Chapter 19

Chronic constipation

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Key points

- Functional constipation affects nearly 12% of the adult population in the world and is more common in women.
- Normal transit constipation is the most common subtype of constipation followed by defecatory disorders and then slow transit constipation.
- Physiological testing of colon transit (e.g., radio-opaque markers, wireless motility capsule) and anorectal functioning (anorectal manometry with balloon expulsion, defecography) can be helpful in subtyping patients with functional constipation.
- Initial treatment includes lifestyle recommendations (exercise, high-fiber diet, fluids) and osmotic laxatives (PEG, Mg), which may be helpful is patients with mild-to-moderate constipation.
- Stimulant laxatives (senna, bisacodyl, picosulfate) are also effective though diarrhea and abdominal pain are common.
- Secretagogues (linaclotide, plecanatide, tenapanor), prokinetics (prucalopride), and osmotic agents (lactulose) are available by prescription and can be effective at improving constipation symptoms.

Introduction

Constipation affects between 3% and 31% of the adult population. For most affected persons, minimal or no intervention is required while for others, it can be challenging to treat and have a negative impact on quality of life. Constipation results in nearly 1 million outpatient office visit per year. While the vast majority of individuals have functional or chronic idiopathic constipation, secondary causes of constipation like systemic or structural diseases should be excluded and in moderate-to-severe cases evaluation of the pelvic floor functioning and colon transit testing should be considered. For patients with mild-to-moderate constipation, lifestyle modification (e.g., exercise), fiber, and osmotic laxatives are sufficient. However, when these maneuvers are not successful or in individuals with more severe symptoms prescription medications may be needed.

Definition/symptoms

Patients presenting with complaints of constipation generally refer to difficulty with bowel movements or a discomfort related to bowel movements including straining, hard stools, and inability to defecate. Importantly only a minority of patients report infrequent stools (i.e., $\leq$3 bowel movements per week) when complaining of constipation. Abdominal symptoms, particularly abdominal bloating and discomfort, are also common. The most widely accepted definition of functional constipation is the Rome IV Criteria (Table 1),[1] which allows for multiple different symptoms related to constipation to be present and requires the presence of at least two of these symptoms to be present in at least 25% of bowel movements. The Rome IV Criteria also requires symptoms to be chronic (i.e., present for at least 3 months, with a symptom onset of 6 months prior to diagnosis). Though the Rome IV Criteria distinguishes between irritable bowel syndrome with constipation (IBS-C) from functional constipation, it is clear from multiple studies that these entities exist on a spectrum and that the symptoms overlap and many individuals migrate between these criteria over time.

Epidemiology

A recent worldwide prevalence study found the prevalence of functional constipation in adults based on the Rome IV criteria to be 11.7% (11.4–12.0).[2] The prevalence of functional constipation was higher in women (15.2%; 14.8–15.7) than in men (8.3%: 8.0–8.6). The prevalence of functional constipation ranged from 1.8% (1.4–2.2) in India to 26.1% (23.6–28.6)

Handbook of Gastrointestinal Motility and Disorders of Gut-Brain Interactions. https://doi.org/10.1016/B978-0-443-13911-6.00009-8

TABLE 1 Rome IV criteria for functional constipation.[1]

(1) Must include 2 or more of the following:[a]
  (a) Straining during more than one-fourth (25%) of defecations
  (b) Lumpy or hard stools (BSFS 1–2) more than one-fourth (25%) of defecations
  (c) Sensation of incomplete evacuation more than one-fourth (25%) of defecations
  (d) Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations
  (e) Manual maneuvers to facilitate more than one-fourth (25%) of defecations (e.g., digital evacuation, support of the pelvic floor)
  (f) Fewer than three spontaneous bowel movements per week
(2) Loose stools are rarely present without use of laxatives
(3) Insufficient criteria for irritable bowel syndrome

[a]*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.*

in Ghana. Within the United States, the prevalence of functional constipation was 8.7% (7.5–10.0). Functional constipation also appears to be more common in individuals with a lower socioeconomic status, advanced age, nonwhite ethnicity, lower levels of education, and a low level of physical activity.

Although common, the majority of individuals with constipation never seek medical attention. Indeed, a Canadian study found that only approximately one-third of individual with constipation seek medical attention for their symptoms. Despite this, between 2007 and 2016, functional constipation resulted in over 1.0 million (95% CI, 0.8–1.2) outpatient visits per year in the United States alone.[3] The frequency of emergency department visits for constipation in the United States increased by 41.5% between 2006 and 2011, with an increase in costs of 121.4% during this time. In a health maintenance organization setting, the mean annual direct healthcare costs for constipation have been estimated to be $7,522, with annual out-of-pocket costs of $390. Women with constipation incur over twice as much in direct medical costs than women without constipation.

A survey conducted in the United States found over half reported that constipation impacted their quality of life (QoL), while over two-thirds reported that constipation affected their performance at work or at school and 12% reported that constipation resulted in absence from work or school in the preceding month.[3] Indeed, constipation is estimated to result in 3.7 million days of restricted activity annually in the United States.

Pathophysiology

Constipation can be classified into three broad categories: normal-transit constipation, slow-transit constipation, and defecatory disorder. A study of more than 1000 patients with chronic constipation in a tertiary care center found normal transit constipation to be the most prevalent form (59%), followed by defecatory disorders (25%) and slow transit constipation (13%). The remaining patient had a combination of defecatory disorders and slow transit (3%).

Normal-transit constipation

In normal-transit constipation, the transit time of stool through the colon within normal limits. The pathophysiology of symptoms in these patients may be due to misperceptions about their bowel frequency, psychosocial distress, among other factors. Whether increased rectal compliance and reduced rectal sensation are effects of chronic constipation or contribute to these patients' failure to experience an urge to defecate is unclear, but most have normal physiologic testing. Overlap with IBS-C is also common.

