYSSYNERGIC DEFECATION AND ANORECTAL BIOFEEDBACK

According to the Rome IV criteria,[5] dyssynergic defecation is present if the criteria for chronic constipation are met, if a dyssynergic pattern of defecation is confirmed by manometry, imaging, or electromyography, and if 1 or more of the following are present: inability to expel an artificial stool (a 50-mL water-filled balloon) within 1 minute, prolonged colonic transit time, inability to evacuate, or 50% or more retention of barium during defecography.[5]

Even though biofeedback has been controversial as a treatment for dyssynergic defecation because of conflicting results in older studies,[76] 3 trials have shown it to be better than placebo, laxatives, and muscle relaxants, with symptomatic improvement in 70% of patients.[77–79]

Biofeedback has been controversial, but trials found it better than placebo, laxatives, and muscle relaxants

Biofeedback therapy involves an instrument-based auditory or visual tool (using electromyographic sensors or anorectal manometry) to help patients coordinate abdominal, rectal, puborectalis, and anal sphincter muscles and produce a propulsive force using their abdominal muscles to achieve complete evacuation. Important components of this therapy include:

- Proper evacuation positioning (brace-pump technique, which involves sitting on the toilet leaning forward with forearms resting on thighs, shoulders relaxed, and feet placed on a small footstool
- Breathing relaxation and training exercises during defecation (no straining, keeping a normal pattern of breathing, and avoiding holding the breath while defecating)
- Use of the abdominal muscles by pushing the abdomen forward, along with relaxation of the anal sphincter.[80]

The anorectal feedback program usually consists of 6 weekly sessions of 45 to 60 minutes each. Limitations of this therapy include unavailability, lack of trained therapists, lack of insurance coverage, and inapplicability to certain patient groups, such as those with dementia or learning disabilities.

SURGERY FOR CHRONIC CONSTIPATION

Surgery for constipation is reserved for patients who continue to have symptoms despite optimal medical therapy.

Total abdominal colectomy and ileorectal anastomosis

Total abdominal colectomy with ileorectal anastomosis is a surgical option for medically intractable slow-transit constipation. Before considering surgery, complete diagnostic testing should be done, including colonic manometry and documentation of whether the patient also has outlet dysfunction.

Even though it has shown excellent outcomes and satisfaction rates as high as 100% in patients with pure slow-transit constipation,[81–83] results in older studies in patients with mixed disorders (eg, slow-transit constipation with features of outlet dysfunction) were less predictable.[84] More recent studies have reported comparable long-term morbidity and postoperative satisfaction rates in those with pure slow-transit constipation and those with a mixed disorder, indicating that careful patient selection is likely the key to a favorable outcome.[85]

Partial colectomies based on segmental colon transit time measurements can also be considered in some patients.[86]

Stapled transanal resection

Stapled transanal resection involves circumferential transanal stapling of the redundant rectal mucosa. It is an option for patients with defecatory disorders, specifically large rectoceles and rectal intussusception not amenable to therapy with pelvic floor retraining exercises.[87]

The efficacy of this procedure in controlling symptoms and improving quality of life is around 77% to 81% at 12 months, though complication rates as high as 46% and disappointing long-term outcomes have been a deterrent to its widespread acceptance in the United States.[88–91]

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