American Gastroenterological Association Technical Review on Constipation

This article has an accompanying continuing medical education activity on page e19. Learning Objective: Upon completion of this exam, successful learners will recognize the importance of a careful clinical assessment in the diagnosis and treatment of constipation, select appropriate diagnostic tests for patients with chronic constipation, and identify therapeutic approaches based on results of diagnostic tests for patients with chronic constipation.

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Constipation is a very common symptom. Prompted by several advances since the last technical review 15 years ago,[1] this update will identify a rational, efficacious, and ideally cost-effective approach to patients with constipation. Toward those objectives, the epidemiology, clinical assessment, diagnostic testing, and management of constipation will be discussed, primarily from the perspective of a practicing gastroenterologist. Constipation in children and secondary constipation (eg, due to spinal cord injury) in adults will not be specifically addressed. This review was prepared by updating the previous technical review with material sourced from recent reviews on chronic constipation,[2–4] supplemented by selected and focused literature searches of peer-reviewed, published studies. Although recommendations are graded based on US Preventive Services Task Force (USPSTF) ratings, formal cost-effectiveness analyses have not been performed. Comparisons of diagnostic approaches, with precise estimates of specificity and sensitivities, also have not been published. Indeed, in some instances, individual diagnostic techniques have not even been standardized.

Definition and Classification of Chronic Constipation

Constipation is a syndrome that is defined by bowel symptoms (difficult or infrequent passage of stool, hardness of stool, or a feeling of incomplete evacuation) that may occur either in isolation or secondary to another underlying disorder (eg, Parkinson's disease). Although many physicians regard constipation as synonymous with reduced stool frequency, others also consider straining to defecate, hard stools, and the inability to defecate at will as constipation.[5] Hence, the Rome III symptom criteria for constipation incorporate several bowel symptoms (Table 1); a diagnosis of defecatory disorders also requires abnormal anorectal test results.[6] Constipation-predominant irritable bowel syndrome (IBS-C) is defined by abdominal discomfort that is temporally associated with 2 of the following 3 symptoms: relief of discomfort after defecation, hard stools, or less frequent stools. Although some patients with constipation also have abdominal discomfort, discomfort is not, in contrast to IBS-C, associated with these features.[7] However, this distinction is of limited utility because patients are often uncertain about the temporal relationship between abdominal discomfort and these features. Moreover, compared with patients with constipation who do not have abdominal pain, patients with constipation who experience pain report poorer overall health and a greater impact of bowel symptoms on quality of life and more somatic symptoms regardless of whether the pain was or was not associated with characteristics of irritable bowel syndrome (IBS).[8] Hence, the presence or absence of abdominal pain may be more useful than other associated features for characterizing phenotypes in chronic constipation.

The American Gastroenterological Association (AGA) and Rome III criteria both emphasize the need to identify defecatory disorders. However, in contrast to the Rome III criteria, the last AGA technical review and this update do not use the term "functional constipation" because a subset of patients with symptom criteria for functional constipation have slow colonic transit. Moreover, in several small studies, slow transit constipation (STC) was associated with a marked reduction in colonic intrinsic nerves and interstitial cells of Cajal,[9,10] that is, it is not truly a functional disorder. Also, as detailed later, IBS-C is associated with various pathophysiological disturbances (eg, slow transit, abnormal colonic sensation). Hence, the AGA criteria rely on assessments of colonic transit and anorectal function to classify patients with constipation into one of 3 groups: normal transit constipation (NTC), STC, and pelvic floor dysfunction or defecatory disorders.

Abbreviations used in this paper: AGA, American Gastroenterological Association; CFTR, cystic fibrosis transmembrane regulator; FDA, Food and Drug Administration; IBS, irritable bowel syndrome; IBS-C, constipation-predominant irritable bowel syndrome; IRA, ileorectal anastomosis; NTC, normal transit constipation; STARR, stapled transanal resection; STC, slow transit constipation.

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Table 1. Definitions of Constipation

Rome III criteria		Criteria used in pharmacologic studies	
Constipation[a]	IBS-C[a]	Constipation[b]	IBS-C[c]
Symptoms for ≥6 months and ≥2 of the following symptoms for more than one-fourth of defecations during the past 3 months: • Straining • Lumpy or hard stools • Sensation of incomplete evacuation • Sensation of anorectal obstruction/blockade • Manual maneuvers to facilitate defecations; <3 defecations/wk • Loose stools are not present, and there are insufficient criteria for IBS	Recurrent abdominal pain or discomfort at least 3 days per month in the past 3 months associated with 2 or more of the following: • Improvement with defecation • Onset associated with change in frequency of stool • Onset associated with change in form (appearance) of stool • <25% of bowel movements were loose stools	<3 SBMs per week and ≥1 of the following symptoms for at least 12 weeks during the preceding 12 months: • Straining in more than one-fourth of defecations • Lumpy or hard stools in more than one-fourth of defecations • Sensation of incomplete evacuation in more than one-fourth of defecations • No loose or watery SBMs (Bristol Stool Form Scale score of 6–7)	<3 SBMs per week and ≥1 of the following symptoms for at least 12 weeks during the preceding 12 months: • Straining in one-fourth or more of defecations • Lumpy or hard stools in one-fourth or more of defecations • Sensation of incomplete evacuation in one-fourth or more of defecations • Mean score of ≥2.0 for daily nonmenstrual abdominal pain or discomfort (5-point scale ranging from 1 = none to 5 = very severe) • Mean of <3 complete SBMs and ≤6 SBMs per week

SBM, spontaneous bowel movements.
[a]Modified from Longstreth et al.[7]
[b]Modified with permission from Lembo et al.[148]
[c]Modified with permission from Johnston et al.[149]

Prevalence and Risk Factors of Constipation

In October 2010, a MEDLINE literature review of the epidemiology of constipation identified 58 full-length articles on the prevalence of constipation in population-based samples of children and adults[4]; another study was not included therein.[8] Subject to the caveats that definitions of constipation vary across studies and that some respondents in these questionnaire-based epidemiologic studies may have had an organic cause for constipation, the median prevalence of constipation was 16% (range, 0.7%–79%) in adults overall and 33.5% in adults aged 60 to 101 years. Most, but not all, studies suggest that the prevalence of constipation is higher in the nonwhite population than in the white population. The prevalence was higher in women (median female-to-male ratio of 1.5:1) and in institutionalized than community-living elderly residents.[11] Women are also more likely to use laxatives and seek health care for their constipation.

Risk Factors for Constipation

There is good agreement as to the risk factors for constipation. Lower socioeconomic status and lower parental education rates are associated with constipation,[12–17] as are less self-reported physical activity,[12,15,16,18,19] medications (Table 2), depression, physical and sexual abuse,[20] and stressful life events.[16,17,21–23] The high prevalence of constipation in nursing home residents is only partly due to adverse drug effects.[24] Constipation was associated with low dietary fiber intake in some,[18] but not other,[25] studies. However, these associations do not necessarily indicate causation. Although it is reasonable to try and modify these risk factors, doing so may not improve bowel function.

Economic Impact and Impact on Quality of Life

Although only a minority (eg, 22% in a US household survey) seek health care for constipation,[26] constipation consumes substantial health care resources because the prevalence is high. Among outpatient clinic visits, constipation is one of the 5 most common physician diagnoses for gastrointestinal disorders.[27] Between 1958 and 1986, an analysis of 4 different surveys (ie, the National Health Interview Survey, the National Hospital Discharge Survey, the National Ambulatory Medical Care Survey, and the Vital Statistics of the United States) estimated that there were approximately 2.5 million ambulatory care physician visits for constipation in the United States every year.[17] More recently, data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey suggest that ambulatory visits for constipation increased from 4 million per annum in 1993 to 1996 (ie, 0.46% of all ambulatory visits) to almost 8 million annually in 2001 to 2004 (ie, 0.72% of all ambulatory visits).[28] Between 2001 and 2004, the most recent epoch for which data are available, these visits were to adult primary care providers (33.4%), pedi-

Table 2. Medications Associated With Constipation

Class	Examples
5-HT_3 receptor antagonists	Ondansetron
Analgesics	
Opiates[a]	Morphine
Nonsteroidal anti-inflammatory agents[a]	Ibuprofen
Anticholinergic agents	belladonna
Tricyclic antidepressants[a]	Amitriptyline > nortriptyline
Antiparkinsonian drugs	Benztropine
Antipsychotics	Chlorpromazine
Antispasmodics[a]	Dicyclomine
Antihistamines[a]	Diphenhydramine
Anticonvulsants[a]	Carbamazepine
Antihypertensives	
Calcium channel blockers	Verapamil, nifedipine
Diuretics[a,b]	Furosemide
Centrally acting	Clonidine
Antiarrhythmics	Amiodarone
Beta-adrenoceptor antagonist	Atenolol
Bile acid sequestrants	Cholestyramine, colestipol
Cation-containing agents	
Aluminum[a]	Antacids, sucralfate
Calcium	Antacids, supplements
Bismuth	
Iron supplements	Ferrous sulfate
Lithium	
Chemotherapy agents	
Vinca alkaloids	Vincristine
Alkylating agents	Cyclophosphamide
Miscellaneous compounds	Barium sulfate, oral contraceptives, polystyrene resins
Endocrine medications	Pamidronate and alendronic acid
Other antidepressants	Monoamine oxidase inhibitors
Other antipsychotics	Clozapine, haloperidol, risperidone
Other antiparkinsonian drugs	Dopamine agonists
Other antispasmodics	Mebeverine, peppermint oil
Sympathomimetics	Ephedrine, terbutaline

5-HT, 5-hydroxytryptamine.
Adapted with permission from Branch RL, Butt TF. Drug-induced constipation. Adv Drug Reaction Bull 2009;257:987–990.
[a]Drugs associated with constipation in community-based studies.[23,205]
[b]Perhaps related to electrolyte disturbances.

atricians (20.9%), and gastroenterologists (14.1%), which is equivalent to approximately 1.12 million patients referred to gastroenterologists for constipation per year. Women and adults aged 65 years and older were more likely to seek consultation than men and younger adults, respectively. To place the 8 million physician visits into perspective, 142,570 people developed colon or rectal cancer and 43,140 people developed pancreatic cancer in the United States in 2010.[29] These relative numbers highlight the problem of effectively identifying patients with colon cancer from among the multitude of patients with constipation. Moreover, they underscore the potential societal benefits of a rational approach to this symptom, such as when it does or does not warrant more extensive investigation.

