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THERAPY IN PRACTICE

Functional Constipation: Individualising Assessment and Treatment

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Abstract
Chronic constipation is one of the five most common symptoms seen by gastroenterologist. In the absence of alarm symptoms, a confident symptom-based diagnosis can often be made using the Rome criteria. Three different subtypes have been identified to date: normal transit constipation, defaecatory disorders and slow transit constipation. Differentiation between these subtypes can be made through functional testing using tests such as anorectal manometry with balloon expulsion and a radio-opaque marker test. In general, patients are initially advised to increase their fluid and fibre intake. When these general lifestyle recommendations do not improve patients' symptoms, a step-wise and add-on treatment approach should be applied. This review summarises the diagnostic criteria to differentiate functional constipation from other causes of chronic constipation. In addition, current drug treatment options, including discussion of new therapeutic targets are discussed. Further, practical treatment approaches (choice and dosing), include discussion of combination/augmentation, treatment failure (adherence/expectations), and relapse prevention are mentioned. Finally, treatment and management of pain and bloating aspects are included.

Key Points

A stepwise clinical evaluation will improve patient outcome through proper subtype identification.

If a patients' symptom does not improve it is always wise to reconsider the diagnosis and re-evaluate the efficacy and side effects of every treatment option.

Before considering surgery in the most difficult patient, combinations of treatments should be considered to achieve the most optimal outcome since slow transit constipation is the rarest of all subtypes.

1 Introduction

Constipation is a term used to describe the presence of different gastrointestinal symptoms such as straining, hard stools, and abdominal discomfort.

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The prevalence of constipation has mainly been evaluated in cross-sectional surveys [1], of which few are available, and have used self-reporting of symptoms or a symptom-based questionnaire for the constipation diagnosis. A large meta-analysis [2] by Suares et al. assessed the prevalence and risk factors for chronic idiopathic constipation in the community. Applying the Rome IV criteria, the pooled prevalence of chronic idiopathic constipation in the global community is 14%; however, when the more stringent Rome III criteria were used, the prevalence was 6.8%. The Rome criteria for chronic constipation are presented in Table 1, together with the criteria for irritable bowel syndrome subtype (IBS-C) constipation. Both disorders show significant overlap in criteria, although for IBS, abdominal pain is the predominant symptom. However, pain and bloating can be present in functional constipation.

As in most other disorders of brain-gut interaction, functional constipation is more prevalent in females. In addition, the prevalence increases slightly with age and is modestly increased in those with a lower socioeconomic status [2].

Chronic constipation can be of primary (intrinsic problems of the colon or anorectal function) or secondary aetiology. Secondary constipation is a result of numerous factors such as organic disease (e.g. mass lesions), diet or drugs (e.g. opioids or antidepressants), and metabolic disorders (e.g. diabetes or hypothyroidism) [3]. Functional

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constipation is of primary origin and is in principle a symptom-based diagnosis. Currently, from a pathophysiological point of view, three different subtypes, which can overlap with each other and other functional gastrointestinal disorders, have been described. These different subtypes are normal transit constipation, slow transit constipation (STC) and rectal evacuation disorders.

This review focuses on the treatment of primary functional chronic constipation in adults, the underlying pathophysiology, the different diagnostic modalities and specific treatments of patients.

2 Materials and Methods

A Pubmed search was performed to identify articles, published in full text and in English. The keywords that were used for this search were 'Constipation', 'Chronic constipation', 'Functional Constipation', 'Irritable Bowel Syndrome', 'Functional bowel disorders', 'Diagnosis', 'Treatment', 'Pellet transit', 'Radiopaque marker', 'Scintigraphy', 'Wireless Motility Capsule', 'Anorectal manometry', 'Rectal hyposensitivity' 'Colonic manometry', 'Over-the-counter', 'Polyethylene Glycol', 'Fibers', 'Osmotic laxatives', 'Bisacodyl', 'Sodium picosulphate', 'Stimulant laxatives', 'Lubiprostone', 'Prucalopride', 'Velusetrag, 'Tegaserod', 'Linaclotide', 'Plecanatide', 'NGM282', 'Naronapride', 'Tenapanor', 'Eloxibat', 'Pelvic floor rehabilitation', 'Biofeedback', 'Surgery'. Further, references of articles were also screened to identify additionally relevant papers.

