



European society of neurogastroenterology and motility guidelines on functional constipation in adults

Jordi Serra^{1,2,3} | Daniel Pohl^{4,5} | Fernando Azpiroz^{1,6} | Giuseppe Chiarioni^{7,8} | Philippe Ducrotté⁹ | Guillaume Gourcerol¹⁰ | A. Pali S. Hungin¹¹ | Peter Layer¹² | Juan-Manuel Mendive¹³ | Johann Pfeifer¹⁴ | Gerhard Rogler^{4,5} | S. Mark Scott^{15,16} | Magnus Simrén¹⁷ | Peter Whorwell¹⁸ | The Functional Constipation Guidelines Working Group

¹Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Badalona, Spain

²Motility and Functional Gut Disorders Unit, University Hospital Germans Trias i Pujol, Badalona, Spain

³Department of Medicine, Autonomous University of Barcelona, Badalona, Spain

⁴Division of Gastroenterology, University Hospital Zurich, Zurich, Switzerland

⁵Department of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland

⁶Digestive System Research Unit, University Hospital Vall d'Hebron, Barcelona, Spain

⁷Division of Gastroenterology B, AOUI Verona, Verona, Italy

⁸UNC Center for Functional GI and Motility Disorders, University of North Carolina, Chapel Hill, NC, USA

⁹Department of Gastroenterology, UMR INSERM 1073, Rouen University Hospital, Rouen, France

¹⁰Department of Physiology, UMR INSERM 1073 & CIC INSERM 1404, Rouen University Hospital, Rouen, France

¹¹General Practice, Faculty of Medical Sciences, Newcastle University, Newcastle, UK

¹²Department of Medicine, Israelitic Hospital, Hamburg, Germany

¹³Sant Adrià de Besòs (Barcelona) Catalan Institut of Health (ICS), La Mina Primary Health Care Centre, Badalona, Spain

¹⁴Department of Surgery, Division of General Surgery, Medical University of Graz, Graz, Austria

¹⁵Neurogastroenterology Group, Centre for Neuroscience, Surgery and Trauma, Blizard Institute, Barts, UK

¹⁶The London School of Medicine & Dentistry, Queen Mary University London, London, UK

¹⁷Department of Internal Medicine & Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

¹⁸Division of Diabetes, Endocrinology & Gastroenterology, Neurogastroenterology Unit, Wythenshawe Hospital, University of Manchester, Manchester, UK

Correspondence

Jordi Serra, Gastroenterology Department, University Hospital Germans Trias i Pujol, 08916-Badalona, Spain.
Email: jserrap.germanstrias@gencat.cat

Funding information

There was no financial support or funding for the development of the guidelines.

Abstract

Introduction: Chronic constipation is a common disorder with a reported prevalence ranging from 3% to 27% in the general population. Several management strategies, including diagnostic tests, empiric treatments, and specific treatments, have been developed. Our aim was to develop European guidelines for the clinical management of constipation.

Design: After a thorough review of the literature by experts in relevant fields, including gastroenterologists, surgeons, general practitioners, radiologists, and experts in gastrointestinal motility testing from various European countries, a Delphi consensus process was used to produce statements and practical algorithms for the management of chronic constipation.

Key Results: Seventy-three final statements were agreed upon after the Delphi process. The level of evidence for most statements was low or very low. A high level of evidence was agreed only for anorectal manometry as a comprehensive evaluation of anorectal function and for treatment with osmotic laxatives, especially polyethylene glycol, the prokinetic drug prucalopride, secretagogues, such as linaclotide and lubiprostone and PAMORAs for the treatment of opioid-induced constipation. However, the level of agreement between the authors was good for most statements (80% or more of the authors). The greatest disagreement was related to the surgical management of constipation.

Conclusions and Inferences: European guidelines on chronic constipation, with recommendations and algorithms, were developed by experts. Despite the high level of agreement between the different experts, the level of scientific evidence for most recommendations was low, highlighting the need for future research to increase the evidence and improve treatment outcomes in these patients.

KEYWORDS

chronic constipation, guidelines, Delphi process, management of constipation

1 | INTRODUCTION

Chronic constipation is a common disorder with a reported prevalence ranging from 3% to 27% in the general population.^{1,2} Its prevalence increases with age^{3,4} and consequently is expected to rise over the next few years,⁵ in parallel with the predicted increase in longevity of the European population. Constipation is a symptom that may have diverse etiologies, and for this reason, several diagnostic approaches and treatment options are available, ranging from simple lifestyle changes and general measures to sophisticated pharmacological treatments and surgical interventions.⁶ In an attempt to unify the health care received by the population across Europe, the European Society of Neurogastroenterology and Motility (ESNM) decided to develop European guidelines to help physicians to take the best decisions to improve the quality of health in patients suffering from common functional and motor disorders. In this document, we present the ESNM guidelines for chronic constipation, which are intended to be a useful tool for the management of this condition in the general population in Europe. In order to produce comprehensive guidelines addressing the different aspects related with constipation, experts from European countries working in related fields developed relevant statements after a thorough review of the available literature, and final recommendations and management algorithms were produced following a Delphi consensus process.

2 | METHODS

2.1 | Participants

A chair (Jordi Serra) and co-chair (Daniel Pohl) were commissioned by the ESNM Steering Committee to develop the guidelines. A panel

Key Points

- Chronic constipation is a common disorder with a reported prevalence ranging from 3% to 27% in the general population. Multiple management strategies, including diagnostic tests, empiric treatments, and specific treatments, are known to be used.
- The aim of the present manuscript was to create European guidelines for the clinical management of constipation, developed by experts in different fields related to constipation across Europe.
- After a full review of the literature, relevant statements, final recommendations, and management algorithms were produced using a Delphi consensus process

of 12 experts from different European countries, constituted by gastroenterologists, surgeons, general practitioners, radiologists, and experts in gastrointestinal (GI) motility testing, was invited by the chairs to participate in the development of the guidelines. Each expert was assigned to develop a specific area of the document (see below) and to establish a team with one or two co-workers to complete the assigned task. The final ESNM guidelines working group was composed of 13 experts and 9 co-authors.

2.2 | The Delphi consensus

Each expert and co-worker conducted a thorough review of the literature in their specific field of expertise. The following areas were covered by the different subgroups: (a) Definition. (b) Pathophysiology: causes and predisposing factors. (c) Diagnostic approach: clinical

approach and basic investigations; functional studies; radiological studies. (d) Treatment: lifestyle and general measures; bulking agents and osmotic laxatives; stimulant laxatives; prokinetics and secretagogues; biofeedback therapy; alternative treatments; probiotics; and surgical treatment. Based on the results of the search, several statements with specific recommendations were produced by each expert and rated according to the level of evidence. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was used to rate the level of evidence and recommendation. In parallel, an algorithm for the management of constipation was developed by the chair. When all the statements had been received from all the authors, a Delphi consensus process was initiated by sending all the statements and algorithms to all the experts for anonymous voting, with progressive refinement and revoting of the reformulated statements.

Finally, each expert wrote the final statements corresponding to the assigned section, including comments, unmet needs, and the literature supporting the evidence of the recommendations, and three algorithms for the management of constipation were produced. The level of agreement between authors for each statement is shown in Figure 1. Algorithms for the management of constipation are in Figures 2-4.

3 | RESULTS

3.1 | Definition

3.1.1 | Statement 1: Constipation is defined as difficult, unsatisfactory, or infrequent defecation

- Level of evidence: Not applicable
- Recommendation: Not applicable
- Level of agreement: 100% (Figure 1).

This definition is consistent with the definitions of chronic constipation used in recent guidelines and in the Rome consensus for functional constipation (FC).^{7,8} The term unsatisfactory evacuation has been chosen as a general and comprehensive term that includes, among others, feeling of incomplete evacuation. The term difficult evacuation includes straining, sensation of anorectal obstruction, and need for manual maneuvers to facilitate evacuation.

3.2 | Pathophysiology

3.2.1 | Causes and predisposing factors

Statement 2: The prevalence of constipation is higher in women

- Level of evidence: High
- Recommendation: Not applicable
- Level of agreement: 100%

Current evidence and literature. The available evidence points toward a clear sex preponderance in women. Most of the studies in a systematic review⁹ reported a predominance of females in the prevalence of constipation. The mean female/male ratio was 1.78 (median 1.58), but differed according to the definition of constipation (1.7 for Rome I, 1.8 for Rome II, and 2.3 for self-reporting of constipation).

Female predominance was also shown in a recent epidemiological study in FC patients based on Rome III Criteria, with a higher prevalence in female (17.4%) compared to male students (12.5%).¹⁰ In univariate logistic regression analysis, FC was significantly associated with sex (odds ratio [OR] 1.48, 95% confidence interval [CI] 1.06-2.06). In a different population of 7251 constipated patients and 7103 controls, Talley et al³ showed an OR of 1.62 (95% CI

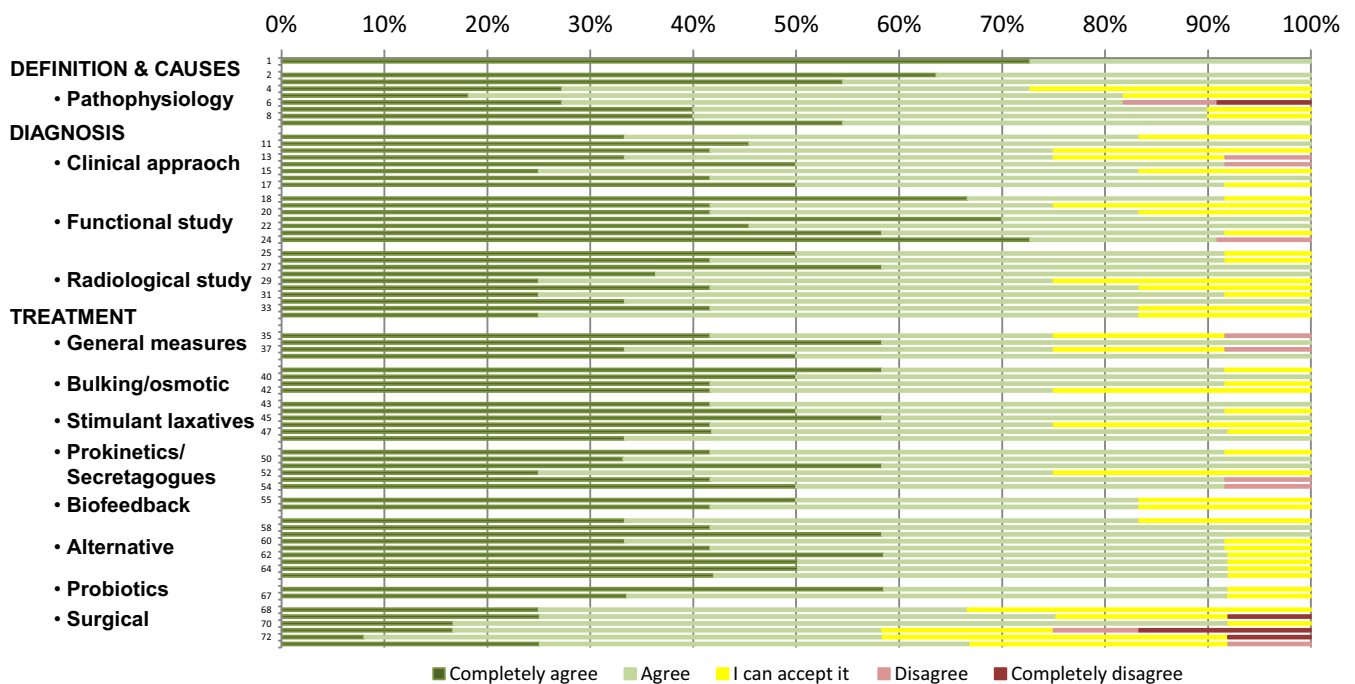


FIGURE 1 Final agreement between the authors for each of the statements produced after the Delphi consensus process

1.49-1.76) in females. This predominance of females has been attributed to hormonal factors, such as a higher risk of constipation during the luteal phase of the menstrual cycle and the effect of progesterone, most notably in pregnancy, and damage to the pelvic floor muscles that may occur in women during childbirth or gynecological surgery. This effect of additional progesterone on colonic transit could also be confirmed in a prospective study by Gonneke et al¹¹ in 49 postmenopausal women.

Additionally, premenopausal women (age 25-49) were shown to have longer transit times than older women (64.0 vs 59.5 hours; difference 4.6 hours, 95% CI 1.1-8.1 hours).¹² This leads to less pronounced gender differences in constipation prevalence in the older population.

Future research/unmet needs. Investigations on further pathophysiological differences except for the hormonal situation between men and women should be done.

Statement 3: The prevalence of constipation increases with age

- Level of evidence: High
- Recommendation: Not applicable
- Level of agreement: 100%

Current evidence and literature. It is generally perceived that the prevalence of constipation increases with age. In a postal health survey in 41 724 Australian women,⁴ the prevalence of constipation was 14.1% (CI 13.5-14.7) in young women (18-23 years), 26.6% (CI 25.9-27.4) in middle-aged women (45-50 years), and 27.7% (CI 26.9-28.5) in older women (70-75 years). In data analyses from the General Practice Research Database (GPRD) in the United Kingdom, Talley et al³ showed a higher OR of constipation in patients >75 years compared to controls (OR 1.96, 95% CI 1.71-2.24).

Future research/unmet needs. The effects of aging on intestinal connective tissue, influence of hormonal status in relation to gut motility, and age-related changes in the microbiome should be evaluated to analyze functional, intestinal, and external structures as underlying causes of constipation and defecation disorders.

Statement 4: A positive family history of constipation predisposes the individual to constipation, including earlier age of onset, longer duration, and higher rate of complications

- Level of evidence: Low
- Recommendation: Not applicable
- Level of agreement: 100%

Current evidence and literature. Genetics and/or epigenetics may play a role in FC. Chan et al¹³ analyzed the clinical characteristics of FC in 118 FC patients and 114 patients without FC according to the Rome II questionnaire. Patients with a positive family history of FC showed younger age at onset (median 11-20 years vs 21-30 years, $P < .001$) and longer duration of constipation (20 ± 14 vs 15 ± 13 , $P = .016$). Additionally, more complications,

for example, symptomatic hemorrhoids, anal fissure and rectal prolapse (54.2% vs 40.4%, $P = .034$); fewer precipitating factors leading to the onset of constipation (35.6% vs 49.1%, $P = .037$); and more frequent use of digital evacuation (27.1% vs 13.2%, $P = .008$) were seen in patients with a positive family history of FC. Another study by Ostwani et al¹⁴ demonstrated significantly higher rates of constipation in siblings or parents of children with functional, habitual constipation than in controls (30% vs 7% and 42% vs 9%, respectively; $P = .001$).

Future research/unmet needs. Genetic and epigenetic studies are needed.

Statement 5: Lower social, economic, and educational levels are associated with a higher prevalence of constipation

- Level of evidence: Low
- Recommendation: Not applicable
- Level of agreement: 100%

Current evidence and literature. In general, individuals of lower social, economic, and educational levels have a tendency toward higher constipation rates. Bytzer et al¹⁵ divided the sample of their questionnaire survey into five socioeconomic classes from 1st (highest) to 5th (lowest). They showed that the standardized prevalence rate (95% CI) for constipation symptoms was lowest in the 1st quintile (2.81 in males and 8.53 in females) compared to the 2nd to 5th quintile (4.03, 6.99, 5.68, and 5.15 in men and 14.06, 13.35, 13.95, and 14.31 in women). Of interest, according to another study,¹⁶ constipation correlated with a low maternal educational level (1.60; 1.08-2.35). However, there may be a composite effect of socioeconomic class and a low fiber intake. In a systematic review including 75 different studies, Allen et al¹⁷ concluded that there was less consumption of fiber, fruit, and vegetables in lower socioeconomic classes.

Future research/unmet needs. Prospective behavioral studies are of interest; however, it will be unlikely to change practice.

Statement 6: After careful exclusion of a defecatory disorder with anorectal function testing including defecography, at least half of patients with functional constipation do not show signs of delayed colonic transit

- Level of evidence: Low
- Recommendation: Not applicable
- Level of agreement: 82%

Current evidence and literature. Different pathophysiological mechanisms may lead to FC. Constipation can be classified into three categories: functional defecatory disorders, normal colonic transit, and slow colonic transit.¹⁸ In a review of medical records, 1411 patients were analyzed between 1994 and 2011 by a single gastroenterologist. The majority (960, 68%) of patients had normal transit constipation (NTC), 390 (28%) had dyssynergic defecation

(DD) (abnormal balloon expulsion test and/or high anal sphincter pressure and/or failure of the anorectal angle to open), and 61 (1%) suffered from slow-transit constipation (STC) (diagnosed by colon transit scintigraphy).¹⁹

Future research/unmet needs. There is still a lack of understanding how best to separate individual patient symptomatology from meaningful pathologic transit. Further research is needed in this area.

Statement 7: There is increased prevalence of rectal hyposensitivity in constipation

- Level of evidence: Very low
- Recommendation: Not applicable
- Level of agreement: 100%

Current evidence and literature. Shekar et al²⁰ demonstrated anorectal hyposensitivity in FC (27%) compared to constipation-predominant irritable bowel syndrome (IBS-C) patients (4%) using 2.5th and 97.5th percentiles for pain threshold for healthy volunteers (18 mm Hg and 42 mm Hg, respectively). Hypersensitivity was seen in 30% IBS-C patients and no FC patients.

Another study by Gladman et al²¹ also showed a higher prevalence of rectal hyposensitivity in patients with constipation (23%) and incontinence associated with constipation (27%) compared to patients with fecal incontinence only (10%) and "others" (patients with anorectal physiologic investigations without constipation or fecal incontinence, 5%).

Future research/unmet needs. Research should be conducted on the mechanisms/pathophysiology of the development of hyposensitivity (primary, secondary) in constipation.

Statement 8: The volume of interstitial cells of Cajal in the sigmoid colon and the neuronal structures within the colonic circular smooth muscle layer are decreased in patients with slow-transit constipation

- Level of evidence: Low
- Recommendation: Not applicable
- Level of agreement: 100%

Current evidence and literature. The pathophysiology of constipation, in particular STC, is not completely understood. Focusing on motility, He et al²² analyzed the role of interstitial cells of Cajal (ICC) in STC patients. They found a significantly decreased volume of ICC in all layers of sigmoid colonic specimens in STC patients compared to controls. Neuronal structures within the colonic circular smooth muscle layer were also decreased.

Future research/unmet needs. Research should be conducted on the mechanisms/pathophysiology of the development of hypo-/dysmotility in constipation. Current studies with histological data come from very select patients with more pronounced symptoms that may not be representative of ordinary constipation. A way to move forward would make use of recent developments such as

full thickness resection devices that allow endoscopic retrieval of representative specimen²³

Statement 9: Evacuation disorders represent an important underlying cause of constipation and should be excluded before diagnosing isolated slow-transit constipation

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Battaglia et al²⁴ showed that, one year after biofeedback therapy, only 20% of patients with STC maintained a beneficial effect compared to 50% of patients with pelvic floor dyssynergia (PFD). In the short term (three-month assessment), both groups showed a significant improvement in abdominal pain, straining, number of evacuations/week, and laxative use. The less effective biofeedback therapy in STC may be due to more complex pathophysiology and multiple involved factors like impairment of propulsive activity²⁵ and physiologic reflexes²⁶ not only in the most distal part of the bowel like in PFD. As not only therapy but also the underlying pathophysiology might be different in FC, PFD should be excluded.

Future research/unmet needs. Pathophysiological studies that can discriminate/predict modifiable and innate factors of FC are needed.

3.3 | Diagnostic approach

3.3.1 | Clinical approach and basic explorations

Statement 10: The diagnosis of constipation can be made mainly on symptoms alone. Objective testing can be performed if considered necessary to identify underlying pathophysiological mechanisms

- Level of evidence: Very low
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Despite very low evidence, most consensus guidelines agree that the diagnosis of constipation in the clinical setting is mainly made on the basis of symptoms alone.^{5,6,27-30} A US survey showed that the most frequent symptoms of chronic constipation were straining, hard stools, abdominal discomfort, bloating, infrequent bowel movements, and feeling of incomplete evacuation after bowel movement.³¹ Hence, the guidelines underscore the importance of a careful history assessing the presence of these symptoms and their duration and progression. Specific validated questionnaires, like the Patient Assessment of Constipation Symptoms (PAC-SYM) questionnaire or the Bristol stool scale, can be used for the clinical evaluation of the patient with constipation.³² Objective testing is recommended when the physician considers it necessary to rule out organic disease, that is, if alarm symptoms are present, or in refractory cases to identify underlying pathophysiology that may help guide treatment.

Statement 11: The most frequent symptoms of chronic constipation are straining and hard stools

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. The prevalence of specific symptoms in chronic constipation has been addressed in systematic reviews and meta-analyses.^{5,6,27-30,33-38} These studies have agreed that straining and hard stools are the most frequent symptoms of chronic constipation.