Between 1958 and 1985, 85% of physician visits for constipation resulted in a prescription for over-the-counter laxatives or cathartics.[17] Using different databases, this figure was 36% during 1993 to 1996 and 22% during 2001 to 2004.[28] Between 1993 and 1996 and between 2000 and 2004, use of bulking agents declined, use of osmotic laxatives increased, and use of stool softeners and stimulant laxatives did not change.[28] The annual direct medical costs for constipation were recently estimated to exceed $230 million,[30] and the costs incurred by women with constipation were double that of women without constipation.[31] The direct costs over 15 years were $64,000 per person with constipation versus $26,000 without. The challenge is estimating what costs must be due to constipation because this study included all costs incurred by people with constipation (ie, costs of any comorbidities were included). Population-based data are lacking as to the number of tests and procedures performed specifically for constipation in the United States. In a study of 51 patients seen in a surgical referral clinic (tertiary care), the average cost of the diagnostic evaluation was $2752.[32] The largest line item was the colonoscopy, which was responsible for more than one-third of the total expenditures. These investigators calculated the cost per patient who benefited from the evaluation to be $11,697.[32] The actual cost of performing colonoscopy is a challenge because this varies from location to location. Economic analyses have suggested that screening for colon cancer is cost-effective,[33] but formal economic analyses of the evaluation of constipation have not been performed. Because it is unlikely that patients with constipation are at lower risk for cancer, the performance of an anatomic evaluation of the colon in patients with constipation is thus likely to also be cost-effective. Constipation may, in fact, indicate a higher risk of colorectal malignancy[33,34]; thus, exclusion of malignancy perhaps is the most cost-effective first step in approaching a patient with constipation. The challenge is to consider the patient's age. Young people with constipation are not likely to have colorectal cancer, but evaluation is cost-effective in those older than 50 years. Of note, guidelines do not clearly state how often an evaluation should be performed in a person with symptoms; the guidelines are based on asymptomatic people.

To summarize these general aspects, constipation is common in the community, with prevalence estimates as high as 28%. A minority of those with constipation seek medical care, but this still accounts for 8 million annual physician visits in the United States. Most people see primary care providers and receive a prescription for laxatives, and they may undergo an anatomic evaluation of the colon. The role of the gastroenterologist is to assist in identifying selected patients with constipation who might benefit from additional testing or more specific treatments. By doing this, scarce health care resources may be used most efficiently.

A comprehensive literature search identified 10 studies, including 4 population-based studies, in which constipation was defined by the Rome criteria and quality of life was evaluated by a generic tool permitting comparisons with other conditions.[35] General health, mental health, and social functioning were impaired in people with con-

stipation compared with healthy controls and more so in hospitalized patients than in the community. Among hospitalized patients, mental and physical subcomponent scores were comparable to those of unstable patients with Crohn's disease. Among people in the community, scores were comparable to those of patients with gastroesophageal reflux, hypertension, diabetes, and depression.[36]

Pathophysiology

Virtually all studies on the pathophysiology of constipation emanate from tertiary centers rather than unselected people in the community.[37–40] Although some patients (ie, up to 50% in some series) with defecatory disorders also have slow colonic transit,[41–43] it is useful to consider mechanisms of STC and defecatory disorders separately. Understanding the pathophysiology of chronic constipation is useful for guiding therapy.

NTC and STC

In these guidelines, (isolated) STC refers to patients who do not have a defecatory disorder. Although slow colonic transit may reflect colonic motor dysfunction, it may also result from inadequate caloric intake.[44] Intraluminal assessments of colonic motility with manometry and a barostat reveal colonic motor dysfunction in some patients with STC.[43,45,46] Manometric disturbances include fewer high-amplitude propagated contractions and reduced phasic contractile responses to a meal and/or to pharmacologic stimuli (eg, bisacodyl or neostigmine).[45,46] However, because healthy subjects have 1 to 15 high-amplitude propagated contractions daily, only patients who have no high-amplitude propagated contractions over a 24-hour period have a true abnormality.[45] Increased nonpropagated or retrogradely propagated sigmoid or rectal phasic pressure activity, which may impede colonic flow, has also been described.[46] High-resolution colonic manometry suggests that there is less spatial overlap between adjacent propagated sequences.[46] Colonic inertia refers to patients with STC who also have markedly reduced or absent responses to a meal and to a pharmacologic stimulus (eg, bisacodyl or neostigmine).[43,47] These colonic motor dysfunctions may be explained by a marked reduction in colonic intrinsic nerves and interstitial cells of Cajal,[9,10] and this should prompt consideration of colonic resection in medically refractory patients who do not have pelvic floor dysfunction, as discussed later.

Barostat measurements revealed reduced fasting and/or postprandial colonic tone and/or compliance in 40% of patients with NTC, 47% with STC, 53% with defecatory disorders and normal transit, and 42% with defecatory disorders and slow transit.[43] In another study, 43% of patients with STC had normal fasting colonic motility and motor responses to a meal and bisacodyl.[48] Together, these observations suggest that normal and slow colonic transit are imperfect surrogate markers for normal and abnormal colonic motor function, respectively. Although NTC has been mistakenly regarded as synonymous with IBS-C, 23% of patients with constipation or IBS-C had delayed colonic transit.[49] Hence, the relationship between colonic transit and motor functions needs to be clarified.

Sensory disturbances in chronic constipation depend on the rate of distention; findings include increased and reduced rectal sensation during rapid and slow distention, respectively.[40] Increased rectal sensitivity is associated with abdominal pain and bloating, suggestive of IBS,[50,51] whereas slow colonic transit is associated with infrequent stools in some,[52] but not all,[53] studies.

Defecatory Disorders

Defecatory disorders are primarily characterized by impaired rectal evacuation, with normal or delayed colonic transit.[6] Conceptually, incomplete rectal evacuation may result from inadequate rectal propulsive forces and/or increased resistance to evacuation; the latter may result from high anal resting pressure ("anismus"), incomplete relaxation,[54] or paradoxical contraction of the pelvic floor and external anal sphincters ("dyssynergia").[42] However, these disturbances and other pseudonyms (eg, outlet obstruction, obstructed defecation) refer to the same disorder. These patterns are not associated with specific clinical features or the response to pelvic floor retraining.[55] Other disturbances in defecatory disorders include rectal hyposensitivity,[56] delayed colonic transit,[43,57] and structural disturbances (eg, excessive perineal descent and rectoceles),[58,59] Excessive straining may weaken the pelvic floor, causing excessive perineal descent, rectal intussusception, solitary rectal ulcer syndrome, and pudendal neuropathy; pudendal neuropathy may weaken the anal sphincters, predisposing to fecal incontinence.[58,60–62]

Several factors limit a precise understanding of the relationship between anorectal sensorimotor dysfunctions and symptoms of disordered defecation. First, even asymptomatic people and some patients with symptoms (eg, rectal pain) other than difficult defecation have dyssynergia, which undermines the significance of this finding.[63,64] Perhaps this reflects the challenges of simulating defecation during anorectal testing. Patients may be restricted by feelings of inadequate privacy, and these voluntary components will, of necessity, vary among patients and even for the same person at different times. Second, these disturbances (eg, dyssynergia, rectoceles) may overlap, limiting an assessment of the contribution of individual disturbances. Third, some features (eg, rectal hyposensitivity and delayed colonic transit) may be consequences rather than causes of obstructed defecation because they may improve after successful biofeedback therapy.[57] Fourth, the findings of different tests (eg, anal manometry, defecography) may not concur and there is no gold standard for the diagnosis. Lastly, other factors, particularly stool form, likely influence expression of symptoms in pelvic floor dysfunction.