Slow-transit constipation

Slow-transit constipation is particularly common in young women. Most patients report infrequent bowel movements with bloating and some pain particularly after a several days without a bowel movement. The onset of symptoms is usually occurs around the time of puberty and results from disordered colonic motor function as demonstrated by delayed emptying

of the proximal colon and fewer high-amplitude propagating contraction (HAPCs) after meals. *Colonic inertia* describes patients with symptoms severe symptoms as demonstrated by the inability to initiate colonic motor activity after a meal or use of laxatives (e.g., bisacodyl).

Defecatory disorders

Functional defecatory disorders (i.e., rectal evacuation disorders) are the result of inability to empty the rectum secondary to an inability to coordinate abdominal, rectoanal, and pelvic floor muscles. Slow-transit constipation can be present as result. This disorder can start childhood but is more often a learned behavior potentially to avoid pain or discomfort associated with passage of stools. Individuals with rectal evacuation disorders can occur from incomplete relaxation of the anal sphincter on attempted defecation or inability to raise intrarectal pressure, or both. On a rare occasion, patients with a rectal evacuation disorder can have structural abnormalities such as rectal intussusception, obstructing rectocele, enterocele, and excessive perineal descent. Rectal evacuation disorders are more common in patients with constipation who report excessive straining and have failed standard medical treatment. Patients with functional defecatory disorders have greater rectal gas volume compared to other subtypes of constipation suggesting that imaging of the rectum (i.e., CT scan) may provide a sensitivity (>70%) and reasonable specificity (>60%) in distinguishing rectal evacuation disorder from other subtypes.[4]

Diagnosis

A detailed history should include details of symptoms including bowel frequency and consistency, straining, incomplete evacuation, and abdominal pain/discomfort and bloating. The presence of alarm features (e.g., unintentional weight loss, rectal bleeding, change in the caliber of stool, severe abdominal pain, or family history of colon cancer) could indicate a

TABLE 2 Secondary causes of constipation.

Mechanical obstruction
Anal stenosis
Colorectal cancer
Extrinsic compression
Rectocele or sigmoidocele
Stricture
Medications
Acetaminophen (>7 tablets weekly)
Antacids (aluminum containing)
Anticholinergic agents (e.g., antiparkinsonian drugs, antipsychotics, antispasmodics, tricyclic antidepressants)
Anticonvulsants (e.g., carbamazepine, phenobarbital, phenytoin)
Antineoplastic agents (e.g., vinca derivatives)
Calcium channel blockers (e.g., verapamil)
Calcium supplements
Diuretics (e.g., furosemide)
5-Hydroxytryptamine$_3$ antagonists (e.g., alosetron)

Continued

TABLE 2 Secondary causes of constipation—cont'd
Iron supplements
NSAIDs (e.g., ibuprofen)
Mu-opioid agonists (e.g., fentanyl, loperamide, morphine)
Metabolic and endocrinologic disorders
Diabetes mellitus
Heavy metal poisoning (e.g., arsenic, lead, mercury)
Hypercalcemia
Hyperthyroidism
Hypokalemia
Hypothyroidism
Panhypopituitarism
Pheochromocytoma
Porphyria
Pregnancy
Neurologic and myopathic disorders
Amyloidosis
Autonomic neuropathy
Chagas' disease
Dermatomyositis
Intestinal pseudo-obstruction
Multiple sclerosis
Parkinsonism
PSS
Shy-Drager syndrome
Spinal cord injury
Stroke

secondary cause of constipation (Table 2) and requires further investigation. In contrast, long duration of symptoms without progression and without alarm features is suggestive of a functional constipation and limited, if any, investigation is warranted. The history should also include a dietary history with specific attention to the amount of daily fiber and fluid intake as well as daily exercise habits. Use of digital maneuvers to facilitate defecation is suggestive of a defecatory disorder. Within the past medical history, obstetric and surgical histories are particularly important. Finally, a detailed review of medication use including over-the-counter and herbal medications is important as many are associated with constipation (Table 3).

TABLE 3 Over-the-counter therapies for CIC.

Agent	Daily dose (g)	Mechanism of action	Comments
Fiber	6–10 g	Increase water and increase bulk and soften stool	Gas, bloating, and distention are common, therefore start low in dose (2–4 g) and titrate gradually. Avoid in patients with fecal impaction
Methylcellulose			Semisynthetic cellulose fiber relatively resistant to colonic bacterial degradation may cause less bloating and flatus
Psyllium	2–4		Soluble fiber that comes from the ground seed husk of the ispaghula plant; forms a gel when mixed with water, sufficient water should be taken. Bloating and flatus are common, gradual titration of dose is often needed
Polycarbophil	4–6		Synthetic fiber from polymer of acrylic acid. Resistant to bacterial degradation
Guar gum	3–6		Soluble fiber extracted from seeds of the leguminous shrub *Cyamopsis tetragonoloba*

The physical examination should exclude major CNS disorders, including spinal lesions. The abdomen should be examined for distention, stool in the colon, or a mass. If the abdomen is distended, a hand should be passed under the lumbar spine while the patient is lying supine to exclude anterior arching of the lumbar spine as a cause of postural bloating.