3 Pathophysiology of Different Constipation Subtypes

Normal transit constipation is thought to be the most prevalent subtype with a prevalence of 4.6% (31% of all those with constipation) [4], although formal confirmation on this statement is lacking. These patients have no evidence of STC or anorectal dysfunction; only subjective symptoms of constipation are present. Overlap of this subtype with IBS-C has been reported, as well as transition from one to the other [5]. The precise pathophysiology underlying this subtype is unknown.

Rectal evacuation disorders make up the second largest subgroup of patients with constipation. An epidemiological study reports a prevalence of 4.6% for outlet obstruction and 3.4% for patients with IBS symptoms and outlet obstruction (combined 55% of total constipated) [4]. Bowel movements require proper coordination between the straining of the abdominal wall muscles, to increase the abdominal pressure and produce a propulsive force, and relaxation of the pelvic floor and anal sphincters to evacuate the stool. Evacuation disorders can present due to disorders of anorectal function, for example dyssynergic defaecation, structural abnormalities such as a rectocele, rectal intussusception or prolapse [6], or even both [7, 8].

Dyssynergic defaecation is the most common subtype of the above. These patients are unable to properly coordinate the required muscle functions to increase the intra-abdominal pressure and relax the anal sphincter due to unknown exact aetiology. In ~ 30% of patients, the problem started during childhood, possibly as a result of pain avoidance, yet in an equal number of patients after a certain life-event such as pregnancy, trauma or back injury, and in the remaining 40% no triggering cause could be found [9]. Of all children presenting with constipation, one-third show persistence of complaints into adulthood [10]. Several phenotypes have been established, which will be explained in more detail. Furthermore, rectal hyposensitivity or impaired rectal sensation is found in 23% [11] even up to 60% [12] of patients with constipation. Whether this hyposensitivity is primary or secondary due to chronic faecal stasis is unclear. In addition, overlap between dyssynergic defaecation, normal transit constipation [13], and STC [14] has been reported, yet improvements in transit and symptoms can occur after biofeedback in these patients [13, 15]. In spite of its high prevalence in patients with constipation, little is known about its clinical relevance. In some patients who report a weakened or absent call for stool [16], it can even be the sole apparent finding.

STC is the least prevalent subtype, with prevalence reports ranging from 15 to 30% [17, 18]. Multiple alterations have been found in these patients such as autonomic dysfunction, dysfunction of colonic smooth muscle activity and colo-colonic reflex, changes in neurotransmitters, and pacemaker activity [3, 19]. These patients have a reduction in overall colonic motility, a reduced or absent rise in colonic motor activity after waking up, an impaired or missing postprandial gastro-colonic response, and absent mass movement contractions, also named high-amplitude propagating contractions, in response to a meal or after administration of a drug [20–23].

A large number of signalling molecules play a role in the modulation of colonic contractile activity. For spontaneous colonic smooth muscle contractions, acetylcholine is the primary stimulant [24]. The release of acetylcholine is mainly controlled by an inhibitory effect of noradrenaline, released by the sympathetic nerve fibres that have shown an abundant colonic presence [25]. Patients with STC display an attenuated or absent motor response to cholinergic stimulation in the descending colon [26]. Another important stimulus for excitatory neuromuscular function is tachykinins. In chronic idiopathic constipation, the effect of neurokinin1-3 receptor

stimulation is reduced compared to health [27]. Vasoactive intestinal peptide (VIP)-containing neurons are present in the human colon and have been shown to mediate descending inhibitory effects [28]. However, reports on VIP have shown conflicting results. In one study, an increase in VIP expression was found in the ascending colon in constipated patients but not in other parts of the colon. However, a number of patients in this series [29] had suspicion for outlet obstruction. In another report, VIP levels were decreased in the sigmoid colon in patients with chronic idiopathic constipation. For peristalsis, the neurotransmitter serotonin is the main mediator [30]. Here, patients with IBS-C, with a low number of stool productions per day, have shown absent to limited 5-hydroxytryptamine (5-HT) meal responses, suggesting a reduced release of 5-HT from enterochromaffin cells [31]. Further, increased levels of nitric oxide have been shown to be present in STC, leading to changes in smooth muscle relaxation and dysmotility [32]. Finally, patients with STC have demonstrated reduction in the number of intrinsic nerves and in the interstitial cells of Cajal [33, 34].