The etiology of defecatory disorders is unclear. Disordered defecation may be conceptualized as maladaptive learning of sphincter contraction, perhaps initiated by

avoidance of pain or trauma[65] or even neglecting the call to defecate. Symptoms may date to childhood; indeed, one-third of children with childhood constipation continue to have severe symptoms beyond puberty.[66] Although obstetric trauma can damage the anal sphincter and pelvic floor, there is no evidence for an association between obstetric trauma and defecatory disorders.[67]

Some people have both slow transit and a defecatory disorder. In these patients, the defecatory disorder cannot be identified by the pattern of delayed colonic transit (eg, regional left-sided vs overall delay).[68] Delayed colonic transit in defecatory disorders may be attributable to physical obstruction to passage of contents by stool, rectocolonic inhibitory reflexes initiated by rectal distention from retained stool,[69] or colonic motor dysfunction, which is unrelated to defecatory disorders.[46]

Clinical Evaluation

The clinical assessment must, in particular, elicit specific symptoms of constipation, clarify which symptoms are distressing, and inquire about medications that can cause (Table 2) or are used to treat constipation. Alarm symptoms include a sudden change in bowel habits after the age of 50 years, blood in stools, anemia, weight loss, and a family history of colon cancer. The timing of symptom onset, particularly relative to potential risk factors (eg, onset during childhood, use of prescription and over-the-counter medications, inadequate dietary calorie and fiber intake, obstetric events, and a history of abuse), should be clarified. As discussed previously, it is essential to characterize bowel habits and elucidate the specific symptoms of chronic constipation. Is the "call to stool" postprandial, initiated by abdominal discomfort and/or by a rectal sensation? Is the call always answered? What maneuvers (eg, straining to begin and/or to end defecation) are used to defecate? Although some symptoms (ie, anal digitation, a sense of anal blockage during defecation, or a sense of incomplete evacuation after defecation) suggest disordered defecation,[70] the evaluation of these symptoms by a questionnaire is not particularly useful for discriminating patients with constipation who have a normal versus an abnormal rectal balloon expulsion test result.[71] Pictorial representations of stool form (eg, by the Bristol Stool Form Scale) and bowel diaries are efficient and reliable methods to characterize bowel habits and are better predictors of colonic transit than self-reported stool frequency.[72,73] Moreover, self-reported stool frequency is unreliable.[74] Stool form also influences the ease of defecation.[75] For example, among women with constipation in the community, straining to begin defecation is more frequent (ie, approximately 40% vs approximately 20%) for hard stools than normal stools.[75] When evacuatory deficits are pronounced, even soft stools and enema fluid may be difficult to pass. After a complete purge, it will take several days for residue to accumulate such that a normal fecal mass will be formed. Hence, it is not uncommon for patients to skip a bowel movement for a few days after a bout of diarrhea. Use of laxatives in patients with constipation can also predispose to alternating constipation and diarrhea, which is common in IBS.[76] In a population study, 7% reported use of laxatives.[77,78]

In addition to bowel disturbances, many patients, particularly those with IBS, have abdominal symptoms (eg, abdominal bloating, distention, or discomfort), nongastroenterological symptoms (eg, fatigue, malaise, fibromyalgia), or psychosocial distress. Many patients rank abdominal bloating, which may be associated with abdominal distention, as their most bothersome symptom.[79]

The clinical assessment should consider diseases to which constipation is secondary (Table 3). A meticulous perineal and rectal examination is very useful for identifying defecatory disorders. Digital rectal examination can gauge anal resting tone. Pelvic contraction is normally accompanied by increased anal tone and a puborectalis "lift" (ie, anterosuperior motion toward the umbilicus); when patients are instructed to "expel the examining finger," both muscles should relax with perineal descent, which is normally 2 to 4 cm.[80,81] Patients with defecatory

Table 3. Common Medical Conditions Associated With Constipation

Drug effects
See Table 2
Mechanical obstruction
Colon cancer
External compression from malignant lesion
Strictures: diverticular or postischemic
Rectocele (if large)
Postsurgical abnormalities
Megacolon
Anal fissure
Metabolic conditions
Diabetes mellitus
Hypothyroidism
Hypercalcemia
Hypokalemia
Hypomagnesemia
Uremia
Heavy metal poisoning
Myopathies
Amyloidosis
Scleroderma
Neuropathies
Parkinson's disease
Spinal cord injury or tumor
Cerebrovascular disease
Multiple sclerosis
Other conditions
Depression
Degenerative joint disease
Autonomic neuropathy
Cognitive impairment
Immobility
Cardiac disease

Adapted from, Locke GR, Pemberton JH, and Phillips SF. AGA technical review on constipation. Gastroentrology 2000;119:1766–1778, with permission from the American Gastroenterological Association.

disorders may have high anal resting tone, as evidenced by increased resistance to insertion of the examining finger into the anal canal, and/or impaired relaxation or paradoxical contraction of the sphincter complex with reduced perineal descent during simulated evacuation. Other possible findings include stool in the rectal vault, fecal soiling on the perianal skin, hemorrhoids, anal fissure(s), a rectocele, or puborectalis tenderness. Among 209 patients (191 men) with chronic constipation, a digital rectal examination performed by a skilled clinician was 75% sensitive and 87% specific for diagnosing dyssynergia as predicted by manometry but only 80% sensitive and 56% specific for predicting an abnormal rectal balloon expulsion test result, which is more useful for diagnosing defecatory disorders.[81] The utility of a digital rectal examination is likely lower for less skilled examiners.

After obtaining a history and conducting a physical examination, physiological testing should be performed in patients with chronic constipation refractory to dietary fiber supplementation and/or over-the-counter laxatives. When the clinical index of suspicion for disordered defecation is high, anorectal testing may be considered sooner, perhaps even before a trial of fiber and over-the-counter laxatives. In addition, a complete blood cell count should be performed. Although fasting serum glucose, sensitive thyroid-stimulating hormone, and calcium levels are often measured, the diagnostic utility and cost-effectiveness of these tests have not been rigorously evaluated and are probably very low.[82] Testing for colon cancer with imaging or endoscopy should be considered for all patients with alarm clinical features (eg, blood in stool, unexplained anemia, weight loss $\geq$10 lb, abdominal or rectal mass), for all patients with constipation refractory to medical management, and for patients aged 50 years or older who have not undergone an age-appropriate colon cancer screening procedure after onset of constipation; this age specification is lower in some patients with a family history of colon cancer. Testing should also be considered in patients with an abrupt change in bowel habits without an obvious cause, recognizing the limitations of defining an abrupt change. Because the prevalence of colonic neoplastic lesions at colonoscopy is comparable in patients with versus without chronic constipation, routine colonoscopy is not warranted for most patients with constipation.[83]

Patients are usually referred for specialty consultation because their symptoms have not responded to fiber supplements and/or over-the-counter laxatives. Given the variability of patient recall, gastroenterologists should consider evaluating symptoms with a bowel diary. Most secondary causes of constipation (Table 3) will be evident after obtaining a history and performing a physical examination. Although celiac disease is not associated with constipation in population-based studies, some patients with celiac disease report constipation at diagnosis and more so after treatment.[84,85] Further laboratory and imaging studies may need to be selectively completed or repeated.

Defecatory disorders, which are by far the most common cause of medically refractory chronic constipation,[86] can often be recognized by a careful clinical assessment and substantiated by anorectal test results. In general, IBS-C is characterized predominantly by abdominal pain, bloating, or feelings of incomplete evacuation in addition to bowel disturbances. Thereafter, assessments of colonic transit, as well as intraluminal assessment of colonic motor activity in selected patients, are useful for identifying when constipation is caused by colonic motor dysfunction.[7]

Diagnostic Tests

Figure 1 in the medical position statement summarizes a preferred approach to diagnostic testing in patients with chronic constipation who have not responded to a high-fiber diet and/or over-the-counter laxatives after organic disorders have been excluded. Anorectal testing with manometry and a rectal balloon expulsion test are at the top of the pyramid and may be considered even before trying laxatives in patients with symptoms that are highly suggestive of pelvic floor dysfunction. In contrast to the previous medical position statement, assessment of colonic transit is not recommended in the early assessment for 2 reasons. First, because up to 50% of patients with defecatory disorders have slow colonic transit, slow transit does not circumvent anorectal testing or exclude the presence of defecatory disorders. Defecatory disorders are treated with pelvic floor retraining regardless of colonic transit. Second, initial therapies (ie, laxatives) for NTC and STC are similar. If necessary, colonic transit and other tests follow.

Diagnostic approaches are compounded by the inherent limitations of anorectal testing, which have been discussed previously. Thus, the tests should be in a setting as private as possible to reduce embarrassment and facilitate cooperation, but ideal conditions are rarely possible. Indeed, these test results may be abnormal even in a small proportion of asymptomatic people. Moreover, false-positive and false-negative test results do occur and there is no single criterion standard diagnostic test for diagnosing defecatory disorders. Hence, test results need to be interpreted in the overall clinical context rather than in isolation. The studies referred to in the algorithm are listed in order of simplicity, cost, and general use.