The rectal examination should be performed to rule out perianal conditions and to assess for defecatory function.[5] The perineum should be observed both at rest and after the patient strains as if to have a bowel movement. Normally, the perineum descends between 1 and 4 cm during straining. With the patient in the left lateral position, descent of the perineum below the plane of the ischial tuberosities (i.e., >4 cm) usually suggests excessive perineal descent. A lack of descent may indicate the inability to relax the pelvic floor muscles during defecation, whereas excessive perineal descent may indicate excessive perineal descent. Rectal prolapse may be detected when the patient is asked to strain though this is best seen by examining the patient in the squatting position. The perianal area should be examined for scars, fistulas, fissures, and external hemorrhoids. Finally, a digital rectal examination should be performed to evaluate the patient for the presence of a fecal impaction, anal stricture, or rectal mass. A patulous anal sphincter may suggest prior trauma to the anal sphincter or a neurologic disorder that impairs sphincter function. Specifically, inability to insert the examining finger into the anal canal may suggest an elevated anal sphincter pressure, and tenderness on palpation of the pelvic floor as it traverses the posterior aspect of the rectum may suggest pelvic floor spasm. The degree of descent of the perineum during attempts to strain and expel the examining finger provides another way of assessing the degree of perineal descent.

Diagnostic tests

Diagnostic testing is usually not necessary for patients who complain of mild symptoms, especially adolescents, young adults, and those without alarm features. Investigations may be indicated for patients in whom there is a suspicion for an organic or structural disorder as a cause of constipation or to elucidate the underlying pathophysiologic mechanisms in patients refractory to standard therapies. Basic laboratory tests such as hemoglobin, CRP, thyroid function, and calcium could be considered if the clinical picture or physical exam are suggestive of a secondary cause for constipation (Table 2). Likewise, colonoscopy is generally not indicated for constipation symptoms in the absence of "alarm" features. Studies suggest that the yield of a colonoscopy in patients with chronic constipation is comparable to patients who undergo colonoscopy for routine colon cancer screening[6] and recent society guidelines recommend against the use of colonoscopy for chronic constipation in the absence of alarm features.[7]

Physiological tests

Physiologic testing can be helpful in patients who do not respond to routine treatment (i.e., fiber and laxatives) in determining the subtype of constipation (Fig. 1). Testing include colonic transit time, anorectal manometry with balloon expulsion and defecography.

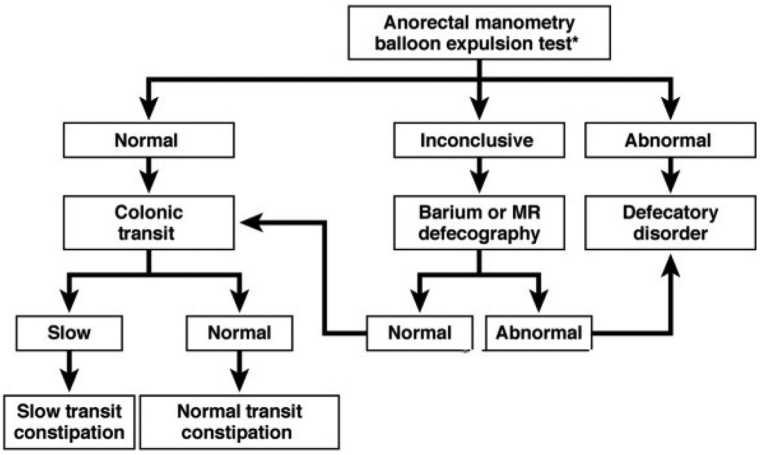

FIG. 1 Role of physiological testing in the evaluation of functional constipation.[8] *Because anorectal manometry, rectal balloon expulsion test may not be available in all practice settings, it is acceptable, in such circumstances, to proceed to assessing colonic transit with the understanding that delayed colonic transit does not exclude a defecatory disorder.

Colonic transit testing

Currently, there are three clinical tests used to assess colonic transit: radiopaque markers, wireless motility capsule, and scintigraphy.

Radiopaque markers can be used to assess colon transit by performing standard X-ray of the abdominal at predetermined times after the patient ingests the radiopaque markers. The easiest method to assess colon transit is to obtain an X-ray 5 days after ingestion of a single capsule containing 24 radiopaque rings. If 5 or more markers are present then the study is considered to be abnormal and consistent with slow transit constipation. Other methods to assess regional transit are also used. Patients should maintain a high-fiber diet and should avoid laxatives, enemas, or medications that may affect bowel function prior to the test. Delayed transit does not exclude the presence of a defecatory disorder, and therefore, anorectal physiological testing should be considered prior to performing radiopaque marker testing (Fig. 2).

Wireless motility capsule (WMC) measures not only colon transit but also whole gut transit, gastric emptying, and small bowel transit. The WMC also measures contractility including the frequency and amplitude of contractions. The procedure is performed by ingesting a WMC (26× 13 mm) following a standardized meal and 50 mL of water. The WMC measures temperature, pH, and pressure as it moves along the GI tract (Fig. 3). Gastric emptying of the WMC occurs with the Phase III migrating motor complex, signifying completion of the postprandial phase and return of the fasting state. Small bowel transit time is determined by a rapid rise in pH when entering the duodenum and by a relatively small decrease in pH in the cecum. Colon transit time is determined by the WMC leaving the body, which is determined by change in temperature and loss of signal from the WMC. The sensitivity and specificity of the WMC are similar to radiopaque marker test in

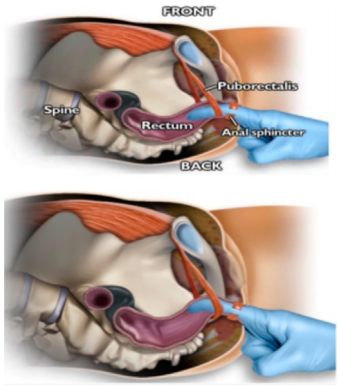

FIG. 2 Schematic of the key anatomy and maneuvers involved in the digital rectal exam of a patient with suspected constipation.[5] *Courtesy of Dr. Satish SC Rao.*