4 Making a Diagnosis

Functional constipation is characterised by nonspecific symptoms. The Rome IV committee has introduced specific criteria [3] for the diagnosis of constipation disorders (Table 1). However, these criteria are mainly intended for use in clinical research and are not always strictly applicable in clinical practice. Finally, symptoms must have been present for the last 3 months and for a minimum of 6 months, this to exclude possible factors that play a role in transient constipation.

In every patient, taking a proper history of patients' symptoms is essential. Excluding alarm symptoms, for example the presence of rectal blood loss, unexplained weight loss, a family history of colorectal cancer or onset of symptoms after the age of 50, requires exclusion of organic abnormalities.

While it is thought that stool frequency is the most characterising symptom for functional constipation, research has shown that stool frequency does not correlate with colonic transit time in patients with fewer than 3 bowel moments per week [35]. Therefore, in clinical practice, a patient's stool consistency should be used as a predictor for the colonic transit time measurements. The Bristol stool form scale is a validated measurement scale on which seven different types of stool are presented [36]. Furthermore, poor correlations have been found for symptoms of constipation (e.g. anorectal blockage, self-digitation, incomplete evacuation) and the presence of dyssynergic defaecation [37, 38].

Careful clinical history taking should be followed by a physical examination in which external central nervous system disorders and spinal lesions should be excluded. Further, examination of the abdomen should be performed with additional attention for distention, palpable hard stool or mass [19]. During inspection, anal fissures, a rectal prolapse and haemorrhoids can be revealed. When performing digital rectal examination, structural abnormalities such as a stricture, rectal mass or faecal impaction can be detected. Further, it can be of value for the detection of dyssynergic defaecation (sensitivity 75–93%, specificity 59–87% [39, 40]). During digital rectal examination, the resting and squeezing tone of the anal sphincter can be evaluated. Thereafter, a patient should be asked to push down, after which a relaxation of the external anal sphincter and puborectalis muscle should occur. In addition, in a normal condition, the perineum descends and abdominal muscles contract. Excessive descent of the perineum beyond this point has been described as the descending perineum syndrome [41], in which there is ballooning of the perineum several centimetres below the bony outlet of the pelvis during a straining effort [42]. Normal physiological perineal descent ranges up to 3 cm. Perineal descent can be evaluated during physical evaluation,

Table 1 Diagnostic criteria [3] for functional constipation and irritable bowel syndrome subtype constipation; for both, criteria must be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Functional constipation	Irritable bowel syndrome subtype constipation (IBS-C)
A. Must include 2 or more of the following, present in >25% of defaecations 1. Straining 2. Lumpy or hard stools (BSFS 1–2) 3. Sensation of incomplete evacuation 4. Sensation of anorectal obstruction/blockage 5. Manual manoeuvers to facilitate (e.g. digital evacuation, support of the pelvic floor) 6. <3 spontaneous bowel movements per week B. Loose stools are rarely present without the use of laxatives C. Insufficient criteria for irritable bowel syndrome	A. Recurrent abdominal pain associated with 2 or more of the following criteria: 1. Related to defaecation 2. Associated with a change in frequency of stool 3. Associated with a change in form (appearance) of stool B. >25% of bowel movements with Bristol stool form types 1–2 and <25% of bowel movements with Bristol stool form types 6–7 C. On average, pain needs to be present ≥1 day per week in the last 3 months

defaecography or magnetic resonance imaging (MRI) [42]. It has been reported that clinical examination does not over or underestimate descent compared to MRI [43]. Clinical symptoms are however a poor predictor for parameters of anorectal dysfunctions [43]. Further diagnostic testing is not always required in patients with constipation. The Rome foundation committee advises to only further test and divide patients in pathophysiology-based subgroups when empirical treatment with laxatives has failed [19]. A systematic, stepwise evaluation of a patient's symptoms and test results is advised (Fig. 1).