Rectal Balloon Expulsion Test

This simple procedure, first described by Preston and Lennard–Jones,[54] evaluates a patient's ability to evacuate a water-filled balloon. It can be performed in isolation or in conjunction with anorectal manometry. The preferred approach is to quantify the time required to expel a rectal balloon in the seated position; depending on the technique, recommended normal values range from less than 1 minute to up to 5 minutes.[87,88] Alternatively, the magnitude of additional passive forces needed to expel the balloon in the lateral decubitus position can be

measured if spontaneous evacuation is not possible.[89] Depending on the technique, patients with pelvic floor dysfunction require more time or more external traction to expel the balloon. In a study of 106 patients with constipation and 24 patients with defecatory disorders diagnosed by defecography, rectal balloon expulsion was 87.5% sensitive and 89% specific with positive and negative predictive values of 64% and 97% for diagnosing defecatory disorders, respectively.[90] This uncontrolled study excluded patients with secondary (eg, medication-induced) chronic constipation. Although defecatory disorders were identified by a deviation in defecographic findings from the anticipated normal appearance, some asymptomatic subjects have abnormal pelvic floor motion by barium defecography.[91] Contrary to the approach in most clinical laboratories, the rectal balloon was inflated by a variable volume, averaging 183 mL, until patients experienced the desire to defecate rather than a fixed volume. Variable distention may compensate for reduced rectal sensation, which is associated with defecatory disorders.[56] However, these 2 techniques (ie, fixed vs variable balloon inflation) have not been compared.

Anorectal Manometry

This procedure has greatest value in (1) excluding Hirschsprung's disease by the presence of a normal rectoanal inhibitory reflex and (2) supporting a clinical impression of defecatory disorders as evidenced by high anal resting pressures, typically ≥90 mm Hg (anismus), with relatively little voluntary augmentation, suggestive of a nonrelaxing pelvic floor/sphincter dysfunction[92] or an abnormal (ie, lower) rectoanal pressure gradient during simulated evacuation. The precise utility of a low rectoanal pressure gradient to diagnose defecatory disorders is unclear because there is considerable overlap in values for this parameter between asymptomatic subjects and patients with defecatory disorders.[42,71,88] Therefore, the rectoanal gradient should not be used in isolation to diagnose defecatory disorders. The methods for anorectal manometry are not standardized and are reviewed extensively elsewhere.[93] Hence, data from center to center cannot be generalized. Both traditional approaches (ie, water-perfused or solid-state manometric sensors) are of comparable utility and generally correlated with high-resolution manometry.[94] In contrast to traditional sensors, high-resolution manometric catheters have several evenly distributed sensors situated along the catheter that straddle the entire anal canal, allowing pressures to be assessed without a pull-through maneuver.

Barium, Scintigraphic, and Magnetic Resonance Defecography

Defecography is particularly useful when the results of anorectal testing are inconsistent with the clinical impression and/or to identify anatomic abnormalities.[6,91,93,95] The most relevant findings in defecatory disorders include inadequate (ie, "spastic" disorder) or excessive ("flaccid perineum," "descending perineum syndrome") widening of the anorectal angle and/or perineal descent during defecation. Excessive straining, internal intussusception, solitary rectal ulcers, rectoceles, and rectal prolapse may also be observed.[96] If the vagina and small intestine are opacified, enteroceles as well as bladder and uterovaginal prolapse can also be visualized. Even before the advent of magnetic resonance imaging, barium defecography was not widely used, perhaps because radiologists have limited enthusiasm for the test and the technique was incompletely standardized.[93] Some asymptomatic subjects have features of disordered defecation. Methodological limitations to barium defecography (eg, limited reproducibility of anorectal angle measurements) can be minimized by standardized techniques.[95] Magnetic resonance defecography avoids radiation exposure and is better for visualizing the bony landmarks, which are necessary for measuring pelvic floor motion, than barium defecography; measurements are reproducible among observers.[59,97] However, in contrast to scintigraphy or fluoroscopy, conventional, closed-configuration magnetic resonance systems permit imaging in the supine position only. With the exception of rectal intussusceptions, for which seated magnetic resonance imaging was superior,[98] supine and seated magnetic resonance using open-configuration magnets are comparable for identifying clinically relevant findings. Scintigraphy can quantify evacuation of artificial stools with minimal radiation exposure.[89] However, anatomic defects may not be as well seen as with barium defecography.

Colonic Transit

Rates at which fecal residue moves through the colon are important determinants of fecal form, which can be categorized from liquid to semi-formed to pellet stools.[72,99] Bowel cleansing shortens colonic transit but does not affect the characterization of patients as having normal or slow colon transit.[100] Hence, it is not necessary to prepare the colon before evaluating colonic transit. Colonic transit is most commonly and inexpensively measured using radiopaque markers (Sitzmarks; Konsyl Pharmaceuticals, Fort Worth, TX). With the Hinton technique, a capsule containing 24 radiopaque markers is swallowed; normally, less than 5 markers should remain in the colon on an abdominal radiograph (110 keV) 5 days later.[101] A more refined approach is to have the patient ingest a capsule containing 24 radiopaque markers on days 1, 2, and 3 and count the markers remaining on a plain abdominal radiograph on days 4 and 7; a total of ≤68 markers remaining in the colon is normal, whereas >68 markers indicates slow transit.[102] The test is reproducible in simple constipation[72] but less so in defecatory disorders and colonic inertia.[103] Hence, as suggested in the algorithm, colonic transit should be reevaluated when necessary.

Less widely used is radionuclide gamma scintigraphy[49,104] or a wireless pH-pressure capsule.[105,106] Radiographic and scintigraphic methods correlate well[72]; scintigraphy requires scanning for 24 or 48 hours versus 5 to

7 days for completing a radiopaque marker assessment.[102] In patients with constipation, the correlation between colonic transit measured by radiopaque markers (on day 5) and the wireless motility-pH capsule is reasonable (correlation coefficient of approximately 0.7).[105] The capsule can also measure colonic motor activity but cannot identify propagation; the clinical utility of assessing colonic motor activity with a capsule is unclear.[106]

Colonic Manometry and Barostat Testing

Colonic manometry or barostat-manometric testing should be considered in patients with medically refractory STC.[43,45,48,107] However, these tests are only available in highly specialized centers with a research interest and their role in management is not well established. Manometry may be conducted under stationary or ambulatory conditions. As detailed in the section on the pathophysiology of STC, a subset of patients with STC has one or more features of colonic motor dysfunctions. A subtotal colectomy should be considered for patients with medically refractory STC who have colonic motor dysfunction but no pelvic floor dysfunction.

This review will not consider tests that are used in clinical research or generally not applicable to practice. These include (1) specific tests of rectal perception of distention or electrical stimuli, (2) electromyography of the external sphincter or puborectalis, and (3) pudendal nerve terminal motor latency. These studies, although of value in highly selected instances or for research purposes, are not part of the standard armamentarium.[93] These investigators also point out the potential role of surface electromyograms in the therapeutic mode of biofeedback.

Putting It Together

At the conclusion of the initial clinical evaluation of patients with constipation, it should be possible to tentatively classify patients into one (or possibly more) of the following categories:

1. NTC with normal colonic transit and defecation; some patients in this group have symptoms of IBS (eg, abdominal pain, bloating, and incomplete defecation)
2. STC when pelvic floor function is normal and there is evidence of slow transit
3. Defecatory disorders (anismus/dyssynergia [failure of relaxation] or descending perineal syndrome and other flaccid disorders)
4. Combination of 2 and 3; clinical observations suggest that some patients also have features of IBS
5. Organic constipation (mechanical obstruction or adverse drug effect; Table 2)
6. Secondary constipation (metabolic disorders; Table 3).

The degree to which some or all of the possibilities listed in Table 3 need to be considered will vary greatly. In some instances, treatment will be available for the primary disorder (hypothyroidism, hypercalcemia, rectal stricture, and so on). When treatment for the primary disorder is not available or is inadequate (eg, scleroderma, amyloidosis, neurologic disease), the challenge of adequate symptomatic treatment remains (see the following text). In most instances, at the level of the primary consultation, it will be sufficient to exclude organic and secondary constipation on clinical grounds and to treat symptomatically. Only some cases will require diagnostic studies for constipation.

Medical Management

The treatment algorithms in the medical position statement encapsulate our suggestions. Tables 4–6 summarize common over-the-counter laxative agents and newer pharmacologic agents for chronic constipation. Since the last review, some drugs (ie, cisapride and tegaserod) have been withdrawn and others have been introduced. Also, there is new evidence supporting the use of common laxative agents.

Adjunctive Approaches

There is no evidence that constipation can be treated by increasing fluid intake unless there is evidence of dehydration.[82] There is evidence that increased physical activity is associated with less constipation.[82,107] Mild physical activity increases intestinal gas clearance and reduces bloating,[108] and moderate to vigorous intensive physical activity (20–60 minutes 3–5 days per week) has been shown to improve symptoms and quality of life in IBS.[109] Although some probiotics may accelerate colonic transit, there are limited data on the impact of probiotics on constipation.[110]

Dietary Fiber Supplementation and Osmotic Laxatives

Systemic reviews suggest that soluble (eg, psyllium or ispaghula) but not insoluble dietary fiber (eg, wheat bran) supplements improve bowel symptoms in chronic constipation[111] and IBS.[112] A review of 4 trials, of which the largest enrolled 201 patients[113] and 3 used psyllium, showed that soluble dietary fiber improved individual bowel symptoms (eg, stool frequency, straining, stool consistency, and sense of incomplete evacuation) in chronic constipation.[111] However, only one study treated patients for more than 4 weeks, outcome measurements differed across trials, and none were at low risk for bias, precluding a formal meta-analysis. A meta-analysis of 17 trials observed that soluble fiber improved global symptoms and symptoms of constipation in IBS but that the effects on abdominal pain were variable.[112] Thereafter, a randomized study in 275 primary care patients observed superior response rates for psyllium (10 g twice daily; 57%), but not bran, compared with placebo (ie, rice flour; 35%) at 1 month. At 3 months, bran was better than placebo.[114] More than 60% of patients randomized to treatment with bran or psyllium reported adverse effects, primarily constipation or diarrhea. Dropout rates for all reasons at 2- and 3-month follow-up were 29% and 40%, respectively.