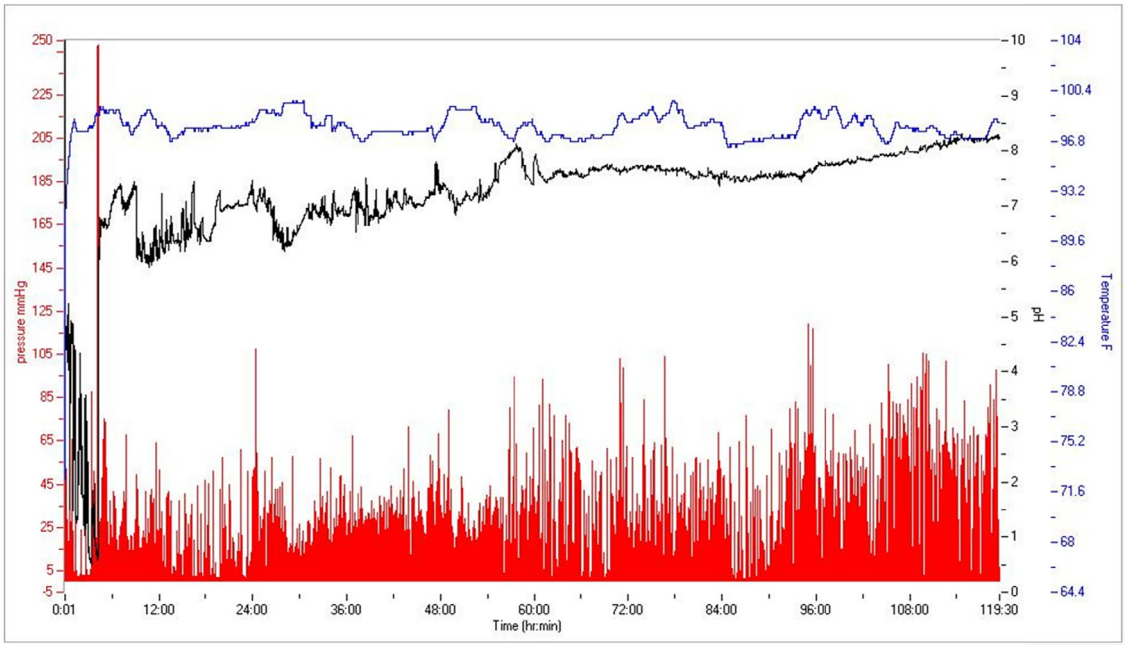

FIG. 3 Wireless motility capsule test in a patient with suspected constipation showing slow colon transit. Wireless motility capsule tracings showing temperature (*blue*), pH (*yellow*), and pressure (*red*). Gastric emptying is determined by the rise in pH that occurs after the capsule leaves the acidic stomach. The subsequent decrease in acid (approximately 1/3 into the study) represents passage of the capsule to the colon. The decrease in pH in the colon is due to bacterial fermentation.

diagnosing slow transit constipation. WMC avoids radiation exposure and generally well tolerated. Its use is not recommended in patients with cardiac pacemakers or defibrillators, swallowing disorders, suspected strictures or fistulas, or in those who are high risk for strictures.

Though not widely available, colonic transit scintigraphy is a useful tool to measure colonic transit time as well regional colonic transit times. Like the WMC, scintigraphy can also be used to measure gastric and small bowel transit times as well. The procedure is performed by measuring radioactive with a gamma camera at specified times after ingestion of a labeled meal (In-DTPA-labeled water with standard ^{99m}Tc egg sandwich or In-labeled activated charcoal particles contained in a capsule). Results are reported as ascending colon emptying, indicating the time for 50% emptying, or overall colonic transit expressed as the geometric center (weighted average of the radioactivity distribution within the colon and stool).

Defecography

Defecography visualizes the pelvic floor anatomy at rest, during sustained squeeze, and on simulated bear down. Defecography assesses the degree of rectal emptying, changes in the anorectal angle, and the extent of perineal descent. The presence of structural abnormalities such as a rectocele, internal mucosal prolapse, intussusception, or a enterocele can also be excluded. Defecography can be performed using fluoroscopy or with MRI. The procedure involves placing contrast into the rectum, and imaging the patient resting, deferring defecation, and straining to defecate. These tests are best performed with the patient sitting on a commode, though this is not often feasible when using MRI. Limitations of this study include variability among radiologists in interpreting studies, inhibition of normal rectal emptying because of patient embarrassment, and differences in texture between barium paste and stool. MRI may be more sensitive for detecting pelvic organ abnormalities such as cystoceles and colpoceles.

Anorectal manometry

Anorectal manometry assesses the anal sphincter pressures at rest, during squeeze, and with simulated defecation. In addition, the anorectal manometry catheter also has a balloon at it tip to allow for balloon distention of the rectum to assess the rectoanal inhibitory reflex, rectal sensation, and compliance. Anorectal manometry is most commonly performed with high-resolution manometry (HRM) catheter or a three-dimensional HRM catheter, which is most suitable for patients with fecal incontinence. A balloon expulsion test is usually performed as part of the anorectal manometry study. The balloon expulsion test is performed by asking the patient to expel a 50-mL water-filled balloon from the rectum while sitting on a

commode in private. Normal values for balloon expulsion are less than 60 s. The International Anorectal Physiology Working Group (IAPWG) recently developed classifications, known as the London Criteria, for abnormal findings on anorectal manometry and balloon expulsion.