4.1 Evaluation of Anorectal and Pelvic Floor Function

Anorectal manometry and the *balloon expulsion test* are physiological tests that can assess rectal evacuation disorders and changes in anal sphincter pressures. For anorectal manometry, different types of catheters exist, yet the most widely used are the water perfused or solid-state catheters. Sphincter pressure changes can be evaluated during rest and during a squeeze. Further, anorectal reflexes and pressure changes can be evaluated during a defaecation attempt. Using anorectal manometry, 4 different types of dyssynergic defaecation have been identified [44] with good reproducibility [45]. High anal sphincter pressure in rest as well as during defaecation, and low rectal pressure and impaired relaxation, have shown increased prevalence in patients with constipation. For the balloon expulsion test, a latex balloon, positioned in the patients' rectum, is filled with 50 mL of water. Thereafter, the patient should be given privacy to try and expel the balloon. Chiarioni et al. found that only a limited number of constipated patients could expel this balloon within one minute [46]. In clinical practice, a one-minute cut off is currently the gold standard [37]. However, recently, Chedid et al. [47] reported that by using this cut off, the sensitivity of this test is limited (sensitivity 39.0%, specificity 93.0%). When reducing the cut off to 22 s, the sensitivity was increased (sensitivity 77.8%, specificity 69.8%). Future prospective studies with biofeedback training are necessary to determine whether this has a positive effect on symptom prognosis, although varying the cut-off for a normal balloon expulsion time did not affect summary sensitivity or specificity in a recent analysis [48]. However, it is a simple tool to exclude the presence of pelvic floor dysfunction (negative predictive value 97%), yet to diagnose, the results of the test should be interpreted with caution (positive predictive value 64%) [37]. Meta-regression analysis was unable to show an effect of left lateral decubitus position or seated position on test performance, although a higher specificity was found in the left lateral position [48]. Finally, up to 90% of healthy individuals have pressure patterns that can be considered abnormal [45].

Another test that can be performed to obtain information on anatomical changes (rectocele, enterocele, intussusception or rectal prolapse) but also on the dynamic function of the anorectal region (dyssynergic defaecation or descending perineum syndrome) is *defaecography*. Contrast defaecography can be performed using barium in combination with fluoroscopy. The patient is asked to expel the barium paste from the rectum while sitting on a commode. Earlier reports have mentioned poor agreements with regard to completeness of evacuation and its contribution to a patients' management was controversial. However, it has the ability to provide information on perineal descent and anorectal function. In addition, rectal intussusception, rectal prolapse, rectocele, and enterocele are possible findings [49]. In some centres, mostly tertiary care, MR defaecography is available which involves no exposure to radiation. However, MR defaecography is usually performed in a supine position, which is thought to be unphysiological and therefore creating extra difficulty for the patient to evacuate the contrast. Yet, MR defaecography has shown to be of good clinical value for the detection of functional and structural abnormal findings in patients suspected to have dyssynergic defaecation. However, the different results (impaired evacuation, abnormal anorectal angle change and paradoxical sphincter contraction) should be interpreted with caution as sensitivity and specificity for findings differ significantly [50].

4.2 Transit Measurements

Assessment of colonic transit can provide objective results and possibly provide insights about the colonic motor function. Its place in the diagnostic workup of patients with functional constipation should be after evaluation of the anorectal region, as this is a more prevalent abnormality and could affect the result of this test when present.

The *radiopaque marker test* is the cheapest and most simple test for assessing colonic transit. For this test, oral administration of radiopaque markers is followed by an abdominal X-ray or fluoroscopy to determine the number of remaining markers. This test is mostly used to determine the colonic transit time. However, it should be noted that a delay in upper gastrointestinal motility can have an impact on the arrival of the makers in the colon. Multiple different protocols for the analysis of whole gut or colonic transit exist. Using the Metcalf method [51], 24 markers are ingested on 3 sequential days, followed by a fluoroscopy picture on Day 4. Using this test, the maximum transit time that can be calculated is 72 h. A protocol [52] that has been described in great detail and has been validated, is the administration of 10 radiopaque markers every morning for 5 days followed by the intake of 5 markers in the morning (8 am) and 5 in the evening (8 pm) on Day 6. On the 7th day, assessment of the remaining markers should be performed.