Table 4. Summary of Medications Commonly Used for Constipation

Type	Generic name	Trade name	Dosage	Side effects	Time to onset of action (*h*)	Mechanism of action
Fiber	Bran	—	1 cup/day	Bloating, flatulence, iron and calcium malabsorption	—	Stool bulk increases, colonic transit time decreases, gastrointestinal motility increases
	Psyllium	Metamucil Konsyl	1 tsp up to 3 times daily	Bloating, flatulence	—	
	Methylcellulose	Citrucel	1 tsp up to 3 times daily	Less bloating	—	
	Calcium polycarbophil	FiberCon	2–4 tablets once daily	Bloating, flatulence	—	
Stool softener	Docusate sodium	Colace	100 mg twice daily		12–72	
Hyperosmolar agents	Sorbitol	—	15–30 mL once daily or twice daily	Sweet tasting, transient abdominal cramps, flatulence	24–48	Nonabsorbable disaccharides metabolized by colonic bacteria into acetic acid and other short-chain fatty acids
	Lactulose	Chronulac	15–30 mL once daily or twice daily	Same as sorbitol	24–48	
	PEG	Golytely Colyte Miralax	8–32 oz once daily	Incontinence due to potency	0.5–1	Osmotically increases intraluminal fluids
Stimulant	Glycerin		Suppository; up to once daily	Rectal irritation	0.25–1	Evacuation induced by local rectal stimulation
	Bisacodyl	Dulcolax	10-mg suppositories or 5–10 mg by mouth up to 3 times/wk	Incontinence, hyperkalemia, abdominal cramps, rectal burning with daily use of suppository form	0.25–1	Bisacodyl and sodium picosulfate are prodrugs that are hydrolyzed by colonic bacteria (sodium picosulfate) or intestinal and colonic brush border enzymes (bisacodyl) to the active metabolite (bis-(p-hydroxyphenyl)-pyridyl-2-methane, which has anti-absorptive/secretory and prokinetic effects
	Picosulfate					Similar to bisacodyl
	Anthraquinones (senna, cascara)	Senokot Perdiem (plain) Peri-Colace	2 tablets once daily to 4 tablets twice daily 1–2 tsp once daily 1–2 tablets once daily	Degeneration of Meissner's and Auerbach's plexus (unproven), malabsorption, abdominal cramps, dehydration, melanosis coli	8–12 8–12 8–12	Electrolyte transport altered by increased intraluminal fluids; myenteric plexus stimulated; motility increases
Saline laxative	Magnesium	Milk of magnesia	15–30 mL once daily or twice daily	Magnesium toxicity, dehydration, abdominal cramps, incontinence	1–3 1–3	Fluid osmotically drawn into small bowel lumen; cholecystokinin stimulated; colon transit time decreases
		Hailey's M-O (with mineral oil)	15–30 mL once daily or twice daily			
Lubricant	Mineral oil	—	15–45 mL	Lipid pneumonia, malabsorption of fat-soluble vitamins, dehydration, incontinence	6–8	Stool lubricated
Enemas	Mineral oil retention enema	—	199–250 mL once daily per rectum	Incontinence, mechanical trauma	6–8	Stool softened and lubricated
	Tap water enema	—	500 mL per rectum	Mechanical trauma	5–15 min	Evacuation induced by distended colon; mechanical lavage
	Phosphate enema	Fleet	1 unit per rectum	Accumulated damage to rectal mucosa, hyperphosphatemia, mechanical trauma	5–15 min	
	Soapsuds enema	—	1500 mL per rectum	Accumulated damage to rectal mucosa, mechanical trauma	2–15 min	

Adapted from Locke GR, Pemberton JH, and Phillips SF. AGA technical review on constipation. Gastroenterology 2000;119:1766–1778, with permission from the American Gastroenterological Association.

Table 5. Newer Pharmacologic Approaches for Constipation

Generic name (chemistry)	Mechanism of action	Metabolism, bioavailability	Pharmacodynamic effects	Clinical trials	Common side effects	Cardiovascular safety[a]
Secretagogues						
Lubiprostone (prostone)[b]	Stimulate intestinal chloride and fluid secretion by activating chloride channels	Intestinal degradation, minimal oral bioavailability	Accelerated small bowel and colonic transit in health	Phases 2 and 3 in CC, IBS-C	Diarrhea, nausea	No arrhythmic effects
Linaclotide	Stimulate intestinal chloride and fluid secretion by activating CFTR	Intestinal degradation, minimal oral bioavailability	Dose-related acceleration of colonic transit in IBS-C	Phases 2 and 3 in CC, IBS-C	Diarrhea	No arrhythmic effects
Serotonin 5-HT_4 receptor agonists						
Prucalopride[c] (benzofuran carboxamide)	High selectivity and affinity for 5-HT_4 receptors; much weaker affinity for human D4 and s1 and mouse 5-HT_3 receptors	Limited hepatic, not CYP3A4	Accelerated colonic transit in health and CC	Phases 2 and 3 in CC	Diarrhea, headache	No arrhythmic activity in atrial cells; inhibits hERG at very high μmol/L concentration; no clinically relevant adverse cardiac effects in large trials (>4000 subjects)

NOTE. Only agents that have been tested in phase 3 clinical trials are included.
CC, chronic constipation.
[a]In addition to the listed effects, none of the agents shown in this table affect QTc in healthy subjects.
[b]Approved by the FDA.
[c]Approved by the European Agency for Evaluation of Medicinal Products.

Taken together, the potential therapeutic benefits, low cost, safety profile, and other potential health benefits of dietary fiber justify consideration of fiber supplementation, either as a standardized fiber supplement (Table 4) or through the diet, as a first step in patients with chronic constipation, particularly in primary care. In contrast to NTC, patients with drug-induced constipation or STC are unlikely to respond to fiber supplementation.[115] Patients should be instructed to begin with 2 daily doses with fluids and/or meals and gradually adjust the dose after a 7- to 10-day period. They should not expect an immediate response (as can be expected with a purgative) but should embark on a program for several weeks. They should also be warned that fiber supplements may increase gaseousness but that the symptoms often decrease after several days. Sometimes gaseousness can be reduced by switching to another fiber supplement.

If more treatment is needed, an inexpensive osmotic agent should be used regularly, supplemented by stimulant laxatives as needed (ie, "rescue" agents). Although there are no head-to-head comparisons of osmotic and stimulant laxatives, osmotic agents may be preferable to stimulant laxatives in patients in whom both agents are equally effective because there is more evidence of short-term and long-term efficacy for certain osmotic agents (ie, polyethylene glycol [PEG]). A meta-analysis of 7 controlled studies (ie, 1141 subjects) evaluating osmotic and stimulant laxatives in chronic idiopathic constipation reported a number needed to treat of 3 (95% confidence interval, 2–4).[2] The 4 main types of osmotic agents include PEG-based solutions, magnesium citrate–based products, sodium phosphate–based products, and nonabsorbable carbohydrates. These hypertonic products extract fluid into the intestinal lumen by osmosis, causing diarrhea. However, the PEG and electrolyte lavage solution used for colonic cleansing, typically not for chronic constipation, is iso-osmotic with plasma; bowel evacuation is by high-volume lavage. Patients can often titrate the dose of these agents such that soft but not liquid stools are achieved. The most evidence supporting efficacy, including a controlled trial with a duration of 6 months, exists for PEG.[2,116–118] Although the marketing label recommends treatment with PEG for a maximum duration of 2 weeks, retrospective series confirm that PEG maintains its efficacy for up to 24 months of treatment.[117,119] Patients prefer PEG preparations without electrolyte supplements[120]; the electrolyte-containing preparation is mainly indicated when a large volume is used for colonic cleansing.[121] Magnesium hydroxide and other salts improve stool frequency and consistency. Absorption of magnesium is limited, and these agents are generally safe. However, there are a few case reports of severe hypermagnesemia after use of magnesium-based cathartics in patients with renal impairment.[122] Sodium phosphate–based bowel cleansing preparations should be avoided because they are associated with hyperphosphatemia, hypocalcemia, and hypokalemia and, in less

Table 6. Comparison of Efficacy of Approved, Over-the-Counter, and Phase 3 Completed but Not Approved Pharmacologic Therapies for Relief of Chronic Constipation and IBS-C

	Chronic constipation			IBS-C		
Agent	Number needed to treat	Number of patients	Quality of evidence	Number needed to treat	Number of patients	Quality of evidence
Soluble fiber	[a]	368[111]	Very low	4.5[114]	275	Moderate
Osmotic and stimulant laxatives	3 (2–4)	1411	High	NA	NA	Moderate[b]
PEG	2.4[117]	573	High	NA	NA	Moderate[b]
Lubiprostone	4 (3–7)	610	Moderate	13[206]	1171	Moderate
Linaclotide	6 (5–8)	2858[207]	Moderate	10[208]	420	Moderate
Prucalopride	6 (5–9)	2639	Moderate	NA	NA	Very low

NOTE. Numbers in parentheses reflect 95% confidence intervals where available. Except where cited otherwise, data for therapeutic efficacy and numbers of patients with chronic idiopathic constipation are obtained from a meta-analysis of several trials.[2]
NA, not available.
[a]Although some trials suggest that dietary fiber is effective in patients with chronic constipation, the efficacy cannot be estimated reliably because the quality of the evidence is very low.
[b]Although no controlled clinical trials have been conducted in patients with IBS-C, indirect evidence from trials in chronic constipation, the mechanism of action of these agents, and clinical experience suggest they are also likely to be effective in patients with IBS-C.

than 1 in 1000 individuals, with acute phosphate nephropathy.[122,123]

In a Cochrane Database review of 10 randomized trials comparing PEG and lactulose, PEG was superior to lactulose for improving stool frequency, stool consistency, and abdominal pain.[124] Among nonabsorbable carbohydrates, lactulose and sorbitol had similar laxative effects but lactulose was associated with more nausea in a randomized crossover study of 30 men[125]; sorbitol is less sweet than lactulose and accelerates proximal colonic emptying.[126,127] Bacterial metabolism of unabsorbed carbohydrate leads to gas production.