Treatment

The initial treatment for constipation is nonpharmacological including lifestyle modifications such as increased physical activity and increased fluid and fiber intake through changes in diet or use of commercial fiber supplements. If these measures fail, pharmacologic agents may be used. If a defecatory disorder is present anorectal biofeedback should be recommended since up to 75% of patients with disordered evacuation respond to biofeedback. In patients who do not improve with lifestyle modifications, the first-line pharmacological therapy (after fiber) is an osmotic laxative (e.g., milk of magnesia, polyethylene glycol) (Table 4).[9] Stimulant laxatives (e.g., bisacodyl, senna derivatives) are generally recommended for patients who do not respond to osmotic laxatives. Prescription pharmacologic agents such as a secretagogue (e.g., lubiprostone, linaclotide, plecanatide, tenapanor) or a promotility agent (e.g., prucalopride, tegaserod) should be considered for patients who have not responded to initial therapy (Table 4).[10] Surgery is rarely required and then only in patients with severe slow transit constipation.

TABLE 4 Pharmacological treatments for constipation.

Type of laxative	Dose	Mechanism of action	Comments
Osmotic laxatives			
Magnesium oxide	15–30 mL once daily	Draws fluid into the intestines	Small amount of magnesium is absorbed therefore not recommended in patients with renal failure. Abdominal cramps are common
Lactulose	15–30 mL once or twice daily	Non-digested disaccharide	Undergoes bacterial fermentation, frequently causes gas and bloating. Not as well tolerated as PEG. Available only by prescription
Polyethylene glycol (PEG)	17–34 g once or twice daily	An inert synthetic polymer that is not absorbed or degraded by bacteria. It retains water thereby softening stool	Generally well tolerated, but can cause nausea and bloating. Better tolerated and more effective than lactulose. Dose should be titrated until stools are soft. Onset of action is generally 2–3 days
Stimulant laxatives			
Senna,	7.5–15 mg once daily	Anthraquinone laxative that acts as a local irritant to colonic sensory nerves causing secretion and motility	Onset is generally 6–12 h. Regular use can brown pigmentation of the colonic mucosa known as pseudomelanosis coli. It is a weaker stimulant than bisacodyl and tends to cause less side effects such as abdominal cramps, diarrhea, and nausea
Bisacodyl	5–10 mg once daily	Diphenylmethane derivative that works in the colon by stimulating neurons to induce motility and increase secretions	Onset is generally 6–12 h. Also used as a suppository/enema for more rapid action. Abdominal pain and diarrhea are common. Generally not recommended for rescue rather than daily use
Sodium picosulfate	5–15 mg once daily	Undergoes bacterial fermentation to the active product which is structurally and functionally similar to bisacodyl	Likely has effects only on the colon. Abdominal cramps and diarrhea are common. Although widely used in Europe, it is currently only available in the USA as part of a colonoscopy preparation

TABLE 4 Pharmacological treatments for constipation—cont'd

Type of laxative	Dose	Mechanism of action	Comments
Secretagogues			
Lubiprostone	24 µg twice daily	Activates chloride channel type 2 channels on the apical surface of the small intestine causing chloride to be secreted in the small intestine followed by water and sodium	Nausea is common, particularly early in the treatment, occurring in up to 31.7% and leading to discontinuation in 5% of patients
Linaclotide	72 µg and 145 µg once daily	Activates guanylate cyclase C (GC-C) receptor on the apical surface stimulating production of cGMP which open CFTR causing chloride to be secreted in the lumen of the intestines followed by water and sodium	Diarrhea is common, occurring in approximately 20% of patients and leading to discontinuation in approximately 4%
Plecanatide	3 mg once daily	GC-C agonist structurally similar to linaclotide though pH dependent	Diarrhea is common occurring in approximately 5% of patients and lead to discontinuation in 3%. After controlling for differences in diarrhea rates in the placebo arm, rates of diarrhea and withdrawals from diarrhea appear to be similar between the two GC-C agonists
Prokinetic agent			
Prucalopride	2 mg once daily	A selective serotonin type 4 (5-HT4) receptor agonist, that stimulates colonic peristalsis (HAPCs), which increases bowel motility and accelerates colonic transit	Headaches occur in 19% of patients leading to discontinuation in approximately 2%. While a causal link with suicidal ideation has not been established, patients should be monitored

Fiber supplementation

Dietary fiber may be effective in relieving mild-to-moderate constipation. Patients with normal transit constipation are more likely to be a responder compared to patients with slow transit constipation or a defecatory disorder. Fiber can undergo bacterial fermentation in the colon, producing gas and bloating. Soluble fibers appear to be better tolerated and more effective than insoluble fibers. Thus, foods rich in soluble fiber include oat bran, nuts, barley, seeds, beans, lentils, peas, some fruits and vegetables, and psyllium fiber supplements should be recommended. Foods that contain insoluble fiber such as wheat bran, whole grains, and some vegetables should be avoided, particularly if side effects such as bloating and cramping are present. Most controlled studies of the effects of fiber have shown that the minimum amount needed to consistently and significantly alter bowel function or colonic transit time is 12 g/day. To improve adherence, patients should be instructed to increase their dietary fiber intake gradually over several weeks to about 25–30 g/day, the current recommended amount for adults.

In addition to dietary fiber, commercially packaged fiber supplements are also available.

Psyllium husk, the outer coat of the ispaghula seed, which comes from the plant Plantago ovata, is a common soluble fiber. Semisynthetic and synthetic bulking agents (methylcellulose and calcium polycarbophil, respectively) are less susceptible to bacterial fermentation and may cause less gas and distention. In general, patients should start at a low dose (2–4 g per day) and increase gradually to 6–10 g per day as needed.

Osmotic and stimulant laxatives

Osmotic laxatives increase water in the colon by creating an intraluminal osmotic gradient and including magnesium, lactulose, and polyethylene glycol.