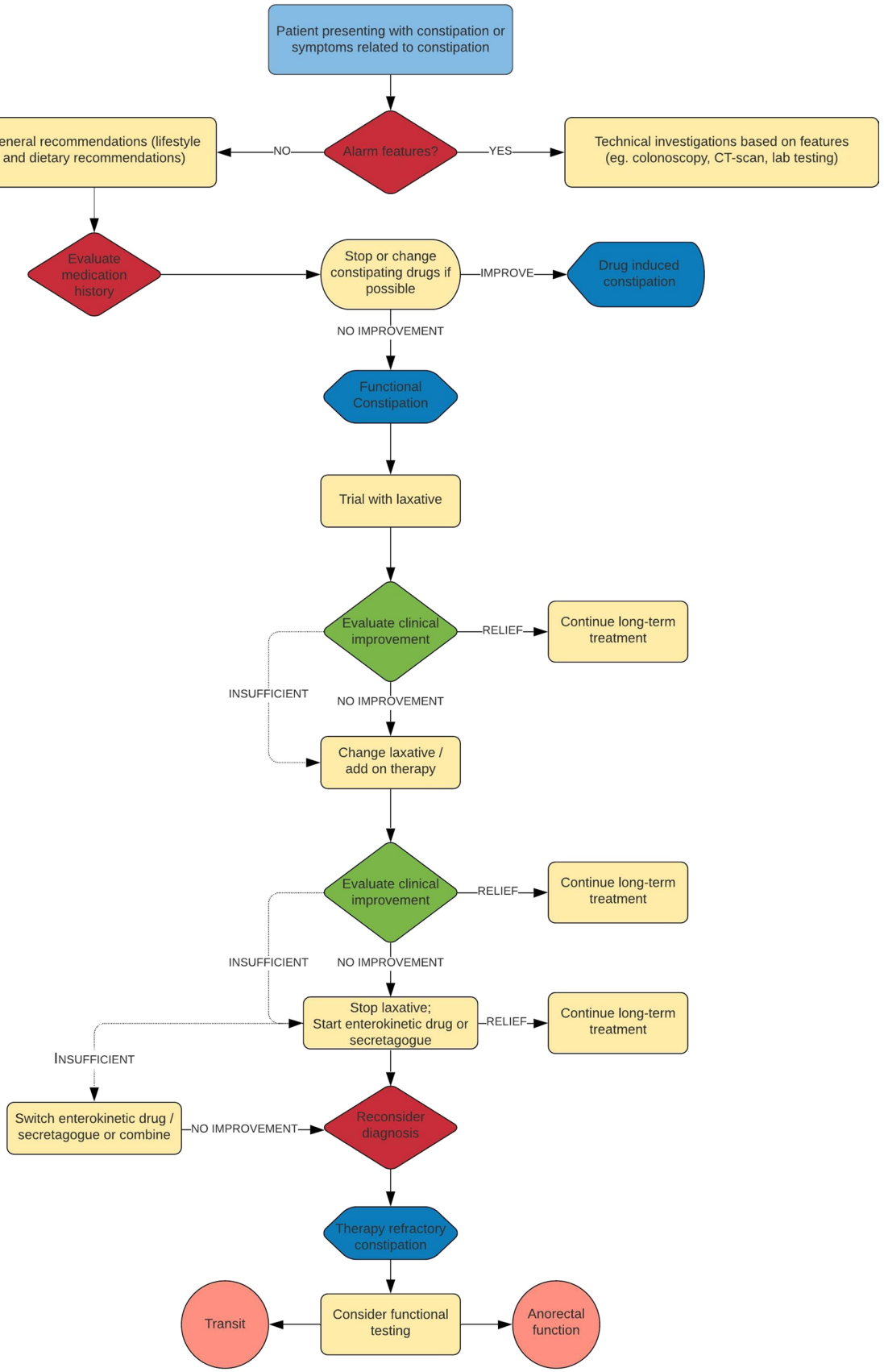

Fig. 1 Functional constipation treatment flowchart

The colonic transit time in days can be determined by dividing the remaining makers by 10. In addition, 4-day protocols should not be performed as these have shown to lack the capacity to discriminate between normal and delayed colonic transit [52, 53]. Normal results of colonic transit time [median (10th–90th percentile)] have been determined and are 1.5 (1.0–3.7) days and 1.3 (0.8–1.9) days for woman and men, respectively [52].

Controversially, the number of remaining markers does not correlate with the symptom severity reported by patients [54]. Another common misconception is that distal location of markers is a reliable sign of dyssynergic defaecation or outlet obstruction. Yet, a rectosigmoid localisation of markers does not correlate with a prolonged balloon expulsion time [55]. Use of these pellets at intervals of one day does not give information on transit through the upper part of the gastrointestinal tract and test results could be influenced by upper gastrointestinal motility disorders.

