

This is a repository copy of An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation.

White Rose Research Online URL for this paper: http://eprints.whiterose.ac.uk/156908/

Version: Published Version

#### Article:

Aziz, I., Whitehead, W.E., Palsson, O.S. et al. (2 more authors) (2020) An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation. Expert Review of Gastroenterology & Hepatology, 14 (1). pp. 39-46. ISSN 1747-4124

https://doi.org/10.1080/17474124.2020.1708718

#### Reuse

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) licence. This licence only allows you to download this work and share it with others as long as you credit the authors, but you can't change the article in any way or use it commercially. More information and the full terms of the licence here: https://creativecommons.org/licenses/

#### Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.





## **Expert Review of Gastroenterology & Hepatology**



ISSN: 1747-4124 (Print) 1747-4132 (Online) Journal homepage: https://www.tandfonline.com/loi/ierh20

# An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation

Imran Aziz, William E Whitehead, Olafur S Palsson, Hans Törnblom & Magnus Simrén

To cite this article: Imran Aziz, William E Whitehead, Olafur S Palsson, Hans Törnblom & Magnus Simrén (2020) An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation, Expert Review of Gastroenterology & Hepatology, 14:1, 39-46, DOI: 10.1080/17474124.2020.1708718

To link to this article: <a href="https://doi.org/10.1080/17474124.2020.1708718">https://doi.org/10.1080/17474124.2020.1708718</a>





#### **REVIEW**

OPEN ACCESS Check for updates



### An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation

Imran Aziza,b, William E Whiteheadc, Olafur S Palssonc, Hans Törnblomd and Magnus Simréncd

<sup>a</sup>Academic Department of Gastroenterology, Sheffield Teaching Hospitals, Sheffield, UK; <sup>b</sup>Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK; Center for Functional Gastrointestinal and Motility Disorders, University of North Carolina, Chapel Hill, North Carolina, USA; dDepartment of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

#### **ABSTRACT**

**Introduction**: Chronic constipation is highly prevalent, affecting between 10% and 15% of the population. The Rome IV criteria categorizes disorders of chronic constipation into four subtypes: (a) functional constipation, (b) irritable bowel syndrome with constipation, (c) opioid-induced constipation, and (d) functional defecation disorders, including inadequate defecatory propulsion and dyssynergic defecation. The initial management approach for these disorders is similar, focusing on diet, lifestyle and the use of standard over-the-counter laxatives. If unsuccessful, further therapy is tailored according to

Areas covered: This review covers the definition, epidemiology, diagnostic criteria, investigations and management of the Rome IV disorders of chronic constipation.

**Expert opinion**: By adopting a logical step-wise approach toward the diagnosis of chronic constipation and its individual subtypes, clinicians have the opportunity to tailor therapy accordingly and improve symptoms, quality of life, and patient satisfaction.

#### ARTICLE HISTORY

Received 16 October 2019 Accepted 20 December 2019

#### KEYWORDS

Rome IV; constipation

#### 1. Introduction

Chronic constipation affects around 10–15% of the population and is amongst the most prevalent gastrointestinal conditions presenting to primary and secondary care. It detrimentally impacts the quality of life and incurs a substantial healthcare burden. The Rome IV criteria categorizes disorders of chronic constipation into four subtypes: (a) functional constipation, (b) irritable bowel syndrome with constipation, (c) opioid-induced constipation, and (d) functional defecation disorders, including inadequate defecatory propulsion and dyssynergic defecation. The initial management approach for these disorders is similar, focusing on diet, lifestyle and the use of standard over-thecounter laxatives. If unsuccessful, further therapy is tailored according to subtype. This review covers the definition, epidemiology, diagnostic criteria, investigations and management of the Rome IV disorders of chronic constipation. This will provide a valuable resource for clinicians to approach and manage constipation in a step-wise and logical manner.

#### 2. Definition

Constipation is used to describe symptoms that relate to difficulties in defecation. These include infrequent bowel movements, hard or lumpy stools, excessive straining, sensation of incomplete evacuation or blockage and, in some instances, the use of manual maneuvers to facilitate

evacuation. Symptoms may be acute, where they typically last less than a week and are commonly precipitated by a change in diet and/or lifestyle (e.g. reduced fiber intake, decreased physical activity, stress, toileting in unfamiliar surroundings). In contrast, chronic constipation is generally defined by symptoms that persist for at least 3 months [1].

#### 3. Epidemiology

Based on a large meta-analysis of 45 population-based surveys, comprising 261,040 adults, the global prevalence of chronic constipation has been estimated at 14% (95% confidence interval 12-17%) [2]. Chronic constipation is more commonly observed in women, older individuals and those of lower socioeconomic status [2,3]. However, it may be argued that due to significant heterogeneity between studies - stemming from differences in sample size, symptom duration, defining criteria, and methods used to collect symptom data - the global prevalence of chronic constipation remains elusive and needs to be addressed through large-scale multinational collaborative studies with uniform research methodology. Recent data from a three- country cross-sectional population-based survey, using the contemporary Rome IV diagnostic questionnaire, have shown the prevalence of chronic constipation to be approximately 9%, with ~6% being accounted for by functional constipation (FC) and the

CONTACT Magnus Simrén 🔯 magnus.simren@medicine.gu.se 🗊 Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden



#### **Article Highlights**

- · The classification of Rome IV functional disorders of chronic constipation is detailed.
- Guidance on how to diagnose and manage the Rome IV functional disorders of chronic constipation in a logical, resourceful, and stepwise manner is provided.
- Future therapies in the pipeline for chronic constipation are discussed.

remaining 3% split evenly between irritable bowel syndrome with constipation (IBS-C) and opioid-induced constipation (OIC) [4]. A global epidemiological study of functional gastrointestinal disorders is currently underway. The population prevalence of functional defecation disorders, including inadequate defecatory propulsion and dyssynergic defecation, is unknown as the diagnosis requires laboratory testing, although in tertiary care centers it can affect up to one-half of chronic constipation cases [5].

