Curr Gastroenterol Rep (2015) 17: 47
DOI 10.1007/s11894-015-0471-z

LARGE INTESTINE (B CASH, SECTION EDITOR)

Chronic Constipation: a Review of Current Literature

Hani Sbahi[1] · **Brooks D. Cash**[1]

Published online: 8 October 2015

Abstract Chronic constipation is a common health condition representing a substantial proportion of primary care visits and referrals to specialist providers. Chronic constipation can have a significant negative effect on health-related quality of life and has been associated with psychological distress in severely affected patients. It has the potential to cause patients to curtail work, school, and social activities. While different pathophysiological mechanisms have been implicated in the development of chronic constipation, in some instances, the causes of chronic constipation are not easily determined. Expenditures for the evaluation and management of chronic constipation represent a significant burden on patients and payers, and it is important for clinicians to have a clear understanding of the different pathophysiological mechanisms associated with constipation, understand the different testing modalities and treatments that are available including their appropriateness and limitations, and tailor that knowledge to the management of individual patients.

Keywords Constipation · Chronic constipation · Management of chronic constipation · Pelvic floor dysfunction · Dyssynergic defecation · Types of constipation

This article is part of the Topical Collection on *Large Intestine*

✉ Hani Sbahi
hsbahi@health.southalabama.edu

Brooks D. Cash
bcash@health.southalabama.edu

[1] Division of Gastroenterology, University of South Alabama, 75 University Boulevard S, Suite 6000-B, Mobile, Al 36688, USA

Introduction

Constipation is a common clinical problem worldwide. The global prevalence of chronic idiopathic constipation is estimated to be approximately 14 % [1]. In North America, the estimated prevalence ranges from 1 to 8 %, disproportionately affecting women and older adults [2, 3]. This is possibly due to a greater degree of self-reporting of symptoms and a higher risk of pelvic floor muscle injury in women, as well as an increased prevalence of comorbid conditions and polypharmacy in older adults. Furthermore, elderly patients are more prone to develop complications of constipation [2, 4]. Constipation is more common in North America and Europe compared to Asian countries, perhaps due to cultural diversity, dietary, genetic, and environmental factors [3]. Despite being such a common clinical syndrome, only 34 % of people with symptoms of chronic constipation consult a physician for their symptoms [5]. Many patients manage their symptoms adequately with non-prescription therapies or lifestyle modifications.

However, some patients' chronic constipation symptoms may be difficult to manage with these approaches, and these individuals are prone to experience significantly impaired health-related quality of life and psychological distress related to their gastrointestinal symptoms [4]. Similar to other functional gastrointestinal disorders, chronic constipation can impair work productivity and limit social activities of affected individuals. Furthermore, chronic constipation represents a significant expenditure of healthcare resources. It is estimated that the annual costs of diagnostic testing for constipation is nearly $7 billion, with an additional $500 million spent on prescription and over-the-counter therapies [5]. In the following discussion, we will review the pathophysiology and common causes of constipation, the role of diagnostic tests, and the evidence regarding available medical options for this common condition.

Definition and Criteria

The general consensus of a "normal" bowel movement frequency is quite broad. Three bowel movements a day or up to three bowel movements a week is generally considered to be within the normal range. While bowel movement infrequency can be distressing to patients, it is the quality of, or difficulty associated with, defecation that is the primary determinant of patient-described constipation. Symptoms such as straining, a sense of incomplete evacuation, hard or lumpy stools, or defecation requiring manual maneuvers to complete can often be elicited from patients who complain of constipation. Constipation can be defined as reduced frequency of defecation and stool passage, hardness of the stool, or feeling of incomplete evacuation that leads to patient dissatisfaction [6, 7•]. It is not uncommon for caregivers and patients to perceive constipation differently, and having a common lexicon regarding constipation symptoms is an important component of successful management of this common condition [8].

In an attempt to standardize the definition of constipation, clinical criteria for chronic (functional) constipation and irritable bowel syndrome with predominant constipation (IBS-C) were developed by the ROME committee, most recently as the ROME III criteria [9] (Table 1). The initial step in the evaluation of constipation is to distinguish chronic constipation from IBS-C, which can be generally defined as abdominal pain or discomfort that is temporally associated with at least two of the following three symptoms: improvement of discomfort with defecation, hard or lumpy stools, and/or infrequent stools [7•, 9]. While patients with chronic constipation may complain of abdominal discomfort, it is not usually the primary complaint as in IBS-C. Despite the attempt to separate these conditions, the distinction between chronic constipation and IBS-C can be difficult in individual patients. Furthermore, the application of these criteria in clinical practice can be restrictive, due to the disparity between clinical criteria-defined constipation and patient self-reported constipation [10].

Chronic Constipation Classification

Chronic constipation can be classified, based on etiology, into primary constipation (also referred to as chronic idiopathic constipation (CIC) or functional constipation) and secondary constipation (attributed to comorbid medical conditions or medications). The distinction between the two types of constipation is important, as interventions aiming at mitigating the constipation-inducing effects of the underlying condition or the offending medication should be the initial step in addressing secondary constipation. Over 900 medications have been linked with the development of constipation, including prescription and over-the-counter medications as well as herbal supplements. Common medications and systemic illnesses implicated in the development of secondary constipation are presented in Table 2 [6, 7•].

Primary Constipation

Normal colonic motility relies on intact colonic peristaltic contractions generated by the interplay of the myenteric plexus, interstitial cells of Cajal, and numerous neurotransmitters [11]. Functionally, CIC can be classified as normal transit constipation (NTC), slow transit constipation (STC), and/or constipation due to rectal evacuation disorders. The pathophysiology associated with the different subtypes of CIC is incompletely understood, and multiple mechanisms have been proposed as potential causes. It is important to understand that patients with CIC may exhibit symptoms due to the overlap of more than one mechanism. Thus, a patient with NTC or STC may also have evidence of rectal evacuation disorders. In

Table 1 ROME III diagnostic criteria for irritable bowel syndrome with constipation and functional constipation

Irritable bowel syndrome with predominant constipation (IBS-C)	Functional constipation
Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with two or more of the following: • Improvement with defecation • Onset associated with a change in frequency of stool • Onset associated with a change in form (appearance) of stool - Hard or lumpy stools (Bristol Stool Scale 1 or 2) ≥25 and loose (mushy) or watery stools (Bristol Stool Scale 6 or 7) <25 % of bowel movements Criteria must be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis	1. The presence of two or more of the following: • Straining during ≥25 % of defecations • Lumpy or hard stools in ≥25 % of defecations • Sensation of incomplete evacuation for ≥25 % of defecations • Sensation of anorectal obstruction/blockage for ≥25 % of defecations • Manual maneuvers to facilitate≥25 % of defecations • Fewer than three defecations per week 2. Loose stools rarely present without the use of laxatives 3. Insufficient criteria for IBS Criteria must be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Adapted from Longstreth G, et al. [9]

Table 2 Medications and medical conditions associated with chronic constipation

Medications associated with constipation	Medical conditions associated with constipation
Anticholinergics: antihistamines (diphenhydramine), antispasmodics (dicyclomine, peppermint oil), antipsychotics (chlorpromazine), tricyclic antidepressants (amitriptyline), antiparkinsonian drugs (benztropine)	Mechanical obstruction: colon cancer, other intra- or extra-intestinal masses, strictures, large rectocele, postsurgical abnormalities
Analgesics: opioids (morphine), nonsteroidal antiinflammatory drugs (ibuprofen)	Metabolic conditions: hypothyroidism, diabetes mellitus, hypercalcemia, hypokalemia, hypomagnesemia, chronic renal insufficiency, pregnancy
Anticonvulsants: carbamazepine	Myopathies: amyloidosis, scleroderma, dermatomyositis, myotonic dystrophy
Antihypertensive drugs: calcium channel blockers (verapamil), diuretics (furosemide), centrally acting drugs (clonidine), beta-blockers (atenolol)	Neuropathies: Parkinson's disease, spinal cord injury, cerebrovascular disease, paraplegia, multiple sclerosis
Antiarrhythmics: amiodarone	Enteric neuropathies: Hirschsprung's disease, chronic intestinal pseudo-obstruction
Other antidepressants: monoamine oxidase inhibitors	Anorectal disorders: anal fissures, anal strictures
5-HT receptor antagonists: (ondansetron)	
Bile acid sequestrants: (cholestyramine, colestipol)	
Cation-containing agents: aluminum (antacids, sucralfate), calcium (antacids, supplements), iron (ferrous sulfate), bismuth, lithium	
Chemotherapeutic agents: vinca alkaloids (vincristine), alkylating agents (cyclophosphamide)	
Sympathomimetics: ephedrine, terbutaline; and many others	

general, successful treatment of rectal evacuation disorders, when present, is a prerequisite to successful management of other forms of CIC when overlap is present.