Another method to calculate colonic transit time and even regional transit times is *colonic scintigraphy*. Krevsky et al. [56] first reported on the technique in 1986, infusing a radiolabelled marker that was released in the caecum. Currently, scintigraphy is another biomarker to measure colonic or even whole gut transit with minimal radiation. Further, scintigraphy has been used in numerous drug trials in the USA, summarised by Camilleri [57], providing grounds for its application in clinical practice. Two different techniques using an oral administration of 111Indium, bound to diethylenetriaminepentaacetic acid [58], and activated charcoal mixed with 111Indium contained within a methacrylate-coated capsule designed to dissolve upon arrival in the alkaline environment of the distal ileum [59], have been investigated. Finally, images made at 24 and 48 h allow for differentiation between health and disease [60].

Another possible measurement tool for gastrointestinal transit is the *wireless motility capsule*. It is approved by the Federal Drug Agency (FDA) for use in patients with suspected delayed gastric emptying and for the evaluation of colonic transit time in patients with chronic idiopathic constipation. It has the potential to provide information about whole gut transit rather than information on one specific region. Hence, it could prevent the need for multiple measurements in one patient. The transit of the capsule through different regions of the gastrointestinal tract is based upon the presence of different pH levels in the different parts of the tract. Normative values for segmental transit measurement in clinical practice have been documented [61]. In addition, measurement of temperature allows for detection of the body exit time. Further, the capsule allows for registration of pressures throughout the gastrointestinal tract; however, this is limited by the presence of just one pressure sensor. Capsule retention is rare, yet a history of pseudo-obstruction or true obstruction are contraindications.

4.3 Colonic Manometry

Colonic manometry can have a role in the final workup of patients with STC and is recommended by the American Neurogastroenterology and Motility Society [62] for selected treatment refractory patients. However, to date, no clear criteria for colonic inertia exist. Detection of colonic neuropathy and myopathy features have been reported [63] and the definitions of different colonic motor patterns [64] have been established in healthy participants. Recently, a translational consensus [65] on terminology and definitions of colonic motility in animals and humans studied by manometric and other techniques has been published to provide an insight and overview in the consolidated terminology used in this field. Finally, the absence of colonic neuropathy (absence of a gastro-colonic response to a meal and the absence of high-amplitude contractions) can be reassuring for patients as up to two-thirds of patients have shown response to aggressive pharmacological and/or biofeedback therapy [63].

5 Different Treatment Modalities for Chronic Constipation

Treatment for chronic constipation depends on the underlying aetiology. The general advice for a patient with constipation is often to withdraw from medication, which has a constipating side effect, when possible, increase fluid intake and increase fibre intake.

5.1 General Recommendations

Dietary fibres are digested carbohydrate polymers and are poorly digested in the small bowel. Therefore, they lead to bulk formation in the colon, drawing water into the colon or they undergo bacterial fermentation [66]. Terms such as ‘soluble’ or ‘insoluble’ are used depending on the interaction of the fibres with water. Psyllium is the main example of soluble fibre, with which most studies have been conducted. It was shown to increase stool frequency, stool weight, consistency and improve pain on defaecation. Surprisingly, colonic transit did not improve [67]. Results from systematic reviews suggest not insoluble fibres such as bran but rather soluble fibres such as psyllium or isaghula improve constipation-associated symptoms [68].

Evidence from health and nutrition examination surveys has shown low liquid consumption to be a predictor for constipation rather than low fibre intake [69], although a very low intake (7 g/day) was associated with a reduction in stool frequency in other reports [70]. Intake of 1 L of a natural mineral water rich in magnesium, sulphate, and calcium has shown efficacy in chronic idiopathic constipation after 1 week of treatment, although the primary endpoint in this