#### 4. Pathophysiology

The pathophysiology of functional disorders of chronic constipation is not completely understood, although the prevailing hypothesis pertains to a disorder of gut-brain interaction with various factors of relevance, either alone or in combination – these include visceral hypersensitivity, abnormalities in sensory/motor function, delayed colonic transit, and altered central perception [6]. Yet, in the instance of OIC, the cause is straightforward with agonism of opioid receptors in the gastrointestinal tract leading to reduced intestinal secretion and motility. In fact, OIC was introduced as a new diagnosis in Rome IV disorders of chronic constipation (compared with previous iterations) and there has been debate as to whether it actually constitutes a functional bowel disorder as the pathophysiology is well known; however, the Rome IV working committee opted to include OIC to help facilitate its recognition and aid further research [6].

#### 5. Diagnostic approach

The approach to chronic constipation is similar to evaluating any other gastrointestinal complaint in that organic etiology (i.e. colorectal cancer, inflammatory bowel disease) should initially be excluded in a cost-effective and judicious manner. This entails taking a thorough clinical history, performing a gastrointestinal examination, and requesting basic laboratory tests. Further investigations to look for an organic pathology should then depend on whether alarm features are present [1].

#### 5.1. Clinical history

The duration and nature of constipation should be established. The Bristol Stool Form Scale (BSFS) is a validated tool that assesses stool consistency on a spectrum of seven types, and can be useful in clinical practice; type 1 and 2 stools denote hard or lumpy stool, whereas type 6 and 7 are indicative of loose or watery stool [1]. The stool consistency has been shown to be a more reliable indicator of colonic transit than stool frequency. The presenting complaint should also elicit for the presence of other gastrointestinal symptoms (e.g. abdominal pain, bloating, and vomiting) as well as enquiring for alarm symptoms, which include unintentional weight loss, rectal bleeding and a family history of colorectal cancer or inflammatory bowel disease [1]. It must also be borne in mind that constipation can arise from neurological disorders such as Parkinson's disease, or medications such as opiates, calcium channel blockers, and tricyclic antidepressants.

#### 5.2. Physical examination

Clinicians should assess for the presence of abdominal masses and lymphadenopathy. The anal orifice should be inspected for fissures or mass lesions. Thereafter, a digital rectal examination should be undertaken to palpate for anorectal strictures and, if unremarkable, proceed to asking the patient to bear down to assess for perineal descent and anal sphincter relaxation; the presence of parodoxical anal contraction may imply dyssynergic defecation, an acquired behavioral disorder of defecation, where an inability to coordinate the abdominal, recto-anal, and pelvic floor muscles during attempted defecation exists [7]. The sensitivity and specificity of digital rectal examination for dyssynergic defecation is 75% and 87%, respectively [8]. As such, further confirmation with anorectal manometry is required and if abnormal can be successfully treated with biofeedback (discussed later).

#### 5.3. Limited laboratory tests

This includes blood tests checking for anemia, inflammation, hypothyroidism, hypercalcemia, and celiac disease [1]. Although celiac disease is commonly perceived as a diarrheal illness, 1 in 10 patients present with constipation [9].

A transabdominal/vaginal ultrasound scan should also be performed in postmenopausal women with recent onset constipation, localized lower abdominal pain, bloating or distension; rarely, ovarian cancer can be the underlying cause.

#### 5.4. Further investigations

- a. A colonoscopy or cross-sectional imaging, to exclude conditions such as colon cancer and inflammatory bowel disease, should be reserved for those in whom alarm features are present based on the aforementioned clinical evaluation. There is little diagnostic yield of performing a colonoscopy for chronic constipation in those without any alarm features [1]. Moreover, a meta-analysis found there to be no association between chronic constipation and the development of colorectal cancer [10].
- b. Balloon expulsion test this is a useful screening tool for a suspected rectal evacuatory disorder, like dyssenergic defecation. The test is done by timing how long it takes a patient to evacuate a rectal balloon, filled with either 50 ml of water or air; in health, most will evacuate within 1-2 min. However, there are important considerations for the balloon expulsion test. It can lack sensitivity as the balloon may not mimic the



patients' regular stool and thus be evacuated even in those with a defecatory disorder. Issues also pertain to specificity, as despite individuals being asked to expel the balloon whilst sitting on a commode behind a private screen, they may still not feel comfortable as it is outside their confines of their own toileting environment. Finally, an abnormal result cannot differentiate between inadequate defecatory propulsion, dyssynergic defecation, and a structural evacuatory disorder. As such, the test is commonly performed and interpreted alongside high-resolution anorectal manometry and defecography [7].

c. Anorectal manometry – this should be undertaken in patients in whom a functional defecation disorder (inadequate defecatory propulsion and/or dyssynergic defecation) is suspected, either following the initial digital rectal examination or when standard medical therapy has failed [7].