Fiber content in the diet seems to play a role in the development of constipation, based upon improvement in self-described constipation of patients with normal colonic transit and anorectal function with bulking agents. Recent data suggests that certain types of dietary fiber might improve colonic transit [12]. However, increasing dietary fiber does not seem to improve symptoms in patients with STC [13]. In these patients, delayed colonic transit leads to more time-dependent water absorption, contributing to hard, lumpy, and difficult to evacuate stool [14]. Additionally, abnormal colonic transit can affect the microbial milieu of the colon, which has been shown to exert an influence on colonic motility, absorption, and secretion [6, 15, 16]. Finally, altered pelvic floor motor and sensory function, as well as behavioral and psychological factors, especially in children and younger adults, have been associated with the development of CIC [6, 16, 17]. These etiologies have been shown to be associated with female gender, increasing age, and lower socioeconomic status [1].

Normal Transit Constipation

In NTC, neuroendocrine and muscular function of the colon is intact. It is the most common form of CIC encountered in clinical practice and is may be referred to as functional constipation [18]. Despite an often "normal" stool frequency and transit rate through the colon, patients with NTC often endorse sensations of difficult or delayed evacuation, hard stools, along with bloating, and abdominal pain or discomfort [19]. These patients may have increased rectal compliance, decreased rectal sensation, or both [11, 18]. This group of patients often responds to therapy with dietary fiber and/or osmotic laxatives [13].

Slow Transit Constipation

Slow transit constipation can affect any age group; however, it most commonly affects younger women with symptoms beginning around puberty [20]. These patients may have impaired colonic propulsive motor activity, an attenuated gastrocolic reflex, and delayed emptying of the proximal colon. There is often a lack of response to dietary fiber and bulk laxatives [13]. The hallmark of STC is dramatically infrequent defecation and the lack of a call to defecate [11]. It is not uncommon for these patients to report one bowel movement or less per week. The exact etiology of STC is poorly understood. Immunohistochemical studies have demonstrated a significant reduction in the density of interstitial cells of Cajal, a loss of myenteric plexus neurons (expressing the excitatory transmitter substance P), and abnormalities in the activity of inhibitory transmitters such as vasoactive intestinal peptide and nitric oxide [21–24]. While most cases of STC are idiopathic, it has been reported after an inciting trigger such as an injury to the pelvic plexus following hysterectomy or childbirth [11, 25, 26]. When STC is intractable to medical therapy, it may be called colonic inertia. A congenital form of STC can arise from Hirschsprung's disease, a condition marked by loss of ganglion cells in the distal colon, most commonly present in infancy or early childhood, although in less severe forms can become evident later in life [27].

Rectal Evacuation Disorders

Rectal evacuation disorders refer to difficulty in expelling stool from the rectum. This condition can arise as a result of structural obstruction/abnormality (e.g., anal stenosis, neoplasms, rectocele, intussusception, mucosal prolapse, or anal fissures), or more commonly, as a functional defecatory disorder. Functional defecation disorders result from inadequate

rectal propulsive forces, paradoxical anal contraction, and/or inadequate relaxation of the anal sphincter [28]. Other terms used to describe this condition include pelvic floor dyssynergia, anismus, obstructed defecation, and paradoxical pelvic floor contraction. Clues to functional defecatory disorders include prolonged and excessive straining (even with soft stool), dyschezia, digital manipulation (need for vaginal or perineal pressure to pass a bowel movement), and failure to respond to standard laxative treatment, although historical features have not been shown to be reproducible predictors for rectal evacuation disorders. The ROME III provides formal criteria for functional defecation disorders and dyssynergic defecation [29] (Table 3). Constipation due to rectal evacuation disorders is managed by biofeedback and pelvic floor retraining with reported success rates >70 % [29–32].

Clinical Evaluation

History

The evaluation of a patient with CIC begins with a meticulous medical, surgical, and dietary history addressing comorbid conditions that could be associated with constipation and reviewing medications used by the patient (Table 2). Over-the-counter and alternative and complementary medication use or practices should be evaluated. One of the first steps in evaluation is to differentiate chronic constipation from IBS-C. This can be achieved by applying the symptom-based clinical criteria such as the ROME criteria or the Manning criteria for IBS. A positive diagnosis of IBS-C using these criteria, in the absence of alarm features, can avoid expensive, invasive, and generally low-yield diagnostic testing [33]. It is important to determine the onset and duration of symptoms, frequency of bowel movements, consistency of the stool, straining, and stool caliber. The Bristol stool form scale and the Bowel Function Index can be useful adjuncts to help patients describe their stool form more precisely as well as measure their perception of the severity of their symptoms [34]. The Bristol stool form scale may also be helpful to assess the colonic transit time, especially in patients with suspected STC. Bristol stool types 1 and 2 (scybalous or hard, or lumpy stools) correlate with slower colonic transit [9, 35] (Fig. 1). Some authors advocate the use of dietary and stool diaries to assess fiber and fluid intake in addition to defecation frequency and quality [35]. Moreover, clinicians should inquire about any possible precipitating events, as well as associated symptoms such as perianal pain, abdominal pain, and bloating. Prior laxative use including types, doses, frequency, and response are important historical features to ascertain. The clinician should also determine whether the patient has had to resort to digital maneuvers to facilitate defecation. During the initial evaluation, it is important to screen for red flag symptoms or "alarm symptoms" including new-onset constipation after the age of 50 years, rectal bleeding, unintentional weight loss, fever, nausea and vomiting, anemia, or family history of a gastrointestinal malignancy.