Stimulant laxatives (eg, bisacodyl, glycerin suppositories, and sodium picosulfate, which is available in Germany) induce propagated colonic contractions and seem safe even with long-term use; bisacodyl and sodium picosulfate also have antiabsorptive plus secretory effects.[118,128–130] These agents may be used as rescue agents (eg, if patients do not have a bowel movement for 2 days)[131] or more regularly if required. If stimulant suppositories are used, it seems rational to administer them 30 minutes after breakfast in an attempt to synchronize the pharmacologic agent with the gastrocolonic response. In a multicenter study of 468 patients with chronic constipation, sodium picosulfate improved not only stool frequency and consistency but also other symptoms (eg, ease of evacuation) and quality of life compared with placebo.[118] Moreover, abdominal pain was not a major concern (5.6% of patients treated with sodium picosulfate vs 2.2% receiving placebo). Smaller studies suggest that bisacodyl, which works by a mechanism similar to that of sodium picosulfate, is also effective.[131,132] Contrary to earlier studies,[133,134] stimulant laxatives (senna, bisacodyl) do not appear to damage the enteric nervous system.[135,136] Neurologic damage might just as readily be the cause, not the result,[137] and there is now much less reticence to condone long-term use of stimulants.

Among older drugs, one small phase 2 study suggests that the cholinesterase inhibitor pyridostigmine improved symptoms and accelerated colonic transit in patients with type 2 diabetes mellitus and constipation.[138] Cisapride and tegaserod have been withdrawn from the marketplace because of concerns related to cardiovascular safety. Colchicine, which is a cytotoxin used to treat gout and produces diarrhea, should also be avoided because it can cause major neuromuscular complications, particularly when renal function is impaired.[139,140] Although the evidence is very limited (ie, one crossover study in 9 patients with active treatment, washout, and placebo periods of 1 week each), the prostaglandin E_1 analogue misoprostol, which increases gastrointestinal secretion, has been used to manage constipation.[141] Three new classes of agents to manage chronic constipation include intestinal secretagogues and serotonin 5-HT_4 receptor agonists for NTC and STC as well as opioid antagonists, which are specifically developed for opioid-induced constipation.

Intestinal Secretagogues

By stimulating net efflux of ions and water into the intestinal lumen, secretagogues accelerate transit and also facilitate ease of defecation. Both secretagogues for chronic constipation (ie, lubiprostone and linaclotide) increase intestinal chloride secretion by activating channels on the apical (luminal) enterocyte surface (Table 5). To maintain electroneutrality, sodium is also secreted into the intestinal lumen by other ion channels and transporters. Water secretion follows. Lubiprostone is a bicyclic fatty acid derivative derived from prostaglandin E_1[142] that primarily works by activating apical CIC-2 chloride channels. Lubiprostone also activates prostaglandin EP receptors and the apical cystic fibrosis transmembrane regulator (CFTR); the latter also mediates intestinal fluid secretion.[143,144] These secretory effects likely explain why lubiprostone accelerates small intestinal and colonic transit in healthy subjects.[145] Lubiprostone does not affect colonic motor activity in health.[146] Based on studies summarized by Ford and Suares[2] and Schey and Rao,[142] lubiprostone is approved by the Food and Drug Administra-

tion (FDA) at a dosage of 24 μg twice daily for the treatment of chronic constipation and at a lower dosage (8 μg twice daily) for the treatment of women with IBS-C (Table 6). Women of childbearing age should have a negative pregnancy test result before starting treatment and should be capable of complying with effective contraceptive measures.

Linaclotide is a first-in-class 14–amino acid peptide homologous to the heat-stable enterotoxins that cause diarrhea.[147] These heat-stable enterotoxins are also 3-disulfide homologues of the endogenous 2-disulfide paracrine hormones uroguanylin in the small intestine and guanylin in the colon. These compounds act on guanylyl cyclase C, which is selectively expressed in brush border membranes of intestinal mucosa cells from the duodenum to the rectum. Linaclotide activates the intracellular catalytic domain of guanylyl cyclase C, which in turn converts guanosine triphosphate to cyclic guanosine monophosphate, inducing downstream effectors that phosphorylate the CFTR, which opens the CFTR chloride channel and produces a net efflux of ions and water into the intestinal lumen. Linaclotide has minimal oral bioavailability and extraintestinal adverse effects, and it improved symptoms in phase 3 trials in chronic constipation[2,148] and in phase 2 trials in IBS-C.[149] Linaclotide also accelerated colonic transit in patients with IBS-C.[150] The FDA recently approved linaclotide for treating IBS-C and chronic constipation in adults at dosages of 290 and 145 μg daily, respectively. The FDA approval letter also requested additional toxicology studies to better understand why linaclotide caused deaths in neonatal and young juvenile mice but not in older juvenile mice.

Serotonin 5-HT$_4$ Receptor Agonists

Serotonin 5-HT$_4$ receptors are widely distributed on enteric neurons. 5-HT$_4$ receptor agonists induce fast excitatory postsynaptic potentials in intrinsic neurons, release neurotransmitters such as the excitatory acetylcholine, and induce mucosal secretion by activating submucosal neurons. None of the 3 new highly selective 5-HT$_4$ receptor agonists (ie, prucalopride, velusetrag, and ATI-7505) are approved by the FDA. Compared with older 5-HT$_4$ agonists, they have a much higher selectivity and affinity for 5-HT$_4$ receptors. For example, in contrast to tegaserod, it is unlikely that these newer agents have antagonistic effects at 5-HT$_{2B}$ receptors, which may have vascular effects. Also, extensive cardiovascular safety assessments suggest that these compounds do not affect hERG channels or the QTc interval and do not have arrhythmic effects.

Among the 5-HT$_4$ agonists for chronic constipation, the most evidence in humans is available for prucalopride. Prucalopride accelerated gastrointestinal and colonic transit in constipation,[151] and data from 7 randomized controlled trials with 2639 patients showed its efficacy in chronic constipation.[2] The European Agency for Evaluation of Medicinal Products approved the medication for chronic constipation in women in whom laxatives fail to provide adequate relief at a dosage of 2 mg/day in adults and 1 mg/day in the elderly.[152–155]

Bile Acid Transporter Inhibitors

Bile acids, which are not absorbed in the terminal ileum, spill over into the colon, where they are deconjugated and dehydroxylated by colonic microbiota to produce secondary bile acids such as deoxycholic acid, which induces colonic secretion.[156] This phenomenon, which is referred to as choleraic diarrhea, is minimized by ileal bile acid transporters, which normally absorb 97% of bile acids. Following up on a small pilot study,[157] phase 2 studies showed that the ileal bile acid transporter inhibitor A3309 accelerated colonic transit[158] and improved bowel habits in chronic constipation.[159] Responses, as defined by an increase of ≥1 complete spontaneous bowel movements per week over baseline during 4 of 8 treatment weeks, were more frequently observed with A3309 (ie, 58%, 64%, and 75% with the 5-, 10-, and 15-mg doses, respectively) than placebo (33%). The 2 higher doses (10 and 15 mg) significantly improved straining, bloating, and the Bristol Stool Form Scale score from about 2 at baseline to approximately 4 following treatment. Although A3309 was well tolerated, abdominal cramps (27%) and diarrhea (12.5%) were common with the 15-mg dose, and 23% of the patients in this group withdrew from the study. Thus, the 10 mg daily dosage seems to provide the optimum benefit-to-risk ratio for A3309. In addition to improving bowel habits, A3309 also dose-dependently lowered total and low-density lipoprotein cholesterol levels, which may be particularly beneficial for older patients with chronic constipation. Although promising, these results need to be confirmed by larger phase 3 trials.