Statement 12: For diagnosis of functional constipation, the Rome IV criteria are recommended

- Level of evidence: Not applicable
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. The Rome IV criteria include the following symptoms: (a) straining; (b) hard stools (Bristol 1-2); (c) sensation of incomplete evacuation; (d) sensation of anorectal obstruction; (e) need for manual maneuvers to facilitate evacuation; and (f) less than 3 spontaneous bowel movements per week.⁶ Despite differences in the prevalence of each individual symptom, the authors chose to maintain the 25% rule (symptom present in 25% of stool movements) for all symptoms to facilitate the use of the criteria in the clinical setting.^{28,30,37,39} However, in the clinical setting, especially in pragmatic primary care, patients can be diagnosed with FC with no awareness of formal criteria.

Statement 13: For the diagnosis of chronic constipation, patients must not fulfill criteria for IBS. This means not having abdominal pain as the primary symptom

- Level of evidence: Low
- Recommendation: Weak
- Level of agreement: 92%

Current evidence and literature. The differentiation between IBS-C and FC is an area of major controversy. Most authors consider that the presence of abdominal pain is the cornerstone for differentiating between both disorders. However, as recognized in the Rome IV criteria, functional bowel disorders are a spectrum of disorders with great overlap and no clear or definite borders that differentiate them in clinical practice. Hence, bloating and abdominal pain are often seen in patients with constipation. In line with recent recommendations, we believe that the diagnosis of IBS should be considered only when abdominal pain is the main symptom in a patient with constipation, but not when it is just a secondary accompanying symptom.^{6,27,40-42}

Future research/unmet needs. There is a lack of objective biological markers that can differentiate between FC and IBS-C.

Statement 14: In constipated patients on opioid medication, opioid-induced constipation (OIC) should be considered as a differential diagnosis

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 92%

Current evidence and literature. Constipation is a common side effect of opioid use that can affect up to 81% of patients, even with the concomitant use of laxatives.⁴³ Due to the increasing use of opioids in Western countries, there is a strong need to rule out the use of opioids in patients with constipation, especially considering that opioid consumption is not always reported by patients.^{6,28,37,43-45}

However, in these patients, other aspects related to the illness requiring opiates such as anorexia, immobility, and concomitant treatments have also to be considered. Owing to receptor downregulation, the opiate effect on both pain and the bowel declines over time, and finally, the best test of whether opiates are truly responsible is an improvement on discontinuing therapy or response to naloxegol.

Statement 15: A simple blood test should be performed in the evaluation of patients with constipation to identify secondary causes

- Level of evidence: Very low
- Recommendation: Strong
- Level of agreement: 100%.

Current evidence and literature. Observational studies have identified thyroid- and calcium-related disorders as potential causes of constipation. Consequently, several consensus reports^{6,28,29,33-36} emphasize the relevance of a simple blood test including glucose, calcium, and thyroid-stimulating hormone (TSH) in the evaluation of patients with constipation.⁴⁶

Future research/unmet needs. Cost-effectiveness analysis on the value of blood test in patients without other symptoms suggestive of endocrine or metabolic disorders.

Statement 16: The Bristol Stool Form Scale (BSFS) can be used to record stool consistency in patients with constipation

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. The usefulness of the BSFS in assessing constipation has been demonstrated in different studies. Lewis et al²⁶ showed concordance between the whole gut transit time objectively measured with radiopaque markers and the stool form score. The BSFS has been proposed as a reliable indicator of FC that may be particularly useful in assessing patients with some discrepancy between the frequency of bowel movements and stool hardness.^{32,46,47} Even though other aspects related to individual motor patterns or efficiency of water absorption could

influence stool form, the authors agree that the BSFS is a useful but underused tool for clinical practice.

Statement 17: Physical examination in patients with FC should always include digital rectal examination (DRE)

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Digital rectal examination (DRE) is a very important physical examination in the diagnosis of a patient with constipation. DRE can detect stool in the rectal vault, anorectal masses, hemorrhoids, anal fissures, rectal prolapse, and rectoceles that may cause constipation. DRE should be performed at rest, and asking the patient to strain, to identify alterations such as dyssynergic anal contraction, excessive or defective anal descent, or other structural abnormalities that are not apparent at rest.⁴⁸⁻⁵³ However, due to the non-physiological conditions of the DRE, the final diagnosis of an evacuation disorder needs confirmation with functional studies.

3.3.2 | Functional studies

Statement 18: Functional testing in chronic constipation is recommended (where available) when first-line therapeutic measures have failed to improve symptoms

- Level of evidence: Very low
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Patients consulting for constipation should initially be empirically managed with lifestyle and dietary modifications, withdrawal (or reduction) of constipating medications, and fiber supplementation.⁵⁴ Most patients will respond adequately to these first-line therapeutic measures, and therefore, specialized diagnostic evaluation should only be offered to patients in whom these measures fail to improve symptoms.⁴⁸ Advanced functional testing is not available in all settings; however, procedures such as the balloon expulsion test (BET) and whole gut transit evaluation using radiopaque markers may be performed even when resources are limited.⁵⁴

Future research/unmet needs. First-line measures are effective in most patients, but adherence is generally low. Increasing compliance to diet and laxatives is an area for improvement.

Statement 19: Etiological factors to be evaluated in chronic constipation are: defecatory function (abdominal compression/anal relaxation), intrinsic innervation by rectoanal inhibitory reflex (minimal incidence of primary neuropathies and Hirschsprung's disease in adults, but increasing incidence of Chagas disease), colonic transit, and rectal sensation/compliance (in neurological diseases and severe cases)

- Level of evidence: Low
- Recommendation: Strong

- Level of agreement: 100%

Current evidence and literature. The purpose of functional testing is to determine the pathophysiological mechanisms of constipation and subsequently guide therapeutic measures.⁴⁶ Tests evaluating defecatory function, specifically anorectal manometry (ARM), and BET should be the initial investigations, because evacuation disorders are highly prevalent and may be less likely to respond to first-line therapeutic measures.⁵⁵ Other dynamic tests, generally not as widely available as ARM and BET, but providing valuable complementary information on defecatory function, include defecography, electromyography, and ultrasonography. None of the tests are individually sufficient to diagnose a defecation disorder, and therefore, at least two abnormal evacuation tests are considered necessary to diagnose a functional defecation disorder (FDD).⁵⁶

Other primary etiological factors of chronic constipation to be evaluated are intrinsic innervation and colonic transit. In addition, functional testing is also useful to diagnose the consequences of chronic constipation: abnormal rectal compliance and perineal damage.

Future research/unmet needs. Test protocols should be standardized, including instructions to the patient, which have been shown to significantly influence the outcome.⁵⁷ Studies evaluating ARM in healthy volunteers have shown dyssynergic patterns, which have been attributed to the non-physiological position during the test, embarrassment or fear of incontinence.⁵⁸

Statement 20: Anorectal manometry evaluates defecatory function (coordination of abdominal compression and anal relaxation) and intrinsic innervation by the rectoanal inhibitory reflex (primary etiologic factors) and sphincter function and rectal sensitivity/compliance

- Level of evidence: High
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Evaluation of the defecatory maneuver during ARM should demonstrate adequate coordination between the increase in intrarectal pressure and anal relaxation. Weak abdominal compression and inadequate relaxation of the anal canal are the physiological basis of DD, an important cause of functional constipation.⁵⁹

The rectoanal inhibitory reflex (RAIR) depends on the intrinsic innervation of the gut. An abnormal RAIR is typically found in Hirschsprung's disease but may also be detected in other visceral neuropathies such as Chagas disease.⁶⁰ Technical aspects are important when evaluating the RAIR. A common pitfall is insufficient rectal distension in patients with megarectum, which may be overcome by using a barostat to obtain sufficient pressure.⁶¹

Future research/unmet needs. There is significant discrepancy between methods in data acquisition, analysis, and interpretation

of ARM; there is a need for expert international cooperation to standardize ARM.⁶²

Statement 21: High-resolution manometry is as useful as conventional manometry and may be helpful in the interpretation of the defecatory maneuver

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. High-resolution manometry obtains circumferential pressure measurements of the anal canal and distal rectum. Unlike conventional manometry, it may detect asymmetry of the anal pressures at rest or during squeeze.⁶³ In addition, topographical color-contour plots may facilitate interpretation of the defecatory maneuver compared to conventional manometry.⁶⁴ However, no significant differences in the diagnosis of DD have been detected when directly compared.⁶⁵⁻⁶⁷

Statement 22: An abnormal balloon expulsion test is indicative of an impaired defecatory maneuver and may predict a better response to biofeedback therapy

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. The BET measures the capacity and time to evacuate an air- or water-filled balloon from the rectum. This test has been shown to be abnormal in a high proportion of patients with an evacuation disorder,⁶⁸ but as mentioned previously, is not diagnostic as a single test. In fact, agreement with disordered defecation measured with ARM is relatively low. Indeed, the BET may be normal in patients with DD who are able to compensate by excessive straining. The BET has been shown to predict response to biofeedback therapy,^{69,70} although this finding is not uniform in all studies.⁷¹

Future research/unmet needs. There is considerable disagreement between the tests of evacuatory function; diagnostic criteria for impaired defecatory function should be established.⁷²

Statement 23: Rectal compliance is evaluated by the pressure/volume relationship with an air-filled rectal bag. Patients with constipation may have higher rectal compliance than controls

- Level of evidence: Low
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Rectal compliance may be measured by evaluating the pressure/volume relationship during progressive rectal distension with a balloon. For this purpose, the use of a barostat is useful because it allows direct measurement of rectal capacity at fixed pressure levels.⁷³ Increased rectal compliance may

be associated with chronic constipation, particularly in children with megarectum.⁷⁴ Nevertheless, in pediatric constipation, increased rectal compliance has not been shown to increase treatment failure.^{75,76}

Statement 24: Oro-anal transit is most commonly measured by radiopaque markers; interpretation of slow colonic transit is not reliable in the case of functional or organic outlet obstruction

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 91%

Current evidence and literature. The radiopaque marker (ROM) test is the current standard test for the evaluation of oro-anal transit, with the advantages of low cost, simplicity, and wide availability. Unfortunately, protocols are not standardized, and the technique varies widely between centers. Alternatively, the Smart Pill test and scintigraphy may be used to evaluate colonic transit times and have been shown to correlate well with the ROM test.⁷⁷

STC is characterized by a delayed colonic transit time. However, transit time may also be delayed in patients with important fecal retention or with an evacuation disorder, so these must be excluded to identify patients with STC alone.⁷⁸⁻⁸⁰ In patients with FC, transit times have been shown to correlate well with stool consistency/form but poorly with stool frequency and associated symptoms.^{47,81}

Future research/unmet needs. The procedure should be standardized.

3.3.3 | Radiological studies

Statement 25: The recommended test name is 'defecography' (barium or magnetic resonance [MR])

- Level of evidence: Very low
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. The terminology is far from being universally accepted, given the numerous technical variations and the plethora of synonyms for defecography employed since its conception⁸²: "cineradiographic defecography,"⁸³ "cinedefecography,"⁸⁴ "evacuating"⁸⁵ or "evacuation proctography,"²¹ "defecation"⁸⁶ or "defecating proctography,"⁸⁷ "videodefecography,"⁸⁸ and "videoproctography."⁸⁹ However, the term "defecography" has been most commonly reported (~60% of all published articles); it was initially proposed by Mahieu⁹⁰ to more clearly imply that the physiological act of defecation is examined in dynamic conditions analogous to the investigation of deglutition or micturition.

Future research/unmet needs. One of the principle challenges will be to promote standardization of the language and the technique so that results are transferrable between institutions.

Statement 26: Normative data for structural and functional parameters are available for both barium and MR defecography, but are limited in their scope, particularly for MR. There may be considerable overlap in findings between health and disease

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. A total of only four studies have been conducted in ≥ 40 healthy subjects, two using barium [X-ray] defecography (BD)^{91,92} and two using MR defecography (MRD).^{93,94} Regardless of the technique, a consistent criticism of defecography is the acknowledged overlap between health and disease,⁹¹ hampered by a paucity of normative data, which challenges our ability to define 'true' (pathologic) abnormalities.

Future research/unmet needs. The optimal technique for BD and MRD remains to be defined and should be subject to a Working Group initiative. Normative values are only applicable to specific protocols and are mostly derived from female patients (for MRD, data existing for males are derived from a cohort of only 25 subjects in one study⁹³).

Additional comments. Normative data sets have provided evidence of truly pathologic findings (ie, those not seen in health), such as large rectoceles, high-grade intussuscepta, and enteroceles (whole gut or oro-anal).⁹⁵

Statement 27: Adherence to standardized study protocols is necessary

- Level of evidence: Low
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. The prevalence of structural and functional abnormalities detected by defecography is high, but varies considerably across studies, with high heterogeneity depending on technical protocol variations and diagnostic criteria used. For example, several different cutoffs have been used to define (a) dynamic perineal descent (ranging from 2 to 6 cm)^{96,97}; (b) the magnitude of the infolding for rectal intussuscepta (any fold "more than a wrinkling of the mucosa"⁹⁸; ≥ 3 mm⁹⁹; > 4 mm^{84,100}; or > 1 cm^{97,101}); and (c) severity of rectocele based on maximum depth: 2 cm^{93,99,102-107}; 2.5 cm¹⁰⁸; 3 cm^{84,89,109,110}; or 4 cm.^{72,111,112}

Future research/unmet needs. As above, standardization of protocols is a prerequisite for obtaining results that are robust, reproducible, and easily transferable between institutions.

Statement 28: Barium defecography is indicated in patients with refractory symptoms of an evacuation disorder and can accurately delineate several rectal structural abnormalities that often coexist

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. The prevalence of pathologic high-grade (ie, Oxford III and IV) rectoanal intussusceptions and external rectal prolapse (ie, Oxford grade V) on BD is 23.7% (95% CI, 16.8-31.4; based on 13 studies) and 5.3% (95% CI, 3.1-8.0; based on 16 studies), respectively. The prevalence of large (> 4 cm) pathologic rectoceles is 15.9% (95% CI, 10.4-22.2; based on 9 studies). Enterocele and excessive perineal descent are observed in 16.8% (12.7-21.4) and 44.4% (36.2-52.7) of patients, respectively⁹⁵ (numerous references omitted for the sake of brevity).

Future research/unmet needs. As per the points listed above, optimum cutoffs to define true abnormalities (both in terms of anatomical features and in terms of impaired evacuation) need to be refined, based on standardized protocols.

Statement 29: Among commonly performed investigations for symptoms of an evacuation disorder (eg, ARM, BET, sonography), barium defecography can be considered the gold standard for assessment of structural rectal abnormalities

- Level of evidence: Low
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. BD is considered the gold standard for the assessment of posterior compartment disorders, given its capability to dynamically evaluate the rectum during simulated defecation.¹⁰⁸ Its particular advantage over BET and manometry is that it enables characterization of structural abnormalities.^{72,91} BET and manometry are, de facto, unable to provide such information. A total of four studies (including ≥ 40 subjects) have used BD as the reference standard to assess the diagnostic yield of other imaging modalities (ie, echodefecography^{113,114} and dynamic transperineal ultrasound^{115,116}) in diagnosing posterior pelvic floor compartment disorders.

Future research/unmet needs. There is considerable disagreement between the results of various tests used to diagnose evacuation disorders. Diagnosis is test-dependent, which impacts upon patient management. This highlights the need for a reappraisal of both diagnostic criteria, and what represents the 'gold standard' investigation. There is also further scope for research in comparing the results of barium versus MR defecography.

Statement 30: There is no single gold standard investigation for diagnosis of a 'functional' evacuation disorder. Nevertheless, defecography can identify specific causes (eg, ineffective expulsive force, non-relaxing puborectalis, etc [terminology inconsistently reported]), which may guide treatment

- Level of evidence: Low
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. In defecography, the diagnosis of a functional abnormality is made using three possible features,

originally described by Mahieu et al,¹¹⁷ either combined or in isolation: (a) poor opening of the anorectal angle (secondary to poor relaxation or indeed 'paradoxical' contraction of the puborectalis muscle); (b) poor anal sphincter relaxation; and (c) incomplete and/or prolonged evacuation based on percentage of contrast expelled and/or time taken, respectively. Diagnostic criteria and prevalence of functional abnormalities have been provided in 42 studies of ≥ 40 constipated patients, based on either 'a' (n = 22)^{89,100,102,103,107,115,118-133}; 'b' (n = 2)^{109,134}; 'c' (n = 2)^{135,136}; 'a + b' (n = 4)^{96,108,111,137}; 'a + c' (n = 7)^{84,85,113,116,138-140}; 'b + c' (n = 1)¹¹²; or 'a + b+c' (n = 4).^{72,114,141,142} Quantitative meta-analysis of these studies, including four comparative (BD vs MRD) studies, shows a pooled prevalence of 24.1% (95% CI, 20.2-28.4) for BD and 25.9 (14.1-39.6) for MRD.⁹⁵

Future research/unmet needs. There is a need for prospective studies designed to evaluate the utility and cost-effectiveness of different diagnostic modalities to tailor management of constipation, and to determine predictors of response to biofeedback therapy.

Statement 31: Barium defecography is useful in evaluating the outcome of surgical interventions for structural rectal abnormalities, particularly in patients with ongoing or recurrent symptoms

- Level of evidence: Low
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. Three studies have used BD to assess outcomes of stapled transanal rectal resection (STARR).¹⁴³⁻¹⁴⁵ One study compared the results of biofeedback retraining, botulinum toxin type A injection, and partial division of puborectalis (PDPR) in a randomized study of 60 patients with anismus.¹⁴⁶

Future research/unmet needs. Defecography is widely used by the surgical community to direct surgical management in patients with constipation/evacuation disorder, where the operating procedure is directed to reversal of demonstrable posterior compartment abnormalities (eg, rectocele, high-grade intussusception) that are consistent with presentation of symptoms. However, no randomized controlled trials (RCT) or prospective stratified medicine studies are currently available. Such studies are required now more than ever, given that litigation and intense media scrutiny have forced surgeons to rigidly objectify their motivation for offering surgery.

Statement 32: MR defecography is indicated in patients with refractory symptoms of an evacuation disorder and has the advantage of routinely evaluating all pelvic compartments in those with suspected multicompartamental structural defects. However, comparative data with barium defecography are currently limited

- Level of evidence: Low
- Recommendation: Strong
- Level of agreement 100%

Current evidence and literature. A multiplanar, diagnostic assessment of the anterior, middle, and posterior compartments is possible with MRD. Five studies, comprising ≥ 40 study subjects, have compared BD to MRD.^{104,107,108,136,139} BD represented the reference standard in all studies, except one that adopted the results obtained from the joint analysis of BD and MRD as reference.¹⁰⁸ None of these studies followed the Standards for Reporting Diagnostic Accuracy (STARD) guidelines.

Future research/unmet needs. Well-designed diagnostic test accuracy studies following STARD criteria are needed.

Statement 33: MR and barium defecography are complementary and may provide additional diagnostic information when either one is equivocal or incomplete

- Level of evidence: Low
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Compared to BD, MRD allows a thorough assessment of all pelvic floor organs. However, in centers where MRD is the standard test, patients who fail to evacuate should also undergo BD or significant pathology will be missed.¹³⁹

Future research/unmet needs. Further well-designed comparative studies are required.

Statement 34: Barium defecography is likely to be superior to MR defecography in detecting structural posterior pelvic compartment abnormalities leading to obstructed defecation

- Level of evidence: Moderate
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. Pooled results from the five studies (each comprising ≥ 40 study subjects) that have compared BD to MRD^{104,107,108,136,139} show that BD is superior to MRD in the detection of intussusception (pooled prevalence: 57.8% vs. 37.8%; OR, 1.52 [95% CI 1.12-2.14, P = .009]), although BD is associated with higher levels of embarrassment (qualitatively measured among patients), lower tolerance (54.3% vs. 30.0%; OR, 1.73 [95% CI 1.14-2.62, P = .008]),⁹⁵ and higher radiation exposure.

Future research/unmet needs. Well-designed diagnostic test accuracy studies following STARD criteria are required to confirm these findings.

Additional comments. Concerns over the impact of patient test position on diagnostic yield for MRD (supine in closed-magnet configurations, considered non-physiological, vs upright in open-magnet configurations) are yet to be adequately addressed.