Based on anal/rectal resting and squeeze pressures, four specific patterns of anorectal pressure abnormalities can be detected in patients with defecation disorders using high-resolution anorectal manometry. In physiological health, straining evokes rectal contraction and anal sphincter relaxation. However, in dyssynergic defecation, there is a failure to relax the anal sphincter or its paradoxical contraction, and during the anorectal manometry assessment of the rectal propulsive pressure is also assessed to identify those with inadequate defecatory propulsion. As such, the functional defecation disorders can be categorised into the following manometric subtypes, where type I and III describe the typical patterns of dyssynergic defecation [7]:

Type I – Adequate intrarectal propulsive pressure but increased anal sphincter pressure (the latter reflecting paradoxical anal contraction).

Type II – Inadequate intrarectal propulsive pressure and increased anal sphincter pressure.

Type III – Adequate intrarectal propulsive pressure but absent/insufficient anal sphincter relaxation.

Type IV – Inadequate intrarectal propulsive pressure and absent/insufficient anal sphincter relaxation.

 Defecography – this radiological procedure dynamically images the rectum and pelvic floor during attempted

- defecation. Therefore, it can detect structural abnormalities (e.g. rectocele, rectal prolapse, intussusception) and also assess functional parameters such as the anorectal angle at rest and straining. The test has traditionally been done using fluoroscopy although magnetic resonance imaging has recently become available for this purpose, with its advantages being better image resolution and lack of radiation [7].
- b. Colonic transit studies this test is generally reserved for patients who have failed medical therapy, as it may guide further management including consideration of potential surgical intervention. There is little value in testing for colonic transit in patients with untreated dyssynergic defecation, as delayed transit in this setting arises as a secondary epiphenomenon to the rectal evacuatory disorder and will improve once the dyssynergic defecation has been addressed using biofeedback [11].

A simple, cheap, and reliable method of measuring colonic transit is via the radio-opaque marker test. Slight differences in performing the test exist between laboratories, with one validated method being the ingestion of 10 radio-opaque markers per day for six consecutive days, followed by fluoroscopic imaging on the morning of day 7 to count the number of remaining markers; the colonic transit time can then be calculated (in days) by dividing the number of retained markers with the daily dose, i.e. 10 [12]. Alternative methods to measure colonic transit are also available albeit limited to a few specialist research centers. These include colonic scintigraphy, where a patient consumes a radio-labeled meal and timed measurements of residual radioactivity are taken to calculate transit across various GI segments. Another method is the use of wireless motility capsule, which calculates transit times in GI segments through detecting changes in pH [3].

# 6. Subtypes of Rome IV disorders of constipation (Figure 1)

If individuals have had symptoms of chronic constipation for the last 3 months (with onset at least 6 months prior), and no organic gastrointestinal pathology, they can be categorized

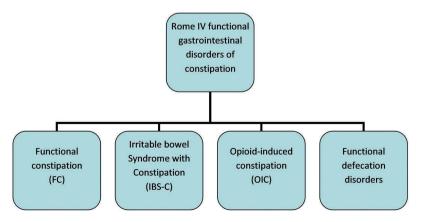


Figure 1. Rome IV disorders of chronic constipation.



according to the Rome IV criteria into one of the following diagnoses [1,7]:

- a. Irritable bowel syndrome with constipation (IBS-C) characterized by abdominal pain at least 1 day per week, where the pain is associated with at least two of the following:
  - (i) Change in stool frequency → toward infrequent bowel movements.
  - (ii) Change in stool form → toward harder stools.
  - (iii) Related to defecation.

Additionally, patients have to have a report that their predominant stool abnormality on days when they have abnormal stools is constipation (at least 25% of all stools Bristol types 1 and 2, and less than 25% types 6 and 7) in order to be diagnosed IBS-C.

- a. Functional Constipation (FC) these patients do not fulfill the criteria for IBS, as abdominal pain is absent/ not predominant or occurs less than 1 day per week. Those who consume opiates should also be excluded from a diagnosis of functional constipation as they rather fit within the realms of opioid-induced constipation. The symptoms of FC must include two or more of the following:
  - (i) Straining more than 25% of defecations.
  - (ii) Lumpy or hard stools (BSFS type 1 or 2) more than 25% of defecations.
  - (iii) Sensation of incomplete evacuation more than one-fourth (25%) of defecations.
  - (iv) Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations.
  - (v) Manual maneuvers to facilitate more than onefourth (25%) of defecations.
  - (vi) Fewer than three spontaneous bowel movements per week.
- b. Opioid-induced constipation (OIC) the diagnostic criteria are similar to that of FC, but with the requisite that new or worsening symptoms of constipation occurred when initiating, changing, or increasing opioid therapy.
- c. Functional defecation disorders (inadequate defecatory propulsion and dyssynergic defecation) – These patients must satisfy the criteria for IBS-C or FC, but also demonstrate features of impaired rectal evacuation as demonstrated by two of the following three tests:
  - (i) Abnormal balloon expulsion test
  - (ii) Abnormal anorectal evacuation pattern with anorectal manometry (or anal surface electromyography (EMG)
  - (iii) Impaired rectal evacuation on defecography, but without structural lesions

#### 7. Treatment

Constipation should be managed in a logical step-wise manner. This encompasses establishing simple conservative measures followed, as appropriate, by pharmacological therapy with or without biofeedback. Very rarely is surgical intervention needed.