Physical Examination

A comprehensive examination is important, including a neurological assessment, to identify systemic conditions that could be contributing to the symptoms of constipation. During the abdominal examination, it is important to identify abdominal tenderness, abdominal masses, and the presence of stool [35]. A careful perineal and digital rectal examination (DRE) is very important and can be the most revealing part of the evaluation [35]. It includes a careful inspection of the perineum to identify external thrombosed hemorrhoids, anal fissures, excoriations, or evidence of pruritus ani. Additionally, observing the perineum while the patient strains facilitates the assessment of appropriate perineal descent (at least 2 cm), leakage of stool, gaping anus, prolapse of internal hemorrhoids, or thrombosis of external hemorrhoids [35]. Digital rectal examination with palpation of the anal canal can identify hard stool, masses, anterior rectocele, hemorrhoids, or pain suggestive of an anal fissure. DRE can also permit assessment of neurologic integrity and pelvic floor muscle

Table 3 ROME III diagnostic criteria for functional defecation disorders and dyssynergic defecation

Functional defecation disorders	Dyssynergic defecation
1. The patient must satisfy diagnostic criteria for functional constipation 2. During repeated attempts to defecate must have at least two of the following: a. Evidence of impaired evacuation, based on balloon expulsion test or imaging b. Inappropriate contraction of the pelvic floor muscles (i.e., anal sphincter or puborectalis) of less than 20 % relaxation of basal resting sphincter pressure by manometry, imaging, or EMG c. Inadequate propulsive forces assessed by manometry or imaging Criteria must be fulfilled for the last 3 months with symptoms onset at least 6 months prior to diagnosis	- Inappropriate contraction of the pelvic floor or less than 20 % relaxation of basal resting sphincter pressure with adequate propulsive forces during attempted defecation

Adapted from Bharucha et al. [29]

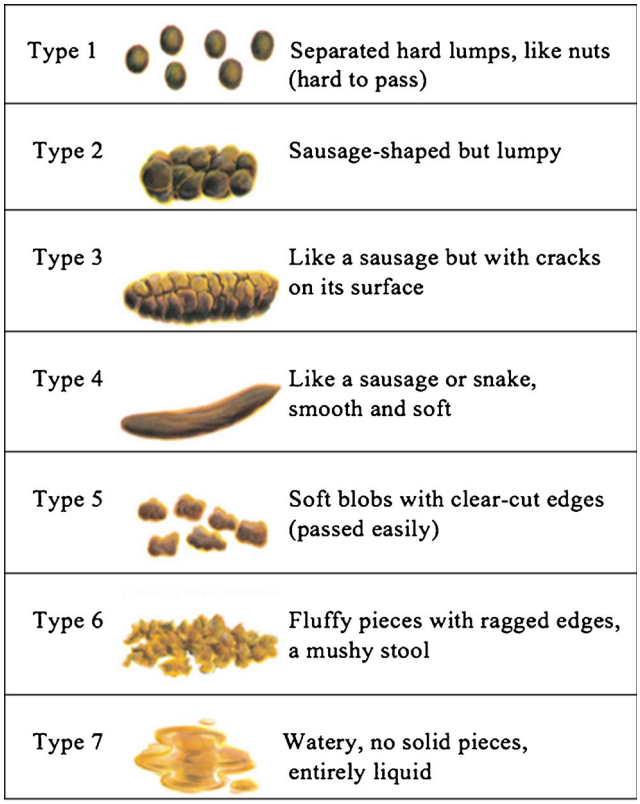

Fig. 1 The Bristol stool form scale

dysfunction or tenderness. During the DRE, the patient should be asked to push and bear down simulating defecation, while the examiner's other hand is placed on the abdomen to assess the push effort. Normally, the anal sphincter and puborectalis should relax with descent of the perineum, while the abdominal muscles contract during simulated defecation. A tightening of the sphincters is suggestive of pelvic floor dysfunction (PFD) and is considered a reliable tool to identify dyssynergia in patients with chronic constipation, facilitating selection of patients for further physiologic testing such as defecography and anorectal manometry [35, 36].

Diagnostic Testing

A complete blood count, chemistry panel, and thyroid function tests are often done in clinical practice to exclude metabolic diseases contributing to chronic constipation. Beyond these tests, additional testing is rarely necessary or required. In fact, the yield of routine diagnostic testing of patients with chronic constipation without alarm symptoms is low [7•, 37]. The American College of Gastroenterology (ACG) Chronic Constipation Task Force recommends against routine diagnostic testing in chronic constipation in the absence of alarm symptoms and suggests that the initial approach to chronic constipation should be empiric treatment [38]. Colonoscopy should be reserved for those who meet the appropriate colon cancer screening guideline recommendations and for patients with alarming symptoms (rectal bleeding, heme-positive stool, iron deficiency anemia, abnormal weight loss, and obstructive symptoms) [39, 40]. The evidence to support the utility of plain abdominal X-ray, barium enema, and anorectal ultrasound in the evaluation of chronic constipation is poor, and these tests should not be routinely obtained [41]. If constipation is refractory to dietary fiber and/or standard laxative therapy, or if PFD or slow transit constipation is highly suspected, physiologic studies focusing on colonic transit and evacuation mechanics may be useful.

Physiologic Testing

Defecography

Defecography involves placing 150 mL of contrast material into the rectum to allow the anorectal region to be studied at rest and during attempted defecation using fluoroscopy and a specialized toilet. It can identify functional abnormalities suggestive of PFD. Additionally, defecography can help identify structural abnormalities such as rectocele, rectal prolapse, intussusception, intraluminal masses, as well as allowing assessment of the residual stool in the rectum after defecation [6, 42]. The disadvantages to this test include radiation exposure, limited availability or radiologic interpretation training, patient embarrassment and reticence to undergo or fully participate in the test, inconsistent methodology, and interobserver bias [41].

Rectal Balloon Expulsion Test

Rectal balloon expulsion testing is performed using a water-filled balloon (FECOM) placed in the rectum and can be performed in the office setting. Once inserted, the patient is escorted to a toilet, given privacy, and instructed to expel the balloon into a toilet from the sitting position. The test is considered normal if the balloon can be expelled within 5 min, although most people with intact defecatory function should be able to expel it in less than a minute [7•, 35, 41]. This simple and inexpensive test provides an initial assessment of the rectal sensory and motor function and can identify patients with elevated sensory threshold volume or rectal hyposensitivity [43]. The disadvantage of this test includes lack of standardization [41]. In clinical practice, it is typically used to identify patients with defecatory disorders and can identify patients with dyssynergia, although the test itself is insufficient to make the diagnosis of dyssynergic defecation [41, 44]. This test is often used in conjunction with anorectal manometry.

Anorectal Manometry

High-resolution anorectal manometry has largely replaced traditional approaches (water-perfused and solid-state manometric sensors). It provides a comprehensive assessment of anorectal pressures at rest and during simulated defecation, and can provide information on rectal sensation and reflex activation of the pelvic floor [41, 45•]. The test is performed using a rectal probe with strain gauge transducers attached to a compliant balloon and a pressure-recording device. The patient is positioned in the left lateral position with the knees flexed. After a digital rectal exam, the lubricated probe is gently placed into the rectum. A baseline measurement of the anorectal pressures is performed first, followed by a volitional squeeze measurement, cough reflex test, attempted defecation, simulated defecation, rectal sensation testing, rectoanal inhibitory reflex (RAIR), as well as rectal balloon expulsion test. A full and detailed description of the test is covered elsewhere [45•]. The normal response to attempted defecation is a rise in the intrarectal pressure with a simultaneous decrease in the intra-anal pressure. Impaired expulsion forces, paradoxical anal contraction, impaired anal relaxation, or a combination of these abnormalities presents the basis for dyssynergic defecation [41]. Absent RAIR is associated with Hirschsprung's disease or intrinsic neuroenteropathy, such as in diabetics [46, 47].

Colonic Transit Study

Unlike the tests above which are aimed at diagnosing defecatory disorders, a colonic transit study evaluates the rate of stool movement through the colon (slow, normal, or rapid colonic transit). Ostensibly, colonic transit testing is meant to assess whether constipation is due to a delay in delivering the stool to the rectum or out of the rectum [48]. Three methods exist to measure colon transit: (1) solid, radiopaque marker ingestion followed by an abdominal radiograph, (2) scintigraphic colonic transit testing, and (3) ingestion of a wireless motility capsule with subsequent tracking its movement [35, 48]. Due to lower cost, wider availability, and safety, the radiopaque marker colonic transit is most commonly used in clinical practice. In one of the simplest methods using this approach, a single capsule containing 24 plastic radiopaque markers (Sitzmarks; Konsyl Pharmaceuticals, Fort Worth, TX) is ingested in the morning of day 1, and an abdominal X-ray is taken on the day of capsule ingestion and 120 h later (day 6). In subjects with normal colonic transit, there should be less than 20 % of markers retained and visible on the abdominal X-ray at day 6. Retention of more than 20 % of markers at day 6 may be indicative of STC [35, 41]. However, this test is inexact, and it is important to exclude rectal evacuation disorders prior to making the diagnosis of STC, as up to two thirds of patients with dyssynergia may retain more than 20 % of markers at day 6 [35, 41, 49].