Comparison of Pharmacologic Agents for Chronic Constipation

Consistent with recent reviews, this technical review recommends a therapeutic trial of traditional approaches (ie, fiber supplementation, osmotic laxatives, stimulant laxatives), which are effective, safe, and generally inexpensive, before newer agents (secretagogues, serotonin 5-HT$_4$ receptor agonists) are considered for managing chronic constipation.[3] Meta-analyses,[2] systematic reviews,[111] and the only head-to-head comparative study[160] suggested that some traditional approaches are as effective as newer agents for treating patients with chronic constipation (Table 6). Table 6 utilizes the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which is based on the quality of evidence and magnitude of benefit, to grade therapies into 4 categories (ie, high, moderate, low, or very low).[161] Several points deserve emphasis. First, end points differed across studies; hence, these numbers may not be strictly comparable. For example, most trials with prucalopride and linaclotide have been anchored by complete spontaneous bowel movements, whereas the studies of lubiprostone were anchored by complete, not complete

spontaneous, bowel movements. However, the criteria for therapeutic response were more stringent in the latter. Second, with the exception of soluble fiber, there is more evidence for efficacy in chronic constipation than in IBS-C. Although lubiprostone and linaclotide have been used in patients with IBS-C, there are no large high-quality trials of PEG, other osmotic or stimulant laxatives, or prucalopride in patients with IBS-C. Nonetheless, based on indirect evidence (ie, the mechanism of action of these agents and clinical experience suggesting efficacy in IBS-C), these agents are probably effective also in patients with IBS-C; the grade has been downgraded by a notch to reflect a lack of direct evidence. Third, the evidence for efficacy is strongest for osmotic and stimulant laxatives. Fourth, there are several well-designed clinical trials showing that lubiprostone, linaclotide, and prucalopride are efficacious for patients with chronic constipation and that lubiprostone and linaclotide are also efficacious for patients with IBS. The evidence to support the use of these newer agents for these indications is rated as moderate, primarily because (1) the pooled estimate of the magnitude of reduced risk (ie, for treatment vs placebo), as suggested by the upper bound of the 95th percentile confidence interval, was relatively low (ie, 12% for prucalopride, 20% for lubiprostone, and 13% for linaclotide) in chronic constipation and (2) the 95% confidence interval for reduced risk was relatively wide or imprecise for lubiprostone in chronic constipation and IBS-C. Fifth, because refractoriness to traditional agents (eg, laxatives) was not, with the exception of several studies with prucalopride, an entry criterion in most studies, the incremental utility of newer agents over traditional approaches, which is the critical question in clinical practice, requires further study. Sixth, anorectal functions and colonic transit were not evaluated in most therapeutic trials; hence, it is unclear if an inadequate response to therapy can be explained by pelvic floor dysfunctions or colonic motor dysfunctions.

Management of Defecatory Disorders

Defecatory disorders should be managed by biofeedback-aided pelvic floor retraining. Using visual or auditory feedback of anorectal and pelvic floor muscle activity, which are typically recorded by surface electromyographic sensors or manometry, patients learn to appropriately increase intra-abdominal pressure and relax the pelvic floor muscles during defecation. Thereafter, patients practice by expelling an air-filled balloon, assisted if necessary by the application of external traction to a catheter attached to the balloon. In patients with reduced rectal sensation, sensory retraining, in which patients learn to recognize weaker sensations of rectal filling, may also be provided. Although therapy may also include measures to improve pelvic floor contraction (ie, Kegel exercises), the emphasis in patients with defecatory disorders is on appropriately coordinating abdominal and pelvic floor motion during evacuation.

Regrettably, biofeedback therapy is not widely used to manage defecatory disorders, perhaps primarily because the benefits of pelvic floor retraining, as shown by controlled trials, are not widely recognized and the expertise is not widely available. Contrary to an earlier study,[162] more recent controlled trials show that pelvic floor retraining is more effective in defecatory disorders, as evidenced by an abnormal rectal balloon expulsion test result, than in isolated STC; 71% of patients with dyssynergic defecation but only 8% of patients with isolated STC achieved adequate relief after biofeedback therapy[57] (Table 7). Moreover, colonic transit normalized after biofeedback therapy in 65% of patients with disordered defecation but only 8% of patients with STC, reinforcing the concept that delayed colonic transit may be secondary to pelvic floor dysfunction.[57] Three controlled studies showed that biofeedback therapy is more effective than PEG,[163] sham feedback,[164] or diazepam[165] in defecatory disorders. These trials used 5 to 6 training sessions lasting 30 to 60 minutes at 2 weekly intervals. Alternatively, daily sessions can be provided over a shorter duration. The skill and experience of the therapist and the patient's motivation are critical factors influencing the response to biofeedback therapy. Dietitians and behavioral psychologists should also participate in this therapy as necessary. Third-party coverage for biofeedback therapy in defecatory disorders has improved over time. For example, the Centers for Medicare & Medicaid Services in many regions now consider biofeedback therapy as medically necessary for treating adults with severe constipation due to pelvic floor dysfunction that has not responded to more conservative treatment measures. When biofeedback therapy is denied for patients with defecatory disorders, physicians should strongly consider appealing the decision because many insurance carriers have not reviewed their policies since the advent of controlled studies showing that pelvic floor retraining is more effective than laxatives for defecatory disorders.

Role of Surgery

Surgical intervention in patients with constipation is generally divided into procedures for documented STC and those for defecatory disorders. Patients should be referred to surgery only after nonsurgical measures have failed and symptoms compromise activities of daily living.

Subtotal Colectomy for STC

Abdominal colectomy and ileorectal anastomosis (IRA) should be strongly considered in patients with medically refractory STC who do not have pelvic floor dysfunction or a diffuse upper gastrointestinal dysmotility.[37–39] Importantly, patients are advised that IRA treats the primary symptoms of constipation (infrequent and difficult evacuation) but may not improve other symptoms, such as abdominal pain and bloating, which patients associate with constipation but often persist postoperatively. This observation likely partially explains the

Table 7. Controlled Trials of Behavioral Treatment for Defecatory Disorders in Adults

Reference	Patients (n)	Behavioral treatment	Design and comparator	Main results
Bleijenberg and Kuijpers, 1994[209]	DD (20)	Intra-anal EMG BF	RCT vs balloon training	Symptoms improved: BF (73%) vs balloon (22%)
Koutsomanis et al, 1995[210]	Constipation (60); DD (47)	EMG and rectal balloon BF	RCT vs muscular coordination training + balloon	Symptoms improved to a similar extent in both arms
Heymen et al, 1999[211]	Constipation (36)	4 anal EMG BF arms	RCT	Relative to baseline, EMG BF alone was as effective as EMG + balloon training, home training, or both
Glia et al, 1997[212]	DD (20)	Perianal EMG BF	RCT vs pressure BF + balloon training	Symptoms improved to a similar extent in both arms
Chiarioni et al, 2005[57]	STC (52); DD (32), mixed (6), STC alone (12)	Anal EMG and balloon BF to teach relaxation	Open trial + abdominal muscle training to teach straining	At 6 months, symptom response (>3 bowel movements/wk) in 71% of the group with puborectalis dyssynergia vs 8% of the group with STC; improvements were maintained at 24 months of follow-up; improved defecation dynamics
Chiarioni et al, 2006[163]	DD (99)	BF	RCT vs PEG (14.6–29.2 g/day) + counseling	At 6 months, major clinical improvement in 80% of the BF group versus 20% of the PEG group; results sustained for 2 y
Rao et al, 2007[164]	DD (77)	BF	RCT vs sham (relaxation prescription)	88% (BF) satisfactory response vs 48% on control; improved defecation dynamics
Heymen et al, 2007[165]	DD (84)	EMG BF + pelvic floor exercises	3-arm RCT vs diazepam or placebo 1–2 h before attempt to defecate	Adequate relief of constipation: 70% (BF) vs 23% (diazepam) vs 38% (placebo); more unassisted bowel movements and reduced strain
Farid et al, 2009[213]	DD (48)	Balloon pressure BF	RCT; botulinum toxin A to external anal sphincter	1-month improvement: BF (50%) vs botulinum toxin A 71% (P = .008); 1-year improvement: 25% vs 33%
Simon and Bueno, 2009[214]	Elderly DD (30)	EMG BF	Counseling on behavioral mechanisms in defecation	Improved symptoms and EMG results in the biofeedback group at 4 wk and 2 mo

DD, defecatory disorders; EMG, electromyography; BF, biofeedback; RCT, randomized controlled trial.
Adapted from Camilleri M and Bharucha AE. Behavioral and new pharmacological treatments for constipation: getting the balance right. Gut 2010;59:1288–1296, with permission from BMJ Publishing Group Ltd.[3]

quite variable outcomes seen in many series of patients who underwent subtotal colectomy in the 1980s and 1990s. Moreover, in most of these same studies, patients did not undergo objective tests of pelvic floor function or tests that quantified colonic transit; patients thus underwent subtotal colectomy for "undocumented" constipation and may instead have had IBS-C, which is poorly managed by IRA (see the following text).

With subtotal colectomy, the colon is removed to the level of the sacral promontory, the rectum is elevated carefully to preserve the presacral nerves, and the anastomosis is made to the highest third of the rectum.[37,39] Anastomosis to the sigmoid colon results invariably in persistence or recurrence of STC,[37] while conversely, an anastomosis to the middle or lower third of the rectum may result in high stool frequencies and sometimes fecal incontinence.