3.4 | Treatment

3.4.1 | Lifestyle and general measures

Statement 35: Exercise has neither a positive nor a negative effect on constipation

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 92%

Current evidence and literature. The literature does not delineate between functional constipation, chronic constipation, or constipation per se. The data are conflicting but largely against benefit from exercise alone for constipation. One study of secondary school pupils (hence, largely normal subjects), which used bowel evacuations less than every two days as the criterion, concluded that constipation was associated with “insufficient” exercise or sedentary behavior, and that this was dose-related to the amount of exercise taken.¹⁴⁷ Similarly, in an education-led program in 35 women with chronic constipation, there was an improvement in their Bristol Stool scores and symptoms.¹⁴⁸ However, the intervention was multilayered, consisting of advice on diet, fluids, and counseling. Conversely, in a study of healthy men over 35 days, intervention with experimentally controlled bed rest, stool consistency, and bowel symptoms was not influenced by physical inactivity.¹⁴⁹ In another study conducted over six weeks in patients with idiopathic constipation, exercise levels and constipation were assessed. The level of exercise did not correlate with constipation indices and the conclusion was that physical activity to the extent considered “regular exercise” did not play a role in the management of idiopathic constipation.¹⁵⁰ While data do indicate that GI transit times may be accelerated by exercise, this does not translate into outcomes in constipation. Although subjects with the slowest resting transit rates may show the largest exercise effects in mouth-to-cecum transit time, this is not necessarily reflected in constipation symptoms.^{151,152}

A review in 2011, which included two small randomized placebo-controlled trials and two cohort studies concluded that lifestyle modification to prevent or treat constipation, was not substantiated by evidence.¹⁵³ No systematic reviews exist for exercise and constipation, but exercise appears to be associated with a range of health benefits for people of all ages.^{150,152,154} A further review in 2011 confirmed conflicting evidence, again largely against the effect of exercise for constipation, with studies showing inconsistent effects.¹⁵⁵ However, physical activity was noted to improve quality of life (QoL) in some subjects in some studies and was associated with improved QoL and a decrease in symptom severity.¹⁵⁶

Future research/unmet needs. Evaluation of the level of exercise needed to maintain good general health and gastrointestinal health in individual people (Figures 2-4).

Statement 36: In patients who are not dehydrated, additional fluid intake alone does not have a positive effect on constipation

- Level of evidence: Low

- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Medical advice frequently stresses the importance of “good” fluid intake for general health and, in particular, to manage constipation. There are no clear definitions of what constitutes an adequate or therapeutic level of fluid intake in people with constipation. While there may be an association between “inadequate” fluid intake or dehydration and constipation, there is a lack of evidence to support that increased fluids alone are of benefit.^{148,154,156} In a study of 833 elderly patients with a mean age of 74 years, it was noted that 71% already drank six or more glasses of water daily and that there was no difference between them in terms of bowel symptoms and the 29% who drank less fluids.¹⁵⁷ In a 2011 review, only one RCT and one observational study was noted, with the RCT showing benefit from fluids only in the presence of additional fiber.¹⁵³ Thus, the evidence in relation to increased fluid intake alone, as being positive for the management of constipation, is sparse.

Future research/unmet needs. Larger, well-defined interventional studies should be done to provide data on appropriate intake for patients with constipation.

Statement 37: Dietary fiber alone within the normal (regular) diet helps functional constipation

- Level of evidence: Low
- Recommendation: Weak
- Level of agreement 92%

Current evidence and literature. This section relates to normal or regular intake of dietary components, essentially fiber, and does not relate to therapeutic supplements. However, much of the literature relates to fiber supplements and laxatives, and there is a paucity of data about lifestyle dietary measures geared to FC. A 2011 review concluded that, while increasing dietary fiber may help constipation caused by fiber deficiency, it should not be assumed that fiber deficiency is the main source of the problem.¹⁴⁸ Consuming a high fiber diet alone may not be as effective as combining it with increased fluid intake. The overall evidence for increased dietary fiber (as opposed to recommended or prescribed fiber) is weak, although the effect may be enhanced if increased fluids are included.^{148,153,156,158}

Future research/unmet needs. Interventional and observational studies in patients are needed.

Statement 38: Overall lifestyle measures may be of value in some patients to improve constipation, quality of life, and contribute toward better health

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

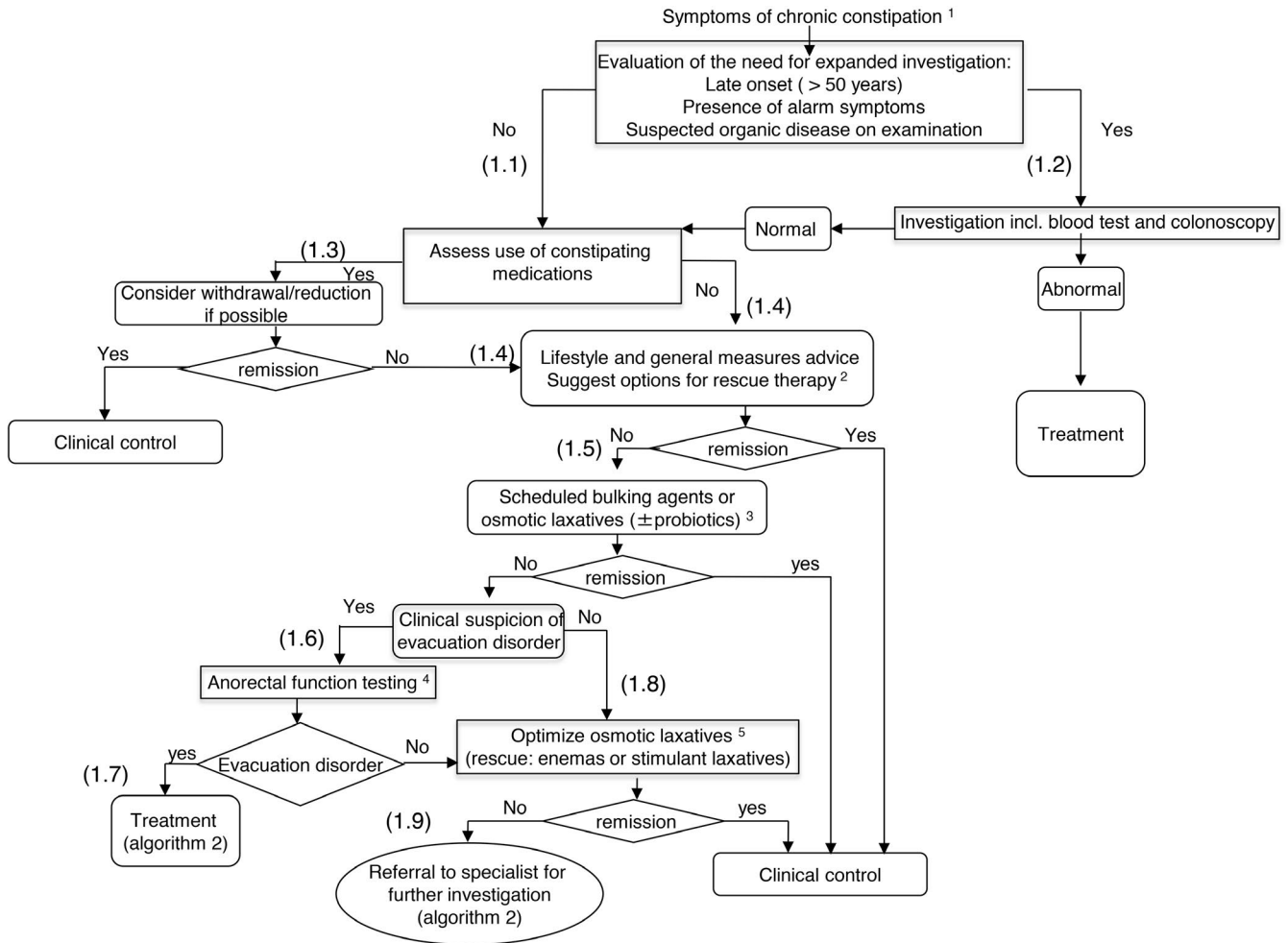


FIGURE 2 Algorithm 1. Management of constipation. First-line management of patients presenting with constipation at any level of the healthcare system. ¹Defined as difficult, unsatisfactory, or infrequent defecation for at least the previous 3 mo. ²Rescue therapy may include suppositories or rectal enemas, if accepted by the patient, or the use of fiber or osmotic laxatives on demand. Level of evidence very low. Recommendation strong. ³Use of probiotics seems promising; however, no strong evidence yet. ⁴When available, anorectal function testing may be indicated at this stage when there is clinical suspicion of an evacuation disorder (manual maneuvers, hemorrhoids, prolapse or rectocele, painful evacuation, etc). ⁵Alternatively, other treatments like prokinetics or secretagogues could be tried

Current evidence and literature. With regard to overall lifestyle modification (combined factors), most studies consist of interventions or studies of fiber intake, fluids, and exercise, but some also have additional factors such as counseling or individualized care. The effect of each of these is difficult to separate out. For example, an Egyptian study of 23 elderly patients with FC included group discussions about dietary patterns, fluid intake, physical activity, and the use of laxatives.¹⁵⁹ There was no control group, but the lifestyle modification education significantly reduced the severity of the FC and recorded improvements in QoL. Combined with data from other studies, this suggests that there is overall benefit from a combination of lifestyle measures, both in constipation and in the QoL measures.^{156,158} To this can be added the benefits from a more active lifestyle in terms of general health. While the data are not robust, this would seem a reasonable approach in the practical management of patients.

Future research/unmet needs. More studies are needed on overall lifestyle and gastrointestinal health.

3.4.2 | Bulking agents and osmotic laxatives

Statement 39: Bulking agents, in particular soluble fiber, are effective in the management of chronic constipation

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Despite the fact that bulking agents, in the form of either soluble or insoluble fiber, have relatively little support from large RCTs in patients with chronic constipation, these agents are often recommended as first-line treatment options for patients with chronic constipation. This is

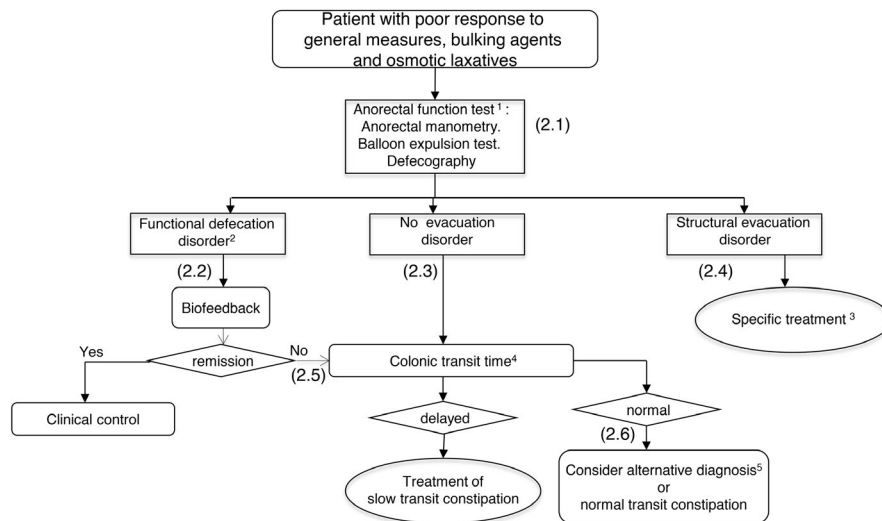


FIGURE 3 Algorithm 2. Further investigation of constipation. ¹Anorectal function testing with manometry should ideally include a balloon expulsion test. Depending on local availability and expertise, defecography could also be performed at this stage (either barium or magnetic resonance). ²According to the Rome IV consensus, functional defecation disorder (FDD) is defined as: (I). The patient must satisfy diagnostic criteria for functional constipation and/or irritable bowel syndrome with constipation. (II). During repeated attempts to defecate, there must be features of impaired evacuation, as demonstrated by 2 of the following 3 tests: (a) Abnormal balloon expulsion test. (b) Abnormal anorectal evacuation pattern with manometry or anal surface EMG. (c). Impaired rectal evacuation by imaging. Subcategories for FDD: (a) 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^b. (b) Diagnostic Criteria for Dyssynergic Defecation. Inappropriate contraction of the pelvic floor as measured with anal surface EMG or manometry with adequate propulsive forces during attempted defecation^b. Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis. These criteria are defined by age- and sex-appropriate normal values for the technique. ³Before considering any surgical correction, evaluate the feasibility of biofeedback treatment as the option with the least side effects. ⁴Evaluation of colonic transit time can be useful in patients without evacuation disorders, and in patients with persistent constipation after treated evacuation disorders. ⁵This means according to Rome IV: Chronic constipation due to "Disease-related," "Medication-induced" or "IBS-C." At this stage, further investigation or symptomatic treatment will be considered

influenced by the safety and low cost of this approach, and some efficacy data from trials, together with long-standing clinical experience with these agents. In a systematic review evaluating the effects of fiber in the management of chronic idiopathic constipation, only six RCTs were found to be eligible: four used soluble fiber (three psyllium, one inulin, and maltodextrin) and two used insoluble fiber (one bran and one fiber-rich rye bread). Soluble fiber led to improvements in global symptoms (86.5% vs. 47.4%), straining (55.6% vs. 28.6%), pain on defecation, and stool consistency, an increase in the mean number of stools per week (3.8 stools per week after therapy compared with 2.9 stools per week at baseline), and a reduction in the number of days between stools. In particular, the effect of psyllium was convincing with a Number-Needed-to-Treat (NNT) of 2 (95% CI 1.6-3), and with no statistically significant heterogeneity between the three psyllium studies.¹⁶⁰ Evidence for any benefit of insoluble fiber was conflicting, mainly based on small patient numbers and few eligible studies. As a follow-up of this systematic review, the American College of Gastroenterology (ACG) recommended, based on these six trials, that fiber and soluble fiber in particular are effective in the management of chronic constipation.⁸ Soluble and insoluble fiber are also frequently used in patients with IBS, but the status of fiber in general in IBS is far from straightforward.¹⁶⁰⁻¹⁶⁶

Insoluble fiber may exacerbate symptoms and provide little relief in patients with IBS, but soluble fiber and psyllium, in particular, seem to provide relief in this condition.¹⁶⁷⁻¹⁶⁹ These latter effects appear to relate to the relief of constipation, which further supports the use of soluble fiber in patients with constipation, either FC or IBS-C.

Future research/unmet needs. Large, high-quality trials using modern clinical trial methodology are needed.

Statement 40: The usefulness of bulking agents, in particular insoluble fiber, in patients with chronic constipation is limited by adverse events, particularly bloating, distension, flatulence, and cramping

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Bulking agents, for example psyllium, bind water and prevent absorption of water from the lumen. This leads to increased small bowel water and increased colonic volumes.¹⁷⁰ These effects can explain both the positive effects of bulking agents, that is, increased stool frequency, and potential side effects. Adverse events, particularly bloating, distension, flatulence,

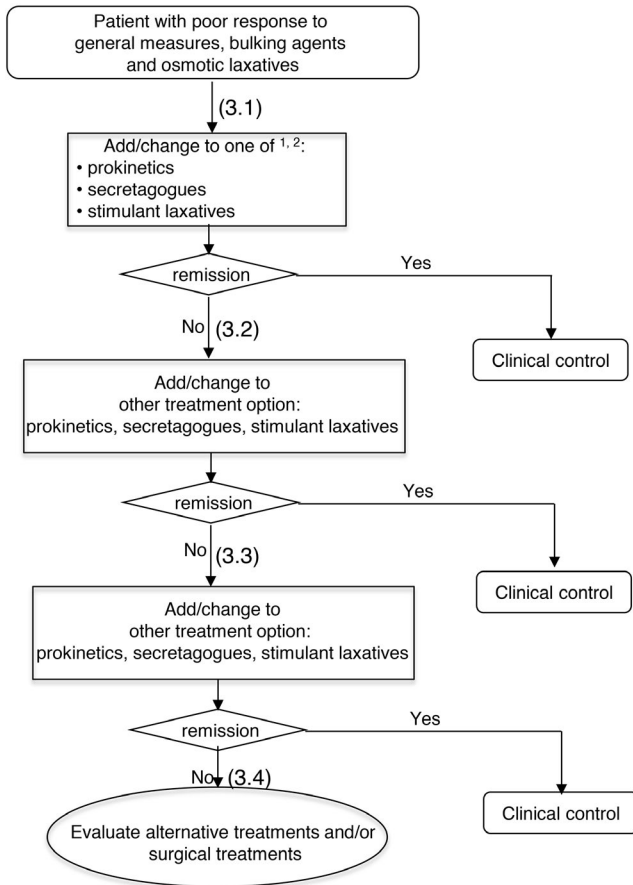


FIGURE 4 Algorithm 3. Treatment of constipation not caused by an evacuation disorder and refractory to first-line management. ¹The first choice will depend on the patient's characteristics, like coexistence of abdominal pain or distension, cost/efficacy evaluation, and local preferences. ²As rescue therapy, stimulant laxatives may be used, as well as suppositories, rectal enemas, or rectal irrigation

and cramping, may limit the use of insoluble fiber, especially if increases in fiber intake are not introduced gradually.^{8,160-169,171}

Future research/unmet needs. Strategies to use fiber to reduce side effects should be defined, and comparisons with other agents used to treat constipation.

Statement 41: Saline laxatives, especially polyethylene glycol (PEG), are effective in treating symptoms of constipation in patients with chronic constipation

- Level of evidence: Strong
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. The evidence supporting the usefulness of saline laxatives, especially polyethylene glycol (PEG), is strong. There are several large, high-quality trials supporting the fact that PEG is superior to placebo in improving symptoms in patients with chronic constipation, with a NNT of 3 (95% CI 2-4).^{8,172-180}

Moreover, a Cochrane analysis also concluded that PEG is superior to lactulose in patients with chronic constipation, resulting in more frequent stools, looser stools, and less abdominal pain. PEG also increases the number of spontaneous complete bowel movements, improves stool consistency, and reduces severity of straining, without clearly affecting abdominal pain, in patients with IBS-C, further supporting its usefulness to treat constipation. The most common side effects with PEG are diarrhea and abdominal pain, but not all trials find these to be more common in patients treated with PEG compared to the placebo group.

Future research/unmet needs. Direct head-to-head comparisons with newer agents treating constipation are needed.

Statement 42: Lactulose is efficacious in the treatment of patients with chronic constipation

- Level of evidence: Low
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. Clinical experience suggests that the osmotic properties of the unabsorbed mono/disaccharides and sugar alcohols lactulose, lactitol, mannitol, and sorbitol benefit patients with chronic constipation, but evidence from high-quality RCTs supporting this is largely absent. Few RCTs exist and these have a high risk of bias and moderate heterogeneity between studies, but suggest a positive effect of lactulose versus placebo in chronic constipation with a NNT of 4 (95% CI 2-7).^{8,172,181,182} Moreover, side effects such as abdominal cramping and bloating limit their clinical usefulness. Also dried plums, which contain sorbitol, but also dietary fibers and polyphenols, may be useful for constipation. This was demonstrated in a randomized controlled trial, where dried plums were found to be safe, palatable and more effective than psyllium for the treatment of mild-to-moderate constipation.¹⁸³ At least part of the effect on constipation may be explained by the sorbitol content, which act as an osmotic laxative.

Future research/unmet needs. High-quality trials assessing the effects of the unabsorbed mono/disaccharides and sugar alcohols lactulose, lactitol, mannitol, and sorbitol are needed, including comparisons with newer agents for the treatment of constipation.

3.4.3 | Stimulant laxatives

Statement 43: Bisacodyl is effective in the management of chronic constipation

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Bisacodyl is a diphenyl methane derivative hydrolyzed by intestinal and bacterial enzymes to a deacetylated active metabolite that induces high amplitude

propagative contractions of the colon and stimulates intestinal secretion.¹⁸⁴ It is usually given orally at a dose of 5-10 mg daily in a coated tablet that dissolves in the colon to ensure a local effect, or as a suppository given at a dose of 10 mg daily. In healthy volunteers, bisacodyl significantly accelerated emptying of the ascending colon, although overall transit was not modified.¹⁸⁵ In 2005, a systematic review of the literature found that stimulant laxatives, including bisacodyl, had a level III of evidence and were rated as a grade C recommendation,¹⁸⁶ while the American College of Gastroenterology Chronic Constipation Task Force underlined that high-quality data were lacking to make a recommendation about the efficacy of stimulant laxatives for the management of chronic constipation.¹⁸⁷ Since then, only one randomized, double-blind placebo-controlled study comparing the efficacy of daily use of bisacodyl in chronic constipation has been conducted. In this study, performed in 368 patients with chronic constipation defined by Rome III criteria, oral bisacodyl at 10 mg once daily increased the frequency of both bowel movements and complete spontaneous bowel movements over a 4-week period.

Statement 44: The use of bisacodyl in patients with chronic constipation is often well-tolerated

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Constipation-related QoL was also improved in the bisacodyl group compared with placebo.¹⁸⁸ Of note, six adverse events leading to drug discontinuation were recorded in the placebo-treated group, versus 44 in the bisacodyl-treated group, the most frequent being diarrhea and abdominal pain. However, the occurrence of serious adverse events was similar (<2%) in both groups. A second randomized-double-blind placebo-controlled study showed the efficacy of bisacodyl (10 mg once daily for 3 days) to acutely relieve chronic constipation by increasing the frequency of bowel movements and softening stool consistency.¹⁸⁸ An open-label RCT conducted in two groups of patients with chronic constipation treated with either pyridostigmine or bisacodyl showed that both treatments achieved an increase in bowel movements per week compared to baseline, with greater efficacy with pyridostigmine compared to bisacodyl.¹⁸⁹

Future research/unmet needs. Controlled studies evaluating the efficacy of bisacodyl in FC over 4 weeks of treatment are lacking and should be conducted. Whether the association of bisacodyl with an osmotic laxative is superior to bisacodyl alone or an osmotic laxative alone has yet to be investigated.