#### 7.1. General conservative approach

As with all functional gastrointestinal disorders, patients must receive a clear understanding of the diagnosis and not merely be told what has been excluded. An effective physicianpatient relationship is a cornerstone of successful management of chronic constipation. The physician should listen actively to identify the patient's concerns and their understanding of the disorder. It is important to set realistic goals and to involve the patient in treatment decisions rather than issuing directives. This approach improves patient satisfaction, compliance with the therapy outlined, and reduces subsequent physician visits [6].

Initial therapy includes basic lifestyle and dietary modifications, which may suffice in relieving the symptoms of chronic constipation. Commonly, patients are told to increase their fluid intake, although there is no evidence supporting this concept unless the patient is dehydrated. A randomized controlled study in patients with chronic constipation found that those allocated to 2 L of mineral water per day had increased stool frequency compared to the group allocated ad libitum fluid intake (~1 L per day); however, the findings may be confounded by the mineral water containing magnesium, which has a laxative effect [13]. Exercise is recommended for chronic constipation, with a systematic review and meta-analysis of nine randomized controlled trials – involving 680 participants – supporting its benefit and feasibility [14]. The effects of exercise may be through modulation of anti-inflammatory and anti-oxidative mechanisms [15]. Hence, patients should be encouraged to increase their physical activity as tolerated, starting with simple recommendation to take a 20-min walk (e.g. roughly 1 mile) each day; in particular in light of other potential health benefits with this recommendation.

Supplementing the diet with fiber can be of benefit as it serves to enhance the water-holding properties of the stool, form gels to provide stool lubrication, and provide bulk for the stool and stimulate peristalsis. However, the benefit appears to be limited to soluble fiber (i.e. psyllium and ispaghula husk) with a number needed to treat of 7, and not insoluble fiber such as bran [16,17]. Moreover, patients should be recommended to start adding a low dose of 3-4 g daily and build gradually as tolerated to a dosage of 20-30 g/day in total, as the fermentable properties within fiber may aggravate abdominal pain and bloating.

#### 7.2. Pharmacological therapies

#### 7.2.1. Standard laxatives

Laxatives are commonly used as first-line pharmacological therapy as they are cheap and readily available over the counter. A meta-analysis of six randomized controlled trials found osmotic laxatives to be superior to placebo for FC, with a number needed to treat of 3 [18]. In head-to-head comparisons, polyethylene glycol was superior to lactulose (another osmotic laxative) and non-inferior to prucalopride (a prosecretory agent discussed below) [19,20]. There is a paucity of studies

evaluating osmotic laxatives in IBS-C, other than polyethylene glycol, where a randomized controlled trial demonstrated its superiority over placebo with regards to improving stool frequency, stool consistency and straining; however, no differences were seen between the treatment arms in terms of improvement of abdominal pain although both groups did improve relative to baseline [21]. Osmotic laxatives are typically well tolerated but can cause dose-dependent side effects of bloating, gas, and loose stools.

Stimulant laxatives are also commonly used should osmotic laxative fail. However, data is mainly limited to FC, where a number needed to treat of 3 has been reported [17]. Two relatively recent randomized controlled trials, using modern clinical trial design and outcome assessment, found bisacodyl and sodium picosulphate to be superior to placebo [22,23]. There is a paucity of data for other stimulant laxatives in FC, including the commonly used senna. There is also a lack of high-quality clinical data evaluating stimulant laxatives in IBS-C, although they are commonly used also in this patient group to treat constipation. The most common adverse effects associated with stimulant laxatives are abdominal pain, cramping, and loose stools.

#### 7.2.2. Secretagogues (prosecretory agents)

Luminally acting prosecretory agents have been evaluated in patients with either FC or IBS-C, where they can be used as second-line therapy after standard laxatives. Those available for use in current clinical practice are Linaclotide, Plecanatide, and Lubiprostone.

Linaclotide and Plecanatide are minimally absorbed guanylate cyclase-C agonists. Activation of this receptor on colonic epithelial cells leads to increased intracellular production of cyclic guanosine monophosphate. In turn, this has a dual mode of action, comprising (a) salt and water secretion into the intestinal lumen, and (b) attenuation of visceral afferent pain signaling. Hence, the physiological mode of action of linaclotide and plecanatide is to improve stool consistency and frequency, and reduce abdominal pain. Randomized controlled trials have demonstrated their superiority compared to placebo for the treatment of FC and IBS-C [24-30]. The role of linaclotide in OIC is being evaluated in a phase II randomized, controlled trial [ClinicalTrials.gov identifier: NCT02270983]. When patients are commenced on the guanylate cyclase-C agonists, they should be made aware that stool frequency can increase within a week, but that relief of abdominal pain and bloating (if present) lags behind and can take up to 8-12 weeks. Diarrhea is the most common adverse effect, reported by up to 20% of patients, but can be reduced by taking the medication at least 30-60 min before breakfast. Linaclotide is available in many countries around the globe, whereas plecanatide is currently available only in the United States.