trial was not met [71]. The general recommendation is to increase fibre intake slowly, up to a maximum of 35 g/day. Yet, side effects such as bloating, distension and flatulence can hamper its use. Combined data from three trials provided some evidence of a beneficial effect when compared to placebo with a number needed to treat (NNT) of 2 [72]. Further, one randomised trial [73] has shown possible benefits of dried plums over psyllium for the treatment of constipation. In addition, a short 2-week trial [74] has shown superiority of psyllium over docusate sodium, a stool softener, which is available as an over-the-counter drug. However, it could be expected that over half of patients do not respond to increased fibre intake. Suspicion of STC, a defaecatory disorder, and drug-induced constipation are associated with reduced efficacy [75]. Furthermore, no research has been done on a fermentable oligosaccharide, disaccharide, monosaccharide and polyol (FODMAP)-restricted diet in patients with functional constipation. However, patients are often not satisfied with the effect of fibres on bloating (80%), predictability of treatment effect (79%), and relieve of symptoms of constipation (66%) and constipation itself (50%) [76]. Finally, large epidemiological study results have shown constipation to be more prevalent in those with little physical activity [70, 77] but more importantly in those who ate fewer calories [77].

5.2 Pharmacological Treatment Options

5.2.1 Over-the-counter Laxatives

When lifestyle advice does not resolve or improve the patients' symptoms sufficiently, *osmotic laxatives* are generally recommended. Water secretion or retention in the colon is obtained by poorly absorbed ions, creating an osmotic gradient leading to improvements in stool consistency and frequency. The efficacy of *polyethylene glycol* (PEG 3350) has been shown in multiple studies [78–81] up to 6 months duration when compared to placebo. For the use of PEG, a NNT of 3 has been determined [72]. Use of single daily doses of 17 g [80, 81], 26 g [82] or twice daily (bid) 250 mL solutions [78, 79] are effective.

Lactulose is a synthetic disaccharide, which arrives in the colon undigested and is thereafter fermented by the colonic microbiome causing the pH of the colon to fall. It has shown to increase the frequency, weight, volume, and water content of stools and produced stools of softer consistency [83], with a good treatment response [84]. In a head-to-head trial [82], low-dose PEG (13–39 g/day) has been shown to be superior to lactulose (10–30 mg/day). Side effects such as abdominal pain, bloating and flatus are comparable in prevalence for lactulose and PEG [82]. It is recommended to start with a low dose of PEG 3350 (13 g/day) and gradually increase the dose up to 39 g/day if necessary, to prevent rapid onset of side effects.

Stimulant laxatives are mostly prescribed as the next step in the treatment of functional constipation. One of the most used and well known stimulant laxatives is *bisacodyl*, which increases water and electrolyte secretion in the colon, and prevents the reabsorption of water [85]. In addition, stimulant laxatives initiate high-amplitude propagating contractions in the colon [86], and accelerate colonic transit in healthy individuals [87] or induce high-amplitude propagating contractions [22]. They are often used as rescue treatment in many of current randomised controlled trials [88]. *Sodium picosulphate* has been shown to improve bowel function and symptoms [89, 90], similar to bisacodyl [89], with sustained improvement [89] over a 4-week period in patients with chronic constipation. Both are prodrugs that convert into the same active metabolite, bis-(*p*-hydroxyphenyl)-pyridyl-2-methane in the gut. Dose reduction from 18 to 9 drops for sodium picosulphate [90] and from 10 to 5 mg for bisacodyl [91] can help reduce side effects in patients with good efficacy. Finally, prevalence of expected side effects such as abdominal pain, diarrhoea and headache declined largely after the initial week of treatment with bisacodyl (week 1: 57%, week 4: 5%) [91]. Contrary to what has been thought, results from animal research suggest against damage to intestinal tissue [92] and myenteric neurons [93] due to senna or anthraquinones. The above are first-line treatments in constipation due to their wide-spread availability and low costs.

5.2.2 Prosecretory Agents

Currently, three prosecretory agents are available: lubiprostone, linaclotide, plecanatide and tenapanor. Their mechanism of action is through an increased secretion of intestinal chloride by activating enterocyte surface channels. Through a net increased efflux of ions and water into the intestinal lumen, transit is accelerated as well as the ease of defaecation [94].

Lubiprostone is a bicyclic fatty acid compound and derived from prostaglandin E1 metabolites. Its mode of action is through the activation of chloride channels (ClC_2), leading to increased Cl^- transport into the colonic lumen, resulting in increased fluid secretion.

