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## Review article: diagnosis, management and patient perspectives of the spectrum of constipation disorders.

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# Review article: diagnosis, management and patient perspectives of the spectrum of constipation disorders

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## Summary

**Background:** Chronic constipation is a common, heterogeneous disorder with multiple symptoms and pathophysiological mechanisms. Patients are often referred to a gastroenterology provider after laxatives fail. However, there is limited knowledge of the spectrum and management of constipation disorders.

**Aim:** To discuss the latest understanding of the spectrum of constipation disorders, tools for identifying a pathophysiologic-based diagnosis in the specialist setting, treatment options and the patient's perspective of constipation.

**Methods:** Literature searches were conducted using PubMed for constipation diagnostic criteria, diagnostic tools and approved treatments. The authors provided insight from their own practices.

**Results:** Clinical assessment, stool diaries and Rome IV diagnostic criteria can facilitate diagnosis, evaluate severity and distinguish between IBS with constipation, chronic idiopathic constipation and dyssynergic defecation. Novel smartphone applications can help track constipation symptoms. Rectal examinations, anorectal manometry and balloon expulsion, assessments of neuromuscular function with colonic transit time and colonic manometry can provide mechanistic understanding of underlying pathophysiology. Treatments include lifestyle and diet changes, biofeedback therapy and pharmacological agents. Several classes of laxatives, as well as prokinetic and prosecretory agents, are available; here we describe their mechanisms of action, efficacy and side effects.

**Conclusions:** Constipation includes multiple overlapping subtypes identifiable using detailed history, current diagnostic tools and smartphone applications. Recognition of individual subtype(s) could pave the way for optimal, evidence-based treatments by a gastroenterology provider.

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## 1 | INTRODUCTION

Constipation affects 15%-20% of the global population and carries a major health care burden.<sup>1,2</sup> The pathophysiology of chronic constipation is complex, exemplified by varying classifications. Patients often present with similar, overlapping symptoms.<sup>3,4</sup> Therefore, differentiation and appropriate classification of constipation types guides treatment selection.<sup>4,5</sup> Constipation is classified as primary or secondary, depending on the underlying cause.<sup>3,4</sup> Secondary constipation is associated with organic disease (eg, colonic stricture, mass or malignancy), medication use (eg, opioids, anti-cholinergic medications) or an underlying condition (eg, metabolic, thyroid or diabetic disorders), while primary constipation is a consequence of neuromuscular dysfunction of the colon or anorectal sensory-motor function.<sup>3,6</sup>

The complexity of primary constipation—and failure to respond to first-line treatments (eg, lifestyle changes and laxatives)—is why patients are referred to gastrointestinal (GI) specialists.<sup>5</sup> Constipation disorders are sometimes difficult to manage, and patients are often dissatisfied with their treatment.<sup>7</sup> Symptoms of constipation can be secondary to GI pathology, such as colonic strictures, advanced colorectal polyps or neoplasms, necessitating an age-appropriate colon cancer screening. Failure to address constipation disorders may result in symptom progression over time.<sup>8</sup>

IBS with constipation (IBS-C), functional constipation or chronic idiopathic constipation (CIC) and defecatory disorders—especially dyssynergic defecation—comprise the most common spectrum of primary constipation disorders.<sup>9</sup> IBS-C, CIC and dyssynergic defecation have overlapping symptoms.<sup>8</sup> Another growing problem is opioid-induced constipation (OIC) and, although a secondary cause of constipation, significant new knowledge in the pathophysiology and treatment of OIC is helpful for GI specialists to consider when differentiating from a primary constipation diagnosis.<sup>10</sup> Our purpose is to provide an up-to-date review on the spectrum of primary constipation disorders, focusing on understanding pathophysiology, diagnostic and clinical assessment tools, and pharmacologic and bio-feedback therapies.

## 2 | METHODS

For this review, during the period from February 2020 through December 2020, literature searches were conducted using PubMed, CINAHL and Embase to identify publications reporting on the pathophysiology, diagnostic criteria, diagnostic tools and approved treatments for constipation. Various combinations of search terms were used for IBS-C, CIC or functional constipation and defecation disorder. Review of the reference lists from the above searches provided additional references, as did additional targeted searches. In summary, 171 references were selected for inclusion in this review due to their relevance to the scope of this manuscript and based on the authors' insight, research experience and clinical practices in managing constipation.

## 3 | PATHOPHYSIOLOGY

The pathophysiology of constipation is multifactorial and varies between patients. Patients with primary constipation are classified as having one of the three overlapping subtypes: defecatory disorders, slow-transit constipation or normal transit constipation.<sup>3,4,11</sup>

Defecatory disorders are often associated with underlying dys-synergic defecation, characterised by impaired rectal evacuation from inadequate rectal propulsion forces, high anal resting pressure and/or paradoxical contraction of the anal sphincter and pelvic floor muscles during defecation or incomplete relaxation.<sup>3,4,11,12</sup> Dyssynergic defecation results from uncoordinated contraction of the abdominal and pelvic floor muscles.<sup>13,14</sup> Difficulty defecating may also be compounded by anatomical abnormalities (eg, rectoceles, intussusception) or altered rectal sensitivity.<sup>3,11</sup>

Primary slow colonic transit constipation can be caused by neuromuscular dysfunction of the colon wall that is not associated with other disorders or underlying systemic diseases.<sup>3,11</sup> Colonic motor disturbances, or myopathies, are associated with low-amplitude contraction resulting in reduced propulsion and colonic stasis leading to water reabsorption and stool hardening, accompanied by a reduced feeling of the need to defecate.<sup>3,11</sup> Colonic neuropathy, associated with disorganised or uncoordinated contraction, may include abnormal colonic sensation contributing to abdominal pain and bloating and altered neuromuscular signalling in and/or to the colonic wall.<sup>3,11</sup> The colons of patients with chronic constipation have shown a reduced number of intrinsic nerves and interstitial cells of Cajal and a decreased response to cholinergic stimulation.<sup>3,11</sup> Evidence suggests that methane gas accumulation in the GI tract, or intestinal methanogenic overgrowth, is associated with reduced colonic transit and slow transit constipation<sup>15</sup>; however, a separate study presented conflicting data where breath methane excretion was not associated with slow colonic transit.<sup>16</sup> The prevalence of methane-producing flora—and baseline methane levels—is significantly higher in patients with delayed colonic transit than with normal transit, and negatively correlate with colonic transit.<sup>17</sup>

The pathophysiology of CIC and IBS-C is multifactorial, involving visceral hypersensitivity, neuropathy along the afferent gut-brain axis, altered bile acid metabolism, neurohormonal regulation, immune dysfunction, gut microbiota dysbiosis, alterations in the epithelial barrier, secretory properties and brain and gut dysfunction.<sup>18-20</sup> These diagnoses of primary constipation are not exclusive, as patients may have co-existing defecation disorder, slow transit, CIC or IBS-C.<sup>3,11</sup> Consequently, with an unrecognised or untreated dyssynergia (or an overlapping rectal evacuation disorder), there is a potential for secondary delays in colonic transit.

Approximately, 40% of opioid-using patients report OIC regardless of opioid potency.<sup>21</sup> Without treatment, opioid-related bowel disorders, mainly constipation, significantly decrease the quality of life (QoL) and daily activities.<sup>22</sup> The robust interaction of opioids with  $\mu$ -receptors in the enteric nervous system, rather than effects of opioids in the central nervous system, results in decreased








GI transit, stimulation of non-propulsive activity, increased anal tone, decreased intestinal secretion, increased fluid adsorption and decreased rectal sensitivity. The net effort of these mechanisms induced by opioids is to cause constipation and bowel-based dysfunctions.<sup>10</sup>

## 4 | DIAGNOSTIC TOOLS

The term 'constipation' is non-specific, referring to a constellation of patient-reported symptoms describing a bowel function disturbance.<sup>23,24</sup> However, clinicians should be able to characterise

constipation's varied features.<sup>23,24</sup> Visual images of stool form, specifically the Bristol Stool Form Scale (BSFS; Figure 1), and bowel diaries are reliable methods to characterise bowel habits. A self-administered mobile phone app, Constipation Stool Diary, provides information about constipation symptoms that a patient can keep prospectively for 1-2 weeks, reducing recall bias and improving treatment response monitoring (Figure 2).<sup>25</sup>

Symptoms of chronic constipation alone do not accurately predict the underlying pathophysiology or response to treatment.<sup>26</sup> Providers should be familiar with 'alarm features' that suggest a more serious underlying health issue (eg, occult colon cancer), so appropriate testing (eg, colonoscopy) can be arranged. Alarm features include bloody stools, anaemia or iron deficiency, unintentional weight loss and family history of colorectal cancer.<sup>5,27</sup>

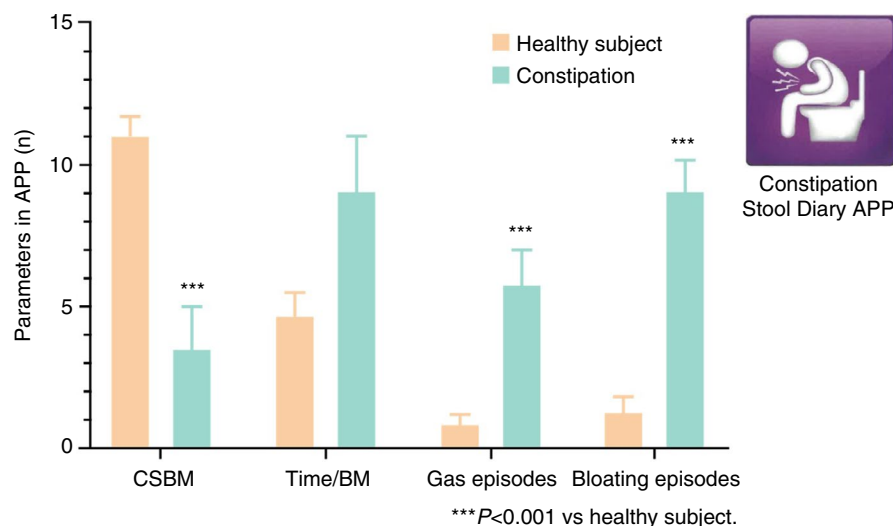
Type 1		Separate hard lumps, like nuts
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces.

**FIGURE 1** Bristol Stool Form Scale. Copyright 2000 © by Rome Foundation. All Rights Reserved

### 4.1 | Diagnostic criteria

Chronic constipation can be diagnosed via Rome IV criteria, which incorporate patient-reported symptoms, stool consistency, physical examination and motility study findings (Table 1).<sup>28</sup> In addition to stool frequency, stool shape and consistency are also key components of the diagnostic criteria, and the BSFS is recommended for characterising stool appearance (Figure 1).<sup>3,28,29</sup> The BSFS describes seven stool consistency categories correlating with colonic transit time.<sup>29</sup> Longer transit times are associated with lower BSFS scores. Sensations of incomplete emptying, straining, use of digital manoeuvres for evacuation of stool and abdominal bloating/distension can indicate underlying constipation.<sup>4</sup>

Before diagnosing primary constipation, gastroenterology providers should first rule out secondary causes of constipation. A thorough medication history can identify exacerbating medications, opioids and anti-cholinergic medications. Secondary constipation may also be a result of diabetes mellitus, chronic renal disease, dehydration, Parkinson's disease, Ehlers-Danlos syndrome or other connective tissue disorders.<sup>3,30,31</sup>



Constipation Stool Diary APP

**FIGURE 2** Parameters in Constipation Stool Diary in constipated and healthy subjects. This figure has been reproduced from Yan et al *Gastroenterology* 2020 with permission from Elsevier.<sup>25</sup> BM, bowel movement; CSBM, complete spontaneous bowel movement

**TABLE 1** Rome IV diagnostic criteria for IBS with constipation,<sup>43</sup> functional constipation<sup>43</sup> and functional defecation disorders<sup>28</sup>**IBS with Constipation (IBS-C)**

Criteria fulfilled for the last 3 mo with symptom onset  $\geq 6$  mo prior to diagnosis

Recurrent abdominal pain, on average,  $\geq 1$  d per week in the last 3 mo, associated with two or more of the following criteria:

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form (appearance) of stool

Predominant bowel habits are based on stool form on days with at least one abnormal bowel movement<sup>a</sup>

IBS with predominant constipation: More than one fourth (25%) of bowel movements with BSFS types 1 or 2 and less than one fourth (25%) of bowel movements with BSFS types 6 or 7

*Alternative for epidemiology or clinical practice:* Patient reports that abnormal bowel movements are usually constipation (like type 1 or 2 in the picture of BSFS).