Statement 45: Sodium picosulfate is effective in the management of chronic constipation, at least as a short-term treatment

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Sodium picosulfate is a locally acting stimulant laxative hydrolyzed by the colonic microflora into the same active form as bisacodyl. It therefore has a similar mode of action to bisacodyl, including increased colon peristalsis and secretion. There is only one randomized, double-blind placebo-controlled study comparing the efficacy of sodium picosulfate in chronic constipation.¹⁹⁰ This study was conducted in 367 patients with Rome III-defined FC allocated 2:1 to receive either sodium picosulfate (10 mg/day) or placebo for 4 weeks. The number of complete spontaneous bowel movements (CSBMs) increased from 0.9 to 3.4 per week in the sodium picosulfate-treated group compared with an increase from 1.1 to 1.7 per week in the placebo-treated group.

Future research/unmet needs. Controlled studies evaluating the efficacy of sodium picosulfate in FC over a 4-week treatment period are lacking and should be conducted. Whether the association of sodium picosulfate with an osmotic laxative is superior to sodium picosulfate alone or an osmotic laxative alone is yet to be investigated.

Statement 46: The use of sodium picosulfate in patients with chronic constipation is often well-tolerated

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Constipation-related QoL was also improved after treatment in the sodium picosulfate-treated group compared with placebo. Comparable to bisacodyl, diarrhea, and abdominal pain were the most common adverse events reported compared with placebo. The efficacy of sodium picosulfate was compared with bisacodyl in an open-label RCT involving 144 patients with chronic constipation.¹⁹¹ After 4 weeks of treatment, sodium picosulfate and bisacodyl both achieved a comparable number of bowel movements per week (3.2 in both groups).

Statement 47: Anthraquinones, and particularly senna, are effective in the management of chronic constipation

- Level of evidence: Low
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. This class of laxatives includes mainly sennosides A and B and cascara. Sennosides are transformed by the colonic microbiota into active components¹⁹² They cannot be absorbed and are not excreted in breastmilk. Clinical trials are sparse and have often been conducted in the geriatric population or in patients with OIC. In these trials, the objective was often to demonstrate the additional benefit of combining senna to a bulk or osmotic laxative. The available trials prove their efficacy for increasing the number of stools or improving stool consistency. Senna provided more improvement than bulk or

osmotic laxatives¹⁹³⁻¹⁹⁵ and obtained similar results to magnesium hydroxide,¹⁹⁶ sodium picosulfate,¹⁹⁷ and even lubiprostone.¹⁹⁸

Future research/unmet needs. Blinded controlled studies evaluating the efficacy of anthraquinones are still lacking and should be performed.

Statement 48: Anthraquinones, and particularly senna, are often well-tolerated in patients with chronic constipation

- Level of evidence: Moderate
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. Anthraquinones have been linked with the development of melanosis coli, which is a brown pigmentation of the colonic mucosa due to collections of lipofuscin-containing macrophages.^{199,200} It is now established that this pigmentation has no clinical significance.¹⁹⁹ An increased risk of colorectal cancer has also been discussed. In a prospective study of 84 577 females, no association between laxative use and colorectal cancer was found.²⁰¹

3.4.4 | Prokinetics and secretagogues

Statement 49: The serotonin (5-HT)-4 agonist prucalopride has prokinetic action in the entire gut and is effective in the management of chronic constipation, including conditions refractory to conventional laxatives

- Level of evidence: High
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. The serotonin (5-HT)-4 agonist prucalopride has been shown to be effective in severe chronic constipation refractory to laxatives and has been approved in Europe for this indication for several years.²⁰²⁻²⁰⁷ It is highly receptor-selective and has no cardiologic side effects. Other related substances play no practical role in the treatment of chronic constipation at this time; examples include cisapride, which is no longer available as it had been associated with QT prolongation, torsades de pointes, and cardiac arrest, thought to be due to its binding and inactivation of a potassium channel encoded by the hERG gene; mosapride (established only for the upper GI tract); and molecules such as velusetrag (no current clinical trials available despite positive data from an earlier phase-2 study) and naronapride (currently being evaluated); for review compare Prichard DO & Barucha AE, Recent advances in understanding and managing chronic constipation. *F1000Res.* 2018 Oct 15;7. pii: F1000 Faculty Rev-1640. <https://doi.org/10.12688/f1000research.15900.1>. eCollection 2018. PMID: 30364088.

Future research/unmet needs. Predictors of response are poorly defined. In particular, the relevance of different pathomechanism of constipation (eg, slow vs. normal transit) has not been clarified. The

potential therapeutic role of prucalopride in other segments of the GI tract should be further elucidated.

Statement 50: Acetylcholinesterase inhibitors exert prokinetic effects in the intestine, but currently have no practical role in the management of chronic constipation

- Level of evidence: Moderate
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. Acetylcholinesterase inhibitors exert prokinetic action by inhibiting degradation of acetylcholine, thus amplifying its effects in the enteric nervous system (ENS) and in GI smooth muscle. Distigmine (and related substances) have their use in (often refractory, and usually acute or protracted) motility disturbances, such as colonic acute pseudoobstruction, postoperative ileus, etc.²⁰⁸ On an individual basis, they may be useful in selected cases of CC refractory to other established treatments. Indeed, a small trial reported similar efficacy as bisacodyl.¹⁸⁹ Overall, they have limited use in chronic constipation. This is also due to their low specificity, with effects on both muscarinic and nicotinic receptors, and because they have been associated with multiple systemic, secretory, and serious cardiologic side effects.^{209,210} Acotiamide is a new acetylcholinesterase inhibitor with additional antimuscarinic effects, available in Japan and currently being evaluated in Europe and the United States for functional dyspepsia²¹¹; there are no data for chronic constipation.

Future research/unmet needs. Their therapeutic potential in defined subtypes of constipation disorders is not well defined and thus they are possibly under-utilized.

Statement 51: Peripherally Acting μ -Opioid Receptor Antagonists (PAMORA) have prokinetic properties by reversing the inhibitory effects of μ -opioid analgesics on GI motility and are effective in the management of opioid-induced chronic constipation

- Level of evidence: High
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Peripherally Acting μ -Opioid Receptor Antagonists (PAMORA) inhibit the peripheral effects of μ -opioid analgesics on bowel functions such as reduced GI motility and secretion, and increased fluid absorption.²¹²⁻²¹⁴ True PAMORA (naloxegol, methylnaltrexone, alvimopan, naldemedine) do not pass the blood-brain barrier and are effective in the treatment of OIC without affecting the central analgesic effects.²¹⁵⁻²²⁵ The systemic opioid antagonist naloxone if administered as slow release formula may also inhibit intestinal opioid effects with little/no systemic action due to the high first pass effect in the liver, it is available as a fixed combination tablet with oxycodone.^{226,227}

Future research/unmet needs. As there are limited data on combination treatments, further studies should be done.

Statement 52: Peripherally Acting μ -Opioid Receptor Antagonists (PAMORA) have prokinetic properties even in the absence of opioid therapy and may potentially be effective in constipation not caused by opioids

- Level of evidence: Low
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. A high-quality RCT²²⁸ demonstrated that in healthy subjects the PAMORA alvimopan not only reversed opioid-induced inhibition of small bowel and colon transit, but also significantly accelerated colonic transit in the absence of opioid co-treatment. These findings suggest that μ -opiate mechanisms participate in the physiologic regulation of colonic motility, independent of opioid-induced modulation.

Future research/unmet needs. The therapeutic potential of PAMORA in chronic constipation subtypes not induced by opioids should be investigated.

Statement 53. The guanylate cyclase C receptor agonist linaclotide is effective and safe in the management of chronic constipation and IBS-C

- Level of evidence: High
- Recommendation: Strong
- Level of agreement: 92%

Current evidence and literature. Linaclotide acts as an oral guanylate cyclase C receptor agonist, increases intracellular cyclic guanosine monophosphate (cGMP) levels, and thus fluid secretion into the intestinal lumen, which in turn accelerates gastrointestinal transit velocity. At a dose of 290 μ g/d, it significantly improves chronic constipation with a RR of response to treatment of 1.95 [1.3-2.9] and a NNT of 7. In addition, it has been licensed as treatment for IBS-C as it also improves abdominal symptoms commonly associated with CC, such as bloating or pain^{229,230} due to decreasing effects on visceral hypersensitivity.^{229,230} Linaclotide may cause diarrhea as its most frequent side effect, but has a very low risk of major systemic adverse responses due to its local action in the intestinal lumen and low bioavailability.^{172,231}

Statement 54: The chloride channel activator lubiprostone is effective in the management of chronic constipation and IBS-C, but has limited availability in the majority of European countries

- Level of evidence: High
- Recommendation: Strong
- Level of agreement: 92%

Current evidence and literature. Lubiprostone is a chloride channel activator and induces intra-intestinal water and chloride

secretion, and accelerates transit. In RCTs in patients with chronic constipation and IBS-C, lubiprostone was associated with significantly improved symptoms^{213,232-236} with a therapeutic benefit of 7.8%, and a NNT of 12.8.²³⁷ Lubiprostone may cause nausea and has been suspected to promote abortion rates in animal studies due to its prostaglandin properties.^{213,232-236} Hence, it is mostly used as reserve medication and has not been approved in most European countries so far.

Future research/unmet needs. The optimal target group and side effects should be defined more clearly. Limited or no availability in most European countries.

3.4.5 | Biofeedback therapy

Statement 55: Biofeedback is the preferred treatment for constipation due to functional defecation disorders whenever dedicated expertise is available, regardless of abnormal bowel transit

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Biofeedback is a conditioning treatment where information about a physiological process is converted to a simple signal to enable the patient to learn to control the disordered function.²³⁸ Recently, instrumented biofeedback has been reported to ameliorate symptoms and accelerate bowel transit by improved defecation effort in over 70% of STC due to DD, while isolated STC did not benefit.⁷⁸ This study provided support for the specific therapeutic contribution of biofeedback therapy and heralded three pivotal RCTs addressing its effectiveness in FDDs.²³⁹⁻²⁴¹ These pivotal trials were adequately sized and included only severe, refractory constipation due to DD diagnosed by physiology testing, regardless of abnormal colon transit in most of them. Biofeedback therapy has been consistently reported to be superior to controlled treatment modalities, including sham biofeedback, placebo pill, muscle relaxant drugs (diazepam), and osmotic laxatives.^{239,240} Improved anorectal physiology correlated with successful outcomes, supporting a specific mechanism of action of biofeedback that differed from psychotherapy interventions and simple education. Biofeedback was effective in the long term and devoid of side effects, as confirmed by a recent open-label trial with a follow-up interval extended up to 4 years.^{239,240,242,243} In the pivotal trials, a complex protocol addressing the defecation effort as a whole using dedicated instruments was employed²³⁹⁻²⁴¹; this seems relevant to the successful outcome of biofeedback therapy, as simpler protocols were less effective than alternative treatments in FDDs.¹⁴⁶ In addition, constipation symptoms associated with isolated anatomical disruption of the pelvic floor seem to benefit little from retraining.²⁴⁴ Factors that may predict successful outcome of biofeedback therapy are: baseline harder stool consistency, digital

maneuvers to facilitate defecation, shorter duration of laxative use, higher resting anal sphincter pressure, and failure to expel a rectal balloon.^{69,245} Comorbid slow colonic transit is not a contraindication to retraining, as it has been repeatedly shown that improved defecation effort is effective on normalizing bowel transit in the vast majority of DD patients.^{78,245} Finally, the patient's willingness to participate, motivation and therapist's skill are all considered relevant to a successful outcome, although these are generally not specifically addressed.²⁴⁶

Future research/unmet needs. Other RCTs of biofeedback for constipation due to inadequate rectal propulsion with or without DD should be conducted. They should include both subjective and objective outcome measures, such as structural alterations of the pelvic floor. RCTs comparing simple bowel retraining measures to instrumented biofeedback for constipation due to FDDs are needed. RCTs for constipation due to FDDs aimed at standardizing biofeedback protocols for DD and inadequate rectal propulsion are also required, and RCTs comparing biofeedback with conservative care for constipation due to structural alterations of the pelvic floor.

Statement 56: Habit training is an effective treatment option for chronic constipation non-responsive to standard care whenever dedicated expertise is available

- Level of evidence: Low
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. Habit training, also called bowel retraining or pelvic floor retraining, has been developed to address constipation as a multifactorial disorder with a particular focus on the pelvic outlet. Habit training is generally not provided according to a standardized protocol and is mostly a nurse-led treatment option.^{247,248} It involves dietary advice to improve stool consistency and to maximize the gastro-colic response in order to ease defecation.^{247,248} Patients can be given basic gut anatomy and function training to gain an appreciation of how psychological and social stresses may influence gut functioning, as well as advice about the frequency and length of toilet visits and posture. Simple pelvic floor exercises and abdominal muscular coordination training to improve the pushing effort are relevant treatment components in all protocols.^{247,248} However, habit training is not like biofeedback, where information about a physiological process is presented to enable mastering of a disordered function.²⁴⁶ Some centers provide this treatment approach in all resistant chronic constipation, regardless of etiology.²⁴⁸ However, a pelvic floor retraining protocol was prescribed as sole treatment for 22% of constipated Italian patients consulting specialized care.²³⁹ The recently published St Mark's experience has shed some light on habit training given to constipated patients non-responsive to conservative care.²⁴⁹ A retrospective analysis of data from 347 mostly female constipated subjects (median age, 50 years) showed an improvement in symptoms in 62.5% and in the QoL score in 40.2% of the patients at the end of

treatment. Multivariate analysis demonstrated that increasing age, the number of sessions attended, and non-irrigation constipation were independent predictors of treatment satisfaction.²⁴⁸ No side effects were reported. The same group undertook an historical RCT comparing electromyography (EMG) on straining and rectal balloon biofeedback to abdomino-pelvic muscular coordination training and balloon feedback in a series of 60 adults with functional constipation unresponsive to conservative management.²⁵⁰ After only two unsatisfactory sessions, patients who were judged unable to respond were switched to the alternative treatment, thus biasing the results. At the end of treatment, approximately 50% of patients in both groups rated their symptoms as significantly improved. The outcome did not correlate with colon transit time, the presence of FDD, or other functional and clinical variables.²⁵⁰ No other RCTs have attempted to duplicate the results in the adult population.

In conclusion, habit training is an appealing treatment option for chronic constipation, regardless of etiology. It is a safe and affordable treatment option. Dedicated expertise is essential to perform it, but costly pretreatment testing is apparently not required. It comprises a non-drug, non-instrumental, holistic approach that is likely to appeal to patients with functional gastrointestinal disorders. However, it is not an evidence-based treatment and results from RCTs are pending before consistently endorsing it for all refractory constipation patients.²⁵¹

Future research/unmet needs. RCTs comparing habit training to instrumented biofeedback for constipation due to FDDs including both subjective and objective outcome measures should be conducted. RCTs comparing habit training to laxatives and different habit training protocols for chronic constipation are also needed, and RCTs comparing habit training with biofeedback for constipation due to structural alterations of the pelvic floor.

3.4.6 | Alternative treatments

Statement 57: Chinese herbal medicine improves bowel function in functional constipation, but it is not known which formulation is best

- Level of evidence: Low
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. A large proportion of patients with constipation have tried alternative remedies,^{252,253} partly because of the misconception that laxatives damage the bowel in some way or make it lazy. In addition, many patients like to think that they are treating their constipation in a more 'natural' way and, therefore, food or plant extracts that are thought to have a laxative effect are very popular.

Alternative remedies are also often used by patients with IBS, and there are more studies for this condition than for FC.²⁵⁴⁻²⁵⁶

This raises the possibility of using data derived from IBS-C patients. However, the outcome measures used in these studies on alternative treatments in IBS tend to be more global, rather than

reporting the actual effect on bowel function. Furthermore, even in those studies that divide patients into different bowel function subtypes, the outcomes are also usually global, rather than necessarily reporting specifically on change in stool form or frequency. Despite these drawbacks, where there is a lack of data with respect to the effect of alternative treatments in chronic constipation, it seems reasonable to consider extrapolating results from studies reporting results from IBS-C to chronic constipation.

In contrast to most other alternative approaches to treating constipation, Chinese herbal medicines have been the subject of more recent research in reasonably well-designed controlled trials. The results from these trials have shown consistently encouraging results.²⁵⁷⁻²⁶² However, the formulation of these products can vary, making it difficult to create specific recommendations on their use.

Future research/unmet needs. Many of the alternative remedies for the treatment of constipation have been available for many years, but very few have been subjected to the scrutiny of a modern clinical trial. This situation is unlikely to change in the future, as it is doubtful that funding for research of these established, but largely unproven approaches, will be forthcoming. Many of these preparations contain multiple components, and it would be useful to know whether all of the components are necessary for a clinical effect.

Statement 58: There is insufficient evidence to recommend acupuncture for the treatment of functional constipation

- Level of evidence: Very low
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. Studies on acupuncture in any disorder are always criticized because of the difficulty in finding an appropriate control group. A systematic review of IBS acupuncture studies was inconclusive,²⁶³ and there have been too few studies on constipation in the English literature to draw any firm conclusions.^{258,264} However, a systematic review of the Chinese literature suggests that acupuncture may be beneficial in constipation, although the authors commented that the studies had methodological flaws.²⁶⁵

Future research/unmet needs. Better designed trials are necessary before a final decision can be made about the utility of acupuncture in constipation.

Statement 59: There is insufficient evidence to recommend moxibustion for the treatment of functional constipation

- Level of evidence: Very low
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. Moxibustion is a technique for applying heat to acupuncture points and is widely used in Asian countries. A systematic review of its use in constipation published in 2010 was inconclusive and a subsequent study was negative.^{266,267}

Future research/unmet needs. Further trials are unlikely to provide enough new information to change practice.

Statement 60: There is insufficient evidence to recommend herbal remedies for the treatment of functional constipation

- Level of evidence: Very low
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. It has been suggested that Iberogast (STW 5) may be beneficial in IBS,²⁶⁸ but there are no data on its use in constipation. Other studies on herbal preparations are either conflicting, negative, or of poor quality according to our understanding of medicine.^{252,269-273}

Future research/unmet needs. Better designed trials are necessary and in particular emphasis should be placed on determining the relative contribution of the multiple constituents of these preparations to the clinical effect.

Statement 61: Abdominal massage may have an effect in functional constipation, but the way it is performed needs to be standardized before it can be recommended

- Level of evidence: Very low
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. Abdominal massage would appear to be an attractive approach to managing constipation, as it should be a safe and cheap option in which the patient can engage. Trials show some effect, although the methodology of the older trials is questionable. In contrast, the more recent studies are better designed and still show an effect.^{252,274-277}

Future research/unmet needs. More uniform and confirmatory studies using a standardized approach should be performed before abdominal massage can be recommended.

Statement 62: Behavioral approaches such as psychotherapy, cognitive behavioral therapy, and hypnotherapy may improve quality of life and coping in functional constipation, but there is no research evidence to suggest that they directly improve bowel function in this disorder

- Level of evidence: Very low
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. Behavioral treatments such as psychotherapy, cognitive behavioral therapy, and hypnotherapy have all been shown to be effective in IBS.²⁷⁸ It therefore seems reasonable to assume that, at the very least, they might improve coping and QoL in patients with FC.

Future research/unmet needs. The specific effect of behavioral treatments on constipation has not been investigated, and there are no studies on the use of any these behavioral approaches in FC.

Statement 63: Despite a lack of good research evidence, rectal suppositories are frequently used to treat constipation and probably have some effect. They are not associated with any obvious risks

- Level of evidence: Low
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Glycerin or bisacodyl suppositories are frequently used as over-the-counter remedies for FC. However, there has been no good quality research on the subject, although studies that have been undertaken suggest an effect.^{154,279}

Future research/unmet needs. Further trials on assessing the utility of these well-used remedies would be welcome.

Statement 64: Rectal enemas are frequently used to aid evacuation of the distal colon and rectum, although there is no research evidence to support their use. However, a trial of enemas is probably justified in patients in whom all other measures have failed. They should be avoided in people at risk of fluid or electrolyte imbalance, such as those with cardiac or renal disease

- Level of evidence: Low
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Enemas have been used for centuries to treat constipation, but unfortunately there have been no studies on their use in chronic constipation. They continue to be widely used and are available in ready-made delivery systems containing between 5 and 150 mL of fluid. The larger volume products should be avoided in the elderly or patients with renal or cardiac disease because of the potential for fluid overload or electrolyte problems, especially with phosphate enemas.^{154,279,280}

Future research/unmet needs. Further well-designed trials on assessing the utility of enemas would be welcome.