Lubiprostone is a chloride-channel activator that stimulates intestinal fluid secretion. A meta-analysis of nine randomized controlled trials, comprising 1468 patients, found lubiprostone to be superior to placebo with regards to improving the symptoms of FC and IBS-C; however, the beneficial effect was seen at 1 month but was no longer significant at 3 months [31]. Lubiprostone has also been shown to be superior to placebo in patients with OIC [32,33]. Diarrhea and nausea are the most common side effects (~8%), and to limit these, the drug should be taken with food.

#### 7.2.3. 5HT4 agonists (prucalopride)

Serotonin (5-hydroxytryptamine, 5-HT) accelerates gastrointestinal motility, and Prucalopride exerts its effect through being a 5HT4 receptor agonist. An integrated analysis of six randomized controlled trials, comprising 2484 patients with functional constipation, demonstrated that prucalopride was superior to placebo toward achieving at least 3 spontaneous bowel movements per week [34]. There have been no randomized controlled trials of prucalopride in IBS-C although a number of studies in FC have reported improvements in abdominal pain, discomfort and bloating. Prucalopride has also been shown to be superior to placebo in patients with OIC [35]. Prucalopride has a favorable safety and tolerability profile. Even though common side effects include diarrhea and headache, these symptoms normally disappear within the first week of treatment, which is important to inform the patient about when initiating the therapy.

#### 7.2.4. Peripherally acting mu-opioid receptor antagonists (PAMORAs)

Opioids exert their analgesic effects by crossing the bloodbrain barrier and binding to opioid receptors within the central nervous system. However, the GI tract is also abundant with opioid receptors and their agonism leads to reduced intestinal secretion and motility, giving rise to OIC. Indeed, OIC occurs in 51-87% of patients receiving opioids for cancer and between 41% and 57% patients receiving opioids for chronic non-cancer pain [36]. PAMORAs (i.e. nalexagol, naldemedine, methylnaltrexone) alleviate the symptoms of OIC by blocking the mu-opioid receptors within the GI tract, but as they do not cross the blood-brain barrier they do not diminish the central analgesic effect of opioids nor induce withdrawal symptoms. A systematic review and network meta-analysis of randomized controlled trials has found PAMORAs to be superior to placebo for the treatment of OIC [37]. A recent European expert consensus statement on OIC advises PAMORAs to be prescribed if standard laxatives have failed, which will be the case in up to 50% of cases [36]. As previously mentioned, there is also data from randomized controlled trials supporting the use of prucalopride and lubiprostone in OIC, although where they fit into the treatment algorithm for this purpose is debatable; these may be tried after standard laxatives but before proceeding to a PAMORA, although a recent consensus opinion suggests they be added onto a PAMORA if needed [36].

#### 7.2.5. Future drug therapies

Elobixibat is an ileal bile acid transporter inhibitor. It induces a state of bile acid malabsorption, thereby increasing the colonic bile acid pool and leading to increased stool frequency and looser stool consistency. Results from a randomized, double-blind, placebo-controlled, phase 3 trial and an open-label, single-arm, phase 3 trial conducted in Japan found that elobixibat resolved the symptoms of FC in the short-term, and was well tolerated with both short-term and long-term



treatment [38]. This drug is currently approved only in Japan for the treatment of chronic constipation. A small randomized controlled trial of 29 women with IBS-C found that chenodeoxycholate (a delayed release oral form of bile acid which increases the colonic bile acid pool), was superior to placebo with regards to accelerating colonic transit time and improving bowel function [39]. Further trials are needed for both elobixibat and chenodeoxycholate.

Other drugs in the pipeline for FC include the 5HT-4 agonists, velusetrag, and naronapride, for which clinical efficacy data is thus far limited to phase 2 trials [40,41]. Another drug of interest is tenapanor, a first-in-class, small-molecule inhibitor of the gastrointestinal sodium hydrogen exchanger 3, which increases intestinal fluid volume and transit. A doubleblind placebo-controlled phase 2 trial found tenapanor to significantly increase stool frequency and reduce abdominal symptoms in patients with IBS-C [42]. Further trials are awaited.

#### 7.3. Other treatments

#### 7.3.1. Anorectal biofeedback

This is a behavioral training technique that can be used effectively to manage individuals with dyssynergic defecation, with a response rate of approximately 70%. Importantly, biofeedback can also improve slow transit constipation that can arise as a secondary phenomenon to dyssynergic defecation. The procedure entails patients having an anorectal manometry or EMG probe inserted and, via live monitors, being educated on their abnormal anorectal defecatory behavior, followed by instruction in appropriate reversal techniques. The emphasis is to re-learn proper toileting behavior, which during attempted defecation is to enhance push effort (increase intraabdominal and rectal pressure) and relax the pelvic floor muscles. Randomized controlled trials have shown biofeedback to be superior to sham feedback and standard therapy (i.e. laxatives) for dyssynergic defecation [43,44]. The limitations of biofeedback for dyssynergic defecation pertain to its availability in selected centers only and the need for multiple clinic visits. A recent randomized controlled trial found homebased biofeedback to improve bowel symptoms and physiology similar to office-based biofeedback; this cost-effective approach may substantially broaden the availability and use of this treatment [45,46].

#### 7.3.2. Transanal irrigation

This is generally a safe intervention used predominantly in the context of neurogenic bowel dysfunction. It may be considered in individuals with FC in whom pharmacological therapies have failed and before any irreversible surgical measures are undertaken. The procedure is, however, time consuming as most patients need to perform it every second day and the time spent at each procedure is 30-45 min. A prospective evaluation noted that although transanal irrigation can improve bowel function and quality of life, more than onethird of patients discontinue treatment within the first year, of whom one half cite inadequate response [47].