**Functional constipation (Chronic idiopathic constipation [CIC])**

Criteria fulfilled for the last 3 mo with symptom onset at least 6 mo prior to diagnosis

1. Must include two or more of the following:

- Straining during more than one fourth (25%) of defecations
- Lumpy or hard stools (BSFS 1-2) more than one fourth (25%) of defecations
- Sensation of incomplete evacuation more than one fourth (25%) of defecations
- Sensation of anorectal obstruction/blockage more than one fourth (25%) of defecations
- Manual manoeuvres to facilitate more than one fourth (25%) of defecations (eg, digital evacuation, support of the pelvic floor)
- Fewer than three spontaneous bowel movements per week

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

3. Insufficient criteria for IBS-C

**Functional defecation disorders**

Criteria fulfilled for the last 3 mo with symptom onset at least 6 mo prior to diagnosis

1. The patient must satisfy diagnostic criteria for functional constipation and/or IBS-C

2. During repeated attempts to defecate, there must be features of impaired evacuation, as demonstrated by two of the following three tests:

- Abnormal balloon expulsion test
- Abnormal anorectal evacuation pattern with manometry or anal surface electromyography
- Impaired rectal evacuation by imaging

3. Subcategories F3a and F3b apply to patients who satisfy criteria for a functional defecation disorder F3a. Diagnostic criteria for inadequate defecatory propulsion

Inadequate propulsive forces as measured with manometry with or without inappropriate contraction of the anal sphincter and/or pelvic floor muscles<sup>b</sup>

F3b. Diagnostic criteria for dyssynergic defecation

Inappropriate contraction of the pelvic floor as measured with anal surface electromyography or manometry with adequate propulsive forces during attempted defecation<sup>b</sup>

Abbreviations: BSFS, Bristol Stool Form Scale; CIC, chronic idiopathic constipation; IBS-C, IBS with constipation.

<sup>a</sup>IBS subtypes related to bowel habit abnormalities can only be confidently established when the patient is evaluated off medications used to treat bowel habit abnormalities.

<sup>b</sup>These criteria are defined by age- and sex-appropriate normal values for the technique.

Primary chronic constipation can be further investigated by multiple tests. Defecatory disorders are evaluated by digital rectal examination, rectal balloon expulsion, anorectal manometry and defecography.<sup>5,6,27</sup>

or dyssynergic defecation.<sup>3,11,29,33,34</sup> If constipation is fibre- and laxative refractory, then physiological testing should be considered.<sup>29</sup>

Often, patients will have already attempted self-treatment with fibre and laxatives before seeing a health care provider.<sup>26</sup>

## 4.2 | Physical examination

Comprehensive abdominal and thorough digital rectal examinations are useful in evaluating chronic constipation.<sup>11,32</sup> Close inspection of the perianal region can reveal excoriations, haemorrhoids, fissures or masses. A lubricated finger in the anal canal can assess anal sphincter tone. Placing one hand on the lower abdomen while a finger is inserted into the anal canal assesses rectoanal incoordination

## 4.3 | Functional tests

High-resolution anorectal manometry and balloon expulsion testing are simple, inexpensive and the first anorectal physiological tests recommended for patients with laxative-refractory CIC or suspected dyssynergic defecation, with high sensitivity for detecting dyssynergia and rectal hypersensitivity or hyposensitivity.<sup>4,11,28,32</sup>

#### 4.3.1 | Balloon expulsion test

The balloon expulsion test is an office-based test assessing a patient's ability, based on time taken, to expel a water- or air-filled balloon inserted into the rectum.<sup>28,32,35,36</sup> Standardisation is lacking and methodology differs between GI motility laboratories,<sup>32,35</sup> but an expulsion time longer than 1-2 minutes is generally considered abnormal.<sup>28</sup> An uncontrolled study of patients with constipation and defecation disorders illustrated that the balloon expulsion test may identify patients with dyssynergic defecation.<sup>37</sup> Some GI motility laboratories use the balloon expulsion test to screen for dyssynergic defecation. However, a normal test does not always exclude defecatory dysfunction, and correlation with other anorectal physiological testing and defecography is lacking.<sup>5,11,29,38</sup> Patient demographics can also affect test results: males typically have a shorter expulsion time, and expulsion time lengthens with increasing age.<sup>35</sup> Therefore, corresponding tests of anorectal physiological function should be obtained.<sup>28,29</sup>

#### 4.3.2 | Anorectal manometry

Anorectal manometry assesses anorectal pressure changes during rest and simulated defecation of an intrarectal balloon, sphincter tone and rectoanal reflexes (which evaluate intrinsic and extrinsic innervation, and rectal compliance and sensitivity).<sup>5,28,29,32</sup> Although more expensive, high-resolution anorectal manometry using a six-sensor, solid-state probe permits easier calibration and shorter procedure time compared to conventional water-perfused anorectal manometry.<sup>39</sup> Anorectal manometry is useful in diagnosing dyssynergic or disordered defecation and other neuromuscular and sensory problems, and identifying patients who may benefit from biofeedback therapy.<sup>5,32,40,41</sup>

While effective and widely used, anorectal manometry has limitations. Substantial variations in clinical practice in methodologies used for the balloon expulsion test and anorectal manometry<sup>32,36</sup> demand prompt efforts to standardise testing protocols.<sup>36,40</sup> A standardised protocol of high-resolution anorectal manometry can characterise dyssynergic defecation subtype of rectoanal incoordination and guide therapists providing corrective biofeedback therapy treatment.<sup>36</sup> Furthermore, patient cooperation is key,<sup>11</sup> the procedure may be embarrassing<sup>11</sup> and test performance may not accurately replicate the actual act of defecation.<sup>28</sup> If the balloon expulsion or anorectal manometry test fails to diagnose or exclude a strongly suspected defecatory disorder, defecography is recommended.<sup>11,28</sup>

#### 4.3.3 | Defecography

Defecography examines both the function and structure of the anorectum and the pelvic floor during voluntary defecation.<sup>28,29</sup> Defecography is performed in specialist centres, using X-ray

(barium) or magnetic resonance imaging.<sup>28,32,35</sup> X-ray defecography assesses rectal wall structure and pelvic floor motion while seated. Magnetic resonance imaging defecography evaluates all pelvic compartments in the semi-recumbent position, which may not replicate the everyday practice of defecation.<sup>35</sup> These tests can determine if chronic constipation is associated with incomplete anal opening, impaired puborectalis relaxation or contraction, abnormal perineal descent and anatomical abnormalities (eg, rectocele, prolapse or intussusception).<sup>5,29</sup>

### 4.4 | Assessing colonic transit time

Slow colonic transit time can contribute to constipation and is assessed by measuring the time taken for content to move through the GI system.<sup>32</sup> Colonic transit assessment is recommended in the evaluation of laxative-refractory constipation.<sup>11,32</sup> Specialist centres evaluate colonic transit time either by radiopaque markers, wireless motility capsules or by scintigraphy.<sup>5,11,27,28,42</sup> Colonic transit tests should be performed while the patient is not taking a laxative.<sup>43</sup>

#### 4.4.1 | Radiopaque marker test

Radiopaque marker testing is widely accessible, non-invasive, inexpensive and the most common option for assessing colonic transit time.<sup>5,28,29,42</sup> In a radiopaque marker test, the patient ingests a dissolvable capsule containing 20-50 plastic markers.<sup>42</sup> The radiopaque markers are visible on X-ray. Transit time is calculated from abdominal radiographic images captured at set time points in the days following capsule ingestion.<sup>42</sup> Variations in the radiopaque marker test are used in gastroenterology clinical practice.<sup>42</sup> The most commonly applied method involves administering a capsule containing 20-24 markers on day 1, followed by abdominal radiograph imaging after 5 days<sup>29,42</sup>; retention of >20% of ingested markers indicates slow colonic transit.<sup>29</sup>

#### 4.4.2 | Wireless motility capsule test

Wireless motility capsules enable radiation-free, continuous monitoring of the intraluminal pH, pressure and temperature while passing through the GI tract.<sup>29,42,44</sup> Signals from the capsule are transmitted to a receiver the patient wears. After capsule ingestion following an overnight fast, patients record events (eg, meals, bowel movements, symptoms) over 3-5 days by pressing a receiver button and maintain a diary.<sup>44</sup> Results have demonstrated good correlation with radiographic tests.<sup>28,44,45</sup> Wireless motility capsules provide a comprehensive picture with other regional GI transit times (gastric emptying time, small-bowel transit time) and whole-gut transit time.<sup>44,46</sup> The capsule measures colonic transit time by detecting pH changes while moving through the gut.<sup>29,44</sup>



Demographics and study protocols can influence test findings.<sup>47</sup> Transit times are shorter among males and can vary with the menstrual cycle.<sup>47</sup>

#### 4.4.3 | Scintigraphy

Scintigraphy uses repeated imaging of ingested radioisotopes over consecutive days to calculate overall and regional colonic transit times.<sup>29,42</sup> A range of  $\gamma$ -emitting isotopes, administered in varying vehicles, may be used.<sup>42</sup> Scintigraphy testing is conducted at a few specialised centres, due to the need for specialist equipment and use of short-lived radioactive isotopes.<sup>42</sup>

#### 4.4.4 | Colonic manometry

In cases of severe slow-transit constipation and suspected colonic inertia, ambulatory 24-hour colonic manometry following a standardised protocol can help distinguish between underlying colonic myopathy and neuropathy, facilitating appropriate management.<sup>48</sup> Like scintigraphy, colonic manometry is limited to a few, specialised centres.

### 5 | DIAGNOSTIC FEATURES

#### 5.1 | Chronic idiopathic constipation

CIC is estimated to affect 14% of the global population.<sup>1</sup> Patients with CIC may report lumpy or hard stools (BSFS type 1-2) and infrequent bowel movements (<3 per week). Straining and abdominal bloating may be present. Pain may also be present, but it would not be predominant.<sup>43</sup> Evaluation of patient's history may find sensation of incomplete evacuation or anorectal obstruction, and patients may report using manual manoeuvres to facilitate defecations. Discussion with the patient may reveal limited physical activity, QoL complaints, attempted use of laxatives and infrequent loose stools without the use of laxatives. A rectal examination and routine blood tests would likely be normal and there may be no immediate indication of alarm features or physical abnormalities. More invasive diagnostic tests may be necessary if symptoms are not relieved with prescription therapy. In patients with laxative-refractory constipation, colonic transit assessment may be informative.

#### 5.2 | IBS with constipation

Approximately 5.2% of the North American population is estimated to experience IBS-C.<sup>49</sup> In order to diagnose IBS-C based on the Rome IV criteria, a review of the patient's medical history would reveal recurrent abdominal pain associated with defecation, reductions in stool frequency and/or a change in stool consistency.<sup>43</sup> Assessment

of a patient's stools via BSFS would reveal more than 25% of bowel movements with BSFS types 1 or 2 and less than 25% of bowel movements with BSFS types 6 or 7.<sup>43</sup> Predominant abdominal pain would likely distinguish IBS-C from CIC. Laxatives may help improve bowel movement frequency, but they may not improve abdominal symptoms (eg, bloating and pain). Digital rectal examination, anorectal manometry and balloon expulsion would determine the coexistence of disordered or dyssynergic defecation.

#### 5.3 | Defecatory disorder

As with CIC, patients may have infrequent and hard bowel movements, bowel movements associated with excessive straining, or a feeling of incomplete evacuation, and may use digital evacuation manoeuvres. Laxatives may not improve feelings of incomplete evacuation, straining and hard stools. A detailed history may reveal natural birth experience in women. Digital rectal examination, rectal balloon expulsion, anorectal manometry and defecography would help diagnose defecatory disorders.<sup>27</sup> In a digital rectal examination, a patient may have a normal sphincter tone at rest, but when asked to push and bear down may exhibit paradoxical contraction of anal sphincter with no perineal descent, suggesting dyssynergia.<sup>34</sup> The patient may be unable to pass the balloon expulsion test,<sup>37</sup> and results from anorectal manometry would show consistency with dyssynergic defecation. Biofeedback therapy using visual manometry-based feedback would likely be helpful.