Colonic Manometry

Colonic manometry provides a complete assessment of the overall motor activity of the colon at rest, during sleep, after waking, after meals, and after provocative stimulation (drugs, meal, or balloon distention). The test involves placing a colonic manometry catheter either through nasal intubation with migration of the probe into the colon, guide wire assisted, water-perfused probe placement, or retrograde direct probe placement [35]. This test is typically indicated for intractable constipation unresponsive to medical therapy without evidence of a rectal evacuation disorder. In such a scenario, it can guide surgical intervention including placement of diverting stoma, resection of a portion of the colon, or formation of a conduit for administration of antegrade enemas, as well as permits evaluation of the function of the excluded colon before possible closure of a diverting ostomy. Other indications for colonic manometry include evaluation of chronic intestinal pseudo-obstruction and clarification of the pathophysiology of persistent symptoms in patients with suspected Hirschsprung's disease after removal of the aganglionic segment. Colonic manometry is not widely available and is typically performed in tertiary care and research settings.

Medical Management of Chronic Constipation

Several therapeutic approaches exist for the management of chronic constipation (can be used in primary and secondary constipation) ranging from over-the-counter stool softeners to more recently developed pharmaceutical options. Despite the different available medications for chronic constipation, a significant number of patients are dissatisfied with the treatment results [50, 51]. Constipation secondary to a medical condition or a constipating medication should be managed by addressing the primary condition contributing to the development of constipation. Patients with chronic constipation due to PFD should be referred for biofeedback therapy, which has been shown to be an effective therapy that can result in improvement in quality of life in this patient group [52, 53•].

Dietary and Lifestyle Modifications

Patients with chronic constipation should generally be encouraged to increase water and fiber content in the diet and engage in regular modest exercise. The data supporting these lifestyle modifications is scant. Several studies have evaluated the relationship between increasing water intake alone and its effect on chronic constipation and have failed to demonstrate

convincing data to support the concept that increasing oral fluid intake can successfully treat the symptoms of constipation [54]. While physical activity may have an effect on bowel function and motility, controlling of other variables such as diet and personality limits the ability to draw conclusions on whether exercise is a meaningful treatment for chronic constipation. A diet high in fiber leads to increases in stool weight and accelerates intestinal transit, thereby increasing stool frequency [55]. Lack of dietary fiber may be a contributing factor in the development of constipation, and existing data, although limited, suggests that increasing fiber intake along with modest exercise is associated with reduction in the incidence of constipation [54, 56]. Additional dietary and lifestyle modifications are probably helpful for some patients with mild constipation. However, most patients referred to a gastroenterology specialist setting have more severe and chronic constipation, have often tried and failed these interventions, and are expecting additional and different management options.

Traditional Laxatives

Bulk Laxatives

Apart from dietary sources of fiber, medicinal bulking agents in the form of natural soluble fiber (e.g., psyllium and wheat dextrin), semisynthetic fiber (e.g., methylcellulose), and synthetic polymers (e.g., polycarbophil) can be used as safe and well-tolerated first-line agents in the management of chronic constipation. Fiber traps water in the gastrointestinal lumen, increasing stool weigh (bulk) and decreasing consistency. It also stimulates colonic motility and reduces transit time. Bulking agents are most effective in NTC. A standard initial dose is one heaping tablespoon of bulking agent in 8 oz of water, ideally in the morning. Abdominal distention and bloating are common adverse effects of bulking agent therapy, especially initially. This may limit their effective use in patients with bloating as one of the main complaints accompanying constipation. Bloating may be mitigated in some patients by lowering the dose and slowly increasing the amount of bulking agent ingested or by switching to a semisynthetic or synthetic agent [57].

Stool Softeners and Lubricants

Stool softeners and lubricants are anionic surfactants with emulsifying, detergent-like properties that are meant to increase the water content and lubricate the stool in order to ease defecation [55, 58]. They appear to be more effective than placebo at increasing bowel movement frequency and overall symptom improvement in patients with occasional or short-duration constipation; however, data is limited and conflicting regarding their effectiveness in the management of chronic constipation [55, 59]. Sodium dioctyl sulfosuccinate and liquid paraffin are examples of stool softeners. Liquid paraffin and mineral oil can interfere with absorption of fat-soluble vitamins and, in rare circumstances, have been associated with aspiration and lipoid pneumonia. These agents should be avoided in patients with oropharyngeal dysphagia [58, 59].

Osmotic Laxatives

The class of osmotic laxatives includes osmotic salts, also referred to as saline laxatives (e.g., magnesium hydroxide, magnesium citrate, magnesium sulfate, magnesium phosphate, and sodium phosphate salts), poorly absorbed sugars (e.g., lactulose and sorbitol), and polyethylene glycol. These agents work by osmotically inducing water movement into the intestinal lumen leading to a softer, more voluminous stool. Although osmotic salts are ingested as hypertonic solutions, osmotic equilibrium occurs as water is retained or secreted into the gut lumen. There is a potential with some osmotic laxatives for electrolyte absorption into the plasma, leading to a variety of electrolyte imbalances (e.g., hypermagnesemia or hyperphosphatemia), and these agents are not generally recommended for the treatment of chronic constipation in patients with renal compromise or cardiac insufficiency [57].

Lactulose is a synthetic disaccharide (galactose–fructose) and is nonabsorbable in humans due to the lack of intestinal fructosidase. Rather, it undergoes fermentation by colonic bacteria with resultant production of hydrogen, methane, carbon dioxide, water, lactic acid, and fatty acids. These products of fermentation lead to the osmotic effect of lactulose and stimulate intestinal secretion and motility. The production of gas from the process of bacterial fermentation also leads to the abdominal bloating and flatulence commonly observed with lactulose ingestion [57]. The evidence to support the sustained use of lactulose in the treatment of chronic constipation is scant, and its adverse effects limit its use [60].

Polyethylene glycol electrolyte solution (PEG 3350, MiraLax, Braintree Laboratories, Inc., Braintree, MA) is an electrolyte-balanced preparation that osmotically retains water molecules in the intestinal lumen, softening the stool and increasing its volume. While PEG 3350 is approved for short-term use of 2 weeks or less, it has been shown to be an effective therapy for chronic constipation [61]. It has also been shown to be safe and effective in the treatment of secondary chronic constipation due to constipating medications (Table 2) [57, 62]. A typical starting dose for PEG 3350 is 17 g (one capful) dissolved in 8 oz of water. However, PEG 3350 has been studied at substantially larger daily doses and appears to be safe and effective therapy for a substantial proportion of patients with constipation [63]. Common adverse effects include abdominal cramps, flatulence, and nausea.

Stimulant Laxatives

Stimulant laxatives act by facilitating neurotransmitter release within the colonic myenteric plexus, leading to increased intestinal motility. Additionally, they can alter fluid and electrolyte flow leading to increased intestinal secretions [59]. This class of laxatives includes diphenylmethane derivatives (bisacodyl, sodium picosulfate) and anthraquinone derivatives (senna, cascara, sagrada, and aloe). In placebo-controlled trials, bisacodyl and sodium picosulfate have been shown to increase stool frequency, improve stool consistency, and decrease the symptoms of constipation and the use of recue medications [64, 65]. Stimulant laxatives are generally well tolerated and generally do not cause electrolyte disturbances at appropriate doses, but have been associated with abdominal discomfort and cramps. Anthraquinones are associated with the development of Melanosis coli, a harmless discoloration of the colonic mucosa resulting from macrophage apoptosis and pigment deposition within months of regular use [54, 57]. Stimulant laxatives were once thought to cause damage to the myenteric plexus; however, subsequent rigorous studies demonstrated that such damage to the colon is unlikely at recommended doses [54, 57].