#### 7.3.3. Nerve stimulation

Sacral nerve stimulation was initially reported to be of benefit in refractory cases of chronic constipation with pooled treatment success ranging between 57% and 86% [48]. However, this data was derived from poor quality, open-label observational studies and has since been refuted by two welldesigned double-blind sham-controlled studies [49,50]. Moreover, a favorable response to sacral nerve stimulation cannot be reliably predicted from temporary peripheral nerve evaluation, with a positive and negative predictive value of 50% and 78%, respectively [49]. Additionally, of those who appear to reap benefit from sacral nerve stimulation, the effect is short-lasting as >80% fail treatment within the first few years of long-term follow-up [51]. Finally, sacral nerve stimulation is an invasive surgical procedure with morbidity rates (lead displacement, pain, wound infection, and hematoma) ranging between 13% and 34%, with overall device removal rate between 8% and 23% [48]. In summary, sacral nerve stimulation for refractory chronic constipation is an expensive, invasive procedure which lacks proven benefit. Of late, there has been interest in percutaneous tibial nerve stimulation as a less invasive approach for refractory chronic constipation, although observational studies have yielded conflicting results, with randomized controlled trials yet to be performed [52,53].

#### 7.3.4. Colonic surgery

Colonic resections (i.e. ileorectal anastomosis or ileostomy) are rarely indicated and should only be considered as a last resort in patients with intractable FC, in whom there is clear evidence of slow transit and where pharmacological therapies have failed despite being of optimal dosage and duration. The evidence of benefit of colonic resections is weak and almost exclusively derived from observational studies. A systematic review of 40 articles, providing outcome data in 2045 patients, reported that colectomy may benefit some patients with FC but at the cost of substantial short- and long-term morbidity [54]. Complications occur in 25% of patients. Recurrent episodes of small bowel obstruction occurred in about 15% of patients in the long term, with significant burden of rehospitalization and frequent recourse to surgery. Hence, current evidence is insufficient to guide patient or procedural selection [54]. Moreover, it should be avoided in those with panenteric dysfunction, and neither does it have a role in IBS-C, OIC or dyssynergic defecation.

#### 8. Conclusion

Rome IV disorders of chronic constipation are prevalent and incur considerable health impairment and health-care utilization. The last decade has seen an increase in the repertoire of pharmacological therapies available for the treatment of chronic constipation. By adopting a logical step-wise approach toward the diagnosis of chronic constipation and its individual subtypes, clinicians have the opportunity to tailor therapy accordingly and improve symptoms, quality of life, and patient satisfaction.



#### 9. Expert opinion

In this article, we have reviewed the existing literature and recommendations for management of patients with constipation. Today, most patients with constipation do not undergo physiologic testing, but decisions about treatment and management are based on the clinical history. Moreover, available treatment options often treat the symptoms unsatisfactorily in a large proportion of patients. With the current knowledge about constipation and the available therapies, using a step-wise approach seems reasonable, as well as saving physiologic testing for the more severe and treatment refractory patients. However, in the future, enhanced understanding of the mechanisms underlying constipation and access to better therapies will hopefully allow personalized therapeutic strategies based on better knowledge about physiologic abnormalities in the individual patients. This will require anorectal and colonic physiology characterization in more individuals with constipation, but whether this will lead to optimized treatment in these patients needs to be tested in prospective clinical trials. Furthermore, most of the physiologic tests used today to differentiate between the different types of constipation are invasive and with moderate specificity and sensitivity. Hence, there is certainly an unmet need to better characterize patients with constipation, with less invasive and more accurate methods than those used today, or through optimization of available methods. We foresee progress in this area within the coming years, which will facilitate patient management of large groups of patients in gastroenterology and primary care practices. Moreover, in addition to the development of new treatment options, optimized use of available constipation treatments, with more personalized dosing and potential combination of treatment options with different mode of actions, is another area where progress is also needed in order to help our patients more efficiently. Constipation is a relevant symptom with a pronounced negative effect on the quality of life in large groups of patients. Many patients also testify that these problems are not taken seriously by health-care professionals, and frequently not managed appropriately. Our patients deserve better management options for constipation; we need to make this happen! This can partly be done by standard use of existing methods and available treatment options, but can be further improved by refinement of these, together with the development of new diagnostic and treatment modalities. The future for patients with constipation looks bright!

#### **Funding**

This paper was not funded.

#### **Declaration of interest**

M Simrén has received unrestricted research grants from Danone, Glycom, and Ferring Pharmaceuticals, and served as a Consultant/Advisory Board member for AstraZeneca, Danone, Nestlé, Almirall, Allergan, Albireo, Biocodex Glycom, Kyowa Kirin, Menarini, and Shire, and as a speaker for Tillotts, Menarini, Takeda, Kyowa Kirin, Biocodex, AlfaSigma, Shire, Allergan, and Almirall.

H Törnblom has served as Consultant/Advisory Board member for Almirall and Shire.

O S Palsson has received salary support from research grants from Takeda Pharmaceuticals, Salix Pharmaceuticals, Glycom A/S, the Rome Foundation

and from a consulting agreement with Ironwood Pharmaceuticals, and an educational grant provided by Takeda Pharmaceuticals, and received a speaker honorarium in an educational program supported by Ironwood Pharmaceuticals and Takeda Pharmaceuticals.