Statement 65: Uncontrolled studies suggest that transanal irrigation improves constipation, especially where laxatives have failed. The risk of perforation is very low

- Level of evidence: Low
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. Transanal irrigation using commercially available kits is being increasingly used for the management of bowel dysfunction, including FC. A systematic review and meta-analysis of the available uncontrolled studies in FC suggested a 50% response rate, which is comparable to that obtained with pharmacological agents.²⁸¹ Theoretically, this technique could lead to perforation, but a separate study addressing this possibility has suggested this risk is very low.²⁸² Active or suspected diverticulitis are contraindications and previous rectal or pelvic surgery increases the chances of perforation. Good instruction on how to use the technique is essential.²⁸³ Colonic irrigation using large volumes of fluid is very popular as a private service but is not offered within healthcare systems. It is not recommended as there is no clinical or research evidence to support its use and it is potentially dangerous.

Future research/unmet needs. Controlled trials of transanal irrigation in chronic constipation are needed.

3.4.7 | Modulation of microbiota

Statement 66. There is insufficient evidence to recommend fecal microbiota transfer (FMT) for routine treatment of functional constipation

- Level of evidence: Low
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. A change in the fecal microbiota composition has been described in IBS patients. This has supported the assumption that fecal microbiota transfer (FMT) may be a therapeutic approach, particularly in patients with diarrhea and IBS.

Only a few well-designed clinical studies have been performed in IBS patients. Johnsen et al²⁸⁴ reported on a double-blind, randomized, placebo-controlled, parallel-group, single-center study in 90 patients with IBS with diarrhea alone or with diarrhea and constipation as defined by the Rome III criteria. Patients were randomly assigned (2:1) to receive either active or placebo FMT. The primary endpoint was symptom relief of more than 75 points assessed by the IBS Severity Scoring System (IBS-SSS) 3 months after FMT. Sixty-five percent of patients receiving active treatment versus 43% of patients receiving the placebo showed symptom relief 3 months after FMT ($P = .049$); however, a separate analysis for the patients who also had constipation symptoms was not performed. Halkjaer et al²⁸⁵ performed a randomized, double-blind placebo-controlled trial to compare FMT versus placebo in 52 adult patients with moderate-to-severe IBS. The FMT was given orally via capsules. The investigators found a significant improvement in the IBS-SSS score in the treatment group after 3 months ($P = .012$) in favor of the placebo and not the FMT. This could indicate that the route of administration is crucial (colonoscopy versus oral administration). As patients with oral FMT also had persistent changes in their colonic microbiota composition, it

may be concluded that altering the gut microbiota is not sufficient to obtain clinical improvement in IBS.²⁸⁵ No subgroup analysis is available for IBS-C in this study.

Few studies with a number of methodological limitations have studied FMT in chronic constipation without IBS diagnosis. Ding et al report an improvement in about a third of patients after three months.²⁸⁶ However, patients were treated with vancomycin prior to FMT and used 2 liters of macrogol solution for bowel lavage. No sham control or placebo group was studied making it hard to conclude on the effectiveness of FMT. In a randomized trial, Tian and colleagues provided evidence for superiority of FMT given by nasoduodenal tube for six consecutive days: The clinical improvement rate (ITT) was 53.3% vs. 20.0%, $P = .009$. The observation period was 12 weeks. The control group received no tube and no placebo transplant but only conventional treatment consisting of education, behavioral strategies, and oral laxatives. No long-term follow-up data are available, and the difference between the treatments makes it again hard to draw solid conclusions.²⁸⁷ Zhang and co-workers performed another uncontrolled trial on FMT in 29 patients.²⁸⁸ After 6 FMTs per patient, they reported clinical remission at week 4 in 69.0% of patients. After one year 48.3% of the patients continued to have at least three complete spontaneous bowel movements per week. Again, the lack of a control group makes it hard to interpret these results.

Given the uncertainties in the definitive effect of FMT for the optimal route of administration, optimal choice of donor, optimal frequency of application, long-term outcome, and the lack of randomized, placebo/sham controlled trials, there is insufficient evidence to support such an approach in routine clinical practice.

Future research/unmet needs. A number of different case reports and case series have been published; however, controlled trials are sparse. In patients with constipation, well-designed trials are lacking and should be performed.

Statement 67. There is some limited evidence for a positive effect of probiotic preparations on acceleration of intestinal transit time and improvements in stool frequency in both children and adults. However, studies are generally of high heterogeneity and the optimal species/strains are unknown. Therefore, there is no sufficient evidence to recommend a specific probiotic preparation/strain for the treatment of functional constipation

- Level of evidence: Low
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. Moreira et al found no difference in an RCT comparing an intervention group receiving a probiotic fermented milk beverage with a control group receiving non-probiotic milk in 49 female patients with chronic constipation.²⁸⁹ Interestingly, the consumption of milk resulted in an improvement in constipation symptoms, regardless of the probiotic culture.²⁸⁹ In a well-designed RCT, Spiller et al reported a positive effect of *Saccharomyces cerevisiae*

in patients with IBS-C.²⁹⁰ The study included 379 patients who received either 1000 mg of the probiotic or placebo for 12 weeks. While there was no overall benefit of *S cerevisiae* on IBS symptoms and well-being in the total study population, a significant improvement was observed in the IBS-C subjects with respect to abdominal pain/discomfort and bloating.²⁹⁰ However, this subgroup analysis had not been planned initially. Mezzasalma et al, in a randomized, double-blind, three-arm parallel-group trial in 150 IBS-C patients who received either a daily oral dose of two probiotic mixtures or placebo (for 60 days) found a higher response rate in the two treatment groups.²⁹¹ An increase in bowel movement frequency, improvement in stool consistency, and reduction in abdominal bloating were reported in 70%, 60%, and 47% of patients in a study with the probiotic preparation VSL#3, which contains 8 different bacterial strains.²⁹²

Older studies have been summarized in a 2014 meta-analysis by Ford, Quigley, and co-authors, who selected 43 RCTs.²⁹³ In their analysis, probiotics had beneficial effects on abdominal pain, bloating, and flatulence scores in general.²⁹³ In only two RCTs that focused on constipation, limited beneficial effects were described (mean increase in number of stools per week = 1.49; 95% CI = 1.02-1.96).^{294,295}

The RCTs studied different bacterial preparations for different treatment periods, with or without PEG, with different endpoints. This obvious high heterogeneity of even the well-designed clinical trials prevents a recommendation on a specific probiotic preparation/strain for the treatment of FC.

Future research/unmet needs. RCTs need to be performed for well characterized probiotic preparations that focus selectively either on IBS-C or FC patients. Too many post hoc subgroup analyses have been performed that had no primary focus on constipation. Additional microbiota analyses should be required to evaluate whether an impact on microbiota composition is associated with symptom relief.

3.4.8 | Surgical treatment

Statement 68. Surgical treatment options, both resecting and non-resecting, might be considered for selected patients if all other conservative treatments show no effect

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. Surgical interventions for chronic constipation are, and should be, rare. If all other conservative treatment fails, there is a surgical option.^{296,297} Surgical interventions should be offered as a last resort and should be carefully considered.

Future research/unmet needs. RCTs are lacking, there are few cases, and data in observational studies are inconsistent. RCTs should be performed and patient selection for procedures should be improved.

Additional comments. If no other treatment achieves improvement and the patient is experiencing severe symptoms, then surgery can help to ease them as a final option. However, decision for surgical treatment option includes acceptance of any possible surgery related morbidity (wound infection, hernia formation, revision surgery) including even mortality. This has to be pointed out carefully to the patient during the informed consent discussion.

Statement 69: Surgical treatment should only be offered after performing physiological tests and only if the cause for the chronic constipation lies within the colon and/or rectum (slow-transit constipation, evacuation disorder)

- Level of evidence: Low
- Recommendation: Strong
- Level of agreement: 100%

Current evidence and literature. We do not recommend performing any surgical intervention without a thorough physiological examination.^{49,298}

Future research/unmet needs. RCTs are lacking, there are few cases, and data are inconsistent in observational studies. RCTs should be performed and patient selection for procedures should be improved.

Additional comments. Surgery is always the last resort. With this statement, we want to stress that before considering surgery, physiological testing is critical to plan for the right surgical treatment. And of course, ONLY after all other treatment options have failed.

Statement 70: PEC/Malone antegrade colonic enema is a non-resecting surgical treatment to flush the large intestine orthograde through an appendiceal stoma for highly selected patients suffering from slow-transit constipation

- Level of evidence: Very low
- Recommendation: Weak
- Level of agreement: 100%

Current evidence and literature. Only observational studies are available. Due to the low number of cases and lack of RCTs, there is no recommendation for this procedure. In rare cases, the procedure is successful. A recent study showed no improvement in QoL and the procedure also has a high complication rate.²⁹⁹⁻³⁰²

Future research/unmet needs. RCTs should be performed in adults. Very rarely performed procedure.

Additional comments. The level of recommendation is “weak” because the literature mainly focuses on pediatric patients and the complication rate in adults is high; overall, the number of adult patients is low. Performing RCTs in this setting is not feasible. However, it is a procedure worth trying before performing more radical approaches such as a definitive stoma or colectomy. Therefore, we suggest this procedure before radical surgery.

Statement 71: Continuous direct nerve stimulation (SNS/SNM) can ease symptoms in patients suffering from chronic constipation (slow-transit constipation and/or evacuation disorder) and is the least invasive surgical option for patients after all conservative treatment has failed. The success rate might be low, but the low complication rate justifies the intervention

- Level of evidence: Low
- Recommendation: Weak
- Level of agreement: 75%

Current evidence and literature. Three recent RCTs with n ~ 40-50 reported that SNS did not significantly improve (increase) the frequency of bowel movements.³⁰³⁻³⁰⁶ However, SNS stimulates afferent and efferent nerves which might contribute to better awareness and consecutively ease complaints. Of all surgical therapy options, SNS is the least invasive, and despite a low success rate, SNS also has a low complication rate which may justify its application in selected patients. Patients might choose SNS over colectomy or definitive stoma.

Future research/unmet needs. Three recent RCTs are available. Better patient selection seems to be the main goal for further studies.

Additional comments. The evidence level is too “low for a strong recommendation,” but it may be worth trying before performing more invasive surgery.

Statement 72: Total or segmental colectomy can be an effective treatment in highly selected patients with normal upper GI function and slow-transit constipation who do not respond to medical treatment and have normal evacuatory function

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 91%

Current evidence and literature. In segmental colonic resection, a targeted open or laparoscopic resection of the ineffective bowel segment is performed to improve transit time. Patients with an isolated megasigmoid profit most from segmental colonic resection. Total colectomy (open or laparoscopically performed) can be done by resecting or preserving the ileo-cecal valve (ileorectal anastomosis [IRA] vs. caecorectal anastomosis [CRA]). Complications occur in approximately 24% of cases, the most common being small bowel obstruction. However, reported patient satisfaction is high.³⁰⁷ Significant psychological disorders seem to have a negative effect on the colectomy.

Future research/unmet needs. In comparison with all other surgical procedures for constipation, colectomies are well studied.

Additional comments. Worldwide, definitive stoma formation is probably the most frequently used surgical option for severe constipation (due to costs and lack of physiological testing).

Statement 73: Surgery can be an effective treatment for patients who suffer from an evacuation disorder due to structural causes (ie, intussusception, rectocele, rectal prolapse, descending perineum syndrome) proven by imaging after failed conservative treatment

- Level of evidence: Moderate
- Recommendation: Strong
- Level of agreement: 92%

Current evidence and literature. The surgical method is chosen depending on the pathology. In the case of intussusception, rectocele or prolapse, a STARR or internal Delorme procedure can be done. Patients show a decrease in the Longo's Obstructed defecation Score (ODS). There is virtually no evidence in the literature to support rectocele resection performed trans-anally, vaginally, or transperineally, with or without levatorplasty.³⁰⁸⁻³¹⁰

Future research/unmet needs. At present, there are mostly observational studies and the evidence level is low.

4 | DISCUSSION

This document presents guidelines created by the ESNM for the management of chronic constipation. Following a careful Delphi process, 73 statements were produced and graded according to the level of evidence and the strength of recommendation using the GRADE method. Three algorithms were also developed for the management of constipation. The first algorithm is for first-line management of chronic constipation (Figure 2); the second for further investigation of patients with an unsatisfactory response to first-line management (Figure 3); and the third is for the treatment of constipation not caused by an evacuation disorder and which is refractory to first-line management (Figure 4). In addition to recommendations for the practical management of constipation, unmet needs were identified and future research lines proposed.

In order to develop these comprehensive guidelines that we hope will be useful across Europe, we included experts in different fields who manage constipation, including general practitioners, gastroenterologists, experts in neurophysiology and motility, radiologists, and surgeons, originally from eight European countries. In general, the authors discovered only moderate or low levels of evidence for most of the evaluated items (Table 1). Among the diagnostic studies, only the usefulness of anorectal manometry for the comprehensive evaluation of anorectal function showed a high level of evidence.⁵⁹⁻⁶¹ Among the therapeutic alternatives, only treatment with saline laxatives, especially polyethylene glycol,^{8,172,181,182} the prokinetic drug prucalopride,²¹²⁻²²⁷ secretagogues like linaclotide and lubiprostone,^{48,69,78,238-251,311-315} and PAMORAs for the treatment of opioid-induced constipation^{172,229-231} showed high levels of evidence. Despite the different backgrounds of the panel members and the lack of studies with high levels of evidence, an excellent level of agreement between the experts was obtained for most items, as observed in Figure 1. All but four statements were completely agreed/

agreed upon by 70% or more of the authors (Figure 1). These four items were related to the surgical management of constipation, with the greatest disagreement on the use of continuous direct nerve stimulation (SNS/SNM) for the treatment of this condition. Three newly published RCTs have shown no benefit for SNS/SNM on stool frequency in patients with chronic constipation,³⁰³⁻³⁰⁶ and several of the panel considered that there was no place for this treatment modality. Nonetheless, other authors proposed a trial of SNS/SNM before more aggressive surgical treatment is considered, mainly due to the low rate of side effects of the technique.

In contrast to prokinetics and secretagogues, the evidence for the efficacy of alternative treatments and probiotics was "low" or "very low" in all cases. Consequently, the strength of the recommendation to use these treatments is generally "weak." One exception was the use of suppositories and rectal enemas, which are strongly recommended despite the low scientific evidence in the literature, mainly because both treatments have been safely used for years worldwide.^{154,271-280} For the remaining treatment modalities, the authors found at least moderate evidence of their efficacy. However, the need for studies is great in most areas, and the final recommendations are the result of a mixture of tradition, personal experience and rational use of resources, and the available evidence. In this regard, in some cases the guideline is a compromise between what is traditionally used in different settings and the acceptance of different treatments in different regions. For example, rectal enemas or anal irrigation may have varying acceptance in different countries, and the choice of stimulant laxatives, prokinetics, or secretagogues may depend on local tradition or on local costs and access to specific drugs.

Of note, and despite some minor differences, the present guidelines are largely consistent with previous publications.^{8,48,54,316,317} The Guideline of the American College of Gastroenterology published in 2014⁸ also recommends bulking agents, osmotic and stimulant laxatives, prokinetics and secretagogues, despite different levels of evidence between the treatments, but with a weak degree of recommendation for non-pharmacological treatments like biofeedback therapy or probiotics. However, these European guidelines give a strong recommendation for biofeedback as the preferred treatment strategy for constipation in functional defecation disorders whenever dedicated expertise is available, regardless of abnormal bowel transit. The World Gastroenterology Organization Guideline published in 2010⁵⁴ differentiated between countries with high and low technical resources. For that reason, the colonic transit time test with radiopaque markers, which is cheap and easy to perform, was considered a first-line option. In the present guidelines, measurement of colonic transit time is suggested after an evacuation disorder has been excluded, as this may delay the colonic transit time and produce misleading results.⁷⁸⁻⁸⁰ The American Gastroenterological Association (AGA) guidelines released 2013⁴⁸ considered that radiological examinations for evacuation disorders (defecography) should be performed when anorectal manometry and the balloon expulsion

test are inconclusive. However, considering different levels of access to motility and sophisticated radiological explorations in European countries, we decided to put the various radiological and manometric investigations for evacuation disorders at the same level in the algorithm.

In the present guideline, the authors reached the consensus that when an evacuation disorder is suspected in patients non-responding to first-line therapy with bulking agents/osmotic laxatives, evaluation of an evacuation disorder with functional studies could help to discriminate patients that could benefit from biofeedback therapy, before a costly chronic treatment with prokinetics and/or secretagogues is started. However, we acknowledge that this recommendation may be controversial, and treatment with secretagogues or prokinetics at this stage could also be considered before future studies comparing the cost-effectiveness of these strategies are available.

An important issue on which all authors agreed was the lack of consistent terminology in this area, resulting in considerable confusion in the medical community. Hence, the terms functional constipation, chronic constipation, defecation disorder, evacuation disorder, outlet obstructed evacuation, dyssynergic defecation, etc, have been used in the literature to describe sometimes the same and, at other times, completely different phenomena. After discussion, the authors of these guidelines reached the consensus that the term chronic constipation be used for all types of constipation with a duration greater than 3 months, and the terms slow-transit constipation or normal transit constipation only when objective evidence has been obtained from transit studies. In relation to evacuation disorders, the generic term "evacuation disorder," which encompasses both structural and functional causes is used, and the specific terms "functional defecation disorder," as defined by the Rome IV consensus, and "structural defecation disorder" are used to differentiate between both types of evacuation disorders.

The aim of the guidelines is to provide a practical tool for physicians all over Europe for the management of patients with chronic constipation. These guidelines have addressed mainly the general adult population with chronic idiopathic constipation. Specific

groups such as those with constipation secondary to neurological disorders or to spinal cord injury, or constipation associated with special conditions like pregnancy have not been addressed in the present document. Likewise, the treatment of specific complications like fecaloma, disimpaction, or incontinence secondary to constipation has not been covered here either.

In conclusion, these ESNM guidelines for the management of chronic constipation are presented as a practical tool for the management of adult patients with constipation. They provide sequential algorithms for a progressive diagnostic and management process. This starts with initial first-line assessment and management using general measures and bulking or saline laxatives, followed by more comprehensive diagnostic procedures and more intensive treatment modalities in those patients who fail to respond to first-line treatments.

ACKNOWLEDGMENTS

The authors thank the ESNM Steering Committee and ESNM secretary Magdalena Mara for their support. This article is dedicated to the memory of Professor Philippe Ducrotté, who passed away a few months before this manuscript was submitted for publication. The authors salute his leadership, mentoring, academic contributions, and friendship.

The Functional Constipation Guidelines Working Group includes: Ariadna Aguilar and Noemi Caballero (Motility and Functional Gut Disorders Unit, University Hospital Germans Trias i Pujol, and Department of Medicine, Autonomous University of Barcelona, Badalona, Spain), Valeria Schindler (Division of Gastroenterology, University Hospital Zurich, Zurich, Switzerland; Department of Gastroenterology and Hepatology, University Hospital of Zurich, University of Zurich, Zurich, Switzerland), Stefan-Lucian Popa (2nd Medical Department, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania), Carolina Malagelada (Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas CIBERehd; Digestive System Research Unit, University Hospital Vall d'Hebron, Barcelona, Spain), Viola Andresen (Department

	Level of evidence				Recommendation	
	High	Moderate	Low	Very low	Strong	Weak
Clinical approach	0	67	16,5	16,5	67	33
Functional studies	14	43	29	14	100	0
Radiological studies	0	30	60	10	67	33
General measures	0	50	50	0	75	25
Bulking/osmotics	25	50	25	0	75	25
Stimulant	0	83	17	0	67	33
Prokinetics/secretagogues	67	16.5	16.5	0	67	33
Biofeedback	0	50	50	0	50	50
Alternative treatments	0	0	44	56	22	78
Probiotics	0	0	100	0	0	100
Surgical treatment	0	50	33	17	83	17

TABLE 1 Level of evidence and strength of recommendation of the different statements related to diagnostic approaches and treatment groups (%)

of Medicine, Israelitic Hospital, Hamburg, Germany), James E Waha (Department of Surgery, Division of General Surgery, Medical University of Graz, Austria), Ugo Grossi (Neurogastroenterology Group, Centre for Neuroscience, Surgery and Trauma, Blizard Institute, Barts and The London School of Medicine & Dentistry, Queen Mary University London, UK), Stuart A Taylor (Centre for Medical Imaging, University College London, UK), Hassan SS (Division of Diabetes, Endocrinology & Gastroenterology, University of Manchester, UK).