Newer Agents

Secretagogues

Lubiprostone is a poorly absorbed bicyclic fatty acid derived from prostaglandin E1 and is approved by the Food and Drug Administration (FDA) for chronic idiopathic constipation, opioid-induced constipation (OIC), and IBS-C in adult women. Lubiprostone activates the type-2 chloride channel (ClC-2), located on the apical surface of enterocytes, and possibly works on cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels as well [66]. Activation of ClC-2 leads to increases in intestinal fluid secretion without changing serum electrolyte levels. This leads to softening of the stool and enhanced stool passage [60, 67]. In addition to its effect on chloride channels, lubiprostone has been hypothesized to affect the smooth muscles of the gastrointestinal (GI) tract and may be associated with a dose-dependent increase in pyloric sphincter tone, potentially contributing to the development of nausea, an adverse event that has been noted in phase 3 clinical trials with this agent [67]. In multiple large, randomized, placebo-controlled clinical trials of lubiprostone in patients with IBS-C, CIC, and OIC, lubiprostone was associated with increases in spontaneous bowel movements (SBM) compared to placebo as well as significant improvements in straining effort, stool consistency, and global satisfaction with bowel function. It also showed significant and persistent improvement in constipation severity, bloating, abdominal discomfort, and improved quality of life with long-term administration in patients with CIC [68, 69, 70•, 71, 72•]. Lubiprostone is available in two dosages. The recommended dose for CIC and OIC is 24 μg twice daily, and the recommended dose for female patients with IBS-C is 8 μg twice daily [67]. Mild to moderate nausea is the most commonly reported adverse effect occurring in up to nearly 30 % of patients taking lubiprostone 24 μg twice daily. The rate of nausea development appears to be substantially mitigated with lower doses and administration in a fed state. Hence, it is recommended to take lubiprostone with food to minimize nausea. Dyspnea is an uncommon idiopathic adverse effect associated with lubiprostone and warrants discontinuation of therapy. Because of fetal loss observed with one animal model, it was recommended that women of childbearing age be tested for pregnancy prior to starting lubiprostone when it was initially marketed. However, this recommendation is no longer present in the prescribing information, and there have been no substantiated reports of fetal risk with lubiprostone over 9 years of availability. As with any medication, use during pregnancy requires a risk-benefit analysis. Lubiprostone is rated as FDA pregnancy category C. It is not clear whether lubiprostone is excreted in breast milk [67].

Linaclotide is FDA-approved for the treatment of CIC and IBS-C in adults. Linaclotide is a 14-amino acid peptide that mimics the endogenous intestinal peptides guanylin (15-amino acids) and uroguanylin (16-amino acids). They bind to and activate the guanylate cyclase-C (GC-C) receptors on the surface of enterocytes. The activation of this receptor leads to increases in intracellular cyclic guanosine monophosphate (c-GMP) levels, causing the cystic fibrosis transmembrane conductance regulator (CFTR) to allow chloride and bicarbonate secretion into the intestinal lumen with inhibition of sodium absorption. The net effect of these events is the secretion of water into the gut lumen resulting in softening of the stool and enhanced stool passage [73]. Several large, randomized, placebo-controlled clinical trials have shown linaclotide to be effective in achieving complete spontaneous bowel movements (CSBM) and SBM. A CSBM is an end point that includes the patient's qualitative assessment of completeness of a bowel movement and provides a more rigorous assessment of stool frequency than SBM, which is simply a bowel movement without the aid of a laxative. Linaclotide was also shown to improve stool frequency and consistency in patients with CIC in these trials [74–76]. Similarly, linaclotide has been shown to be effective in the management of patients with IBS-C, improving the frequency of CSBM and SBM and decreasing abdominal pain. Secondary outcomes observed with linaclotide included improved stool consistency, bloating, and straining [74, 77–79]. The linaclotide dose for CIC is 145 μg daily, while the dose for IBS-C is 290 μg daily. Unlike lubiprostone, it is recommended to take linaclotide in a fasting state. The most commonly reported adverse event

is mild to moderate diarrhea, typically reported within the first 4 weeks of therapy. Other notable reported adverse events include flatulence, abdominal pain, and abdominal distension [73]. Linaclotide, like lubiprostone, is FDA pregnancy category C.

Plecanatide is an investigational GC-C agonist, similar to linaclotide, that can bind to transmembrane enteric receptors stimulating increased c-GMP, leading to activation of the CFTR and eventually increasing intestinal secretion of fluid and chloride [55, 80]. In a phase I trial assessing safety and tolerability of escalating doses of plecanatide, it appeared to be safe and well tolerated up to the highest single dose use (48.6 mg). Adverse events were mostly GI related, suggesting that it acts locally in the GI tract. This was supported by minimal systemic absorption noted in this trial. Adverse events were comparable to placebo with mild to moderate diarrhea being the most commonly reported side effect in subjects receiving plecanatide [81]. Plecanatide was recently evaluated in a phase 2, double-blind, placebo-controlled, dose escalation, and repeated dose trial for CIC. Spontaneous bowel movement and CSBM, stool consistency, straining, abdominal discomfort, and overall relief were all improved with plecanatide [55, 82]. Diarrhea was the most common adverse event in this trial and was more common with plecanatide than placebo. A phase 3 trial assessing safety and efficacy of plecanatide with CIC is underway [55].

5-HT_4-Receptor Agonists

Serotonin (5-hydroxytryptamine) is a key regulator of gastrointestinal motility and secretion. It triggers intestinal peristalsis through activation of 5-HT_4 receptors in the enteric nervous system. Tegaserod, cisapride, and prucalopride are examples of 5-HT_4-receptor agonists. Their use is associated with stimulation of colonic and intestinal peristalsis. Tegaserod and cisapride have been withdrawn from the market. Prucalopride is approved in Europe for the treatment of chronic constipation in women who failed to respond to laxative therapy and appears to be safe and well tolerated [58].

Bile Acid Agents

Elobixibat is a novel oral agent classified as an ileal bile acid transporter (IBAT) inhibitor that inhibits ileal absorption of bile acids leading to increased flow of bile into the colon. The osmotic activity of this increased delivery of bile acids leads to increased colonic fluid and electrolyte secretion and accelerated colonic transit [55, 83, 84]. In a multicenter, randomized, double-blind, placebo-controlled, phase IIb study evaluating the efficacy and safety of three doses of elobixibat in CIC, elobixibat significantly increased spontaneous bowel movements during week 1 (the primary end point), an effect that was maintained over 8 weeks of treatment. It also significantly improved secondary end points including weekly CSBM, stool consistency, straining, and bloating. It is generally well tolerated and adverse events were largely GI in origin, including diarrhea and abdominal pain. These adverse events appeared to be dose related and accounted for most of the discontinuations in the study [55, 85]. Additional trials are needed to assess sustained efficacy and adverse events with elobixibat.

Chenodeoxycholate

Treatment of gallstones and cholestatic liver disease with bile acids has been consistently associated with diarrhea as a side effect. Utilizing this side effect, Zinsmeister et al. conducted a double-blind, placebo-controlled study on 36 female patients with IBS-C. Patients were randomized to treatment with placebo and chenodeoxycholic acid at two doses, 500 or 1000 mg daily for 4 days, to evaluate the effect of chenodeoxycholate on colonic transit and bowel function. Colonic transit was significantly accelerated compared to placebo. Furthermore, looser stool consistency, increased stool frequency, and greater ease of passage were noted with chenodeoxycholic acid compared to placebo. The most common adverse effects noted were lower abdominal cramps/pain [86]. Larger studies are needed to evaluate the effectiveness and safety of chenodeoxycholate in the treatment of CIC.