### 6 | TREATMENT

The initial management approach to IBS-C and CIC tends to be similar, but therapy response varies between the two conditions.<sup>9</sup> For example, stimulant laxatives and polyethylene glycol (PEG) can be effective for CIC but not for IBS-C.<sup>9</sup> The symptomatology of defecatory disorders, such as dyssynergic defecation, can overlap with IBS-C and CIC; however, symptoms of excessive straining, feeling of incomplete evacuation and use of digital manoeuvres to defecate are more prevalent. Defecatory disorders are less likely to respond to laxative therapy and more likely to require biofeedback therapy.<sup>2</sup>

#### 6.1 | Lifestyle and dietary modifications

Initial therapy for chronic constipation includes lifestyle and dietary modifications (eg, increasing fluid and fibre intake) and physical activity.<sup>28,29,32</sup> Little evidence suggests that increasing fluid intake alone improves stool consistency among adequately hydrated patients.<sup>28,29,50</sup> Instead, increased fluid intake is most beneficial when combined with additional fibre in patients with mild constipation.<sup>28,32,50</sup>

Increasing fibre intake, which should be done gradually to prevent abdominal distension,<sup>11,28,32</sup> may improve constipation by

stimulating the gut mucosa to secrete water and mucus and improve stool consistency by increasing its water-holding capacity.<sup>29</sup> However, not all constipation patients benefit from additional dietary fibre.<sup>50</sup> Insoluble fibre (eg, fibre in wheat bran and whole grains) may worsen symptoms of abdominal pain, distension and flatulence in some patients.<sup>28,29,32</sup> Fruit fibre (eg, prunes<sup>51</sup>) or mixed soluble fibre<sup>52</sup> has demonstrated a short-term efficacy in the management of chronic constipation, somewhat better than psyllium. In a recent randomised controlled trial of natural treatments for CIC in 79 patients, kiwifruit, psyllium and prunes were found to be effective.<sup>53</sup>

Physical activity has been associated with reduced GI transit times.<sup>50</sup> Although exercise alone does not appear to improve constipation, patients report improved QoL and a reduction in symptom severity.<sup>50</sup>

## 6.2 | Pharmacological therapy

### 6.2.1 | Laxatives

Laxatives are an inexpensive, widely available and often over-the-counter (OTC) treatment option for chronic constipation refractory to lifestyle and dietary modifications.<sup>11,32</sup> Laxatives can improve stool consistency, increase stool frequency and reduce defecation straining.<sup>54</sup>

#### *Osmotic laxatives*

Osmotic laxatives, such as PEG, lactulose, sorbitol, glycerol and magnesium salts, contain non-absorbable ions or molecules.<sup>28,32</sup> These compounds create an osmotic gradient that promotes water and electrolyte secretion into the intestinal lumen, increasing faecal volume and improving peristalsis.<sup>29,32</sup> Most studies have focused on PEG, which has demonstrated superiority over placebo and lactulose in improving symptoms of chronic constipation.<sup>29,50</sup> PEG treatment shows greater resolution of constipation symptoms,<sup>55,56</sup> improved stool consistency and frequency,<sup>55-57</sup> shorter GI transit time,<sup>57</sup> less straining,<sup>55-57</sup> and less severe abdominal bloating and pain compared with placebo.<sup>55</sup> PEG is also better than lactulose in improving stool consistency and frequency, reducing abdominal pain, and need for additional constipation-related treatment.<sup>58,59</sup> Improvements in bowel movements, stool consistency and straining with PEG treatment have also been observed in patients with IBS-C, though abdominal pain is largely unaffected.<sup>50,60,61</sup> Osmotic laxatives are generally well tolerated.<sup>32,55,60</sup> The most common adverse events (AEs) are abdominal pain and distension, diarrhoea, nausea, flatulence and vomiting.<sup>28,56,57,61</sup> Magnesium compounds should be used with caution in patients with renal impairment.

#### *Stimulant laxatives*

Stimulant laxatives are recommended after patients have failed to respond to osmotic laxatives.<sup>11,29</sup> Diphenylmethane derivatives (eg, bisacodyl, sodium picosulfate) and anthraquinones (ie, sennosides, cascara) are inactive, non-absorbable glycosides that stimulate fluid,

electrolyte secretion and peristalsis upon activation by glycosidases in the colon.<sup>28,29,32,50</sup> Stimulant laxatives are commonly used for patients with CIC and IBS-C, though large controlled studies are lacking.<sup>29,50</sup> Both bisacodyl and sodium picosulfate can improve stool consistency and frequency, straining and QoL compared with placebo in CIC patients in randomised controlled trials.<sup>62-64</sup> The most common AEs with stimulant laxatives include diarrhoea, abdominal pain, nausea, vomiting and headache.<sup>28,32,62</sup>

### 6.2.2 | Prokinetic and prosecretory agents

Table 2 and Figure 3 detail the mechanisms of action by which the following types of prokinetic and prosecretory agents improve constipation symptoms.

#### *Guanylate cyclase-C receptor agonists*

Guanylate cyclase-C (GC-C) receptors are transmembrane proteins expressed by intestinal epithelial cells and help maintain bowel function by regulating fluid and electrolyte balance in the gut.<sup>65</sup> Activated GC-C receptors facilitate the production of an ion gradient between the intestinal membrane and intestinal lumen that promotes net water movement into the gut<sup>27,66</sup> by simultaneous activation of cystic fibrosis transmembrane conductance regulator channels and inhibition of sodium/hydrogen exchanger isoform 3 channels.<sup>65,67</sup> Furthermore, GC-C receptor activation helps maintain the intestinal mucosal barrier, prevent inflammation and attenuate visceral pain sensations.<sup>67</sup>

The GC-C receptor is activated by the hormones uroguanylin and guanylin and by heat-stable enterotoxins produced by diarrhoeagenic bacteria.<sup>67</sup> Uroguanylin and guanylin both have two disulphide bonds resulting in a flexible structure with active forms stabilised at a specific pH.<sup>67</sup> Uroguanylin binds more readily to GC-C receptors in slightly acidic conditions of the duodenum and jejunum (pH 5-6), while guanylin binds to GC-C receptors in more neutral to slightly basic conditions of the ileum and the colon (pH 7-8).<sup>65,67</sup> In contrast to uroguanylin and guanylin, heat-stable enterotoxins produced by diarrhoeagenic bacteria are stabilised by a third disulphide bond, producing a more stable and higher affinity structure.<sup>67</sup> Heat-stable enterotoxins lack pH-sensitive amino acids, allowing for GC-C binding throughout the GI tract without being affected by gut pH.<sup>67</sup>

GC-C also helps regulate pain experienced in patients with chronic constipation, especially those with IBS-C.<sup>26,68</sup> Activation of GC-C inhibits nociception in the gut, reducing pain.<sup>68</sup> GC-C is a target for pharmacological therapy because activating this receptor can increase fluid secretion and accelerate colonic transit time, restoring normal bowel function.<sup>65,68</sup> Furthermore, a recent report has demonstrated reduced uroguanylin levels in IBS-C and CIC patients when compared to healthy control subjects during fasting and after meals.<sup>69</sup>

Linacotide, a synthetic analogue of exogenous diarrhoeagenic bacterial heat-stable enterotoxins, and plecanatide, a synthetic



**TABLE 2** Mechanism of action of pharmacological treatments for chronic constipation

Drug	Recommended dose <sup>a</sup>	Mechanism of action		Efficacy	Adverse events
Polyethylene glycol	Non-prescription	Osmotic laxative	<ul style="list-style-type: none"><li>Creates an osmotic gradient that promotes water and electrolyte secretion into the intestinal lumen</li></ul>	<ul style="list-style-type: none"><li>Improves stool consistency and frequency<sup>55,57</sup></li><li>Reduces straining<sup>55,57</sup></li></ul>	<ul style="list-style-type: none"><li>Abdominal pain and distension, diarrhoea, nausea, flatulence, vomiting<sup>28,29,56,61</sup></li></ul>
Bisacodyl	Non-prescription	Stimulant laxative	<ul style="list-style-type: none"><li>Stimulates water and electrolyte secretion, and peristalsis</li></ul>	<ul style="list-style-type: none"><li>Improves stool consistency and frequency, straining and QoL<sup>62-64</sup></li></ul>	<ul style="list-style-type: none"><li>Diarrhoea, abdominal pain, nausea, vomiting, headache<sup>28,32,62</sup></li></ul>
Sodium picosulfate	Non-prescription				
Anthraquinones	Non-prescription				
Plecanatide	CIC or IBS-C: 3 mg q.d.	GC-C agonist	<ul style="list-style-type: none"><li>Increases intracellular cyclic guanosine monophosphate, creating an ion gradient that promotes fluid secretion</li><li>Inhibits colon nociception</li></ul>	<ul style="list-style-type: none"><li>Improves stool consistency and frequency, reduces straining and abdominal discomfort, improves QoL<sup>54,70-82</sup></li><li>Reduces abdominal pain, bloating and cramping<sup>71-73,78,80-83</sup></li></ul>	<ul style="list-style-type: none"><li>Diarrhoea<sup>54,70-82,84,85</sup></li></ul>
Linaclotide	CIC: 145 mcg q.d. and 72 mcg q.d. IBS-C: 290 mcg q.d.				
Prucalopride	CIC: 2 mg q.d. <sup>b</sup>	5-HT <sub>4</sub> agonist	<ul style="list-style-type: none"><li>Accelerates GI motility</li></ul>	<ul style="list-style-type: none"><li>Improves constipation symptoms, including stool consistency and frequency, straining QoL<sup>96-98,167</sup></li></ul>	<ul style="list-style-type: none"><li>Nausea, abdominal pain, diarrhoea, headache<sup>54,96-98,101,102</sup></li><li>Cardiovascular events<sup>93</sup></li></ul>
Tegaserod	IBS-C: 6 mg b.i.d. <sup>c</sup>				
Tenapanor	IBS-C: 50 mg b.i.d.	Sodium/hydrogen exchanger isoform 3 inhibitor	<ul style="list-style-type: none"><li>Creates an ion gradient that promotes water and sodium secretion into the intestinal lumen</li></ul>	<ul style="list-style-type: none"><li>Improves constipation symptoms, including stool consistency and frequency, and abdominal pain<sup>103</sup></li></ul>	<ul style="list-style-type: none"><li>Diarrhoea<sup>103</sup></li></ul>
Lubiprostone	CIC: 24 mcg b.i.d. IBS-C: 8 mcg b.i.d. <sup>d</sup>	Type-2 chloride channel activator	<ul style="list-style-type: none"><li>Creates an ion gradient that promotes water and sodium secretion into the intestinal lumen</li></ul>	<ul style="list-style-type: none"><li>Improves stool consistency and frequency, reduces straining, bloating and pain<sup>54,113-122</sup></li></ul>	<ul style="list-style-type: none"><li>Nausea, diarrhoea<sup>54,113-118,121,122</sup></li></ul>

Abbreviations: b.i.d., twice daily; CIC, chronic idiopathic constipation GC-C, guanylate cyclase-C; GI, gastrointestinal; IBS-C, IBS with constipation; q.d., once daily; QoL, quality of life.

<sup>a</sup>Prescription doses are based on US Food and Drug Administration approval. Not all prescription therapies are approved outside the United States; treatment options should take into account therapy availability.

<sup>b</sup>Indicated for patients with CIC (2 mg q.d.) or for patients with severe renal impairment (1 mg q.d.)

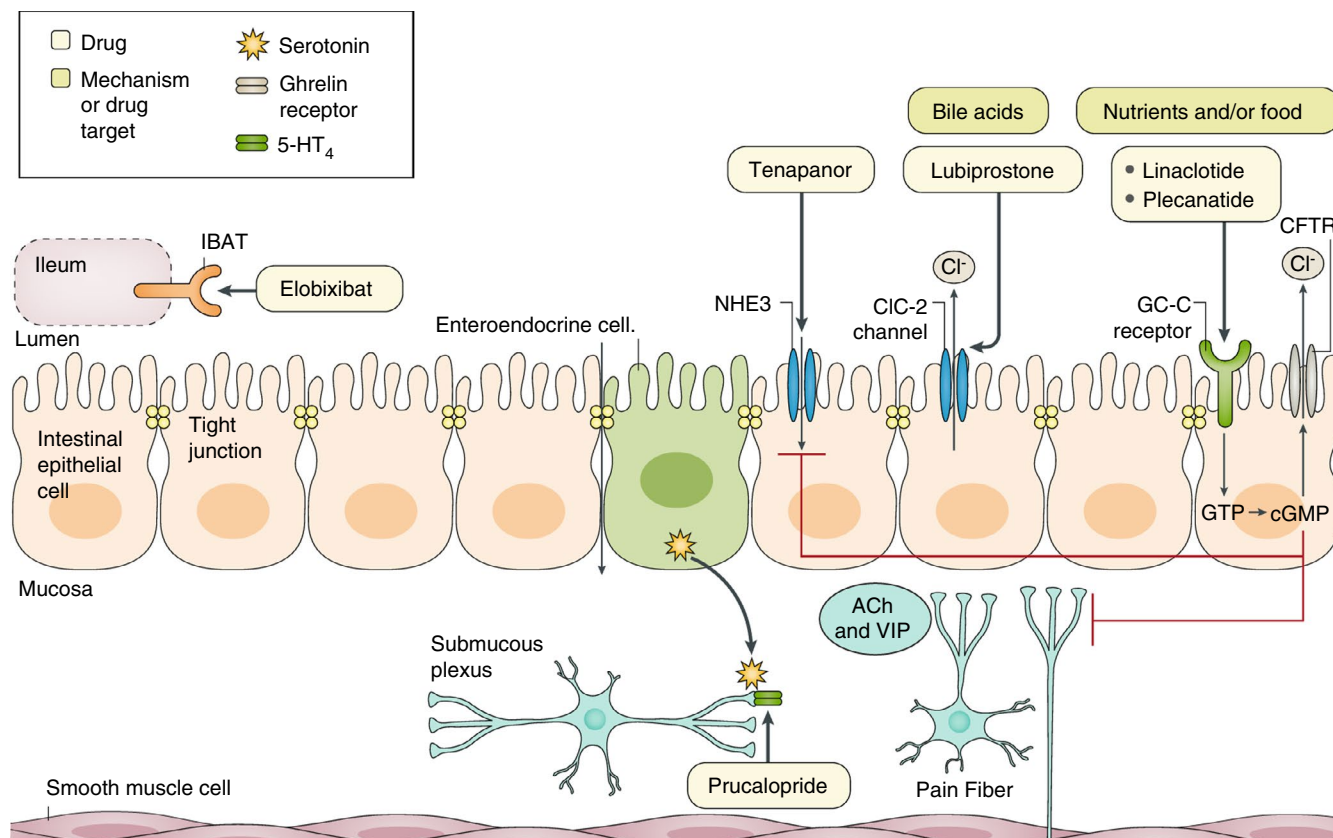
<sup>c</sup>Indicated for women aged <65 y.