Magnesium

Although commonly used, there have been few randomized placebo-controlled trials with magnesium for the treatment of constipation. A recent study found magnesium oxide 0.5 g three times a day for 28 days to be superior to placebo for overall

symptom response (68.3% vs. 11.7%) and similar to senna 0.5 g twice daily, which had a response rate of 69.2%. A small percentage of magnesium is actively absorbed in the small intestine and therefore hypermagnesemia can occur in patients with renal failure.

Lactulose

Lactulose is a nonabsorbable synthetic disaccharide that undergoes fermentation by colonic bacteria to yield short-chain fatty acids, hydrogen, and carbon dioxide. Lactulose is effective at relieving the symptoms associated with constipation as demonstrated by a number of clinical trials; however, gas and bloating are common limiting its use clinically.

Polyethylene glycol

Polyethylene glycol (PEG) is a metabolically inert molecule that binds water molecules and does undergo fermentation by colonic bacteria excreted mostly unchanged in the feces. Multiple high-quality studies have demonstrated the efficacy of PEG in the treatment of chronic constipation including a 6-month trial showing no diminution in effectiveness. PEG, which like other osmotic laxatives takes a few days to work, appears to be well tolerated. The most common adverse events of PEG include abdominal bloating and cramps. A recent meta-analysis found polyethylene glycol to be more effective and with fewer associated adverse events than lactulose.[11] A randomized trial also found PEG to be more effective, with a more rapid onset of action, than fiber (i.e., ispaghula 7 g/day). The recommended starting dose of PEG is 17 g per day though this may titrated every 3–4 days as needed to induce soft stools.

Stimulant laxatives

Stimulant laxatives differ from osmotic laxatives in that they begin working within hours rather than days. Stimulant laxatives include anthraquinones (e.g., cascara, aloe, senna) and diphenylmethanes (e.g., bisacodyl, sodium picosulfate). Stimulant laxatives often cause abdominal cramps and diarrhea. The most commonly used stimulant laxative are senna derivatives. As previously discussed, senna 1 g per day is more effective than placebo and similar to magnesium oxide 1.5 g per day in a 28-day randomized trial. In a multicenter randomized trial, bisacodyl 10 mg once daily for 4 weeks resulted in a greater mean number of complete spontaneous bowel movements (CSBMs) per week compared to placebo (5.2 vs. 1.9, $P<0.05$).[12] Bisacodyl also improved straining, feeling of anal obstruction, and stool form. However, side effects such as diarrhea and abdominal pain were common particularly during the first week of treatment resulting in 18% of patients receiving bisacodyl withdrawing from the study. Sodium picosulfate has also been shown to be effective in constipation. In a multicenter trial conducted in Germany, sodium picosulfate 10-mg resulted in a greater mean number of CSBMs per week compared to placebo (3.4 vs. 1.7, $P<0.05$). Sodium picosulfate also improved straining, incomplete evacuation, feeling of anal obstruction, and stool form. Diarrhea was common, reported by 32% of patients receiving sodium picosulfate.

A recent network meta-analysis that compared relative efficacy and side effects of currently available OTC and prescription treatments for CIC found bisacodyl and sodium picosulfate at a dose of 10 mg once daily were most effective at achieving the endpoint of 3 CSBMs per week at 4 weeks.[13] However, bisacodyl was ranked last in terms of adverse events particularly abdominal pain and diarrhea.

Prescription medications

Secretagogues

Secretagogues increase intestinal fluid secretion thereby increasing bowel movement frequency and improving stool consistency by increasing the amount of stool water. There are currently four secretagogues approved for the treatment of CIC. The site of their mechanism of action in the intestinal cells that lining the GI tract is shown in Fig. 4.

Lubiprostone

Lubiprostone is a bicyclic functional fatty acid derived from prostaglandin E1 that acts on the intestinal chloride 2 channels on the luminal surface of the intestinal epithelium causing chloride secretion in the lumen resulting in sodium and water secretion into the lumen. This, in turn, increases the intestinal and colonic motility and improves stool passage. Lubiprostone 24 mcg twice daily is approved by the Federal Drug Administration (FDA) for adults with CIC. Two Phase

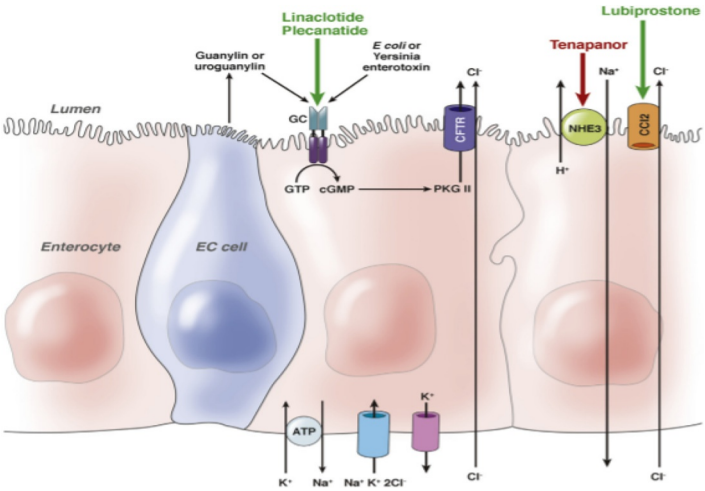

FIG. 4 Mechanism of action of secretagogues for the treatment of constipation.