Opioid Receptor Antagonists

It has been estimated that 50–90 % of patients who use opioids have constipation. This effect is due to opioid-mediated delay in colonic transit, stimulation of nonpropulsive motor activity, increased intestinal tone, prolonged contact time leading to increased fluid absorption, and decreased electrolyte and water secretion into the intestinal lumen [80]. Peripherally acting mu-opioid receptor antagonists (PAMORAs) are used for the treatment of OIC and postoperative ileus. They do not readily cross the blood-brain barrier; thus, they diminish the peripheral mu receptor-mediated effects of opioids such as constipation, nausea, and vomiting, while maintaining analgesic effect [58]. These agents do not have a role in the treatment on non-OIC.

Methylnaltrexone bromide is approved for the treatment of OIC in patients with advanced illness, who are receiving palliative care, when response to first-line laxative therapy has not been sufficient. More recently, it was approved for OIC in adult patients with chronic non-cancer pain. It is administered subcutaneously with a rapid onset of action [87, 88]. It is important to rule out mechanical obstruction prior to administering methylnaltrexone, as there have been reports of intestinal perforation shortly after starting methylnaltrexone [89].

Alvimopan, an orally administered PAMORA, was found to be superior to placebo for OIC [90]. However, due to increased incidence of myocardial infarction in patients treated with alvimopan in a 12-month study compared to placebo, its use is restricted to short-term treatment of postoperative ileus within an accelerated recovery program [91, 92].

Naloxegol is the first approved, orally available PAMORA for OIC in non-cancer pain patients. Phase II and III studies of naloxegol in patients with OIC showed that naloxegol at doses of 12.5 and 25 mg once daily were superior to placebo at increasing SBM without interfering with the centrally mediated analgesic effects of opioids. The most reported adverse events were abdominal pain, diarrhea, nausea, and headache. Naloxegol should not be used in patients with a potential comprise to their blood-brain barrier or those on strong CYP3A4 inhibitors. Dose adjustments should be used in patients on moderate CYP3A4 inhibitors [92].

Biofeedback Therapy and Pelvic Floor Retraining

Biofeedback therapy is considered the most effective treatment for patients with dyssynergic defecation with the main purpose of restoration of a normal pattern of defecation using "operant conditioning" techniques. Pelvic floor retraining is designed to teach patients to relax the pelvic floor while straining to defecate, rather than paradoxically contracting. The goals of biofeedback are to correct the underlying pelvic floor dyssynergia and improve rectal sensory perception. This is achieved by improving abdominal push effort, facilitating pelvic floor relaxation, and expelling artificial stool. Patients typically undergo 4–6 sessions of 1 h each, during which 10–15 maneuvers are attempted per session. A manometric rectal probe is placed to provide instant feedback regarding performance and rectal and anal muscle behavior [93•, 94].

Rao et al. conducted a prospective randomized trial investigating the efficacy of biofeedback (manometric-assisted anal relaxation, muscle coordination, and simulated defecation training) with either sham feedback therapy or standard therapy for constipation (diet, exercise, laxatives) in 77 subjects (the majority were women) with CIC and dyssynergic defecation. Subjects who received biofeedback had a greater number of CSBMs, greater satisfaction with bowel function, and were more likely to discontinue the use of digital maneuvers compared to subjects receiving standard or sham feedback therapy. The symptomatic improvement was also matched by improvement in physiologic characteristics of colorectal function; assessed by anorectal manometry, balloon expulsion, and colonic transit study. The dyssynergic pattern was corrected in 79 % of patients who received biofeedback, while unchanged with the other two therapies [31]. Chiarioni et al. showed that five weekly biofeedback sessions was an effective treatment for PFD, improving patient satisfaction and stool frequency. The improvement was maintained at 24 months of follow-up. However, biofeedback was not beneficial for patients with isolated slow transit constipation [94]. In another study, these investigators evaluated the response in patients with chronic, severe PFD (who failed treatment with fiber plus enemas or suppositories up to twice weekly) to five weekly biofeedback sessions vs. polyethylene glycol plus five weekly counseling sessions in preventing constipation. They found that five biofeedback sessions were more effective than continuous PEG for treating PFD, and benefits lasted at least 2 years [30]. Hence, biofeedback should be the treatment of choice for patients with PFD.

Conclusion

Chronic constipation represents a common and important health problem. Clinicians should understand the common etiologies and pathophysiology behind chronic constipation and be able to differentiate between the different types utilizing appropriate history taking, physical examination, and available testing modalities. Numerous therapeutic interventions are available for the medical management of chronic constipation, and clinicians should tailor treatment based on the most likely etiology, patient response, and concomitant symptoms. Some experts advocate a step-wise management approach, initiating therapy with lifestyle modifications and bulking agents, proceeding to over-the-counter laxatives, and then to prescription agents in refractory patients. There are times in clinical practice when combination therapy may be required to improve patient symptoms and satisfaction, but this has not been adequately studied or documented in the medical literature to provide recommendations. Newer agents that have shown promising results in clinical trials and practice are now available, and additional novel agents are in various stages of development.

Compliance with Ethics Guidelines

Conflict of Interest Hani Sbahi declares no conflict of interest.