<sup>d</sup>Indicated for women aged ≥18 y.

uroguanylin analogue, are GC-C agonists approved by the US Food and Drug Administration for the treatment of CIC and IBS-C.<sup>66</sup> In clinical studies, linaclootide and plecanatide significantly improved stool consistency and frequency, and reduced straining, in patients with CIC or IBS-C.<sup>54,70-81</sup> Patients also report improvements in abdominal discomfort, constipation severity and QoL,<sup>54,70,73-79,82,83</sup> with sustained efficacy over 24 and 52 weeks of treatment.<sup>82</sup> Linaclootide and plecanatide also reduce abdominal pain, bloating and cramping in patients with IBS-C.<sup>71,72,78,80-83</sup> Improvements in IBS-C symptoms were maintained over 12 and 26 weeks of treatment.<sup>83</sup> Japanese patients with IBS-C may require a higher dose of linaclootide, possibly due to differences in GC-C polymorphisms, bacterial proteases that metabolise linaclootide and/or diet compared with Western patients.<sup>82</sup>

Linaclootide and plecanatide are well tolerated. Diarrhoea is the most frequent AE, but is generally mild or moderate in severity

and occurs during the first 4 weeks of treatment.<sup>54,70-82,84,85</sup> No head-to-head trials have been conducted, and so direct comparisons cannot be made between the products; however, rates of diarrhoea reported in clinical trials of linaclootide were higher relative to those in plecanatide trials.<sup>71,73,76-79</sup> While this may be related to the similarity of plecanatide to endogenous uroguanylin and linaclootide to heat-stable enterotoxins,<sup>67</sup> there were also differences between the plecanatide and linaclootide study designs that should be considered. Linaclootide, but not plecanatide, trials permitted dose interruptions (ie, patients could halt treatment to resolve a diarrhoea AE), which may have contributed to artificially lower rates of discontinuation due to diarrhoea. Additionally, while in both trials any verbatim report of 'diarrhoea' was recorded as an AE, in plecanatide studies, an extra level of scrutiny was added. When a patient reported increased stool frequency or looser stools, an assessment of 'bothersome' was made to determine if



**FIGURE 3** Mechanism of action of agents used for the treatment of constipation. This figure has been modified from Simrén et al *Nature Reviews Gastroenterology & Hepatology* 2018 with permission from Springer Nature Customer Service GmbH: Wiley.<sup>171</sup> ACh, acetylcholine; CFTR, cystic fibrosis transmembrane conductance regulator; CIC-2, type-2 chloride channel; GC-C, guanylate cyclase-C; IBAT, ileal bile acid transporter; NHE3, sodium/hydrogen exchanger 3; VIP, vasoactive intestinal polypeptide

this report should be recorded as diarrhoea AE or a desired effect of the drug.<sup>86</sup>

#### Serotonin agonists

Serotonin (5-hydroxytryptamine) is a gut neurotransmitter that promotes motility via several serotonin receptor subtypes in the GI tract.<sup>28,87</sup> Serotonin controls gut smooth-muscle contractions and relaxations.<sup>88</sup> Patients with IBS-C may have dysfunctional serotonin neurotransmission in the gut.<sup>87,88</sup> In a healthy individual, serotonin plasma levels increase after food consumption; however, in IBS-C patients, there may be limited or no response.<sup>88,89</sup> Alternatives in serotonin transporter gene polymorphism in IBS and in constipation have been reported.<sup>90</sup> This dysfunctional serotonin signalling may be associated with altered colonic transit.<sup>89</sup> In patients with slow-transit constipation, levels of serotonin-immunoreactive cells are significantly lower, so cell secretory indexes are decreased in these patients' colons.<sup>91</sup>

Several agents have been developed that target the serotonin receptor 5-HT<sub>4</sub> to promote peristalsis and secretion.<sup>92,93</sup> Prucalopride and velusetrag (currently under clinical investigation) are selective, high-affinity 5-HT<sub>4</sub> agonists that increase GI motility and reduce colonic transit times.<sup>92-94</sup> Earlier 5-HT<sub>4</sub>

agonists, including cisapride and tegaserod, had poor selectivity and low affinity for the 5-HT<sub>4</sub> receptor, were associated with serious cardiovascular AEs, and, consequently, market withdrawal.<sup>92,93</sup> After data re-examination, tegaserod has been re-approved for the treatment of IBS-C in women <65 years old, with a contraindication in patients with a history of cardiovascular issues.<sup>95</sup> In randomised, placebo-controlled phase 3 studies, prucalopride was superior to placebo in improving symptoms, stool consistency and frequency, and reduced straining on defecation in patients with CIC.<sup>96-98</sup> Improvements in disease severity and QoL,<sup>96-98</sup> with patient satisfaction of bowel pattern, were noted and treatment efficacy was maintained for ≥18 months.<sup>99</sup> Prucalopride's efficacy for improving symptoms of constipation was confirmed in several integrated analyses and meta-analyses; however, no evidence has been published demonstrating efficacy for pain so prucalopride is not approved for the treatment of IBS-C.<sup>54,100-102</sup>

Prucalopride-associated AEs include GI complaints (nausea, abdominal pain, diarrhoea), flatulence and headache.<sup>54,96-98,100-102</sup> However, prucalopride is well tolerated, with AEs generally being mild, transient and resolving after the first day of treatment.<sup>96,99,102</sup>

### *Sodium/hydrogen exchanger isoform 3 inhibitors*

Inhibition of GI sodium/hydrogen exchanger isoform 3 expressed on the apical surface of the small intestine and colon reduces absorption of sodium from the small intestines and colon.<sup>103</sup> This results in water secretion into the intestinal lumen, increases intestinal transit time and softens stool consistency. Tenapanor, a sodium/hydrogen exchanger isoform 3 inhibitor, is approved by the US Food and Drug Administration for IBS-C treatment.<sup>103</sup>

In a phase 3 study, patients treated with tenapanor demonstrated improvements in stool frequency and reductions in abdominal pain.<sup>103</sup> Diarrhoea was the most common adverse reaction, with treatment-related diarrhoea reported in 13.3% of tenapanor-treated patients.<sup>103</sup>

### *Bile acid modulation*

Dysfunction in the enterohepatic circulation of bile acids can cause constipation.<sup>87</sup> Bile acids that are not absorbed in the terminal ileum can stimulate water and electrolyte secretion in the colon and directly contribute to colonic motility independent of secretory effects.<sup>104</sup> A subset of patients with IBS-C may exhibit lower bile acid levels in their stools than in those of healthy controls and of patients with diarrhoea-predominant IBS,<sup>87</sup> which may be attributed to altered bile acid synthesis in these patients.<sup>105</sup> Modulation of the bile acid cycle may help treat chronic constipation and involves bile acid supplementation or inhibition of the ileal bile acid transporter. Sodium chenodeoxycholate is a bile salt that can accelerate colonic transit times and improve stool consistency and frequency in patients with chronic constipation, including IBS-C.<sup>106,107</sup>

Elobixibat (approved in Japan) is a minimally absorbed, highly selective ileal bile acid transporter inhibitor. By inhibiting the active reabsorption of bile acids in the ileum, elobixibat increases bile acid concentrations in the colon, promoting fluid secretion and motility.<sup>108</sup> Elobixibat increases stool frequency and improves constipation-associated symptoms, including stool consistency, constipation severity, straining and abdominal bloating in CIC and IBS-C patients.<sup>108-110</sup>

Both sodium chenodeoxycholate and elobixibat are generally well tolerated. AEs are typically mild and GI-related, most commonly abdominal pain and diarrhoea.<sup>107-110</sup> Given elobixibat demonstrates minimal systemic absorption,<sup>110</sup> increased bile acids may stimulate propagated contractions in the colon, resulting in abdominal pain and cramping.<sup>111</sup>

### *Chloride channel activators*

Chloride channels located on intestinal epithelial cells regulate intestinal motility and fluid secretion.<sup>92</sup> Activation of type-2 chloride channels triggers the release of chloride ions into the intestinal lumen.<sup>92</sup> The resulting ion gradient promotes sodium and water release into the lumen, increasing stool volume and GI motility while reducing colonic transit time.<sup>92</sup>

Lubiprostone, a bicyclic fatty acid and a prostaglandin E1 analogue, is a locally acting selective type-2 chloride channel agonist.<sup>28,32,92,112</sup> Lubiprostone has demonstrated efficacy in improving

stool consistency and frequency and in reducing straining, bloating and constipation severity in patients with CIC or IBS-C.<sup>7,54,113-121</sup> Lubiprostone treatment also reduces abdominal pain/discomfort and improves QoL for patients with IBS-C.<sup>115,117,118,120,121</sup> Improvements are maintained with long-term treatment.<sup>113,117,120</sup>

GI-related AEs are most common with lubiprostone treatment (predominantly nausea and diarrhoea), though headaches were also reported.<sup>54,113-118,121,122</sup> AEs tend to be mild or moderate in intensity and short lived.<sup>113-115,117,118,121</sup> A recent study using pooled trial data demonstrated that lubiprostone did not affect electrolyte homeostasis in the short or long term.<sup>123</sup>

### *Opioid receptor antagonists*

The mechanism by which opioid medications induce constipation is complex, involving peripheral and central effects. Peripheral activation of  $\mu$ -opioid receptors in the stomach and intestines inhibits both excitatory and inhibitory neural pathways, diminishing peristalsis and colonic transit time and delaying gastric emptying.<sup>124</sup> Evidence for a central mechanism is supported by a study in rats where intracerebroventricular morphine administration inhibited GI propulsion.<sup>124</sup> In patients with laxative-refractory OIC, opioid receptor antagonists with peripheral or peripheral and central action may be used. Although OIC is a secondary cause of constipation, many of which may be relieved by treating the primary problem, it is the only secondary cause of constipation with specific therapies and is potentially reversible with treatment (unlike other secondary causes). Several therapies for OIC are approved by the US Food and Drug Administration.<sup>125</sup> The American Gastroenterological Association's guidelines on the management of OIC distinguishes between traditional laxatives and peripherally acting  $\mu$ -opioid receptor antagonists and other prescription therapies for this condition. These guidelines recommend traditional laxatives (including PEG) as first-line treatment for OIC, while peripherally acting  $\mu$ -opioid receptor antagonists and other prescription therapies are recommended for patients who fail traditional laxatives.<sup>126</sup> Meta-analysis of the safety and efficacy of current OIC treatments has recently been published.<sup>127</sup>

## **6.3 | Biofeedback therapy for dyssynergic defecation**

Biofeedback therapy is a robust treatment for dyssynergic defecation diagnosed by symptoms and anorectal motility testing, receiving a Grade A recommendation by the American and European Societies of Neurogastroenterology and Motility.<sup>128</sup> Multiple randomised controlled studies have proven that four to six sessions of electromyography or manometry-based biofeedback therapy carries a 70%-80% efficacy rate for dyssynergic defecation compared to standard treatment,<sup>129</sup> diltiazem<sup>130</sup> or laxatives.<sup>131</sup> Furthermore, biofeedback therapy, incorporating rectoanal coordination, simulated defecation and sensory conditioning, is durable, and separate studies have shown a sustained response for 12 and 44 months.<sup>132,133</sup> Severe constipation, digital facilitation of defecation, delayed