W E Whitehead received research grants from Takeda, Ironwood, Salix, and the Rome Foundation; served as a consultant to Biomerica, USA, Ono Pharmaceuticals and Ferring; and received unrestricted educational grants from Takeda and Ferring.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

#### **Reviewer disclosures**

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

#### References

Papers of special note have been highlighted as either of interest (\*) or of considerable interest (\*) to readers.

- Lacy BE, Mearin F, Chang L, et al. Bowel disorders. Gastroenterology. 2016;150(6):1393–1407.
- •• The Rome IV criteria for bowel disorders.
- Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. Am J Gastroenterol. 2011;106(9): 1582–1591. quiz 1581, 1592.
- Camilleri M, Ford AC, Mawe GM, et al. Chronic constipation. Nat Rev Dis Primers. 2017;3:17095.
- Palsson OS, Whitehead WE, van Tilburg MA, et al. Rome IV diagnostic questionnaires and tables for investigators and clinicians. Gastroenterology. 2016;150(6):1481–1491.
- Rao SS, Patcharatrakul T. Diagnosis and treatment of dyssynergic defecation. J Neurogastroenterol Motil. 2016;22(3):423–435.
- Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. Gastroenterology. 2016;150(6):1262–1279.
- 7. Rao SS, Bharucha AE, Chiarioni G, et al. Functional anorectal disorders. Gastroenterology. 2016;150(6):1430–1442.
- The Rome IV criteria anorectal diosorders.
- 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(8):1197–1204.
- Spijkerman M, Tan IL, Kolkman JJ, et al. A large variety of clinical features and concomitant disorders in celiac disease - A cohort study in the Netherlands. Dig Liver Dis. 2016;48(5):499–505.
- Power AM, Talley NJ, Ford AC. Association between constipation and colorectal cancer: systematic review and meta-analysis of observational studies. Am J Gastroenterol. 2013;108(6): 894–903. quiz 904.
- Chiarioni G, Salandini L, Whitehead WE. Biofeedback benefits only patients with outlet dysfunction, not patients with isolated slow transit constipation. Gastroenterology. 2005;129(1):86–97.
- Törnblom H, Van Oudenhove L, Sadik R, et al. Colonic transit time and IBS symptoms: what's the link? Am J Gastroenterol. 2012;107 (5):754–760.
- 13. Anti M, Pignataro G, Armuzzi A, et al. Water supplementation enhances the effect of high-fiber diet on stool frequency and laxative consumption in adult patients with functional constipation. Hepatogastroenterology. 1998;45(21):727–732.
- Gao R, Tao Y, Zhou C, et al. Exercise therapy in patients with constipation: a systematic review and meta-analysis of randomized controlled trials. Scand J Gastroenterol. 2019;54(2):169–177.
- Hajizadeh Maleki B, Tartibian B, Mooren FC, et al. Low-to-moderate intensity aerobic exercise training modulates irritable bowel syndrome through antioxidative and inflammatory mechanisms in women: results of a randomized controlled trial. Cytokine. 2018;102:18–25.



- 16. Suares NC, Ford AC. Systematic review: the effects of fibre in the management of chronic idiopathic constipation. Aliment Pharmacol Ther. 2011;33(8):895-901.
- 17. Ford AC, Moavvedi 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;109(Suppl 1):S2-26. guiz S27.
- Overview of avialable treatments for IBS and constipation and recommendations from ACG about their use.
- 18. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. Gut. 2011:60(2):209-218.
- 19. Attar A, Lémann M, Ferguson A, et al. Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation. Gut. 1999;44(2):226-230.
- 20. Cinca R, Chera D, Gruss HJ, et al. Randomised clinical trial: macrogol/PEG 3350+electrolytes versus prucalopride in the treatment of chronic constipation - a comparison in a controlled environment. Aliment Pharmacol Ther. 2013;37(9):876-886.
- 21. Chapman RW, Stanghellini V, Geraint M, et al. Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. Am J Gastroenterol. 2013;108(9):1508-1515.
- 22. 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(4):897-903.
- 23. Kamm MA, Mueller-Lissner S, Wald A, et al. Oral bisacodyl is effective and well-tolerated in patients with chronic constipation. Clin Gastroenterol Hepatol. 2011;9(7):577-583.
- 24. Chev WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol. 2012;107(11):1702-1712.
- 25. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med. 2011;365(6):527-536.
- 26. Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol, 2012;107(11):1714-1724, quiz p.1725.
- 27. Quigley EM, Tack J, Chey WD, et al. Randomised clinical trials: linaclotide phase 3 studies in IBS-C - a prespecified further analysis based on European medicines agency-specified endpoints. Aliment Pharmacol Ther. 2013;37(1):49-61.
- 28. Brenner DM, Fogel R, Dorn SD, et al. Efficacy, safety, and tolerability of plecanatide in patients with irritable bowel syndrome with constipation: results of two phase 3 randomized clinical trials. Am J Gastroenterol, 2018:113(5):735-745.
- 29. DeMicco M, Barrow L, Hickey B, et al. Randomized clinical trial: efficacy and safety of plecanatide in the treatment of chronic idiopathic constipation. Therap Adv Gastroenterol. 2017;10(11):837-851.
- 30. Miner PB, Koltun WD, Wiener GJ, et al. A randomized phase III clinical trial of plecanatide, a Uroguanylin analog, in patients with chronic idiopathic constipation. Am J Gastroenterol. 2017;112(4):613-621.
- 31. Li F, Fu T, Tong WD, et al. Lubiprostone is effective in the treatment of chronic idiopathic constipation and irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. Mavo Clin Proc. 2016:91(4):456-468.
- 32. Cryer B, Katz S, Vallejo R, et al. A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. Pain Med. 2014;15(11):1825-1834.
- 33. Jamal MM, Adams AB, Jansen JP, et al. A randomized, placebo-controlled trial of lubiprostone for opioid-induced constipation in chronic noncancer pain. Am J Gastroenterol. 2015;110(5):725-732.
- 34. 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(8):2357–2372.
- 35. Sloots CE, Rykx A, Cools M, et al. Efficacy and safety of prucalopride in patients with chronic noncancer pain suffering from opioid-induced constipation. Dig Dis Sci. 2010;55(10):2912-2921.