Brooks D. Cash reports personal fees from Takeda, Actavis, Astra Zeneca, Ironwood, and Sucampo, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Suares N, Ford A. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. Am J Gastroenterol. 2011;106(9):1582–91.
2. McCrea G, Miaskowski C, Stotts N, et al. A review of the literature on gender and age differences in the prevalence and characteristics of constipation in North America. J Pain Symptom Manag. 2009;37(4):737–45.
3. Mugie S, Benninga M, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. Best Pract Res Clin Gastroenterol. 2011;25(1):3–18.
4. Dennison C, Prasad M, Lloyd A, et al. The health-related quality of life and economic burden of constipation. PharmacoEconomics. 2005;23(5):461–76.
5. Sanchez MI, Bercik P. Epidemiology and burden of chronic constipation. Can J Gastroenterol. 2011;25(Suppl B):11B–5B.
6. Basilisco G, Coletta M. Chronic constipation: a critical review. Dig Liver Dis. 2013;45(11):886–93.
7.• Bharucha A, Pemberton J, Locke G. American Gastroenterological Association technical review on constipation. Gastroenterology. 2013;144(1):218–38. **A valuable comprehensive review of chronic constipation**.
8. Herz M, Kahan E, Zalevski S, et al. Constipation: a different entity for patients and doctors. Fam Pract. 1996;13(2):156–9.
9. Longstreth G, Thompson W, Chey W, et al. Functional bowel disorders. Gastroenterology. 2006;130(5):1480–91.
10. Gallagher P, O'Mahony D. Constipation in old age. Best Pract Res Clin Gastroenterol. 2009;23(6):875–87.
11. Andromanakos NP, Pinis SI, Al K. Chronic severe constipation: current pathophysiological aspects, new diagnostic approaches, and therapeutic options. Eur J Gastroenterol Hepatol. 2015;27(3):204–14.
12. Xu L, WY W, Jiang J, et al. Clinical benefits after soluble dietary fiber supplementation: a randomized clinical trial in adults with slow-transit constipation. Zhonghua Yi Xue Za Zhi. 2014;94(48):3813–6.
13. Voderholzer W, Schatke W, Mühldorfer B, et al. Clinical response to dietary fiber treatment of chronic constipation. Am J Gastroenterol. 1997;92(1):95–8.
14. Hammer J, Phillips S. Fluid loading of the human colon: effects on segmental transit and stool composition. Gastroenterology. 1993;105(4):988–98.
15. Stephen A, Wiggins H, Cummings J. Effect of changing transit time on colonic microbial metabolism in man. Gut. 1987;28(5):601–9.
16. Penning C, Steens J, van der Schaar P, et al. Motor and sensory function of the rectum in different subtypes of constipation. Scand J Gastroenterol. 2001;36(1):32–8.
17. Rao S, Seaton K, Miller M, et al. Psychological profiles and quality of life differ between patients with dyssynergia and those with slow transit constipation. J Psychosom Res. 2007;63(4):441–9.
18. Lembo A, Camilleri M. Chronic constipation. N Engl J Med. 2003;349(14):1360–8.
19. Mertz H, Naliboff B, Mayer E. Physiology of refractory chronic constipation. Am J Gastroenterol. 1999;94:609–15.
20. Preston D, Lennard-Jones J. Severe chronic constipation of young women: 'idiopathic slow transit constipation'. Gut. 1986;27(1):41–8.
21. He C, Burgart L, Wang L, et al. Decreased interstitial cell of Cajal volume in patients with slow-transit constipation. Gastroenterology. 2000;118(1):14–21.
22. Wedel T, Spiegler J, Soellner S, et al. Enteric nerves and interstitial cells of Cajal are altered in patients with slow-transit constipation and megacolon. Gastroenterology. 2002;123(5):1459–67.
23. Tzavella K, Riepl R, Klauser A, et al. Decreased substance P levels in rectal biopsies from patients with slow transit constipation. Eur J Gastroenterol Hepatol. 1996;8(12):1207–11.
24. Cortesini C, Cianchi F, Infantino A, et al. Nitric oxide synthase and VIP distribution in enteric nervous system in idiopathic chronic constipation. Dig Dis Sci. 1995;40(11):2450–5.
25. Vierhout ME, Schreuder HW, Veen HF. Severe slow-transit constipation following radical hysterectomy. Gynecol Oncol. 1993;51:401–3.
26. MacDonald A, Baxter J, Bessent R, et al. Gastric emptying in patients with constipation following childbirth and due to idiopathic slow transit. Br J Surg. 1997;84(8):1141–3.
27. Barnes P, Lennard-Jones J, Hawley P, et al. Hirschsprung's disease and idiopathic megacolon in adults and adolescents. Gut. 1986;27(5):534–41.
28. Tack J, Müller-Lissner S, Stanghellini V, et al. Diagnosis and treatment of chronic constipation—a European perspective. Neurogastroenterol Motil. 2011;23(8):697–710.
29. Bharucha AE, Wald A, Enck P, et al. Functional anorectal disorders. Gastroenterology. 2006;130(5):1510–8.
30. Chiarioni G, Whitehead WE, Pezza V, et al. Biofeedback is superior to laxatives for normal transit constipation due to pelvic floor dyssynergia. Gastroenterology. 2006;130:657–64.
31. Rao S, Seaton K, Miller M, et al. Randomized controlled trial of biofeedback, sham feedback, and standard therapy for dyssynergic defecation. Clin Gastroenterol Hepatol. 2007;5(3):331–8.
32. Heymen S, Scarlett Y, Jones K, et al. Randomized, controlled trial shows biofeedback to be superior to alternative treatments for patients with pelvic floor dyssynergia-type constipation. Dis Colon Rectum. 2007;50(4):428–41.
33. Henderson P, DiPalma J. Diagnosing irritable bowel syndrome: a changing clinical paradigm. South Med J. 2011;104(3):195–9.
34. Lewis S, Heaton K. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32(9):920–4.
35. Rao S, Meduri K. What is necessary to diagnose constipation? Best Pract Res Clin Gastroenterol. 2011;25(1):127–40.
36. Tantiphlachiva K, Rao P, Attaluri A, et al. Digital rectal examination is a useful tool for identifying patients with dyssynergia. Clin Gastroenterol Hepatol. 2010;8(11):955–60.
37. Rao S, Ozturk R, Laine L. Clinical utility of diagnostic tests for constipation in adults: a systematic review. Am J Gastroenterol. 2005;100(7):1605–15.
38. American College of Gastroenterology Chronic Constipation Task Force. An evidence-based approach to the management of chronic constipation in North America. Am J Gastroenterol. 2005;100 suppl 1:S1–4.
39. Cash BD, Acosta RD, Chandrasekhara V, et al. The role of endoscopy in the management of constipation. Gastrointest Endosc. 2014;80(4):563–5.
40. Gupta M, Holub J, Knigge K, et al. Constipation is not associated with an increased rate of findings on colonoscopy: results from a national endoscopy consortium. Endoscopy. 2010;42(03):208–12.
41. Remes-Troche J, Rao S. Diagnostic testing in patients with chronic constipation. Curr Gastroenterol Rep. 2006;8(5):416–24.
42. Shorvon P, McHugh S, Diamant N, et al. Defecography in normal volunteers: results and implications. Gut. 1989;30(12):1737–49.
43. Gladman M, Aziz Q, Scott S, et al. Rectal hyposensitivity: pathophysiological mechanisms. Neurogastroenterol Motil. 2009;21(5),508-e5.
44. Rao S. Dyssynergic defecation. Gastroenterol Clin N Am. 2001;30(1):97–114.
45.• Rao S, Singh S. Clinical utility of colonic and anorectal manometry in chronic constipation. J Clin Gastroenterol. 2010;44(9):597–609.

A superb review of colonic and anorectal manometry with detailed explanation on the technical aspects of the tests.