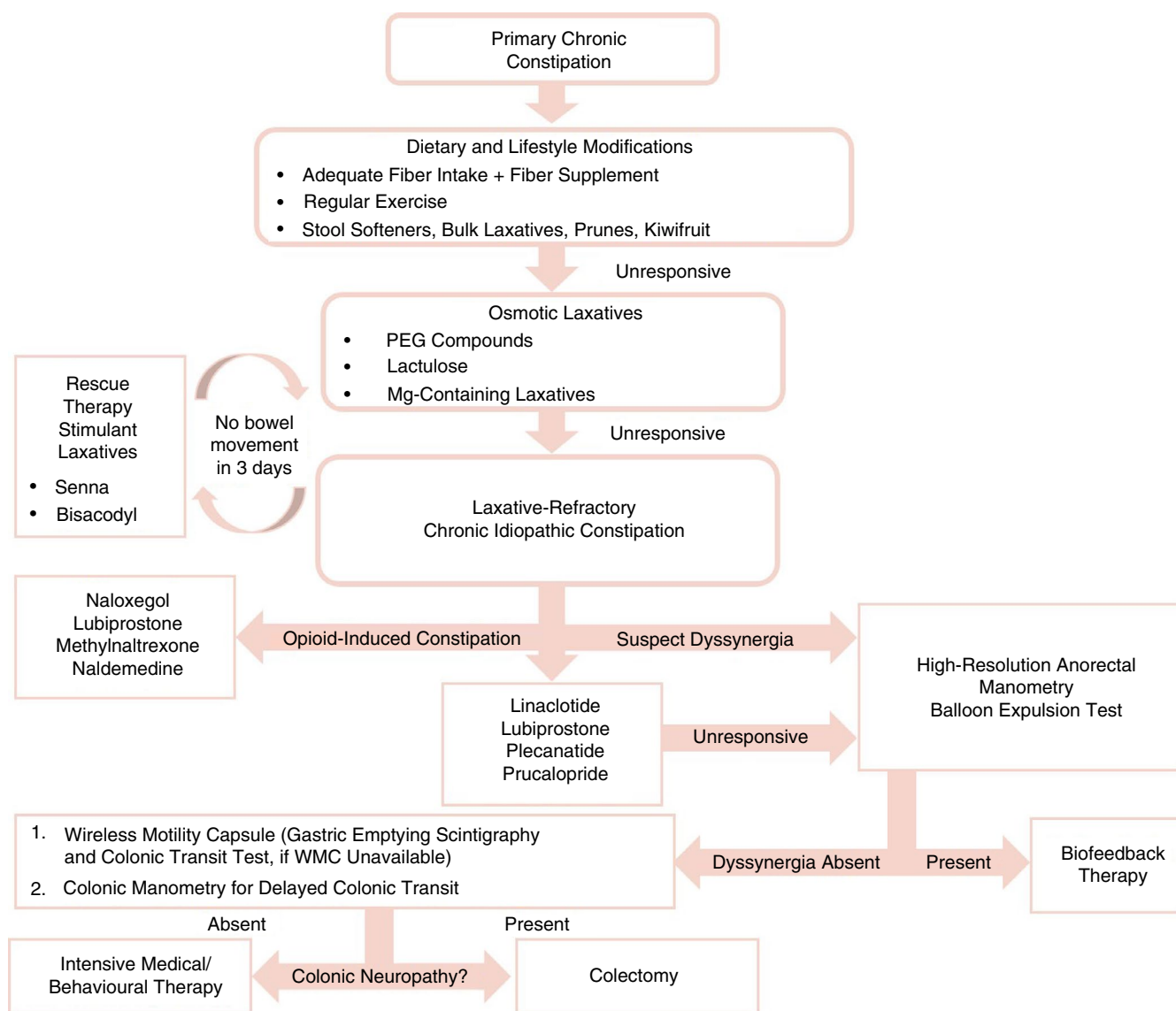
colonic transit, impaired rectal sensation and increased anorectal angle during squeeze are predictors of poor response to biofeedback therapy.<sup>134-136</sup> Standard office-based biofeedback therapy suffers from limitations: the need for skilled staff, multiple visits and limited availability at expert centres. Home biofeedback therapy is appealing for dyssynergic defecation and has similar efficacy in improvement of bowel symptoms and balloon expulsion compared to office-based therapy.<sup>137</sup> Furthermore, home biofeedback therapy is more cost-effective and shows promise for the future.<sup>138</sup>

## 6.4 | Clinical approach to managing patients with constipation

Management algorithms are available to help guide treatment decisions (Figure 4) and a recent meta-analysis evaluating the efficacy of

constipation treatments has been published.<sup>139</sup> First-line treatment for chronic constipation patients failing lifestyle modifications include fibre supplements or osmotic laxatives (such as PEG) on a regular basis, or stimulant laxatives intermittently,<sup>50</sup> which are available to patients as OTC products.<sup>11,28,29,32,140</sup> Indeed, many patients with chronic constipation will use some OTC laxative before consulting a health care provider.<sup>141</sup> Patients try an average of three OTC products before seeking help<sup>141</sup>; however, only half feel satisfied.<sup>7,141</sup>

Primary care providers should refer patients who are laxative refractory or intolerant to treatment to a gastroenterology provider for further assessment.<sup>28,140</sup> Primary care providers may try a promotility agent or prosecretory agent while awaiting gastroenterology evaluation. Gastroenterology providers may further titrate promotility agents or prosecretory agents and/or consider further testing—such as anorectal manometry, barium or magnetic resonance defecography, or colon transit time assessment—to identify



**FIGURE 4** Management algorithm for the treatment of constipation. This figure has been modified from Sharma *Handb Exp Pharmacol*. 2017 with permission by Springer Nature Customer Service GmbH: Wiley.<sup>4</sup> Mg, magnesium; PEG, polyethylene glycol; WMC, wireless motility capsule

the underlying pathophysiology and guide treatment in treatment-refractory patients.<sup>11,28,50</sup> While there is a lack of evidence in the literature to guide a symptom-based therapeutics approach, there is some evidence that different therapies may improve certain underlying mechanisms. For example, biofeedback therapy—a behavioural training technique using visual feedback to correct pelvic floor contractions—is safe, effective and recommended for patients with defecation disorders on the basis of anorectal manometry and defecography findings.<sup>11,29,32,50,140</sup> linaclotide and prucalopride accelerate colonic transit time, and linaclotide and plecanatide improve abdominal pain (and the former has been shown recently to modify afferent gut and brain interactions).<sup>19</sup> Likewise, rectal sensory retraining may be helpful in addition to biofeedback therapy to address both rectal hyper- and hyposensitivity.

A gastroenterology provider may recommend alternative treatments if other treatment options have failed.<sup>50</sup> Acetylcholinesterase inhibitors, such as neostigmine, can dramatically increase GI motility and may be considered in hospitalised patients with colonic pseudo-obstruction; however, its use requires close observation and cardiorespiratory monitoring in the intensive care setting.<sup>50,142</sup> Furthermore, pyridostigmine, an oral acetylcholinesterase inhibitor, may be considered in severe constipation, especially with co-existing autonomic dysfunction in patients who have previously responded to neostigmine or diabetes.<sup>143,144</sup> Oral ingestion of a vibrating capsule alters colonic circadian rhythm and may improve constipation by inducing more complete spontaneous bowel movements.<sup>145</sup> Habit training (bowel or pelvic floor retraining) and psychological interventions (cognitive behavioural therapy, hypnotherapy, psychological therapy) are also recommended for patients failing to respond to standard care.<sup>50,146</sup> Total abdominal colectomy is reserved for rare, severe cases of colonic inertia after all non-surgical options have failed and specialised testing such as colonic manometry suggests underlying colonic neuropathy.<sup>11,32,50,147</sup> Continuous direct nerve stimulation (sacral nerve stimulation) is the least-invasive surgical option available, with fewer complications than other surgeries; however, data demonstrating efficacy are lacking.<sup>50,147</sup> Subcutaneous electrodes can stimulate the sacral nerve to induce propagating contractions and increase stool frequency.<sup>32,147</sup> Antegrade continence enema, an endosurgical procedure where appendicocostomy or caecostomy is created to serve as a conduit to directly administer enemas into the caecum, has been described as an efficacious option to treat faecal incontinence and refractory constipation.<sup>148</sup> The majority of cases and much of the literature are focused on the treatment of children; however, single-centre experiences have described their long-term outcomes in adults.<sup>149–161</sup> A meta-analysis of observational studies, only three of which were prospective, suggested that approximately two thirds of antegrade continence enema procedures for constipation were efficacious, defined by continued use on follow-up or successful resolution of symptoms, and approximately 45% of antegrade continence enema procedures were associated with morbidity, most commonly wound infection and stomal stenosis, with a re-operation rate of >25%.<sup>162</sup> Given the low quality of evidence without randomised controlled

trials and associated morbidity, antegrade continence enema cannot be recommended for treatment of severe constipation.

## 6.5 | Patient perspective

### 6.5.1 | Tools for assessing symptom severity

Patient QoL decreases with severity and duration of constipation and associated symptoms.<sup>7</sup> Furthermore, patients with chronic constipation exhibit significant psychological stress and impaired health-related QoL compared to control subjects.<sup>163</sup> Symptoms reported as most bothersome are often also the most severely perceived.<sup>7</sup> Therefore, treatments focused on these symptoms are important to improve QoL.<sup>7</sup> Improvement in constipation with both secretagogues<sup>73,75–77,79</sup> and biofeedback therapy<sup>138</sup> can improve QoL.

In the absence of objective biomarkers for assessing constipation severity, prospective stool diaries and validated severity scales help assess patient-reported outcomes in clinical trials and manage patients clinically.<sup>164</sup> The most commonly used scales include the Constipation Assessment Scale, Constipation Scoring System, Symptom Severity Score and Patient Assessment Constipation-Symptom (Table 3). These scales assess the presence of constipation, constipation severity and the most bothersome constipation-associated symptoms. Thorough review of stool diaries and responses to severity scales may offer clinicians an opportunity to assess treatment efficacy from the patient's perspective. However, if physical stool diaries and scales are not completed in real time, they may be limited by their dependence on patient recall of bowel habits and symptoms.

New tools are becoming available to support the monitoring of patients with constipation, such as electronic health records, smartphone apps and electronic stool diaries. The National Institutes of Health Patient-Reported Outcomes Measurement Information System is increasingly incorporated into electronic health records as a measure of recording patient-reported outcomes.<sup>164</sup> Within the GI domains of the National Institutes of Health Patient Reported Outcomes Measurement Information System, abdominal pain and constipation, as well as diarrhoea as a potentially treatment-related adverse event, are relevant to patients with constipation.<sup>164</sup>

With smartphone apps and diaries, gastroenterology providers can potentially review patients' symptoms as recorded in real time. The GI Patient Reported Outcomes Measurement Information System scales can be accessed via the MyGiHealth app online and on smartphones, which compare a patient's symptoms scores with those of the general population in the United States and generates a heat map of symptoms.<sup>164</sup> This app can also track changes across time, allowing gastroenterology providers to assess treatment efficacy and facilitate improved outcomes for both providers and patients.<sup>164</sup> The Constipation Stool Diary is an app-based questionnaire used to track patient symptoms and medication use.<sup>25</sup> Apps have demonstrated a level of accuracy comparable to a physical diary and may be patient

**TABLE 3** Commonly used scales for assessing the severity of constipation

Scale	Description	Scoring system	Scoring interpretation
Constipation Assessment Scale <sup>168</sup>	Evaluates eight items: <ul style="list-style-type: none"> <li>• Abdominal distension or bloating</li> <li>• Change in gas passed rectally</li> <li>• Reduced frequency of bowel movements</li> <li>• Oozing liquid stool</li> <li>• Rectal fullness or pressure</li> <li>• Rectal pain with bowel movement</li> <li>• Small stool volume</li> <li>• Inability to defecate</li> </ul>	Each item rated on a 3-point scale: <ul style="list-style-type: none"> <li>• 0 = no problem</li> <li>• 1 = some problem</li> <li>• 2 = severe problem</li> </ul>	Total score range: 0-16 <ul style="list-style-type: none"> <li>• 0 = no constipation</li> <li>• 16 = severe constipation</li> </ul> Score $\geq 1$ indicates constipation
Constipation Scoring System <sup>169</sup>	Evaluates eight items: <ul style="list-style-type: none"> <li>• Frequency of bowel movements</li> <li>• Difficult or painful evacuation</li> <li>• Completeness of evacuation</li> <li>• Abdominal pain</li> <li>• Time per attempt</li> <li>• Type of assistance (none, laxatives, digital/enema)</li> <li>• Number of unsuccessful attempts at evacuation in a 24-h period</li> <li>• Duration of constipation</li> </ul>	Each item rated on a five-point scale: <ul style="list-style-type: none"> <li>• 0 = none of the time</li> <li>• 4 = all the time</li> </ul> One item is rated from 0 to 2	Total score range: 0-30 <ul style="list-style-type: none"> <li>• 0 = normal</li> <li>• 30 = severe constipation</li> </ul> Score $\geq 15$ indicates constipation
Patient Assessment of Constipation-Symptoms <sup>170</sup>	Evaluates 12 items with three subscales: <ul style="list-style-type: none"> <li>• Abdominal (four items)</li> <li>• Rectal (three items)</li> <li>• Stool (five items)</li> </ul>	Each item rated on a 5-point scale: <ul style="list-style-type: none"> <li>• 0 = symptom absent</li> <li>• 1 = mild</li> <li>• 2 = moderate</li> <li>• 3 = severe</li> <li>• 4 = very severe</li> </ul>	Total score range: 0-4 <ul style="list-style-type: none"> <li>• Generated by dividing the total score by the number of questions completed</li> <li>• Higher scores associated with higher symptom burden</li> </ul>

preferred.<sup>165</sup> For example, apps may assist in tracking diet and the symptoms of IBS-C to see if there is a correlation.<sup>166</sup> Administering scales via an app either in the clinic or in the advance of an appointment may also optimise resource use.