- 36. Farmer AD, Drewes AM, Chiarioni G, et al. Pathophysiology and management of opioid-induced constipation: european expert consensus statement. United European Gastroenterol J. 2019;7(1):7–20.
- 37. Luthra P. Burr NE, Brenner DM, et al. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and network meta-analysis. Gut. 2018 May 5. Epub ahead of print.
- Systematic review of treatments for opioid-induced constination.
- 38. Nakajima A, Seki M, Taniguchi S, et al. Safety and efficacy of elobixibat for chronic constipation: results from a randomised, double-blind, placebo-controlled, phase 3 trial and an open-label, single-arm, phase 3 trial. Lancet Gastroenterol Hepatol. 2018;3(8):537-547.
- 39. Rao AS, Wong BS, Camilleri M, et al. Chenodeoxycholate in females with irritable bowel syndrome-constipation: a pharmacodynamic and pharmacogenetic analysis. Gastroenterology. 2010;139 (5):1549-1558. 1558.e1541.
- 40. Goldberg M, Li YP, Johanson JF, et al. Clinical trial: the efficacy and tolerability of velusetrag, a selective 5-HT4 agonist with high intrinsic activity, in chronic idiopathic constipation - a 4-week, randomized, double-blind, placebo-controlled, dose-response study. Aliment Pharmacol Ther. 2010;32(9):1102-1112.
- 41. Camilleri M. Vazquez-Roque Ml. Burton D. et al. Pharmacodynamic effects of a novel prokinetic 5-HT receptor agonist, ATI-7505, in humans. Neurogastroenterol Motil. 2007;19(1):30-38.
- 42. Chey WD, Lembo AJ, Rosenbaum DP. tenapanor treatment of patients with constipation-predominant irritable bowel syndrome: a phase 2, randomized, placebo-controlled efficacy and safety trial. Am J Gastroenterol. 2017;112(5):763-774.
- 43. Chiarioni G, Whitehead WE, Pezza V, et al. Biofeedback is superior to laxatives for normal transit constipation due to pelvic floor dyssynergia. Gastroenterology. 2006;130(3):657-664.
- Landmark paper demonstrating the efficacy of biofeedback to treat pelvic floor dyssynergia.
- 44. Heymen S, Scarlett Y, Jones K, et al. Randomized, controlled trial shows biofeedback to be superior to alternative treatments for patients with pelvic floor dyssynergia-type constipation. Dis Colon Rectum. 2007;50(4):428-441.
- 45. Rao SSC, Valestin JA, Xiang X, et al. Home-based versus office-based biofeedback therapy for constipation with dyssynergic defecation: a randomised controlled trial. Lancet Gastroenterol Hepatol. 2018;3(11):768-777.
  - · Recent clinical trial supporting the use of home-based biofeedback therapy, which has the potential to increase its use in the management of patients with constipation due to anorectal dyssynergia.
- 46. Rao SSC, Go JT, Valestin J, et al. Home biofeedback for the treatment of dyssynergic defecation: does it improve quality of life and is it cost-effective? Am J Gastroenterol. 2019;114(6):938-944.
- 47. Juul T, Christensen P. Prospective evaluation of transanal irrigation for fecal incontinence and constipation. Tech Coloproctol. 2017;21(5):363-371.
- 48. 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(Suppl 3):92-100.
- 49. 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(5):733-740.
- 50. Zerbib F, Siproudhis L, Lehur PA, et al. Randomized clinical trial of sacral nerve stimulation for refractory constipation. Br J Surg. 2017;104(3):205-213.
- 51. Patton V, Stewart P, Lubowski DZ, et al. Sacral nerve stimulation fails to offer long-term benefit in patients with slow-transit constipation. Dis Colon Rectum. 2016;59(9):878-885.
- 52. Kumar L, Liwanag J, Athanasakos E, et al. Effectiveness of percutaneous tibial nerve stimulation in managing refractory constipation. Colorectal Dis. 2017;19(1):45-49.
- 53. Collins B, Norton C, Maeda Y. Percutaneous tibial nerve stimulation for slow transit constipation: a pilot study. Colorectal Dis. 2012;14(4):e165-170.
- 54. Knowles CH, Grossi U, Chapman M, et al. Surgery for constipation: systematic review and practice recommendations: results I: colonic resection. Colorectal Dis. 2017;19(Suppl 3):17-36.