46. Deen K, Premaratna R, Fonseka M, et al. The recto-anal inhibitory reflex: abnormal response in diabetics suggests an intrinsic neuroenteropathy. J Gastroenterol Hepatol. 1998;13(11):1107–10.
47. Vorobyov G, Achkasov S, Biryukov O. Clinical features, diagnostics and treatment of Hirschsprung's disease in adults. Color Dis. 2010;12(12):1242–8.
48. Lin H, Prather C, Fisher R, et al. Measurement of gastrointestinal transit. Dig Dis Sci. 2005;50(6):989–1004.
49. Rao S, Welcher K, Leistikow J. Obstructive defecation: a failure of rectoanal coordination. Am J Gastroenterol. 1998;93(7):1042–50.
50. Johanson J, Kralstein J. Chronic constipation: a survey of the patient perspective. Aliment Pharmacol Ther. 2007;25(5):599–608.
51. Müller-Lissner S, Tack J, Feng Y, et al. Levels of satisfaction with current chronic constipation treatment options in Europe—an internet survey. Aliment Pharmacol Ther. 2012;37(1):137–45.
52. Sahin M, Dogan I, Cengiz M, et al. The impact of anorectal biofeedback therapy on the quality of life of patients with dyssynergic defecation. Turk J Gastroenterol. 2015;26(2):140–4.
53.• Lee H, Boo S, Jung K, et al. Long-term efficacy of biofeedback therapy in patients with dyssynergic defecation: results of a median 44 months follow-up. Neurogastroenterol Motil. 2015. A trial assessing the long-term efficacy of biofeedback therapy in a large group of patients with dyssynergic defecation, concluding that biofeedback therapy is durable and efficacy was maintained for more than 2 years in a sizable proportion of constipated patients with dyssynergic defecation.
54. Muller-Lissner S, Kamm M, Scarpignato C, et al. Myths and misconceptions about chronic constipation. Am J Gastroenterol. 2005;100(1):232–42.
55. Lacy B, Hussain Z, Mearin F. Treatment for constipation: new and old pharmacological strategies. Neurogastroenterol Motil. 2014;26(6):749–63.
56. Dukas L. Association between physical activity, fiber intake, and other lifestyle variables and constipation in a study of women. Am J Gastroenterol. 2003;98(8):1790–6.
57. DiPalma JA. Current treatment options for chronic constipation. Rev Gastroenterol Disord. 2004;4 Suppl 2:S34–42.
58. Tack J. Current and future therapies for chronic constipation. Best Pract Res Clin Gastroenterol. 2011;25(1):151–8.
59. Tack J, Müller–Lissner S. Treatment of chronic constipation: current pharmacologic approaches and future directions. Clin Gastroenterol Hepatol. 2009;7(5):502–8.
60. Cash BD, Lacy BE. Systematic review: FDA-approved prescription medications for adults with constipation. Gastroenterol Hepatol. 2006;2(10):736–49.
61. DiPalma J, Cleveland M, McGowan J, et al. A randomized, multicenter, placebo-controlled trial of polyethylene glycol laxative for chronic treatment of chronic constipation. Am J Gastroenterol. 2007;102(7):1436–41.
62. DiPalma J, Cleveland M, McGowan J, et al. A comparison of polyethylene glycol laxative and placebo for relief of constipation from constipating medications. South Med J. 2007;100(11):1085–90.
63. Di Palma J, Smith J, Cleveland M. Overnight efficacy of polyethylene glycol laxative. Am J Gastroenterol. 2002;97(7):1776–9.
64. Mueller-Lissner S, Kamm M, Wald A, et al. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of sodium picosulfate in patients with chronic constipation. Am J Gastroenterol. 2010;105(4):897–903.
65. Kamm M, Mueller–Lissner S, Wald A, et al. Oral bisacodyl is effective and well-tolerated in patients with chronic constipation. Clin Gastroenterol Hepatol. 2011;9(7):577–83.
66. Schiffhauer E, Vij N, Kovbasnjuk O, et al. Dual activation of CFTR and CLCN2 by lubiprostone in murine nasal epithelia. Am J Physiol Lung Cell Mol Physiol. 2013;304(5):L324–31.
67. Wilson N, Schey R. Lubiprostone in constipation: clinical evidence and place in therapy. Ther Adv Chronic Dis. 2015;6(2):40–50.
68. Johanson J, Morton D, Geenen J, et al. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. Am J Gastroenterol. 2008;103(1):170–7.
69. Fukudo S, Hongo M, Kaneko H, et al. Lubiprostone increases spontaneous bowel movement frequency and quality of life in patients with chronic idiopathic constipation. Clin Gastroenterol Hepatol. 2015;13(2):294–301. **e5**.
70.• Barish C, Drossman D, Johanson J, et al. Efficacy and safety of lubiprostone in patients with chronic constipation. Dig Dis Sci. 2009;55(4):1090–7. **This study assessed the efficacy and safety of lubiprostone in patients with chronic constipation. The authors concluded that lubiprostone produced a bowel movement in the majority of individuals within 24 h of initial dosing, with sustained improvement in frequency and other constipation symptoms over 4 weeks**.
71. Drossman D, Chey W, Johanson J, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome—results of two randomized, placebo-controlled studies. Aliment Pharmacol Ther. 2009;29(3):329–41.
72.• Cryer B, Katz S, Vallejo R, et al. A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. Pain Med. 2014;15(11):1825–34. **In this study, the authors assessed the efficacy and safety of lubiprostone 24 mg twice daily for the treatment of OIC in adult patients with non-cancer pain. The results confirmed superior efficacy of lubiprostone compared to placebo in terms of increasing SBM frequency, improvement in abdominal discomfort, straining, constipation severity, stool consistency, and patient satisfaction. In addition, lubiprostone was well-tolerated with no serious lubiprostone-related adverse events**.
73. Love B, Johnson A, Smith L. Linaclotide: a novel agent for chronic constipation and irritable bowel syndrome. Am J Health Syst Pharm. 2014;71(13):1081–91.
74. Lembo A, Schneier H, Shiff S, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med. 2011;365(6):527–36.
75. Johnston J, Kurtz C, Drossman D, et al. Pilot study on the effect of linaclotide in patients with chronic constipation. Am J Gastroenterol. 2009;104(1):125–32.
76. Lembo A, Kurtz C, MacDougall J, et al. Efficacy of linaclotide for patients with chronic constipation. Gastroenterology. 2010;138(3):886–95. **e1**.
77. Johnston J, Kurtz C, MacDougall J, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. Gastroenterology. 2010;139(6):1877–86. **e2**.
78. Rao S, Lembo A, Shiff S, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol. 2012;107(11):1714–24.
79. Chey W, Lembo A, Lavins B, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol. 2012;107(11):1702–12.
80. Wald A. Constipation. Curr Opin Gastroenterol. 2015;31(1):45–9.
81. Shailubhai K, Comiskey S, Foss J, et al. Plecanatide, an oral guanylate cyclase c agonist acting locally in the gastrointestinal tract, is safe and well-tolerated in single doses. Dig Dis Sci. 2013;58(9):2580–6.
82. Shailubhai K, Barrow L, Talluto C, et al. Plecanatide, a guanylate cyclase c agonist, improves bowel habits and symptoms associated with chronic constipation in a phase IIa clinical study. ACJ. 2011;11(S2):1174.

83. Simrén M, Bajor A, Gillberg P, et al. Randomised clinical trial: the ileal bile acid transporter inhibitor A3309 vs. placebo in patients with chronic idiopathic constipation—a double-blind study. Aliment Pharmacol Ther. 2011;34(1):41–50.
84. Wong B, Camilleri M, McKinzie S, et al. Effects of A3309, an ileal bile acid transporter inhibitor, on colonic transit and symptoms in females with functional constipation. Am J Gastroenterol. 2011;106(12):2154–64.
85. Chey W, Camilleri M, Chang L, et al. A randomized placebo-controlled phase IIb trial of a3309, a bile acid transporter inhibitor, for chronic idiopathic constipation. Am J Gastroenterol. 2011;106(10):1803–12.
86. Rao A, Wong B, Camilleri M, et al. Chenodeoxycholate in females with irritable bowel syndrome-constipation: a pharmacodynamic and pharmacogenetic analysis. Gastroenterology. 2010;139(5): 1549–58. **e1**.
87. Portenoy R, Thomas J, Moehl Boatwright M, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study. J Pain Symptom Manag. 2008;35(5):458–68.
88. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med. 2008;358(22):2332–43.
89. Mackey A, Green L, Greene P, et al. Methylnaltrexone and gastrointestinal perforation. J Pain Symptom Manag. 2010;40(1):e1–3.
90. Ford A, Brenner D, Schoenfeld P. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and meta-analysis. Am J Gastroenterol. 2013;108(10):1566–74.
91. Vaughan-Shaw P, Fecher I, Harris S, et al. A meta-analysis of the effectiveness of the opioid receptor antagonist alvimopan in reducing hospital length of stay and time to GI recovery in patients enrolled in a standardized accelerated recovery program after abdominal surgery. Dis Colon Rectum. 2012;55(5): 611–20.
92. Corsetti M, Tack J. Naloxegol, a new drug for the treatment of opioid-induced constipation. Expert Opin Pharmacother. 2015;16(3):399–406.
93.• Schey R, Cromwell J, Rao S. Medical and surgical management of pelvic floor disorders affecting defecation. Am J Gastroenterol. 2012;107(11):1624–33. **An excellent review of the diagnosis and management of different pelvic floor disorders causing constipation**.
94. Chiarioni G, Salandini L, Whitehead W. Biofeedback benefits only patients with outlet dysfunction, not patients with isolated slow transit constipation. Gastroenterology. 2005;129(1):86–97.