CONFLICT OF INTEREST

Dr Serra acted as consultant/speaker for AB-biotics, Allergan, Bayer, Norgine, Cassen-Recordati, Zespi, and Reckitt Benckiser. Dr Pohl has been consultant/speaker or received research support from Allergan, Medtronic, Permamed, and Sanofi. Dr Azpiroz has acted as a consultant or received research funding from Danone, Clasado, Noventure, and Allergan. Dr Chiarioni acted as consultant/speaker for Aboca, Alfa-Sigma, Allergan, Malesci, Pharmextracta, Kyowa-Kirin, Takeda, and is a member of the Anorectal Committee of the Rome Foundation. Dr Goucerol has acted as consultant or lecturer for Kyowa-Kirin, Allergan, Sanofi, Biocodex, Mayoly-Spindler, Kyowa-Kirin, Laborie, Medtronic. Dr Hungin has served on advisory boards and received funding from Kyowa-Kirin, Shire, Allergan, and Danone in the last three years. Dr Layer has acted as lecturer or consultant for the following companies in the last three years: Abbott, Allergan, Falk, and Nordmark. Dr Mendive has participated in training activities for general practitioners funded by Reckitt Benckiser. Dr Rogler has consulted to Abbvie, Augurix, BMS, Boehringer, Calypso, Celgene, FALK, Ferring, Fisher, Genentech, Gilead, Janssen, MSD, Novartis, Pfizer, Phadia, Roche, UCB, Takeda, Tillots, Vifor, Vital Solutions, and Zeller. Dr Scott acted as a consultant for The Laborie Group and received honoraria for educational/speaking activities. He has received grant funding from Mui Scientific, Bowel & Cancer Research, and The Almond Board of California. Dr Simrén has acted as a consultant for, or received research funding from, the following companies: Danone Nutricia Research, Glycom, Ferring Pharmaceuticals, AstraZeneca, Nestlé, Ammirall, Allergan, Menarini, Albireo, Glycom, Shire, Tillots, Kyowa-Kirin, Takeda, Biocodex, Alimentary Health, and Norgine grants Alfa-Sigma. Dr Whorwell has acted as a consultant for, or received research funding from, the following companies: Allergan, Salix, ironwood Pharmaceuticals, Danone Research, and Chr. Hansen. Dr Andresen has acted as a consultant for Allergan, Bayer, Ferring, Kyowa-Kirin, Nordmark, and Shionogi Hansen. Dr SA Taylor has acted as consultant to Robarts, Dr J. Pfeiffer, Dr A. Aguilar, Dr N. Caballero, Dr U. Grovsi, Dr Hasan, Dr C. Malagelada, Dr Popa, Dr Schindler, and Dr Waha and has no conflicts of interest to declare.

ORCID

Jordi Serra  <https://orcid.org/0000-0003-2120-6270>

Fernando Azpiroz  <https://orcid.org/0000-0002-7327-960X>

Guillaume Gourcerol  <https://orcid.org/0000-0001-8220-9155>

S. Mark Scott  <https://orcid.org/0000-0002-7997-1533>

REFERENCES

- Schmidt FM, Santos VL. Prevalence of constipation in the general adult population: an integrative review. *J Wound Ostomy Continence Nurs.* 2014;41:70-76.
- Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. *Best Pract Res Clin Gastroenterol.* 2011;25:3-18.
- Talley NJ, Jones M, Nuyts G, Dubois D. Risk factors for chronic constipation based on a general practice sample. *Am J Gastroenterol.* 2003;98:1107-1111.
- Chiarelli P, Brown W, McElduff P. Constipation in Australian women: prevalence and associated factors. *Int Urogynecol J Pelvic Floor Dysfunct.* 2000;11:71-78.
- Tack J, Müller-Lissner S, Stanghellini V, et al. Diagnosis and treatment of chronic constipation - a European perspective: Diagnosis and treatment of chronic constipation. *Neurogastroenterol Motil.* 2011;23:697-710.
- Mearin F, Lacy BE, Chang L, et al. Bowel disorders. In: Drossman DA, Chang L, Chey WD, Kellow J, Tack J, Whitehead WE, eds. *ROME IV, Functional Gastrointestinal Disorders-Disorders of gut-brain interactions*, 4th edn. Raleigh, NC: The Rome Foundation; 2016:967-1058.
- Drossman DA, Hasler WL. Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction. *Gastroenterology.* 2016;150:1257-1261.
- Ford AC, Moayyedi P, Lacy BE, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol.* 2014;1:S2-S26.
- Peppas G, Alexiou VG, Mourtzoukou E, Falagas ME. Epidemiology of constipation in Europe and Oceania: a systematic review. *BMC Gastroenterol.* 2008;8:5.
- Lim YJ, Rosita J, Chieng JY, Hazizi AS. The prevalence and symptoms characteristic of functional constipation using Rome III diagnostic criteria among tertiary education students. *PLoS ONE.* 2016;11:e0167243.
- Gonenne J, Esfandyari T, Camilleri M, et al. Effect of female sex hormone supplementation and withdrawal on gastrointestinal and colonic transit in postmenopausal women. *Neurogastroenterol Motil.* 2006;18:911-918.
- Probert CJ, Emmett PM, Heaton KW. Intestinal transit time in the population calculated from self made observations of defecation. *J Epidemiol Community Health.* 1993;47:331-333.
- Chan AO, Lam KF, Hui WM, et al. Influence of positive family history on clinical characteristics of functional constipation. *Clin Gastroenterol Hepatol.* 2007;5:197-200.
- Ostwan W, Dolan J, Elitsur Y. Familial clustering of habitual constipation: a prospective study in children from West Virginia. *J Pediatr Gastroenterol Nutr.* 2010;50:287-289.
- Bytzer P, Howell S, Leemon M, Young LJ, Jones MP, Talley NJ. Low socioeconomic class is a risk factor for upper and lower gastrointestinal symptoms: a population based study in 15 000 Australian adults. *Gut.* 2001;49:66-72.
- Ludvigsson JF. Epidemiological study of constipation and other gastrointestinal symptoms in 8000 children. *Acta Paediatr.* 2006;95:573-580.
- Allen L, Williams J, Townsend N, et al. Socioeconomic status and non-communicable disease behavioural risk factors in low-income

- and lower-middle-income countries: a systematic review. *Lancet Global Health*. 2017;5:e277-e289.
18. Lembo A, Camilleri M. Chronic constipation. *N Engl J Med*. 2003;349:1360-1368.
 19. Nullens S, Nelsen T, Camilleri M, et al. Regional colon transit in patients with dys-synergic defaecation or slow transit in patients with constipation. *Gut*. 2012;61:1132-1139.
 20. Shekhar C, Monaghan PJ, Morris J, et al. Rome III functional constipation and irritable bowel syndrome with constipation are similar disorders within a spectrum of sensitization, regulated by serotonin. *Gastroenterology*. 2013; 145(4):749-757.
 21. Gladman MA, Scott SM, Chan CL, Williams NS, Lunniss PJ. Rectal hyposensitivity: prevalence and clinical impact in patients with intractable constipation and fecal incontinence. *Dis Colon Rectum*. 2003;46:238-246.
 22. He CL, Burgart L, Wang L, et al. Decreased interstitial cell of cajal volume in patients with slow-transit constipation. *Gastroenterology*. 2000;118:14-21.
 23. Valli PV, Pohl D, Fried M, Caduff R, Bauerfeind P. Diagnostic use of endoscopic full-thickness wall resection (eFTR)-a novel minimally invasive technique for colonic tissue sampling in patients with severe gastrointestinal motility disorders. *Neurogastroenterol Motil*. 2018;30:e13153.
 24. Battaglia E, Serra AM, Buonafede G, et al. Long-term study on the effects of visual biofeedback and muscle training as a therapeutic modality in pelvic floor dyssynergia and slow-transit constipation. *Dis Colon Rectum*. 2004;47:90-95.
 25. Bassotti G, Chiarioni G, Germani U, Battaglia E, Vantini I, Morelli A. Endoluminal instillation of bisacodyl in patients with severe (slow transit type) constipation is useful to test residual colonic propulsive activity. *Digestion*. 1999;60:69-73.
 26. Bassotti G, Morelli A, Whitehead WE. Abnormal rectosigmoid myoelectric response to eating in patients with severe idiopathic constipation (slow-transit type). *Dis Colon Rectum*. 1992;35:753-756.
 27. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut*. 1999; 45(Supplement 2):ii43-ii47.
 28. Xin HW, Fang XC, Zhu LM, et al. Diagnosis of functional constipation: Agreement between Rome III and Rome II criteria and evaluation for the practicality: FC diagnosis by Rome III and II criteria. *J Digest Dis*. 2014;15:314-320.
 29. Cook IJ, Talley NJ, Benninga MA, Rao SS, Scott SM. Chronic constipation: overview and challenges. *Neurogastroenterol Motil*. 2009;21(Suppl 2):1-8.
 30. Sood R, Ford AC. Rome IV criteria for FGIDs — an improvement or more of the same?: Diagnosis. *Nat Rev Gastroenterol Hepatol*. 2016;13:501-502.
 31. Johanson JF, Kralstein J. Chronic constipation: a survey of the patient perspective: Patient perspective on constipation. *Aliment Pharmacol Ther*. 2007;25:599-608.
 32. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997;32:920-924.
 33. Storr M, Storr M. Chronic constipation: current management and challenges. *Can J Gastroenterol*. 2011;25(suppl b):5B-6B.
 34. McCallum IJD, Ong S, Mercer-Jones M. Chronic constipation in adults. *BMJ*. 2009; 338(mar20 1):b831-b831.
 35. Basilisco G, Coletta M. Chronic constipation: A critical review. *Digest Liver Dis*. 2013;45:886-893.
 36. Shin JE, Jung H-K, Lee TH, et al. Guidelines for the Diagnosis and Treatment of Chronic Functional Constipation in Korea, 2015 Revised Edition. *J Neurogastroenterol Motil*. 2016;22(3):383-411.
 37. Schmulson MJ, Drossman DA. What is new in Rome IV. *J Neurogastroenterol Motil*. 2017;23:151-163.
 38. Soares 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.
 39. Palsson OS, Whitehead WE, van Tilburg MAL, et al. Development and validation of the Rome IV diagnostic questionnaire for adults. *Gastroenterology*. 2016;150:1481-1491.
 40. Bouchoucha M, Devroede G, Mary F, Bon C, Bejou B, Benamouzig R. Painful or mild-pain constipation? A clinically useful alternative to classification as irritable bowel syndrome with constipation versus functional constipation. *Dig Dis Sci*. 2018;63:1763-1773.
 41. Chandar A. Diagnosis and treatment of irritable bowel syndrome with predominant constipation in the primary-care setting: focus on linaclotide. *Int J Gen Med*. 2017;10:385-393.
 42. Bellini M. Irritable bowel syndrome and chronic constipation: Fact and fiction. *World J Gastroenterol*. 2015;21:11362.
 43. 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. *UEG J*. 2018;6:1254-1266.
 44. Farmer AD, Holt CB, Downes TJ, Ruggeri E, Del Vecchio S, De Giorgio R. Pathophysiology, diagnosis, and management of opioid-induced constipation. *Lancet Gastroenterol Hepatol*. 2018;3:203-212.
 45. Gupta A. Improving the recognition and diagnosis of opioid-induced constipation in clinical practice. *J Fam Pract*. 2015;64 (10 Suppl 1).
 46. Rao SS, Ozturk R, Laine L. Clinical utility of diagnostic tests for constipation in adults: a systematic review. *Am J Gastroenterol*. 2005;100:1605-1615.
 47. Saad RJ, Rao SS, Koch KL, et al. Do stool form and frequency correlate with whole-gut and colonic transit? Results from a multicenter study in constipated individuals and healthy controls. *Am J Gastroenterol*. 2010;105:403-411.
 48. Bharucha AE, Pemberton JH, Locke GR. American gastroenterological association technical review on constipation. *Gastroenterology*. 2013;144:218-238.
 49. Bove A. Consensus statement AIGO/SICCR: Diagnosis and treatment of chronic constipation and obstructed defecation (part I: Diagnosis). *World J Gastroenterol*. 2012;18:1555.
 50. Talley NJ. How to do and interpret a rectal examination in gastroenterology. *Am J Gastroenterol*. 2008;103:820-822.
 51. Soh JS, Lee HJ, Jung KW, et al. The diagnostic value of a digital rectal examination compared with high-resolution anorectal manometry in patients with chronic constipation and Fecal incontinence. *Am J Gastroenterol*. 2015;110:1197-1204.
 52. Rao SSC. Constipation: evaluation and treatment of colonic and anorectal motility disorders. *Gastroenterol Clin North Am*. 2007;36:687-711.
 53. Lam TJ, Felt-Bersma RJF. Clinical examination remains more important than anorectal function tests to identify treatable conditions in women with constipation. *Int Urogynecol J*. 2013;24:67-72.
 54. Lindberg G, Hamid SS, Malferteiner P, et al. World Gastroenterology Organisation global guideline: Constipation—a global perspective. *J Clin Gastroenterol*. 2011;45:483-487.
 55. Videlock EJ, Lembo A, Cremonini F. Diagnostic testing for dys-synergic defecation in chronic constipation: meta-analysis. *Neurogastroenterol Motil*. 2013;25:509-520.
 56. Rao SS, Bharucha AE, Chiarioni G, et al. Functional anorectal disorders. *Gastroenterology*. 2016;150(6):1430-1442.e4.
 57. Heinrich H, Fruehauf H, Sauter M, et al. The effect of standard compared to enhanced instruction and verbal feedback on anorectal manometry measurements. *Neurogastroenterol Motil*. 2013;25(230-7):e163.
 58. Grossi U, Carrington EV, Bharucha AE, Horrocks EJ, Scott SM, Knowles CH. Diagnostic accuracy study of anorectal manometry for diagnosis of dyssynergic defecation. *Gut*. 2016;65:447-455.

59. Rao SS, Patcharatrakul T. Diagnosis and treatment of dyssynergic defecation. *J Neurogastroenterol Motil.* 2016;22:423-435.
60. Salvador F, Mego M, Sánchez-Montalvá A, et al. Assessment of rectocolonic morphology and function in patients with Chagas disease in Barcelona (Spain). *Am J Trop Med Hyg.* 2015;92:898-902.
61. Azpiroz F, Enck P, Whitehead WE. Anorectal functional testing: review of collective experience. *Am J Gastroenterol.* 2002;97:232-240.
62. Carrington EV, Heinrich H, Knowles CH, et al. Methods of anorectal manometry vary widely in clinical practice: Results from an international survey. *Neurogastroenterol Motil.* 2017;29(8):e13016.
63. Carrington EV, Grossi U, Knowles CH, Scott SM. Normal values for high-resolution anorectal manometry: a time for consensus and collaboration. *Neurogastroenterol Motil.* 2014;26:1356-1357.
64. Rasijeffer AMP, Withers M, Burke JM, Jackson W, Scott SM. High-resolution anorectal manometry: A comparison of solid-state and water-perfused catheters. *Neurogastroenterol Motil.* 2017;29(11):e13124.
65. 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.
66. Vitton V, Ben Hadj Amor W, Baumstarck K, Grimaud JC, Bouvier M. Water-perfused manometry vs three-dimensional high-resolution manometry: a comparative study on a large patient population with anorectal disorders. *Colorectal Dis.* 2013;15:e726-e731.
67. Jones MP, Post J, Crowell MD. High-resolution manometry in the evaluation of anorectal disorders: a simultaneous comparison with water-perfused manometry. *Am J Gastroenterol.* 2007;102:850-855.
68. Caetano AC, Santa-Cruz A, Rolanda C. Digital Rectal Examination and Balloon Expulsion Test in the Study of Defecatory Disorders: Are They Suitable as Screening or Excluding Tests? *Can J Gastroenterol Hepatol.* 2016;2016:8654314.
69. Shim LS, Jones M, Prott GM, Morris LI, Kellow JE, Malcolm A. Predictors of outcome of anorectal biofeedback therapy in patients with constipation. *Aliment Pharmacol Ther.* 2011;33:1245-1251.
70. 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.
71. Lee J, Hong KS, Kim JS, Jung HC. Balloon expulsion test does not seem to be useful for screening or exclusion of dyssynergic defecation as a single test. *J Neurogastroenterol Motil.* 2017;23:446-452.
72. Palit S, Thin N, Knowles CH, Lunniss PJ, Bharucha AE, Scott SM. Diagnostic disagreement between tests of evacuatory function: a prospective study of 100 constipated patients. *Neurogastroenterol Motil.* 2016;28:1589-1598.
73. 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.
74. Voskuil WP, van Ginkel R, Benninga MA, Hart GA, Taminiua JA, Boeckxstaens GE. New insight into rectal function in pediatric defecation disorders: disturbed rectal compliance is an essential mechanism in pediatric constipation. *J Pediatr.* 2006;148:62-67.
75. van den Berg MM, Voskuil WP, Boeckxstaens GE, Benninga MA. Rectal compliance and rectal sensation in constipated adolescents, recovered adolescents and healthy volunteers. *Gut.* 2008;57:599-603.
76. van den Berg MM, Bongers ME, Voskuil WP, Benninga MA. No role for increased rectal compliance in pediatric functional constipation. *Gastroenterology.* 2009;137:1963-1969.
77. Rao SS, 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.
78. 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.
79. Shin A, Camilleri M, Nadeau A, et al. Interpretation of overall colonic transit in defecation disorders in males and females. *Neurogastroenterol Motil.* 2013;25:502-508.
80. Quitadamo P, Thapar N, Staiano A, et al. Effect of bowel cleansing on colonic transit time measurement in children with chronic constipation. *J Pediatr.* 2015;167(1440-2):e1.
81. Törnblom H, Van Oudenhove L, Sadik R, Abrahamsson H, Tack J, Simrén M. Colonic transit time and IBS symptoms: what's the link? *Am J Gastroenterol.* 2012;107:754-760.
82. Ekengren K, Snellman B. Roentgen appearances in mechanical rectal constipation. *Acta Radiol.* 1953;40:447-456.
83. Skomorowska E, Henrichsen S, Christiansen J, Hegedus V. Videodefaecography combined with measurement of the anorectal angle and of perineal descent. *Acta Radiol.* 1987;28:559-562.
84. Agachan F, Chen T, Pfeifer J, Reissman P, Wexner SD. A constipation scoring system to simplify evaluation and management of constipated patients. *Dis Colon Rectum.* 1996;39:681-685.
85. Poon FW, Lauder JC, Finlay IG. Technical report: evacuating proctography—a simplified technique. *Clin Radiol.* 1991;44:113-116.
86. Hainsworth AJ, Solanki D, Hamad A, Morris SJ, Schizas AM, Williams AB. Integrated total pelvic floor ultrasound in pelvic floor defaecatory dysfunction. *Colorectal Dis.* 2017;19:O54-O65.
87. Thompson JR, Chen AH, Pettit PD, Bridges MD. Incidence of occult rectal prolapse in patients with clinical rectoceles and defecatory dysfunction. *Am J Obstet Gynecol.* 2002;187(6):1494-1500.
88. Marti R, Deleaval. Rectoceles: value of videodefaecography in selection of treatment policy. *Colorectal Dis.* 1999;1:324-329.
89. Faucheron JL, Dubreuil A. Rectal akinesia as a new cause of impaired defecation. *Dis Colon Rectum.* 2000;43:1545-1549.
90. Bartolo DC, Bartram CI, Ekberg O, et al. Proctography. *Int J Colorectal Dis.* 1988;3:67-89.
91. Palit S, Bhan C, Lunniss PJ, et al. Evacuation proctography: a reappraisal of normal variability. *Colorectal Dis.* 2014;16:538-546.
92. Shorvon PJ, McHugh S, Diamant NE, Somers S, Stevenson GW. Defecography in normal volunteers: results and implications. *Gut.* 1989;30:1737-1749.
93. Goh V, Halligan S, Kaplan G, Healy JC, Bartram CI. Dynamic MR imaging of the pelvic floor in asymptomatic subjects. *Am J Roentgenol.* 2000;174:661-666.
94. Tirumanisetty P, Prichard D, Fletcher JG, Chakraborty S, Zinsmeister AR, Bharucha AE. Normal values for assessment of anal sphincter morphology, anorectal motion, and pelvic organ prolapse with MRI in healthy women. *Neurogastroenterol Motil.* 2018;30(7):e13314.
95. Grossi U, Di Tanna GL, Heinrich H, Taylor SA, Knowles CH, Scott SM. Systematic review with meta-analysis: defecography should be a first-line diagnostic modality in patients with refractory constipation. *Aliment Pharmacol Ther.* 2018;48:1186-1201.
96. Felt-Bersma RJ, Luth WJ, Janssen JJ, and. Meuwissen SG. Defecography in patients with anorectal disorders. Which findings are clinically relevant? *Dis Colon Rectum.* 1990;33:277-284.
97. Renzi A, Izzo D, Di Sarno G, et al. Cine-defecographic findings in patients with obstructed defecation syndrome. A study in 420 cases. *Minerva Chir.* 2006;61:493-499.
98. Klauser AG, Ting KH, Mangel E, Eibl-Eibesfeldt B, Muller-Lissner SA. Interobserver agreement in defecography. *Dis Colon Rectum.* 1994;37:1310-1316.
99. Dvorkin LS, Knowles CH, Scott SM, Williams NS, Lunniss PJ. Rectal intussusception: characterization of symptomatology. *Dis Colon Rectum.* 2005;48:824-831.
100. Ribas Y, Saldana E, Marti-Rague J, Clave P. Prevalence and pathophysiology of functional constipation among women in Catalonia, Spain. *Dis Colon Rectum.* 2011;54:1560-1569.