III trials showed lubiprostone 24 mcg twice daily for 4 weeks increased the number of SBMs compared to placebo (5.9 vs. 4.0 at week 1, $P<0.05$). Lubiprostone also decreased straining, improved stool consistency, and reduced overall severity of symptoms. Nausea was the most common adverse event reported occurring in up to 31.7%, leading to discontinuation in 5% of patients. A 48-week open-label trial found lubiprostone to be generally well tolerated with most side effects occurring relatively early in the onset of treatment.

Linaclotide

Linaclotide activates the guanylate cyclase C receptor on the luminal surface of the intestinal epithelium, resulting in increased levels of cyclic guanosine monophosphate (cGMP) and increased secretion of chloride and bicarbonate into the intestinal lumen. In addition, cGMP appears to reduce visceral hypersensitivity in an animal model. Linaclotide, 72 μg and 145 μg once daily are approved for the treatment of adults with CIC. In two Phase III studies, a greater percentage of patients receiving linaclotide 145 μg once daily met the primary end point (≥3 CSBMs per week and ≥1 from baseline during at least 9 of the 12 weeks) compared to patients receiving placebo (20% vs 5%, $P<0.05$).[14] Linaclotide also increased stool frequency, improved stool consistency, and reduced straining, abdominal bloating, and discomfort as compared with placebo. Diarrhea, the most common adverse event, led to discontinuation in 4% of patients. Linaclotide also appears to be efficacious in improving moderate-to-severe bloating in patients with CIC. A trial comparing linaclotide 72 and 145 μg to placebo found similar efficacy between 72 and 145 μg of linaclotide, which subsequently led to the approval of the 72 μg dose for CIC. Diarrhea occurred in 19.2%, 22.1%, and 7.0% of patients receiving linaclotide 72 and 145 μg and placebo, respectively. Linaclotide is contraindicated in children younger than age 6 and is not recommended in children between 6 and 18 years of age.

Plecanatide

Plecanatide is a guanylate cyclase C agonist mechanistically similar to linaclotide. In contrast to linaclotide, plecanatide is pH sensitive and therefore has a higher affinity to the GC-C receptor in the more acidic environment found in proximal duodenum. Plecanatide 3 mg once daily is approved for the treatment of adults with CIC. In two Phase III trials plecanatide, a greater percentage of patients receiving plecanatide 3 mg once daily met the primary endpoint (>3 CSBMs per week and >1 CSBM over baseline for 9 out of 12 weeks and 3 of the last 4 weeks of the trial) compared to patients receiving placebo (20% vs. 11%, $P<0.05$). Plecanatide also significantly improved stool consistency and stool frequency. Diarrhea was reported in 5.1% of patients and led to discontinuation in 2.7%. Though the rate of diarrhea is lower with plecanatide compared to linaclotide, a meta-regression analysis controlling for differences in diarrhea rates in the placebo arm found similar rates of diarrhea and withdrawals from diarrhea between the two GC-C agonists.[15] Plecanatide is also contraindicated in children younger than age 6 and is not recommended in children between 6 and 18 years of age.

5-HT$_4$ agonists

Prucalopride

Prucalopride, a selective full serotonin type 4 (5-HT4) receptor agonist, that stimulates colonic peristalsis (HAPCs), which increases bowel motility and accelerates colonic transit. Prucalopride also appears to improve gastric emptying in patients with gastroparesis. Prucalopride 2 mg once daily is approved for the treatment of CIC in adults or 1 mg in patients with severe renal impairment (creatinine clearance (CrCL) less than 30 mL/min. In three Phase III trials, a greater percentage of patients receiving prucalopride 2 mg once daily met the primary endpoint ($\geq$3 CSBMs per week) compared to patients receiving placebo (31% vs. 12.0%, $P<0.05$). Prucalopride also improved straining, incomplete evacuation, straining, and constipation severity. The most frequent adverse events for patients receiving prucalopride vs placebo were headaches (19% vs. 9%), abdominal pain (16% vs. 11%), nausea (14% vs. 7%), and diarrhea (13% vs. 5%). In total 5% of patients receiving prucalopride discontinued due to adverse events compared with 3% receiving placebo. Suicidal ideation and attempts have been reported though a causal association has not been established; nevertheless, all patients should be monitored for new onset or worsening of depression or the emergence of suicidal thoughts and behaviors.

Vibrating capsule

The vibrating capsule is a novel device that is activated by electromagnetic signal determines the timing and duration of vibration for each capsule. The vibrating capsule is set to begin vibration within the colon, through potentially stimulating the intestinal wall and inducing peristalsis. The vibrating capsule may augment the physiological effects of waking and meals.[16] In a Phase III trial, a greater percentage receiving the vibrating capsule 5 days a week for 8 weeks achieved an increase of 1 or more CSBMs from baseline for at least 6 out of 8 weeks (39.3% vs. 22.1%, $P = 0.001$). A mild sensation of vibration was reported by 11% of patients but none withdrew from the trial.[17]

Future treatments

Tenapanor

Tenapanor is a minimally absorbed inhibitor of the intestinal sodium/hydrogen exchanger 3 (NHE3) that reduces sodium and phosphate absorption. Tenapanor 50 mg twice daily is currently approved for the treatment of IBS-C where it has been shown to improve bowel function as well as abdominal pain. Tenapanor has yet been studied in CIC.

Tegaserod

Another 5-HT$_4$ receptor agonist was recently reintroduced to the market on a more limited indications due to concerns of cardiovascular side effects. Though several large Phase III trials previous studies showed tegaserod to be effective in chronic idiopathic constipation, it is now approved for use in the US only for women with IBS-C who are under the age of 65 years and without a history of cardiovascular disease (e.g., myocardial infarction, stroke, etc.).