## 6.6 | Summary

CIC and IBS-C are historically classified as idiopathic; however, pathophysiological dysfunctions can be commonly identified in these constipation disorders, which could aid effective management. In addition, pelvic floor disorders such as dyssynergic defecation are common and often may present with overlapping symptoms of infrequent defecation and difficulty with defecation. Gastroenterology providers should be familiar with the constipation subtypes and their underlying pathophysiology, as well as key signalling pathways that may contribute to constipation. Although lifestyle and diet modifications are useful, laxatives remain the first-line treatment of constipation. For laxative-refractory cases, several classes of prokinetic and prosecretory agents are available. Familiarisation with the varied mechanisms of action, expected efficacy and side effects helps to select the appropriate treatment and meet patient expectations. Treatment algorithms are available to guide decision-making. Smartphone apps can help gastroenterology providers and patients track constipation symptoms and treatment response.

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and provided final approval of the version to be published. All the authors approved the final version of this manuscript, including the authorship list.

## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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## REFERENCES

1. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106:1582-1591.
2. Rao SS, Camilleri M. Approach to the patient with constipation. In: Podolsky DK, Camilleri M, Fitz JG, Kalloo AN, Shanahan F, Wang TC, eds. *Yamada's Textbook of Gastroenterology*. Hoboken, NJ: Wiley; 2015:757-780.
3. Serra J, Mascort-Roca J, Marzo-Castillejo M, et al. Clinical practice guidelines for the management of constipation in adults. Part 1: definition, aetiology and clinical manifestations. *Gastroenterol Hepatol*. 2017;40:132-141.
4. Sharma A, Rao S. Constipation: pathophysiology and current therapeutic approaches. *Handb Exp Pharmacol*. 2017;239:59-74.
5. Basilisco G, Coletta M. Chronic constipation: a critical review. *Dig Liver Dis*. 2013;45:886-893.
6. Andrews CN, Storr M. The pathophysiology of chronic constipation. *Can J Gastroenterol*. 2011;25:16b-21b.
7. Johanson JF, Kralstein J. Chronic constipation: a survey of the patient perspective. *Aliment Pharmacol Ther*. 2007;25:599-608.
8. Bellini M, Usai-Satta P, Bove A, et al. Chronic constipation diagnosis and treatment evaluation: the "CHRO.CO.DI.T.E." study. *BMC Gastroenterol*. 2017;17:11.
9. Chey WD. Symposium report: an evidence-based approach to IBS and CIC: applying new advances to daily practice: a review of an adjunct clinical symposium of the American College of Gastroenterology Meeting October 16, 2016 \* Las Vegas, Nevada. *Gastroenterol Hepatol*. 2017;13:1-16.
10. Allen-Brady K, Tuteja AK. Chapter 33 - Opioid-induced bowel disorder and narcotic bowel syndrome. In: Rao SSC, Lee YY, Ghoshal UC, eds. *Clinical and Basic Neurogastroenterology and Motility*. Cambridge, MA: Academic Press; 2020:463-475.
11. Bharucha AE, Dorn SD, Lembo A, Pressman A. American Gastroenterological Association medical position statement on constipation. *Gastroenterology*. 2013;144:211-217.
12. Sharma A, Rao S, Harrison JH. Anorectal function. *Encyclopedia of Gastroenterology*. 2nd edn. Vol. 1. Oxford: Academic Press; 2020:99-104.
13. Patcharatrakul T, Rao SSC. Update on the pathophysiology and management of anorectal disorders. *Gut Liv*. 2018;12:375-384.
14. Rao SS. Dyssynergic defecation. *Gastroenterol Clin North Am*. 2001;30:97-114.
15. Kunkel D, Basseri RJ, Makhani MD, Chong K, Chang C, Pimentel M. Methane on breath testing is associated with constipation: a systematic review and meta-analysis. *Dig Dis Sci*. 2011;56:1612-1618.
16. Wolf PG, Parthasarathy G, Chen J, et al. Assessing the colonic microbiome, hydrogenogenic and hydrogenotrophic genes, transit and breath methane in constipation. *Neurogastroenterol Motil*. 2017;29:1-9.
17. Attaluri A, Jackson M, Valestin J, Rao SS. Methanogenic flora is associated with altered colonic transit but not stool characteristics in constipation without IBS. *Am J Gastroenterol*. 2010;105:1407-1411.
18. Camilleri M, Ford AC. Irritable bowel syndrome: pathophysiology and current therapeutic approaches. *Handb Exp Pharmacol*. 2017;239:75-113.
19. Rao SSC, Xiang X, Yan Y, et al. Randomised clinical trial: linaclotide vs placebo—a study of bi-directional gut and brain axis. *Aliment Pharmacol Ther*. 2020;51:1332-1341.
20. Ghoshal U, Shukla R, Srivastava D, Ghoshal UC. Irritable bowel syndrome, particularly the constipation-predominant form, involves an increase in *Methanobrevibacter smithii*, which is associated with higher methane production. *Gut Liv*. 2016;10:932-938.
21. Andresen V, Banerji V, Hall G, Lass A, Emmanuel AV. The patient burden of opioid-induced constipation: new insights from a large, multinational survey in five European countries. *United European Gastroenterol J*. 2018;6:1254-1266.
22. Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). *Pain Med*. 2009;10:35-42.
23. Rao SS, Rattanakavit K, Patcharatrakul T. Diagnosis and management of chronic constipation in adults. *Nat Rev Gastroenterol Hepatol*. 2016;13:295-305.
24. Bharucha AE, Pemberton JH, Locke GR 3rd. American Gastroenterological Association technical review on constipation. *Gastroenterology*. 2013;144:218-238.
25. Yan Y, Jimenez E, Sharma A, et al. Sa1728 How useful is Constipation Stool APP compared to paper stool diary - randomized study of constipation and healthy subjects. *Gastroenterology*. 2020;158:S-400.
26. Lacy BE, Levenick JM, Crowell M. Chronic constipation: new diagnostic and treatment approaches. *Therap Adv Gastroenterol*. 2012;5:233-247.
27. Rao SSC. Plecanatide: a new guanylate cyclase agonist for the treatment of chronic idiopathic constipation. *Therap Adv Gastroenterol*. 2018;11:1756284818777945.
28. Mearin F, Ciriza C, Minguez M, et al. Clinical Practice Guideline: Irritable bowel syndrome with constipation and functional constipation in the adult. *Rev Esp Enferm Dig*. 2016;108:332-363.
29. Camilleri M, Ford AC, Mawe GM, et al. Chronic constipation. *Nat Rev Dis Primers*. 2017;3:17095.
30. Sharma A, Kurek J, Morgan JC, Wakade C, Rao SSC. Constipation in Parkinson's disease: a nuisance or nuanced answer to the pathophysiological puzzle? *Curr Gastroenterol Rep*. 2018;20:1.
31. Lee YY, Haque M, Lawenko R, Sharma A. Systemic disorders that affect gastrointestinal motility. *Clinical and Basic Neurogastroenterology and Motility*. Cambridge, MA: Academic Press; 2020:601-618.
32. Serra J, Mascort-Roca J, Marzo-Castillejo M, et al. Clinical practice guidelines for the management of constipation in adults. Part 2: diagnosis and treatment. *Gastroenterol Hepatol*. 2017;40:303-316.
33. Tantiplachiva K, Rao P, Attaluri A, Rao SS. Digital rectal examination is a useful tool for identifying patients with dyssynergia. *Clin Gastroenterol Hepatol*. 2010;8:955-960.
34. Rao SSC. Rectal exam: yes, it can and should be done in a busy practice! *Am J Gastroenterol*. 2018;113:635-638.
35. Carrington EV, Scott SM, Bharucha A, et al. Expert consensus document: advances in the evaluation of anorectal function. *Nat Rev Gastroenterol Hepatol*. 2018;15:309-323.
36. Carrington EV, Heinrich H, Knowles CH, et al. The international anorectal physiology working group (IAPWG) recommendations: Standardized testing protocol and the London classification for disorders of anorectal function. *Neurogastroenterol Motil*. 2020;32:e13679.