101. Spazzafumo LP. Rectal constipation and clinical decision-making: multiple correspondence analysis of defecographic findings. *Tech Coloproctol.* 1999;3:117-121.
102. Murad-Regadas S, Peterson TV, Pinto RA, Regadas FS, Sands DR, Wexner SD. Defecographic pelvic floor abnormalities in constipated patients: does mode of delivery matter? *Tech Coloproctol.* 2009;13:279-283.
103. Baek HN, Hwang YH, Jung YH. Clinical significance of perineal descent in pelvic outlet obstruction diagnosed by using defecography. *J Korean Soc Coloproctol.* 2010;26:395-401.
104. Vitton V, Vignally P, Barthet M, et al. Dynamic anal endosonography and MRI defecography in diagnosis of pelvic floor disorders: comparison with conventional defecography. *Dis Colon Rectum.* 2011;54:1398-1404.
105. Piloni V, Tosi P, Vernelli M. MR-defecography in obstructed defecation syndrome (ODS): technique, diagnostic criteria and grading. *Tech Coloproctol.* 2013;17:501-510.
106. Hassan HH, Elnekiyeh AM, Elshazly WG, Naguib NN. Modified MR defecography without rectal filling in obstructed defecation syndrome: Initial experience. *Eur J Radiol.* 2016;85:1673-1681.
107. Martin-Martin GP, Garcia-Armengol J, Roig-Vila JV, et al. Magnetic resonance defecography versus videodefecography in the study of obstructed defecation syndrome: Is videodefecography still the test of choice after 50 years? *Tech Coloproctol.* 2017;21:795-802.
108. Poncelet E, Rock A, Quinton JF, et al. Dynamic MR defecography of the posterior compartment: Comparison with conventional X-ray defecography. *Diagn Interv Imaging.* 2017;98:327-332.
109. Siproudhis L, Ropert A, Vilotte J, et al. How accurate is clinical examination in diagnosing and quantifying pelvic floor disorders? A prospective study in a group of 50 patients complaining of defecatory difficulties. *Dis Colon Rectum.* 1993;36:430-438.
110. Savoye-Collet C, Savoye G, Koning E, Leroi AM, Dacher JN. Defecography in symptomatic older women living at home. *Age Ageing.* 2003;32:347-350.
111. Nielsen MB, Buron B, Christiansen J, Hegedus V. Defecographic findings in patients with anal incontinence and constipation and their relation to rectal emptying. *Dis Colon Rectum.* 1993;36:806-809.
112. Kashyap AS, Kohli DR, Raizon A, Olden KW. A prospective study evaluating emotional disturbance in subjects undergoing defecating proctography. *World J Gastroenterol.* 2013;19:3990-3995.
113. Barthet M, Portier F, Heyries L, et al. Dynamic anal endosonography may challenge defecography for assessing dynamic anorectal disorders: results of a prospective pilot study. *Endoscopy.* 2000;32:300-305.
114. Regadas FS, Haas EM, Abbas MA, et al. Prospective multicenter trial comparing echodefecography with defecography in the assessment of anorectal dysfunction in patients with obstructed defecation. *Dis Colon Rectum.* 2011;54:686-692.
115. Martellucci J, Naldini G. Clinical relevance of transperineal ultrasound compared with evacuation proctography for the evaluation of patients with obstructed defaecation. *Colorectal Dis.* 2011;13:1167-1172.
116. Viscardi A, Ratto C, Parello A. Dynamic transperineal ultrasound in the workup of men with obstructed defecation: a pilot study. *Dis Colon Rectum.* 2012;55:976-982.
117. Mahieu P, Pringot J, Bodart P. Defecography: I. Description of a new procedure and results in normal patients. *Gastrointest Radiol.* 1984;9:247-251.
118. Mahieu P, Pringot J, Bodart P. Defecography: II. Contribution to the diagnosis of defecation disorders. *Gastrointest Radiol.* 1984;9:253-261.
119. Lee HH, Chen SH, Chen DF, Huang CS. Defecographic evaluation of patients with defecation difficulties. *J Formos Med Assoc.* 1994;93:944-949.
120. Karlbom U, Pahlman L, Nilsson S, Graf W. Relationships between defecographic findings, rectal emptying, and colonic transit-time in constipated patients. *Gut.* 1995;36:907-912.
121. Gliá A, Lindberg G, Nilsson LH, Mihocsa L, Akerlund JE. Constipation assessed on the basis of colorectal physiology. *Scand J Gastroenterol.* 1998;33:1273-1279.
122. Stojkovic SG, Ireland IW, Holmfield JH, Sagar PM, Finan PJ. Interobserver variability in the reporting of dynamic evacuation proctography. *Colorectal Dis.* 2000;2:355-358.
123. Bruscianno L, Limongelli P, del Genio G, et al. Clinical and instrumental parameters in patients with constipation and incontinence: their potential implications in the functional aspects of these disorders. *Int J Colorectal Dis.* 2009;24:961-967.
124. Soares FA, Regadas FS, Murad-Regadas SM, et al. Role of age, bowel function and parity on anorectocele pathogenesis according to cinedefecography and anal manometry evaluation. *Colorectal Dis.* 2009;11:947-950.
125. Morandi C, Martellucci J, Talento P, Carriero A. Role of enterocele in the obstructed defecation syndrome (ODS): a new radiological point of view. *Colorectal Dis.* 2010;12:810-816.
126. Bartolo DC, Roe AM, Virjee J, Mortensen NJ, Locke-Edmunds JC. An analysis of rectal morphology in obstructed defaecation. *Int J Colorectal Dis.* 1988;3:17-22.
127. Schouten WR, Briel JW, Auwerda JJ, et al. Anismus: fact or fiction? *Dis Colon Rectum.* 1997;40:1033-1041.
128. Dailianas A, Skandalis N, Rimikis MN, Koutsomanis D, Kardasi M, Archimandritis A. Pelvic floor study in patients with obstructive defecation: influence of biofeedback. *J Clin Gastroenterol.* 2000;30:176-180.
129. Gosselink MJ, Hop WC, Schouten WR. Rectal compliance in females with obstructed defecation. *Dis Colon Rectum.* 2001;44:971-977.
130. Halligan S, Bartram CI. Is digitation associated with proctographic abnormality? *Int J Colorectal Dis.* 1996;11:167-171.
131. Spazzafumo L, Piloni V. Rectal constipation and clinical decision-making: multiple correspondence analysis of defecographic findings. *Tech Coloproctol.* 1999;3:117-121.
132. Bordeianou L, Savitt L, Dursun A. Measurements of pelvic floor dyssynergia: which test result matters? *Dis Colon Rectum.* 2011;54:60-65.
133. Andrade LC, Correia H, Semedo LC, Ilharco J, Caseiro-Alves F. Conventional videodefecography: Pathologic findings according to gender and age. *Eur J Radiol Open.* 2014;1:1-5.
134. Ger GC, Wexner SD, Jorge JM, Salanga VD. Anorectal manometry in the diagnosis of paradoxical puborectalis syndrome. *Dis Colon Rectum.* 1993;36:816-825.
135. Kassis NC, Wo JM, James-Stevenson TN, Maglinte DDT, Heit MH, Hale DS. Balloon expulsion testing for the diagnosis of dyssynergic defecation in women with chronic constipation. *Int Urogynecol J.* 2015;26:1385-1390.
136. Zafar A, Seretis C, Feretis M, et al. Comparative study of magnetic resonance defaecography and evacuation proctography in the evaluation of obstructed defaecation. *Colorectal Dis.* 2017;19:O204-O209.
137. Karlbom U, Nilsson S, Pahlman L, Graf W. Defecographic study of rectal evacuation in constipated patients and control subjects. *Radiology.* 1999;210:103-108.
138. Yeh CY, Pikarsky A, Wexner SD, et al. Electromyographic findings of paradoxical puborectalis contraction correlate poorly with cinedefecography. *Tech Coloproctol.* 2003;7:77-81.
139. Pilkington SA, Nugent KP, Brenner J, et al. Barium proctography vs magnetic resonance proctography for pelvic floor disorders: a comparative study. *Colorectal Dis.* 2012;14:1224-1230.
140. Alves-Ferreira PC, Gurland B, Zutshi M, Hull T. Perineal descent does not imply a more severe clinical disorder. *Colorectal Dis.* 2012;14:1372-1379.

141. Heinrich H, Sauter M, Fox M, et al. Assessment of obstructive defecation by high-resolution anorectal manometry compared with magnetic resonance defecography. *Clin Gastroenterol Hepatol.* 2015;13(1310-7):e1.
142. Seong M-K, Kim T-W. Significance of defecographic parameters in diagnosing pelvic floor dyssynergia. *J Korean Surg Soc.* 2013;84:225-230.
143. Boccasanta P, Venturi M, Spennacchio M, Buonaguidi A, Airoidi A, Roviario G. Prospective clinical and functional results of combined rectal and urogynecologic surgery in complex pelvic floor disorders. *Am J Surg.* 2010;199:144-153.
144. Madbouly KM, Abbas KS, Hussein AM. Disappointing long-term outcomes after stapled transanal rectal resection for obstructed defecation. *World J Surg.* 2010;34:2191-2196.
145. Boenicke L, Jayne DG, Kim M, et al. What happens in stapled transanal rectum resection? *Dis Colon Rectum.* 2011;54:593-600.
146. Faried M, El Nakeeb A, Youssef M, Omar W, El Monem HA. Comparative study between surgical and non-surgical treatment of anismus in patients with symptoms of obstructed defecation: a prospective randomized study. *J Gastrointest Surg.* 2010;14:1235-1243.
147. Huang R, Ho S-Y, Lo W-S, Lam T-H. Physical activity and constipation in Hong Kong adolescents. *PLoS ONE.* 2014;9:e90193.
148. Ayaz S, Hisar F. The efficacy of education programme for preventing constipation in women: Education programme for constipation. *Int J Nurs Pract.* 2014;20:275-282.
149. Coenen C, Wegener M, Wedmann B, Schmidt G, Hoffmann S. Does physical exercise influence bowel transit time in healthy young men? *Am J Gastroenterol.* 1992;87:292-295.
150. Meshkinpour H, Selod S, Movahedi H, Nami N, James N, Wilson A. Effects of regular exercise in management of chronic idiopathic constipation. *Dig Dis Sci.* 1998;43:2379-2383.
151. Robertson G, Meshkinpour H, Vandenberg K, James N, Cohen A, Wilson A. Effects of exercise on total and segmental colon transit. *J Clin Gastroenterol.* 1993;16:300-303.
152. De Schryver AM, Keulemans YC, Peters HP, et al. Effects of regular physical activity on defecation pattern in middle-aged patients complaining of chronic constipation. *Scand J Gastroenterol.* 2005;40:422-429.
153. Leung L, Riutta T, Kotecha J, Rosser W. Chronic constipation: an evidence-based review. *J Am Board Family Med.* 2011;24:436-451.
154. Mueller-Lissner SA, Wald A. Constipation in adults. *BMJ Clin Evid.* 2010;2010:0413.
155. Liu LW. Chronic constipation: current treatment options. *Can J Gastroenterol.* 2011;25(suppl B):22B-28B.
156. American College of Gastroenterology Chronic Constipation Task F. An evidence-based approach to the management of chronic constipation in North America. *Am J Gastroenterol.* 2005;100:S1-S4.
157. Lindeman RD, Romero LJ, Liang HC, Baumgartner RN, Koehler KM, Garry PJ. Do elderly persons need to be encouraged to drink more fluids? *J Gerontol A Biol Sci Med Sci.* 2000;55:M361-M365.
158. Dukas L, Willett WC, Giovannucci EL. Association between physical activity, fiber intake, and other lifestyle variables and constipation in a study of women. *Am J Gastroenterol.* 2003;98:1790-1796.
159. Nour-Eldein H, Salama HM, Abdulmajeed AA, Heissam KS. The effect of lifestyle modification on severity of constipation and quality of life of elders in nursing homes at Ismailia city, Egypt. *J Family Community Med.* 2014;21:100-106.
160. Suares NC, Ford AC. Systematic review: the effects of fibre in the management of chronic idiopathic constipation: Systematic review: effect of fibre in constipation. *Aliment Pharmacol Ther.* 2011;33:895-901.
161. Bijkerk CJ, Muris JWM, Knottnerus JA, Hoes AW, De Wit NJ. Systematic review: the role of different types of fibre in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther.* 2004;19:245-251.
162. Ford AC, Talley NJ, Spiegel BM, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. *BMJ.* 2008;337:a2313.
163. Ashraf W, Park F, Lof J, Quigley EMM. Effects of psyllium therapy on stool characteristics, colon transit and anorectal function in chronic idiopathic constipation. *Aliment Pharmacol Ther.* 2007;9:639-647.
164. Badiali D, Corazziari E, Habib FI, et al. Effect of wheat bran in treatment of chronic nonorganic constipation: A double-blind controlled trial. *Dig Dis Sci.* 1995;40:349-356.
165. Hongisto SM, Paaanen L, Saxelin M, Korpela R. A combination of fibre-rich rye bread and yoghurt containing *Lactobacillus GG* improves bowel function in women with self-reported constipation. *Eur J Clin Nutr.* 2006;60:319-324.
166. Bijkerk CJ, de Wit NJ, Muris JWM, Whorwell PJ, Knottnerus JA, Hoes AW. Soluble or insoluble fibre in irritable bowel syndrome in primary care? Randomised placebo controlled trial. *BMJ.* 2009;339: b3154-b3154.
167. Odes HS, Madar Z. A double-blind trial of a celandin, aloe vera and psyllium laxative preparation in adult patients with constipation. *Digestion.* 1991;49:65-71.
168. López Román J, Martínez González AB, Luque A, et al. Efecto de la ingesta de un preparado lácteo con fibra dietética sobre el estreñimiento crónico primario idiopático. *Nutrición Hospitalaria.* 2008;23:12-19.
169. Fenn GC, Wilkinson PD, Lee CE, Akbar FA. A general practice study of the efficacy of Regulan in functional constipation. *Br J Clin Pract.* 1986;40:192-197.
170. Major G, Murray K, Singh G, et al. Demonstration of differences in colonic volumes, transit, chyme consistency, and response to psyllium between healthy and constipated subjects using magnetic resonance imaging. *Neurogastroenterol Motil.* 2018;30:e13400.
171. Francis C. Bran and irritable bowel syndrome: time for reappraisal. *Lancet.* 1994;344:39-40.
172. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. *Gut.* 2011;60:209-218.
173. 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.
174. DiPalma JA, DeRidder PH, Orlando RC, Kolts BE, Cleveland MVB. A randomized, placebo-controlled, multicenter study of the safety and efficacy of a new polyethylene glycol laxative. *Am J Gastroenterol.* 2000;95:446-450.
175. DiPalma JA, Mv C, 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.
176. 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.
177. Corazziari E. 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.
178. Lee-Robichaud H, Thomas K, Morgan J, Nelson RL. Lactulose versus polyethylene glycol for chronic constipation. *Cochrane Database Syst Rev.* 2010;7:CD007570.
179. Belsey JD, Geraint M, Dixon TA. Systematic review and meta analysis: polyethylene glycol in adults with non-organic constipation:

- Polyethylene glycol in adults with non-organic constipation. *Int J Clin Pract.* 2010;64:944-955.
180. Baldonado YC, Lugo E, Uzcategui AA, Guelrud M, Skornicki J. Evaluation and use of polyethylene glycol in constipated patients. *J Gen Int Med.* 1991;45:294-297.
 181. Wesseliuss-De Casparis A, Braadbaart S, Bergh-Bohlken GE, Mimica M. Treatment of chronic constipation with lactulose syrup: results of a double-blind study. *Gut.* 1968;9:84-86.
 182. Sanders JF. Lactulose syrup assessed in a double-blind study of elderly constipated patients. *J Am Geriatr Soc.* 1978;26:236-239.
 183. Attaluri A, Donahoe R, Valestin J, Brown K, Rao SSC. Randomised clinical trial: dried plums (prunes) vs. psyllium for constipation: Randomised clinical trial: dried plums in constipation. *Aliment Pharmacol Ther.* 2011;33:822-828.
 184. Muller-Lissner SA, Kamm MA, Scarpignato C, Wald A. Myths and misconceptions about chronic constipation. *Am J Gastroenterol.* 2005;100:232-242.
 185. Manabe N, Cremonini F, Camilleri M, Sandborn WJ, Burton DD. Effects of bisacodyl on ascending colon emptying and overall colonic transit in healthy volunteers. *Aliment Pharmacol Ther.* 2009;30:930-936.
 186. Ramkumar D, Rao SS. Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. *Am J Gastroenterol.* 2005;100:936-971.
 187. An, . evidence-based approach to the management of chronic constipation in North America. *Am J Gastroenterol.* 2005;100(Suppl 1):S1-4.
 188. 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.
 189. 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.
 190. 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.
 191. Kienzle-Horn S, Vix JM, Schuijt C, Peil H, Jordan CC, Kamm MA. Comparison of bisacodyl and sodium picosulfate in the treatment of chronic constipation. *Curr Med Res Opin.* 2007;23:691-699.
 192. Lemli J. Metabolism of sennosides—an overview. *Pharmacology.* 1988;36(Suppl 1):126-128.
 193. Marlett JA, Li BU, Patrow CJ, Bass P. Comparative laxation of psyllium with and without senna in an ambulatory constipated population. *Am J Gastroenterol.* 1987;82:333-337.
 194. Kinnunen O, Salokannel J. The carry-over effect on the bowel habit in elderly long-term patients of long-term bulk-forming products containing stimulant laxative. *Acta Med Scand.* 1987;222:477-479.
 195. Passmore AP, Wilson-Davies K, Stoker C, Scott ME. Chronic constipation in long stay elderly patients: a comparison of lactulose and a senna-fibre combination. *BMJ.* 1993;307:769-771.
 196. Kinnunen O, Winblad I, Koistinen P, Salokannel J. Safety and efficacy of a bulk laxative containing senna versus lactulose in the treatment of chronic constipation in geriatric patients. *Pharmacology.* 1993;47(Suppl 1):253-255.
 197. MacLennan WJ, Pooler A. A comparison of sodium picosulfate ("Laxoberal") with standardised senna ("Senokot") in geriatric patients. *Curr Med Res Opin.* 1974;2:641-647.
 198. Marciniak CM, Toledo S, Lee J, et al. Lubiprostone vs Senna in postoperative orthopedic surgery patients with opioid-induced constipation: a double-blind, active-comparator trial. *World J Gastroenterol.* 2014;20:16323-16333.
 199. Muller-Lissner S. Pharmacokinetic and pharmacodynamic considerations for the current chronic constipation treatments. *Expert Opin Drug Metab Toxicol.* 2013;9:391-401.
 200. Willems M, van Buuren HR, de Krijger R. Anthranoid self-medication causing rapid development of melanosis coli. *Neth J Med.* 2003;61:22-24.
 201. Brenner DM. Stimulant laxatives for the treatment of chronic constipation: is it time to change the paradigm? *Gastroenterology.* 2012;142:402-404.
 202. Shin A, Camilleri M, Kolar G, Erwin P, West CP, Murad MH. Systematic review with meta-analysis: highly selective 5-HT4 agonists (prucalopride, velusetrag or naronapride) in chronic constipation. *Aliment Pharmacol Ther.* 2014;39:239-253.
 203. 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.
 204. Tack J, Quigley E, Camilleri M, Vandeplassche L, Kerstens R. Efficacy and safety of oral prucalopride in women with chronic constipation in whom laxatives have failed: an integrated analysis. *UEG J.* 2013;1:48-59.
 205. Camilleri M, Van Outryve MJ, Beyens G, Kerstens R, Robinson P, Vandeplassche L. Clinical trial: the efficacy of open-label prucalopride treatment in patients with chronic constipation - follow-up of patients from the pivotal studies: Clinical trial: long-term prucalopride in chronic constipation. *Aliment Pharmacol Ther.* 2010;32:1113-1123.
 206. 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.
 207. Sajid MS, Hebbar 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.
 208. Ponc RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med.* 1999;341:137-141.
 209. Korsten MA, Rosman AS, Ng A, et al. Infusion of neostigmine-glycopyrrolate for bowel evacuation in persons with spinal cord injury. *Am J Gastroenterol.* 2005;100:1560-1565.
 210. Parthasarathy G, Ravi K, Camilleri M, et al. Effect of neostigmine on gastroduodenal motility in patients with suspected gastrointestinal motility disorders. *Neurogastroenterol Motil.* 2015;27:1736-1746.
 211. Nowlan ML, Scott LJ. Acotiamide: first global approval. *Drugs.* 2013;73:1377-1383.
 212. McNicol ED, Boyce D, Schumann R, Carr DB. Mu-opioid antagonists for opioid-induced bowel dysfunction. *Cochrane Database of Systematic Reviews.* 2008;2:CD006332.
 213. McNicol E, Boyce DB, Schumann R, Carr D. Efficacy and safety of mu-opioid antagonists in the treatment of opioid-induced bowel dysfunction: systematic review and meta-analysis of randomized controlled trials. *Pain Med.* 2008;9:634-659.
 214. Ford AC, Brenner DM, Schoenfeld PS. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and meta-analysis. *Am J Gastroenterol.* 2013;108:1566-1574.
 215. Jansen J-P, Lorch D, Langan J, et al. A randomized, placebo-controlled phase 3 trial (Study SB-767905/012) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. *J Pain.* 2011;12:185-193.
 216. Irving G, Péñzes J, Ramjattan B, et al. A Randomized, Placebo-Controlled Phase 3 Trial (Study SB-767905/013) of Alvimopan for