Elobixibat

Elobixibat is ileal bile acid transporter (IBAT) inhibitor that increases the bile acid concentration in the colon, which increases colon transit and softening of stool by inducing secretion and high-amplitude propagating contractions in the colon. In several Phase III trials, a greater percentage of patients met the primary endpoint ($\geq$3 CSBMs per week and an increase of $\geq$1 CSBM per week from baseline at 12 weeks) compared to patients receiving placebo. Elobixibat has been approved for clinical use in Japan since 2018 though not yet available elsewhere in the world.

Acupuncture

Acupuncture, particularly electroacupuncture (EA), is potentially effective method of treating chronic severe constipation. A large trial (n=1075) found eight sessions of EA at traditional acupoints over 8 weeks increased mean weekly CSBMs by 1.8 (95% CI, 1.61–1.89) compared sham EA at nonacupoints which only increase weekly CSBMs by 0.9 (95% CI, 0.73–0.97) ($P < 0.001$). Importantly, acupuncture-related adverse events during treatment were infrequent in both groups, and all were mild or transient. A meta-analysis of 28 randomized trials found acupuncture also improved

constipation though the quality of evidence in these studies was low. Further studies are needed including in Western countries where acupuncture techniques may differ from eastern countries.

Transcutaneous electrical stimulation (interferential current)

Because colonic electric activity may regulate colonic motility, and therefore, electrical stimulation has the potential to improve constipation-related symptoms. A meta-analysis of transcutaneous electrical stimulation in children with slow transit constipation in children found two randomized trials and four prospective trials found modest improvement of uncertain clinical significance. There was also evidence of bias noted in the studies. Overall, better-designed studies, with larger and more diverse patient populations followed for longer time periods, will be needed in order to reliably determine the efficacy of electrical stimulation therapy in the treatment of this disorder.

Sacral nerve stimulation (SNS)

Sacral nerve stimulation (SNS) is frequently used for fecal incontinence though several trials suggests that it may also be effective for constipation. In a multicenter open-label trial, 62 patients of whom 45 reported improvement with a temporary SNS and proceeded to chronic stimulation. After a mean of 28 (range 1–55) months of follow-up, defecation frequency increased from 2.3 to 6.6 bowel movement per week, and decrease in time spent in toilet (10.5 to 5.7 min). Straining and incomplete evacuation also improved. A subsequent trial involving 44 patients of whom 22 went on to a permanent implant. Four of the 15 were explanted to adverse events and only 5 (11%) of the original group reported sustained improvement after a mean of 24 months (range 4–81). These data suggest that while promising further data is needed prior to recommending SNS for routine use.

Conclusions

Chronic idiopathic constipation is a common disorder that affect adults throughout the world resulting in significant economic costs and negative impact on quality of life. Physiological testing of colon transit and anorectal functioning can assist in identifying individuals who are refractory to initial therapies into subtypes such as normal transit constipation, slow transit constipation, and defecatory disorders. Identifying subtypes can be important particularly since most defecatory disorders are best treated with anorectal biofeedback. Conservative therapy (lifestyle, fiber, fluid) and osmotic laxatives are the recommended initial therapies. Patients who require additional treatments may receive stimulant laxative or prescription therapies such as secretagogues and prokinetic agents.

MCQ's

(1) Which of the following symptom is not part of the Rome IV Criteria for Functional Constipation?
- **(A)** Fewer than three spontaneous bowel movements per week
- **(B)** Hard or lumpy stools
- **(C)** Abdominal pain more than
- **(D)** Incomplete rectal evacuation
- **(E)** Sensation of anorectal obstruction

Answer: C. Abdominal pain is not a feature of the Rome IV Criteria for Functional Constipation. In contrast, in order to meet the Rome IV Criteria for IBS-C patients must experience abdominal pain that is associated with change in bowel frequency or consistency. However, many patients with Functional Constipation experience abdominal pain and bloating. Although Rome IV Criteria requires a mutually exclusive distinction between IBS-C and FC, it is clear that two entities exist along a spectrum and many patients migrate over time from one diagnosis to the other.

(2) Which of the following treatments for Functional Constipation has been shown in a network meta-analysis to be the most effective at increasing the number of complete spontaneous bowel movements (CSBMs) in randomized placebo-controlled trials?
- **(A)** Bisacodyl
- **(B)** Linaclotide
- **(C)** Plecanatide
- **(D)** Prucalopride
- **(E)** Lubiprostone

Answer: A. A recent network meta-analysis that compared relative efficacy and side effects in randomized placebo-controlled trials of currently available treatments for Functional Constipation. This analysis found the stimulant laxatives bisacodyl and sodium picosulfate at a dose of 10 mg once daily to be most effective at achieving the endpoint of 3 CSBMs per week at 4 weeks. However, bisacodyl was ranked last in terms of adverse events particularly abdominal pain and diarrhea resulting approximately 18% of patients withdrawing from the study despite being able to reduce to 5 mg once daily.

(3) Which of the following prescription treatments for Functional Constipation is not a secretagogue?
- **(A)** Linaclotide
- **(B)** Plecanatide
- **(C)** Prucalopride
- **(D)** Lubiprostone

Answer C. Prucalopride is a 5-HT4 agonist, which is not a secretagogue. Activation of the 5-HT4 receptor stimulates intestinal motility. The other medications are secretagogues causing an increase in fluid in the intestines. Linaclotide and plecanatide activate the guanylate cyclase C receptor on the luminal surface of the intestinal epithelium, resulting in increased levels of cyclic guanosine monophosphate (cGMP), which opens the CFTR resulting in the secretion of chloride and bicarbonate into the intestinal lumen and in turn water and sodium. Lubiprostone acts on the intestinal chloride 2 channels on the luminal surface of the intestinal epithelium causing chloride secretion in the lumen resulting in sodium and water secretion into the lumen.

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