37. Minguez M, Herreros B, Sanchiz V, et al. Predictive value of the balloon expulsion test for excluding the diagnosis of pelvic floor dyssynergia in constipation. *Gastroenterology*. 2004;126:57-62.
38. Bharucha AE, Wald A, Enck P, Rao S. Functional anorectal disorders. *Gastroenterology*. 2006;130:1510-1518.
39. Kang HR, Lee JE, Lee JS, et al. Comparison of high-resolution anorectal manometry with water-perfused anorectal manometry. *J Neurogastroenterol Motil*. 2015;21:126-132.
40. Rao SS, Azpiroz F, Diamant N, Enck P, Tougas G, Wald A. Minimum standards of anorectal manometry. *Neurogastroenterol Motil*. 2002;14:553-559.
41. Rao SS. Dyssynergic defecation and biofeedback therapy. *Gastroenterol Clin North Am*. 2008;37:569-586, viii.
42. Sharif H, Devadason D, Abrehart N, Stevenson R, Marciani L. Imaging measurement of whole gut transit time in paediatric and adult functional gastrointestinal disorders: a systematic review and narrative synthesis. *Diagnostics*. 2019;9:221.
43. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology*. 2016;150:1393-1407.e5.
44. Lee YY, Erdogan A, Rao SS. How to assess regional and whole gut transit time with wireless motility capsule. *J Neurogastroenterol Motil*. 2014;20:265-270.
45. Rao SSC, Kuo B, McCallum RW, et al. Investigation of colonic and whole-gut transit with wireless motility capsule and radiopaque markers in constipation. *Clin Gastroenterol Hepatol*. 2009;7:537-544.
46. Rao SSC, Camilleri M, Hasler WL, et al. Evaluation of gastrointestinal transit in clinical practice: position paper of the American and European Neurogastroenterology and Motility Societies. *Neurogastroenterol Motil*. 2011;23:8-23.
47. Wang YT, Mohammed SD, Farmer AD, et al. Regional gastrointestinal transit and pH studied in 215 healthy volunteers using the wireless motility capsule: influence of age, gender, study country and testing protocol. *Aliment Pharmacol Ther*. 2015;42:761-772.
48. Singh S, Heady S, Coss-Adame E, Rao SS. Clinical utility of colonic manometry in slow transit constipation. *Neurogastroenterol Motil*. 2013;25:487-495.
49. Saito YA, Schoenfeld P, Locke GR 3rd. The epidemiology of irritable bowel syndrome in North America: a systematic review. *Am J Gastroenterol*. 2002;97:1910-1915.
50. Serra J, Pohl D, Azpiroz F, et al. European Society of Neurogastroenterology and Motility guidelines on functional constipation in adults. *Neurogastroenterol Motil*. 2020;32:e13762.
51. Attaluri A, Donahoe R, Valestin J, Brown K, Rao SS. Randomised clinical trial: dried plums (prunes) vs. psyllium for constipation. *Aliment Pharmacol Ther*. 2011;33:822-828.
52. Erdogan A, Rao SSC, Thiruvaiyaru D, et al. Randomised clinical trial: mixed soluble/insoluble fibre vs. psyllium for chronic constipation. *Aliment Pharmacol Ther*. 2016;44:35-44.
53. Chey SW, Chey WD, Jackson K, Eswaran S. S0454 Randomized, comparative effectiveness trial of green kiwifruit, psyllium, or prunes in U.S. patients with chronic constipation. *Am J Gastroenterol*. 2020;115:S229.
54. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. *Gut*. 2011;60:209-218.
55. Corazziari E, Badiali D, Bazzocchi G, et al. Long term efficacy, safety, and tolerability of low daily doses of isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in the treatment of functional chronic constipation. *Gut*. 2000;46:522-526.
56. Dipalma JA, Cleveland MV, McGowan J, Herrera JL. A randomized, multicenter, placebo-controlled trial of polyethylene glycol laxative for chronic treatment of chronic constipation. *Am J Gastroenterol*. 2007;102:1436-1441.
57. Corazziari E, Badiali D, Habib FI, et al. Small volume isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in treatment of chronic nonorganic constipation. *Dig Dis Sci*. 1996;41:1636-1642.
58. Lee-Robichaud H, Thomas K, Morgan J, Nelson RL. Lactulose versus polyethylene glycol for chronic constipation. *Cochrane Database Syst Rev*. 2010;(7):Cd007570.
59. Belsey JD, Geraint M, Dixon TA. Systematic review and meta analysis: polyethylene glycol in adults with non-organic constipation. *Int J Clin Pract*. 2010;64:944-955.
60. Awad RA, Camacho S. A randomized, double-blind, placebo-controlled trial of polyethylene glycol effects on fasting and postprandial rectal sensitivity and symptoms in hypersensitive constipation-predominant irritable bowel syndrome. *Colorectal Dis*. 2010;12:1131-1138.
61. Chapman RW, Stanghellini V, Geraint M, Halphen M. Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. *Am J Gastroenterol*. 2013;108:1508-1515.
62. Kamm MA, Mueller-Lissner S, Wald A, Richter E, Swallow R, Gessner U. Oral bisacodyl is effective and well-tolerated in patients with chronic constipation. *Clin Gastroenterol Hepatol*. 2011;9:577-583.
63. Kienzle-Horn S, Vix JM, Schuijt C, Peil H, Jordan CC, Kamm MA. Efficacy and safety of bisacodyl in the acute treatment of constipation: a double-blind, randomized, placebo-controlled study. *Aliment Pharmacol Ther*. 2006;23:1479-1488.
64. Mueller-Lissner S, Kamm MA, Wald A, et al. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of sodium picosulfate in patients with chronic constipation. *Am J Gastroenterol*. 2010;105:897-903.
65. Brancale A, Shailubhai K, Ferla S, Ricci A, Bassetto M, Jacob GS. Therapeutically targeting guanylate cyclase-C: computational modeling of plecanatide, a uroguanylin analog. *Pharmacol Res Perspect*. 2017;5:e00295.
66. Islam BN, Sharman SK, Browning DD. Clinical utility of plecanatide in the treatment of chronic idiopathic constipation. *Int J Gen Med*. 2018;11:323-330.
67. Waldman SA, Camilleri M. Guanylate cyclase-C as a therapeutic target in gastrointestinal disorders. *Gut*. 2018;67:1543-1552.
68. Hannig G, Tchernychev B, Kurtz CB, Bryant AP, Currie MG, Silos-Santiago I. Guanylate cyclase-C/cGMP: an emerging pathway in the regulation of visceral pain. *Front Mol Neurosci*. 2014;7:31.
69. Waldman SA, Tenenbaum R, Foehl HC, Winkle P, Griffin P. Blunted evoked prouroguanylin endocrine secretion in chronic constipation. *Clin Transl Gastroenterol*. 2019;10:e00016.
70. Atluri DK, Chandar AK, Bharucha AE, Falck-Ytter Y. Effect of linaclotide in irritable bowel syndrome with constipation (IBS-C): a systematic review and meta-analysis. *Neurogastroenterol Motil*. 2014;26:499-509.
71. Brenner DM, Fogel R, Dorn SD, et al. Efficacy, safety, and tolerability of plecanatide in patients with irritable bowel syndrome with constipation: results of two phase 3 randomized clinical trials. *Am J Gastroenterol*. 2018;113:735-745.
72. Chey WD, Lembo AJ, Lavins BJ, 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;107:1702-1712.
73. DeMicco M, Barrow L, Hickey B, Shailubhai K, Griffin P. Randomized clinical trial: efficacy and safety of plecanatide in the treatment of chronic idiopathic constipation. *Therap Adv Gastroenterol*. 2017;10:837-851.
74. Lacy BE, Schey R, Shiff SJ, et al. Linaclotide in chronic idiopathic constipation patients with moderate to severe abdominal bloating: a randomized, controlled trial. *PLoS One*. 2015;10:e0134349.

75. Lembo AJ, Kurtz CB, MacDougall JE, et al. Efficacy of linaclotide for patients with chronic constipation. *Gastroenterology*. 2010;138:886-895.e1.
76. Lembo AJ, Schaefer HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. *N Engl J Med*. 2011;365:527-536.
77. Miner PB, Koltun WD, Wiener GJ, et al. A randomized phase III clinical trial of plecanatide, a uroguanylin analog, in patients with chronic idiopathic constipation. *Am J Gastroenterol*. 2017;112:613-621.
78. Rao S, Lembo AJ, Shiff SJ, 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;107:1714-1724; quiz p.1725.
79. Schoenfeld P, Lacy BE, Chey WD, et al. Low-dose linaclotide (72µg) for chronic idiopathic constipation: a 12-week, randomized, double-blind, placebo-controlled trial. *Am J Gastroenterol*. 2018;113:105-114.
80. Videlock EJ, Cheng V, Cremonini F. Effects of linaclotide in patients with irritable bowel syndrome with constipation or chronic constipation: a meta-analysis. *Clin Gastroenterol Hepatol*. 2013;11:1084-1092.e3; quiz e68.
81. Yang Y, Fang J, Guo X, et al. Linaclotide in irritable bowel syndrome with constipation: a Phase 3 randomized trial in China and other regions. *J Gastroenterol Hepatol*. 2018;33:980-989.
82. Fukudo S, Miwa H, Nakajima A, et al. A randomized controlled and long-term linaclotide study of irritable bowel syndrome with constipation patients in Japan. *Neurogastroenterol Motil*. 2018;30:e13444.
83. Quigley EM, Tack J, Chey WD, et al. Randomised clinical trials: linaclotide phase 3 studies in IBS-C - a prespecified further analysis based on European Medicines Agency-specified endpoints. *Aliment Pharmacol Ther*. 2013;37:49-61.
84. Barish CF, Crozier RA, Griffin PH. Long-term treatment with plecanatide was safe and tolerable in patients with irritable bowel syndrome with constipation. *Curr Med Res Opin*. 2019;35:81-85.
85. Barish CF, Griffin P. Safety and tolerability of plecanatide in patients with chronic idiopathic constipation: long-term evidence from an open-label study. *Curr Med Res Opin*. 2018;34:751-755.
86. Griffin PH. Comment on meta analysis by Shah et al. *Am J Gastroenterol*. 2018;113:1395.
87. Niewinna K, Zielinska A, Fichna J. Recent advances in the pharmacological management of constipation predominant irritable bowel syndrome. *Expert Opin Pharmacother*. 2020;21:73-84.
88. Atkinson W, Lockhart S, Whorwell PJ, Keevil B, Houghton LA. Altered 5-hydroxytryptamine signaling in patients with constipation- and diarrhea-predominant irritable bowel syndrome. *Gastroenterology*. 2006;130:34-43.
89. Dunlop SP, Coleman NS, Blackshaw E, et al. Abnormalities of 5-hydroxytryptamine metabolism in irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2005;3:349-357.
90. Bonfiglio F, Liu X, Smillie C, et al. GWAS of stool frequency reveals genes, pathways, and cell types relevant to human gastrointestinal motility and irritable bowel syndrome. *medRxiv*. 2020:2020.2006.2017.20132555.
91. El-Salhy M, Norrgard O, Spinnell S. Abnormal colonic endocrine cells in patients with chronic idiopathic slow-transit constipation. *Scand J Gastroenterol*. 1999;34:1007-1011.
92. Jiang C, Xu Q, Wen X, Sun H. Current developments in pharmacological therapeutics for chronic constipation. *Acta pharmaceutica Sinica B*. 2015;5:300-309.
93. Prichard DO, Bharucha AE. Recent advances in understanding and managing chronic constipation. *F1000Res*. 2018;7:1640.
94. Bouras EP, Camilleri M, Burton DD, Thomforde G, McKinzie S, Zinsmeister AR. Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder. *Gastroenterology*. 2001;120:354-360.
95. In brief: Tegaserod (Zelnorm) returns. *Med Lett Drugs Ther*. 2019;61:72.
96. Camilleri M, Kerstens R, Ryckx A, Vandeplasse L. A placebo-controlled trial of prucalopride for severe chronic constipation. *N Engl J Med*. 2008;358:2344-2354.
97. Quigley EM, Vandeplasse L, Kerstens R, Ausma J. Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation—a 12-week, randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther*. 2009;29:315-328.
98. Tack J, van Outryve M, Beyens G, Kerstens R, Vandeplasse L. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. *Gut*. 2009;58:357-365.
99. Camilleri M, Van Outryve MJ, Beyens G, Kerstens R, Robinson P, Vandeplasse L. Clinical trial: the efficacy of open-label prucalopride treatment in patients with chronic constipation - follow-up of patients from the pivotal studies. *Aliment Pharmacol Ther*. 2010;32:1113-1123.
100. Camilleri M, Piessevaux H, Yiannakou Y, et al. Efficacy and safety of prucalopride in chronic constipation: an integrated analysis of six randomized, controlled clinical trials. *Dig Dis Sci*. 2016;61:2357-2372.
101. Sajid MS, Hebbbar M, Baig MK, Li A, Philipose Z. Use of prucalopride for chronic constipation: a systematic review and meta-analysis of published randomized, controlled trials. *J Neurogastroenterol Motil*. 2016;22:412-422.
102. Tack J, Quigley E, Camilleri M, Vandeplasse L, Kerstens R. Efficacy and safety of oral prucalopride in women with chronic constipation in whom laxatives have failed: an integrated analysis. *United European Gastroenterol J*. 2013;1:48-59.
103. Chey WD, Lembo AJ, Rosenbaum DP. Efficacy of tenapanor in treating patients with irritable bowel syndrome with constipation: a 12-week, placebo-controlled phase 3 trial (T3MPO-1). *Am J Gastroenterol*. 2020;115:281-293.
104. Eswaran S, Guentner A, Chey WD. Emerging pharmacologic therapies for constipation-predominant irritable bowel syndrome and chronic constipation. *J Neurogastroenterol Motil*. 2014;20:141-151.
105. Abrahamsson H, Ostlund-Lindqvist AM, Nilsson R, Simren M, Gillberg PG. Altered bile acid metabolism in patients with constipation-predominant irritable bowel syndrome and functional constipation. *Scand J Gastroenterol*. 2008;43:1483-1488.
106. Bazzoli F, Malavolti M, Petronelli A, Barbara L, Roda E. Treatment of constipation with chenodeoxycholic acid. *J Int Med Res*. 1983;11:120-123.
107. Rao AS, Wong BS, Camilleri M, et al. Chenodeoxycholate in females with irritable bowel syndrome-constipation: a pharmacodynamic and pharmacogenetic analysis. *Gastroenterology*. 2010;139:1549-1558.e1.
108. Chey WD, Camilleri M, Chang L, Rikner L, Graffner H. A randomized placebo-controlled phase IIb trial of a3309, a bile acid transporter inhibitor, for chronic idiopathic constipation. *Am J Gastroenterol*. 2011;106:1803-1812.
109. Nakajima A, Seki M, Taniguchi S, et al. Safety and efficacy of elobixibat for chronic constipation: results from a randomised, double-blind, placebo-controlled, phase 3 trial and an open-label, single-arm, phase 3 trial. *Lancet Gastroenterol Hepatol*. 2018;3:537-547.
110. Kumagai Y, Amano H, Sasaki Y, et al. Effect of single and multiple doses of elobixibat, an ileal bile acid transporter inhibitor, on chronic constipation: a randomized controlled trial. *Br J Clin Pharmacol*. 2018;84:2393-2404.
111. Nakajima A, Seki M, Taniguchi S. Determining an optimal clinical dose of elobixibat, a novel inhibitor of the ileal bile acid transporter,