- opioid-induced bowel dysfunction in patients with non-cancer pain. *J Pain*. 2011;12:175-184.
217. Mehta N, O'Connell K, Giambone GP, Baqai A, Diwan S. Efficacy of methylnaltrexone for the treatment of opioid-induced constipation: a meta-analysis and systematic review. *Postgrad Med*. 2016;128:282-289.
 218. Kolbow J, Modess C, Wegner D, et al. Extended-release but not immediate-release and subcutaneous methylnaltrexone antagonizes the loperamide-induced delay of whole-gut transit time in healthy subjects. *J Clin Pharmacol*. 2016;56:239-245.
 219. Bull J, Wellman CV, Israel RJ, Barrett AC, Paterson C, Forbes WP. Fixed-Dose Subcutaneous Methylnaltrexone in Patients with Advanced Illness and Opioid-Induced Constipation: Results of a Randomized, Placebo-Controlled Study and Open-Label Extension. *J Palliat Med*. 2015;18:593-600.
 220. Nalamachu SR, Pergolizzi J, Taylor R, et al. Efficacy and tolerability of subcutaneous methylnaltrexone in patients with advanced illness and opioid-induced constipation: a responder analysis of 2 randomized, Placebo-Controlled Trials. *Pain Practice*. 2015;15:564-571.
 221. Webster LR, Yamada T, Arjona Ferreira JC. A Phase 2b, randomized, double-blind placebo-controlled study to evaluate the efficacy and safety of naldemedine for the treatment of opioid-induced constipation in patients with chronic noncancer pain. *Pain Medicine*. 2017;18:2350-2360.
 222. Lawson R, Ryan J, King F, Goh JW, Tichy E, Marsh K. Cost Effectiveness of Naloxegol for Opioid-Induced Constipation in the UK. *Pharmacoeconomics*. 2017;35:225-235.
 223. Tack J, Lappalainen J, Diva U, Tummala R, Sostek M. Efficacy and safety of naloxegol in patients with opioid-induced constipation and laxative-inadequate response. *UEG J*. 2015;3:471-480.
 224. Yuan C-S, Foss JF, Osinski J, Toledano A, Roizen MF, Moss J. The safety and efficacy of oral methylnaltrexone in preventing morphine-induced delay in oral-cecal transit time*. *Clin Pharmacol Ther*. 1997;61:467-475.
 225. Yuan C-S, Foss JF, O'Connor M, Toledano A, Roizen MF, Moss J. Methylnaltrexone prevents morphine-induced delay in oral-cecal transit time without affecting analgesia: A double-blind randomized placebo-controlled trial*. *Clin Pharmacol Ther*. 1996;59:469-475.
 226. Webster L, Chey WD, Tack J, Lappalainen J, Diva U, Sostek M. Randomised clinical trial: the long-term safety and tolerability of naloxegol in patients with pain and opioid-induced constipation. *Aliment Pharmacol Ther*. 2014;40:771-779.
 227. Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for Opioid-Induced Constipation in Patients with Noncancer Pain. *N Engl J Med*. 2014;370:2387-2396.
 228. Gonne J, Camilleri M, Ferber I, et al. Effect of Alvimopan and Codeine on Gastrointestinal Transit: A Randomized Controlled Study. *Clin Gastroenterol Hepatol*. 2005;3:784-791.
 229. Nelson AD, Camilleri M, Chirapongsathorn S, et al. Comparison of efficacy of pharmacological treatments for chronic idiopathic constipation: a systematic review and network meta-analysis. *Gut*. 2017;66:1611-1622.
 230. 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.
 231. 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.
 232. 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.
 233. 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: lubiprostone for chronic constipation. *Aliment Pharmacol Ther*. 2007;25:1351-1361.
 234. Johanson JF, Drossman DA, Panas R, Wahle A, Ueno R. Clinical trial: phase 2 study of lubiprostone for irritable bowel syndrome with constipation: Clinical Trial: Lubiprostone For IBS With Constipation. *Aliment Pharmacol Ther*. 2008;27:685-696.
 235. Camilleri M, Bharucha AE, Ueno R, et al. Effect of a selective chloride channel activator, lubiprostone, on gastrointestinal transit, gastric sensory, and motor functions in healthy volunteers. *Am J Physiol-Gastrointest Liver Physiol*. 2006;290:G942-G947.
 236. Pennington B, Marriott ER, Lichtlen P, Akbar A, Hatswell AJ. The cost effectiveness of lubiprostone in chronic idiopathic constipation. *Pharmacoecon Open*. 2018;2:241-253.
 237. Shah E, Pimentel M. Evaluating the functional net value of pharmacologic agents in treating irritable bowel syndrome. *Aliment Pharmacol Ther*. 2014;39:973-983.
 238. Chiarioni G, Whitehead WE. The role of biofeedback in the treatment of gastrointestinal disorders. *Nat Clin Pract Gastroenterol Hepatol*. 2008;5:371-382.
 239. 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.
 240. 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.
 241. 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.
 242. 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.
 243. 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.
 244. Lehur PA, Stuto A, Fantoli M, et al. Outcomes of stapled transanal rectal resection vs. biofeedback for the treatment of outlet obstruction associated with rectal intussusception and rectocele: a multicenter, randomized, controlled trial. *Dis Colon Rectum*. 2008;51:1611-1618.
 245. Patcharatrakul T, Valestin J, Schmeltz A, Schulze K, Rao SSC. Factors associated with response to biofeedback therapy for dyssynergic defecation. *Clin Gastroenterol Hepatol*. 2018;16:715-721.
 246. Chiarioni G. Biofeedback treatment of chronic constipation: myths and misconceptions. *Tech Coloproctol*. 2016;20:611-618.
 247. Etherson KJ, Horrocks EJ, Scott SM, Knowles CH, Yiannakou Y. A national biofeedback practitioners service evaluation: focus on chronic idiopathic constipation. *Front Gastroenterol*. 2017;8:62-67.
 248. Iqbal F, Askari A, Adaba F, et al. Factors associated with efficacy of nurse-led bowel training of patients with chronic constipation. *Clin Gastroenterol Hepatol*. 2015;13:1785-1792.
 249. Bellini M, Usai-Satta P, Bove A, et al. Chronic constipation diagnosis and treatment evaluation: the "CHRO.CO.DI.TE". study. *BMC Gastroenterol*. 2017;17(1):11.
 250. Koutsomanis D, Lennard-Jones JE, Roy AJ, Kamm MA. Controlled randomised trial of visual biofeedback versus muscle training without a visual display for intractable constipation. *Gut*. 1995;37:95-99.

251. Norton C, Emmanuel A, Stevens N, et al. Habit training versus habit training with direct visual biofeedback in adults with chronic constipation: study protocol for a randomised controlled trial. *Trials*. 2017;18.
252. Wang X, Yin J. Complementary and alternative therapies for chronic constipation. *Evid-Based Complement Alternat Med*. 2015;2015:1-11.
253. Peng W, Liang H, Sibbritt D, Adams J. Complementary and alternative medicine use for constipation: a critical review focusing upon prevalence, type, cost, and users' profile, perception and motivations. *Int J Clin Pract*. 2016;70:712-722.
254. Rahimi R. Herbal medicines for the management of irritable bowel syndrome: A comprehensive review. *World J Gastroenterol*. 2012;18:589.
255. Grundmann O. Complementary and alternative medicines in irritable bowel syndrome: An integrative view. *World J Gastroenterol*. 2014;20:346.
256. Shen Y-HA, Nahas R. Complementary and alternative medicine for treatment of irritable bowel syndrome. *Can Fam Physician*. 2009;55:143-148.
257. Bensoussan A, Kellow JE, Bouchier SJ, et al. Efficacy of a Chinese herbal medicine in providing adequate relief of constipation-predominant irritable bowel syndrome: a randomized controlled trial. *Clin Gastroenterol Hepatol*. 2015;13:1946-1954.e1.
258. Zhang C, Guo L, Guo X, Li G, Guo X. Short and long-term efficacy of combining Fuzhengliqi mixture with acupuncture in treatment of functional constipation. *J Tradit Chin Med*. 2013;33:51-59.
259. Huang C-H, Su Y-C, Li T-C, et al. Treatment of constipation in long-term care with chinese herbal formula: a randomized, double-blind placebo-controlled trial. *J Alternat Complement Med*. 2011;17:639-646.
260. Jia G, Meng M-B, Huang Z-W, et al. Treatment of functional constipation with the Yun-chang capsule: A double-blind, randomized, placebo-controlled, dose-escalation trial: YCC for treating FC. *J Gastroenterol Hepatol*. 2010;25:487-493.
261. Cheng C-W, Bian Z-X, Zhu L-X, Wu JCY, Sung JJY. Efficacy of a Chinese herbal proprietary medicine (Hemp Seed Pill) for functional constipation. *Am J Gastroenterol*. 2011;106:120-129.
262. Bian ZX, Cheng CW, Zhu LZ. Chinese herbal medicine for functional constipation: a randomised controlled trial. *Hong Kong Med J*. 2013;19(Suppl 9):44-46.
263. Manheimer E, Wieland LS, Cheng K, et al. Acupuncture for irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol*. 2012;107:835-847.
264. Xue Q, Li N, Liu Z, Wang C, Lu J. Efficacy of electroacupuncture in the treatment of functional constipation: A randomized controlled pilot trial. *Chinese J Integ Med*. 2015;21:459-463.
265. Zhang T, Chon TY, Liu B, et al. Efficacy of acupuncture for chronic constipation: a systematic review. *Am J Chinese Med*. 2013;41:717-742.
266. Lee MS, Choi T-Y, Park J-E, Ernst E. Effects of moxibustion for constipation treatment: a systematic review of randomized controlled trials. *Chinese Med*. 2010;5:28.
267. Park J-E, Sul J-U, Kang K, Shin B-C, Hong K-E, Choi S-M. The effectiveness of moxibustion for the treatment of functional constipation: a randomized, sham-controlled, patient blinded, pilot clinical trial. *BMC Complement Altern Med*. 2011;11:124.
268. Ottillinger B, Storr M, Malfertheiner P, Allescher H-D. STW 5 (Iberogast®)—a safe and effective standard in the treatment of functional gastrointestinal disorders. *Wien Med Wochenschr*. 2013;163:65-72.
269. Cirillo C, Capasso R. Constipation and botanical medicines: an overview: constipation and botanical medicines. *Phytother Res*. 2015;29:1488-1493.
270. Elsagh M, Fartookzadeh MR, Kamalinejad M, et al. Efficacy of the *Malva sylvestris* L. flowers aqueous extract for functional constipation: A placebo-controlled trial. *Complement Therap Clin Pract*. 2015;21:105-111.
271. Iturrino J, Camilleri M, Wong BS, Linker Nord SJ, Burton D, Zinsmeister AR. Randomised clinical trial: the effects of daikenchuto, TU-100, on gastrointestinal and colonic transit, anorectal and bowel function in female patients with functional constipation. *Aliment Pharmacol Ther*. 2013;37:776-785.
272. van Tilburg MAL, Palsos OS, Ringel Y, Whitehead WE. Is ginger effective for the treatment of irritable bowel syndrome? A double blind randomized controlled pilot trial. *Complementary Therapies in Medicine*. 2014;22:17-20.
273. Brinkhaus B, Hentschel C, Keudell CV, et al. Herbal medicine with curcuma and fumitory in the treatment of irritable bowel syndrome: A randomized, placebo-controlled, double-blind clinical trial. *Scand J Gastroentero*. 2005;40:936-943.
274. Lämäs K, Lindholm L, Engström B, Jacobsson C. Abdominal massage for people with constipation: a cost utility analysis: Abdominal massage for people with constipation. *J Adv Nurs*. 2010;66:1719-1729.
275. Lämäs K, Lindholm L, Stenlund H, Engström B, Jacobsson C. Effects of abdominal massage in management of constipation—A randomized controlled trial. *Int J Nurs Stud*. 2009;46:759-767.
276. Silva CAG, Motta MEFA. The use of abdominal muscle training, breathing exercises and abdominal massage to treat paediatric chronic functional constipation. *Colorectal Dis*. 2013;15:e250-e255.
277. Sinclair M. The use of abdominal massage to treat chronic constipation. *J Bodywork Movement Therap*. 2011;15:436-445.
278. Ford AC, Quigley EMM, Lacy BE, et al. Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol*. 2014;109:1350-1365.
279. Paré P, Bridges R, Champion MC, et al. Recommendations on chronic constipation (including constipation associated with irritable bowel syndrome) treatment. *Can J Gastroenterol*. 2007;21(Suppl B):3B-22B.
280. Mendoza J, Legido J, Rubio S, Gisbert JP. Systematic review: the adverse effects of sodium phosphate enema: systematic review: adverse effects of sodium phosphate enema. *Aliment Pharmacol Ther*. 2007;26:9-20.
281. Emmett CD, Close HJ, Yiannakou Y, Mason JM. Trans-anal irrigation therapy to treat adult chronic functional constipation: systematic review and meta-analysis. *BMC Gastroenterol*. 2015;15:139.
282. Christensen P, Krogh K, Perrouin-Verbe B, et al. Global audit on bowel perforations related to transanal irrigation. *Tech Coloproctol*. 2016;20:109-115.
283. Emmanuel AV, Krogh K, Bazzocchi G, et al. Consensus review of best practice of transanal irrigation in adults. *Spinal Cord*. 2013;51(10):732-738.
284. Johnsen PH, Hilpusch F, Cavanagh JP, et al. Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial. *Lancet Gastroenterol Hepatol*. 2018;3:17-24.
285. Halkjaer SI, Christensen AH, Lo BZS, et al. Faecal microbiota transplantation alters gut microbiota in patients with irritable bowel syndrome: results from a randomised, double-blind placebo-controlled study. *Gut*. 2018;67(12):2107-2115.
286. Ding C, Fan W, Gu L, et al. Outcomes and prognostic factors of fecal microbiota transplantation in patients with slow transit constipation: results from a prospective study with long-term follow-up. *Gastroenterology Report*. 2018;6:101-107.
287. Tian H, Ge X, Nie Y, et al. Fecal microbiota transplantation in patients with slow-transit constipation: A randomized, clinical trial. *PLoS ONE*. 2017;12:e0171308.

288. Zhang X, Tian H, Gu L, et al. Long-term follow-up of the effects of fecal microbiota transplantation in combination with soluble dietary fiber as a therapeutic regimen in slow transit constipation. *Sci China Life Sci.* 2018;61:779-786.
289. Moreira TR, Leonhardt D, Conde SR. Influence of drinking a probiotic fermented milk beverage containing bifidobacterium animalis on the symptoms of constipation. *Arq Gastroenterol.* 2017;54:206-210.
290. Spiller R, Pelerin F, Cayzele Decherf A, et al. Randomized double blind placebo-controlled trial of *Saccharomyces cerevisiae* CNCM I-3856 in irritable bowel syndrome: improvement in abdominal pain and bloating in those with predominant constipation. *United European Gastroenterol J.* 2016;4:353-362.
291. Mezzasalma V, Manfrini E, Ferri E, et al. A randomized, double-blind, placebo-controlled trial: the efficacy of multispecies probiotic supplementation in alleviating symptoms of irritable bowel syndrome associated with constipation. *Biomed Res Int.* 2016;2016:1-10.
292. Kim SE, Choi SC, Park KS, et al. Change of fecal flora and effectiveness of the short-term VSL#3 probiotic treatment in patients with functional constipation. *J Neurogastroenterol Motil.* 2015;21:111-120.
293. Ford AC, Quigley EM, Lacy BE, et al. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. *Am J Gastroenterol.* 2014;109:1547-1561.
294. Mazlyn MM, Nagarajah LH, Fatimah A, Norimah AK, Goh KL. Effects of a probiotic fermented milk on functional constipation: a randomized, double-blind, placebo-controlled study. *J Gastroenterol Hepatol.* 2013;28:1141-1147.
295. Choi SC, Kim BJ, Rhee PL, et al. Probiotic fermented milk containing dietary fiber has additive effects in ibs with constipation compared to plain probiotic fermented milk. *Gut Liv.* 2011;5:22-28.
296. Knowles CH, Grossi U, Horrocks EJ, et al. Surgery for constipation: systematic review and practice recommendations: Graded practice and future research recommendations. *Colorectal Dis.* 2017;19(Suppl 3):101-113.
297. Arebi N, Kalli T, Howson W, Clark S, Norton C. Systematic review of abdominal surgery for chronic idiopathic constipation: Surgical outcomes in constipation. *Colorectal Dis.* 2011;13:1335-1343.
298. Pfeifer J. Surgical options to treat constipation: A brief overview. *Rozhl Chir.* 2015;94:349-361.
299. Bove A. Consensus statement AIGO/SICCR diagnosis and treatment of chronic constipation and obstructed defecation (Part II: Treatment). *World J Gastroenterol.* 2012;18:4994.
300. 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.
301. Meurette G, Lehur PA, Coron E, Regenet N. Long-term results of Malone's procedure with antegrade irrigation for severe chronic constipation. *Gastroentérologie Clinique et Biologique.* 2010;34:209-212.
302. Sturkenboom R, van der Wilt AA, van Kuijk SMJ, et al. Long-term outcomes of a Malone antegrade continence enema (MACE) for the treatment of fecal incontinence or constipation in adults. *Int J Colorectal Dis.* 2018;33(10):1341-1348.
303. Dinning PG, Hunt L, Patton V, et al. Treatment efficacy of sacral nerve stimulation in slow transit constipation: a two-phase, double-blind randomized controlled crossover study. *Am J Gastroenterol.* 2015;110:733-740.
304. Patton V, Stewart P, Lubowski DZ, Cook IJ, Dinning PG. Sacral Nerve Stimulation Fails to Offer Long-term Benefit in Patients With Slow-Transit Constipation. *Dis Colon Rectum.* 2016;59:878-885.
305. Pilkington SA, Emmett C, Knowles CH, et al. Surgery for constipation: systematic review and practice recommendations: Results V: Sacral Nerve Stimulation. *Colorectal Dis.* 2017;19:92-100.
306. Zerbib F, Siproudhis L, Lehur PA, et al. Randomized clinical trial of sacral nerve stimulation for refractory constipation. *Br J Surg.* 2017;104:205-213.
307. Knowles CH, Grossi U, Chapman M, Mason J. Surgery for constipation: systematic review and practice recommendations. *Colorectal Dis.* 2017;19:17-36.
308. Grossi U, Horrocks EJ, Mason J, et al. Surgery for constipation: systematic review and practice recommendations: Results IV: Recto-vaginal reinforcement procedures. *Colorectal Dis.* 2017;19:73-91.
309. Grossi U, Knowles CH, Mason J, et al. Surgery for constipation: systematic review and practice recommendations: Results II: Hitching procedures for the rectum (rectal suspension). *Colorectal Dis.* 2017;19:37-48.
310. Mercer-Jones M, Grossi U, Pares D, et al. Surgery for constipation: systematic review and practice recommendations: Results III: Rectal wall excisional procedures (Rectal Excision). *Colorectal Dis.* 2017;19:49-72.
311. Constipation WA. Advances in diagnosis and treatment. *JAMA.* 2016;315:185.
312. Rao SSC, Bharucha AE, Chiarioni G, et al. Anorectal Disorders. *Gastroenterology.* 2016;150(6):1430-1442.e4.
313. Chiarioni G, Kim SM, Vantini I, Whitehead WE. Validation of the balloon evacuation test: reproducibility and agreement with findings from anorectal manometry and electromyography. *Clin Gastroenterol Hepatol.* 2014;12:2049-2054.
314. Chiarioni G. Biofeedback therapy for dyssynergic defecation. *World J Gastroenterol.* 2006;12:7069.
315. Burnett CA. Nurse management of intractable functional constipation: a randomised controlled trial. *Arch Dis Child.* 2004;89:717-722.
316. Mearin F, Ciriza C, Mínguez M, et al. Guía de práctica clínica del síndrome del intestino irritable con estreñimiento y estreñimiento funcional en adultos: tratamiento. (Parte 2 de 2). *SEMERGEN - Medicina de Familia.* 2017;43:123-140.
317. Serra J, Mascort-Roca J, Marzo-Castillejo M, et al. Guía de práctica clínica sobre el manejo del estreñimiento crónico en el paciente adulto. Parte 2: Diagnóstico y tratamiento. *Gastroenterología y Hepatología.* 2017;40:303-316.

How to cite this article: Serra J, Pohl D, Azpiroz F, et al. European society of neurogastroenterology and motility guidelines on functional constipation in adults. *Neurogastroenterol Motil.* 2019;00:e13762. <https://doi.org/10.1111/nmo.13762>