Controversy exists regarding hemicolectomy and targeted segmental resection for STC. Although results for IRA are superior to those for segmental colectomy in several studies, 2 small studies in patients in whom left, right, or subtotal colectomy[37–39,166] based on segmental transit time measurements were performed reported good results.[167,168]

In properly selected patients, prompt and sustained relief of STC is achieved by IRA.[37–39,166,169,170] A nonrobust outcome measure, "satisfaction," is reported in between 90% and 100% of patients after IRA.[37,166,167,171] Recently, quality of life results after IRA for STC using validated outcome measures showed impressive results that were sustained over time.[166] In general, poorer outcomes in terms of satisfaction are reported by investigators who did not perform complete physiological assessments of their patients; patients with delayed colonic transit and no pelvic floor dysfunction report higher rates of satisfaction and better function[37,39,167] than those who underwent surgery based on history and physical examinations alone.[172,173] Several series have established the safety and efficacy of performing abdominal colectomy and ileorectostomy using either purely laparoscopic or hand-assisted techniques.[174–176] Counterbalancing increased operative time is the cosmetic advantage of tiny incisions and accelerated recovery times in this generally younger cohort of patients.

Although we found that patients with STC and concomitant upper gastrointestinal dysmotility did well after IRA,[177] others have cautioned against this approach.[173,178]

Complications occur in patients undergoing IRA for constipation, just as they can occur in any patient undergoing abdominal surgery; ileus, small bowel obstruction, anastomotic leakage, and wound infections all occur, but not at rates any higher than expected.[37,166] Small bowel obstruction is the most common complication after IRA, occurring in 10% to 70% of patients,[37,179] and can affect patients either early or late in their postoperative course. Most such episodes are managed conservatively and do not require reoperation.

Finally, there have been no objective predictors of success identified in patients with STC undergoing IRA, although outcomes in properly selected patients have been predictably good.[166]

Other Surgical Approaches for STC

Antegrade colonic enemas[180] ensure colonic emptying by infusing water into the colon either through an appendiceal conduit or indwelling cecostomy catheter.[180,181] This procedure has been mostly used in children with neurogenic constipation, and there is limited experience in adults.[182] In patients with severe bloating and abdominal pain accompanying STC, a venting ileostomy may help ascertain if symptoms are attributable to the small intestine or colon. If symptoms do not improve with a venting ileostomy, an IRA would not be indicated.[183] Constructing a colostomy instead of an ileostomy in these situations is ill advised, because colonic transit is slow and persistent constipation may occur.

Sacral Nerve Stimulation

The use of sacral nerve stimulation to treat the symptoms of constipation (caused by slow transit, pelvic floor dysfunction, or both) has gained credence in Europe as experience has widened. In the largest multicenter study, 45 of 62 patients with medically refractory chronic constipation proceeded to permanent stimulation; 39 patients had improved symptoms (ie, ≥50% reduction in straining during defecation, sense of incomplete evacuation after defecation, or an increase in bowel frequency from less than 3 to 3 or more bowel movements per week).[184] Of 27 patients in whom colonic transit was evaluated at baseline, 20 had delayed colonic transit; only 9 had delayed transit after therapy.[184] In contrast, another study of 19 patients reported that only 42% of patients with a mix of slow transit and pelvic floor dysfunction had improved symptoms with sacral nerve stimulation.[185] Moreover, approximately 60% of patients undergoing sacral nerve stimulation for constipation experienced one or more "events"; the 2 most common were loss of efficacy and pain.[186] More than one-third of patients required surgical reintervention or discontinuation of treatment altogether.[186] Sacral nerve stimulation for the treatment of constipation is not approved by the FDA for use in the United States.

Surgery and Pelvic Floor Injection of Botulinum Toxin for Pelvic Floor Dysfunction

Older surgical approaches addressing pelvic floor dysfunction (anismus, paradoxical puborectal muscle contraction) consisted of dividing the puborectalis muscle or performing a postanal repair.[187,188] Neither is effective. Based on small, uncontrolled studies, injection of botulinum toxin into the puborectalis muscle, which is variably effective,[189,190] cannot be recommended for managing defecatory disorders.

Stapled Transanal Resection

The stapled transanal resection (STARR) procedure was developed to address the problem of obstructed defecation caused by 2 anatomic abnormalities: rectal intussusception (occult rectal prolapse) and rectoceles. Rectoceles traditionally are managed operatively if the defect is large, fills preferentially on a defecating proctogram, and is managed by the patient stenting the posterior wall of the vagina.[191] Rectal intussusception has traditionally been treated by pelvic floor retraining for lack of an efficacious alternative.[192,193]

The STARR procedure involves stapling the redundant rectal mucosa associated with a rectocele and intussusception. The aim is to cure the symptoms by resecting the redundant tissue, but the link between symptoms and actual anatomic abnormalities is tenuous.[194] It is quite probable that anatomic abnormalities, such as intussusception and complete rectal prolapse, are actually caused by the underlying disorder of function (impaired pelvic floor relaxation and excessive straining), which is not corrected by the procedure. Although a large randomized, prospective, multicenter trial observed that STARR was superior to pelvic floor retraining using biofeedback therapy, it is unclear what proportion of patients had pelvic floor dysfunction at baseline because rectal balloon expulsion was not evaluated at baseline; anal pressures were measured but not provided.[195] There are discrepancies between improvement in symptoms and anatomy; symptoms may improve despite modest effects on anatomic disturbances[196–198] and vice versa.[199]

Complications include pelvic sepsis, fistula, peritonitis, bowel perforation, pain, and bleeding,[197,200,201] which has prompted pleas that only qualified surgeons perform STARR.[201] Finally, the long-term outcomes of patients even ideally suited for STARR are somewhat disappointing.[202] The operation has failed to gain widespread acceptance in the United States.

Pouch of Douglas protrusion,[203] which is often confused with rectal intussusception and full-thickness rectal prolapse, is best addressed with sacrocolpopexy and is usually performed in conjunction with other gynecologic procedures in patients with pelvic floor abnormalities such as cystoceles, rectoceles, and enteroceles and vaginal vault prolapse.[204]

Summary of the Surgical Approach to Patients With Constipation (Grade of Recommendation)

Patients with STC who fail to respond to optimal medical management are candidates for colectomy and ileorectostomy. In a referred population undergoing stringent physiological testing, only about 3% are actually candidates for this procedure. Thus, among the population at large with constipation, only a tiny fraction will ever be suitable candidates for ileorectostomy. Patients with both pelvic floor dysfunction and STC should have their pelvic floor function addressed by pelvic floor retraining and, if constipation persists, should be offered

IRA.[39] Patients with pelvic floor dysfunction alone should undergo pelvic floor retraining, patients with a physiologically significant rectocele should undergo a repair, and patients with rectal intussusception should undergo pelvic floor retraining. Until STARR becomes a safe, reproducible, effective, and durable procedure, it should be performed on a protocol basis.

Conclusions

Based on the preceding review, an algorithmic approach to patients with constipation can be devised. See Algorithms 1 to 3 in the preceding medical position statement.

After the initial history and physical examination, it should be provisionally possible to classify patients into one of several subgroups. Standard blood tests (complete blood cell count, thyroid-stimulating hormone, calcium) are widely used and inexpensive. The yield of these tests has not been evaluated but is likely very low. Whether these tests should be routinely performed in all patients is debatable. When appropriate, a colonic structural evaluation (colonoscopy or flexible sigmoidoscopy and barium enema or computed tomographic colonography) should be performed to rule out organic causes of the constipation. Patients with known neurologic conditions need these to be addressed. If the initial evaluation is normal or negative, an empiric trial of fiber (and/or dietary changes) can be followed by over-the-counter osmotic or stimulant laxatives. Many patients will obtain symptom relief with these measures, which are safe for long-term use. Patients who fail to respond to this initial approach are appropriate candidates for more specialized testing. Pelvic floor dysfunction needs to be excluded by performing anorectal manometry and a balloon expulsion study, followed by defecography if necessary. Biofeedback therapy is the cornerstone for managing pelvic floor dysfunction. A simple and inexpensive radiopaque marker study will identify STC, which should be treated with aggressive laxative programs and, where available, prokinetic agents. Truly refractory patients may be considered for surgery, although few will qualify after more extensive physiological studies.

Many patients will have normal studies, and most will meet the criteria for IBS-C. The hope is that most of these patients can be managed with laxatives and reassurance. As with other functional gastrointestinal disorders, psychological conditions need to be considered as contributing factors. Key to their adequate management is identification of the predominant symptom: is this constipation or the associated symptoms (bloating, pain, nausea, and so on)?

Unfortunately, the clinical effectiveness and the cost-effectiveness of this algorithmic approach have not been assessed. The structural evaluation, at least in older patients, is likely cost-effective on the basis of identifying colon cancer and adenomatous polyps. Laxatives, biofeedback, and surgery have all been shown to be effective in treating selected patients. Community-based physicians will likely perform the evaluation sequentially, whereas tertiary centers may need to test more simultaneously for patient convenience. Many of the specific points of our algorithm may be debated, and different algorithms certainly have not been compared for clinical or cost benefits. The goal of this review was to guide practicing gastroenterologists through rational and efficacious approaches to patients with constipation.

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Conflicts of interest

The authors disclose the following: Mayo Clinic and A. E. Bharucha have a financial interest in a new technology related to anal manometry. A. E. Bharucha has been a consultant for Helsinn Therapeutics and Asubio Pharmaceuticals. G. R. Locke has been a consultant for Ironwood Pharmaceuticals, Movetis, Salix Pharmaceuticals, and ProStrakan, Inc.

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