- in Japanese patients with chronic constipation: a phase II, multicenter, double-blind, placebo-controlled randomized clinical trial. *J Gastroenterol*. 2018;53:525-534.
112. Bassil AK, Borman RA, Jarvie EM, et al. Activation of prostaglandin EP receptors by lubiprostone in rat and human stomach and colon. *Br J Pharmacol*. 2008;154:126-135.
  113. Lembo AJ, Johanson JF, Parkman HP, Rao SS, Miner PB Jr, Ueno R. Long-term safety and effectiveness of lubiprostone, a chloride channel (CIC-2) activator, in patients with chronic idiopathic constipation. *Dig Dis Sci*. 2011;56:2639-2645.
  114. Johanson JF, Morton D, Geenen J, Ueno R. 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;103:170-177.
  115. Johanson JF, Drossman DA, Panas R, Wahle A, Ueno R. Clinical trial: phase 2 study of lubiprostone for irritable bowel syndrome with constipation. *Aliment Pharmacol Ther*. 2008;27:685-696.
  116. Barish CF, Drossman D, Johanson JF, Ueno R. Efficacy and safety of lubiprostone in patients with chronic constipation. *Dig Dis Sci*. 2010;55:1090-1097.
  117. Chey WD, Drossman DA, Johanson JF, Scott C, Panas RM, Ueno R. Safety and patient outcomes with lubiprostone for up to 52 weeks in patients with irritable bowel syndrome with constipation. *Aliment Pharmacol Ther*. 2012;35:587-599.
  118. Li F, Fu T, Tong W-D, et al. Lubiprostone is effective in the treatment of chronic idiopathic constipation and irritable bowel syndrome. *Mayo Clin Proc*. 2016;91:456-468.
  119. Fukudo S, Hongo M, Kaneko H, Ueno R. Efficacy and safety of oral lubiprostone in constipated patients with or without irritable bowel syndrome: a randomized, placebo-controlled and dose-finding study. *Neurogastroenterol Motil*. 2011;23:544-e205.
  120. Fukudo S, Hongo M, Kaneko H, Takano M, Ueno R. Lubiprostone increases spontaneous bowel movement frequency and quality of life in patients with chronic idiopathic constipation. *Clin Gastroenterol Hepatol*. 2015;13:294-301.e5.
  121. Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome—results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther*. 2009;29:329-341.
  122. Johanson JF, Ueno R. Lubiprostone, a locally acting chloride channel activator, in adult patients with chronic constipation: a double-blind, placebo-controlled, dose-ranging study to evaluate efficacy and safety. *Aliment Pharmacol Ther*. 2007;25:1351-1361.
  123. Rao SSC, Lichtlen P, Habibi S. Effects of lubiprostone, an intestinal secretagogue, on electrolyte homeostasis in chronic idiopathic and opioid-induced constipation. *J Clin Gastroenterol*. 2020;32(11). Publish Ahead of Print. <https://doi.org/10.1097/MCG.0000000000001385>
  124. Leppert W. The role of opioid receptor antagonists in the treatment of opioid-induced constipation: a review. *Adv Ther*. 2010;27:714-730.
  125. Viscusi ER. Clinical overview and considerations for the management of opioid-induced constipation in patients with chronic non-cancer pain. *Clin J Pain*. 2019;35:174-188.
  126. Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S. American Gastroenterological Association Institute Guideline on the medical management of opioid-induced constipation. *Gastroenterology*. 2019;156:218-226.
  127. Vijayvargiya P, Camilleri M, Vijayvargiya P, Erwin P, Murad MH. Systematic review with meta-analysis: efficacy and safety of treatments for opioid-induced constipation. *Aliment Pharmacol Ther*. 2020;52:37-53.
  128. Rao SS, Benninga MA, Bharucha AE, Chiarioni G, Di Lorenzo C, Whitehead WE. ANMS-ESNM position paper and consensus guidelines on biofeedback therapy for anorectal disorders. *Neurogastroenterol Motil*. 2015;27:594-609.
  129. Rao SSC, Seaton K, Miller M, et al. Randomized controlled trial of biofeedback, sham feedback, and standard therapy for dyssynergic defecation. *Clin Gastroenterol Hepatol*. 2007;5:331-338.
  130. Heymen S, Scarlett Y, Jones K, Ringel Y, Drossman D, Whitehead WE. Randomized, controlled trial shows biofeedback to be superior to alternative treatments for patients with pelvic floor dyssynergia-type constipation. *Dis Colon Rectum*. 2007;50:428-441.
  131. Chiarioni G, Whitehead WE, Pezza V, Morelli A, Bassotti G. Biofeedback is superior to laxatives for normal transit constipation due to pelvic floor dyssynergia. *Gastroenterology*. 2006;130:657-664.
  132. Rao SSC, Valestin J, Brown CK, Zimmerman B, Schulze K. Long-term efficacy of biofeedback therapy for dyssynergic defecation: randomized controlled trial. *Am J Gastroenterol*. 2010;105:890-896.
  133. Lee HJ, Boo SJ, Jung KW, et al. Long-term efficacy of biofeedback therapy in patients with dyssynergic defecation: results of a median 44 months follow-up. *Neurogastroenterol Motil*. 2015;27:787-795.
  134. Patcharatrakul T, Gonlachanvit S. Outcome of biofeedback therapy in dyssynergic defecation patients with and without irritable bowel syndrome. *J Clin Gastroenterol*. 2011;45:593-598.
  135. Chiarioni G, Salandini L, Whitehead WE. Biofeedback benefits only patients with outlet dysfunction, not patients with isolated slow transit constipation. *Gastroenterology*. 2005;129:86-97.
  136. Shin JK, Cheon JH, Kim ES, et al. Predictive capability of anorectal physiologic tests for unfavorable outcomes following biofeedback therapy in dyssynergic defecation. *J Korean Med Sci*. 2010;25:1060-1065.
  137. Rao SSC, Valestin JA, Xiang X, Hamdy S, Bradley CS, Zimmerman MB. Home-based versus office-based biofeedback therapy for constipation with dyssynergic defecation: a randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2018;3:768-777.
  138. Rao SSC, Go JT, Valestin J, Schneider J. Home biofeedback for the treatment of dyssynergic defecation: does it improve quality of life and is it cost-effective? *Am J Gastroenterol*. 2019;114:938-944.
  139. Luthra P, Camilleri M, Burr NE, Quigley EMM, Black CJ, Ford AC. Efficacy of drugs in chronic idiopathic constipation: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol*. 2019;4:831-844.
  140. Tse Y, Armstrong D, Andrews CN, et al. Treatment algorithm for chronic idiopathic constipation and constipation-predominant irritable bowel syndrome derived from a Canadian national survey and needs assessment on choices of therapeutic agents. *Can J Gastroenterol Hepatol*. 2017;2017:8612189.
  141. Harris LA, Horn J, Kissous-Hunt M, Magnus L, Quigley EMM. The Better Understanding and Recognition of the Disconnects, Experiences, and Needs of patients with Chronic Idiopathic Constipation (BURDEN-CIC) study: results of an online questionnaire. *Adv Ther*. 2017;34:2661-2673.
  142. Soufi-Afshar I, Moghadamnia A, Bijani A, Kazemi S, Shokri-Shirvani J. Comparison of pyridostigmine and bisacodyl in the treatment of refractory chronic constipation. *Caspian J Intern Med*. 2016;7:19-24.
  143. Bharucha AE, Low PA, Camilleri M, Burton D, Gehrking TL, Zinsmeister AR. Pilot study of pyridostigmine in constipated patients with autonomic neuropathy. *Clin Auton Res*. 2008;18:194-202.
  144. Bharucha AE, Low P, Camilleri M, et al. A randomised controlled study of the effect of cholinesterase inhibition on colon function in patients with diabetes mellitus and constipation. *Gut*. 2013;62:708-715.
  145. Rao SSC, Lembo A, Chey WD, Friedenberg K, Quigley EMM. Effects of the vibrating capsule on colonic circadian rhythm and bowel



- symptoms in chronic idiopathic constipation. *Neurogastroenterol Motil.* 2020;32:e13890.
146. NICE Guidance: Irritable bowel syndrome in adults: diagnosis and management. 2008. <https://www.nice.org.uk/guidance/cg61>. Date Accessed: March 10, 2020.
  147. Hussain ZH, Everhart K, Lacy BE. Treatment of chronic constipation: prescription medications and surgical therapies. *Gastroenterol Hepatol.* 2015;11:104-114.
  148. Griffiths DM, Malone PS. The Malone antegrade continence enema. *J Pediatr Surg.* 1995;30:68-71.
  149. Lees NP, Hodson P, Hill J, Pearson RC, MacLennan I. Long-term results of the antegrade continent enema procedure for constipation in adults. *Colorectal Dis.* 2004;6:362-368.
  150. Portier G, Ghouti L, Kirzin S, Chauffour M, Lazorthes F. Malone antegrade colonic irrigation: ileal neoappendicostomy is the preferred procedure in adults. *Int J Colorectal Dis.* 2006;21:458-460.
  151. Teichman JM, Zabihi N, Kraus SR, Harris JM, Barber DB. Long-term results for Malone antegrade continence enema for adults with neurogenic bowel disease. *Urology.* 2003;61:502-506.
  152. Meurette G, Lehur PA, Coron E, Regenet N. Long-term results of Malone's procedure with antegrade irrigation for severe chronic constipation. *Gastroenterol Clin Biol.* 2010;34:209-212.
  153. Duchalais E, Meurette G, Mantoo SK, et al. Percutaneous endoscopic caecostomy for severe constipation in adults: feasibility, durability, functional and quality of life results at 1 year follow-up. *Surg Endosc.* 2015;29:620-626.
  154. Uno Y. Introducer method of percutaneous endoscopic cecostomy and antegrade continence enema by use of the Chait Trapdoor cecostomy catheter in patients with adult neurogenic bowel. *Gastrointest Endosc.* 2006;63:666-673.
  155. Gerharz EW, Vik V, Webb G, Leaver R, Shah PJ, Woodhouse CR. The value of the MACE (Malone antegrade colonic enema) procedure in adult patients. *J Am Coll Surg.* 1997;185:544-547.
  156. Biyani D, Barrow E, Hodson P, Watson AJ, MacLennan I. Endoscopically placed caecostomy buttons: a trial ACE procedure. *Colorectal Dis.* 2007;9:373-376.
  157. Hirst GR, Arumugam PJ, Watkins AJ, et al. Antegrade continence enema in the treatment of obstructed defaecation with or without faecal incontinence. *Tech Coloproctol.* 2005;9:217-221.
  158. Altomare DF, Rinaldi M, Rubini D, et al. Long-term functional assessment of antegrade colonic enema for combined incontinence and constipation using a modified Marsh and Kiff technique. *Dis Colon Rectum.* 2007;50:1023-1031.
  159. Poirier M, Abcarian H, Nelson R. Malone antegrade continent enema: an alternative to resection in severe defecation disorders. *Dis Colon Rectum.* 2007;50:22-28.
  160. Worsoe J, Christensen P, Krogh K, Buntzen S, Laurberg S. Long-term results of antegrade colonic enema in adult patients: assessment of functional results. *Dis Colon Rectum.* 2008;51:1523-1528.
  161. Whiteley I, Stewart P. Antegrade continence enema (ACE) in adults: a review of long-term outcomes and complications from a single institution. *Aust N Z Continence J.* 2020;26.
  162. Chan DS, Delicata RJ. Meta-analysis of antegrade continence enema in adults with faecal incontinence and constipation. *Br J Surg.* 2016;103:322-327.
  163. Rao SSC, Seaton K, Miller MJ, et al. Psychological profiles and quality of life differ between patients with dyssynergia and those with slow transit constipation. *J Psychosom Res.* 2007;63:441-449.
  164. Almario CV, Spiegel BMR. Employing irritable bowel syndrome patient-reported outcomes in the clinical trenches. *Clin Gastroenterol Hepatol.* 2018;16:462-466.e2.
  165. Yan Y, Karunaratne T, Jimenez E, et al. Electronic APP vs. paper form stool diary for fecal incontinence: 2877. *Am J Gastroenterol.* 2019;114:S1577-S1578. (2019 ACG Annual Meeting Abstracts).
  166. Zia J, Schroeder J, Munson S, et al. Feasibility and usability pilot study of a novel irritable bowel syndrome food and gastrointestinal symptom journal smartphone app. *Clin Transl Gastroenterol.* 2016;7:e147.
  167. Johanson JF, Wald A, Tougas G, et al. Effect of tegaserod in chronic constipation: a randomized, double-blind, controlled trial. *Clin Gastroenterol Hepatol.* 2004;2:796-805.
  168. Sharma S, Agarwal B. Scoring systems in evaluation of constipation and obstructed defecation syndrome (ODS). *J Int Med Sci Acad.* 2012;25:57-59.
  169. McCrea HJ, Ment LR. The dianeonategnosis, management, and postnatal prevention of intraventricular hemorrhage in the preterm. *Clin Perinatol.* 2008;35:777-792, vii.
  170. Frank L, Kleinman L, Farup C, Taylor L, Miner P Jr. Psychometric validation of a constipation symptom assessment questionnaire. *Scand J Gastroenterol.* 1999;34:870-877.
  171. Simrén M, Tack J. New treatments and therapeutic targets for IBS and other functional bowel disorders. *Nat Rev Gastroenterol Hepatol.* 2018;15:589-605.

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