In two randomised controlled trials, in which in total 242 [95] and 237 patients [96] were included, lubiprostone 24 µg bid, which is the currently recommended dose, improved the weekly average number of spontaneous bowel movements (lubiprostone: 5.69, placebo: 3.4695/ lubiprostone: 5, placebo: 3.596). During all treatment weeks, significant improvements in stool consistency, straining, and constipation severity occurred [95, 96]. Further, a bowel movement could be expected within 24–48 h

of the initial dosing with lubiprostone [95, 96]. However, use of lubiprostone during 3 months was not associated with a significant reduction in abdominal pain scores compared to baseline [95]. The primary endpoint, change in pain scores during the 1st month, was reached. Side effects of lubiprostone are mostly related to the gastrointestinal system, and were rated as mild or moderate by patients [95]. The most commonly reported adverse drug reactions were nausea (19.8%), diarrhoea (9.7%), abdominal distension (6.9%), headache (6.9%), and abdominal pain (5.2%) during 48-week follow-up [97]. The FDA and European Medicines Agency (EMA) have approved use of lubiprostone (24 µg) in chronic idiopathic constipation.

Linaclotide activates guanylate cyclase C (GC-C) receptors on the luminal surface of the intestinal epithelium. This activation leads to generation of increased levels of cyclic guanosine monophosphate (cGMP) and thereby altered secretory function through increased expressions of the cystic fibrosis transmembrane receptor [98]. This effect is homologous to that seen in patients with an *Escherichia coli* infection, where heat-stable enterotoxins cause diarrhoea. GC-C is available in brush border membranes of intestinal mucosa cells, ranging from the duodenum to the rectum [94]. In addition, preclinical models in mice and a post-hoc analysis in humans have shown that linaclotide use is associated with a reduction in abdominal pain experience, thought to occur due to the inhibition of nociceptors by cGMP [99].

Lembo et al. have conducted two randomised controlled trials [100], in which improvements in symptoms of constipation with the 290 µg (19.4% and 16.0% of patients improved) and 145 µg dose (19.4% and 21.3% of patients improved) were seen. Further, improvements in bowel symptoms, abdominal symptoms (discomfort and bloating), and constipation severity were found in these trials. However, due to diarrhoea, 4.2% of patients discontinued the medication. Therefore, a low-dose linaclotide trial [101] (72 µg and 145 µg) was conducted in patients with chronic idiopathic constipation. A significantly larger number of patients on linaclotide met the primary endpoint [≥ 3 complete spontaneous bowel movements (CSBMs) and an increase of ≥ 1 CSBMs per week from baseline in the same week for ≥ 9 of 12 weeks] and had a sustained response. Further, the use of linaclotide (≤ 104 weeks) was shown to be safe in a pooled analyses [102] of six randomised controlled trials.

A 12-week phase 3b trial [103] in patients with chronic idiopathic constipation reported improvement (mean improvement from baseline) of bloating in patients using linaclotide (145 µg: 34.9%, 290 µg: 34.3%, placebo: 22.7%; $p < 0.001$). This already occurred in the first week of treatment and continued for the entire treatment period.

Although pain is not considered part of the Rome IV criteria for functional constipation, symptoms of different functional bowel disorders can overlap and can be more or less predominant. Therefore, a post hoc analysis [104] of pooled data from earlier Phase 3 trials was conducted reporting prevalence of 91%, 96%, and 97% of the 1271 patients with some level of abdominal pain, discomfort, and bloating, respectively. For both their subpopulations (none-mild and moderate-severe), both doses of linaclotide (145 µg and 290 µg) were able to improve patients' symptoms of abdominal pain.

The FDA approved the use of linaclotide in chronic constipation; the EMA only approved its use in IBS subtype constipation. Use of the low dose (72 µg) in the USA was able to reduce the prevalence of diarrhoea by half (2.4%) and was thereby mild in most of the patients.

Plecanatide is an analogue of uroguanylin, which in turn can bind and activate GC-C receptors, with similar effects to linaclotide as described above. The net result of plecanatide is decreasing sodium-hydrogen exchanger activity, resulting in increased fluid secretion into the intestinal lumen to increase stool consistency and volume [105]. Miner Jr et al. conducted a double-blind randomised controlled trial [105], showing sustained efficacy of plecanatide (3 mg and 6 mg) over a period of 12 week with significant improvements in quality of life, when compared to placebo. Use of plecanatide was able to increase CSBMs and SBMs frequency, stool consistency, straining, and other symptoms such as discomfort and bloating, associated with chronic idiopathic constipation. Similar to linaclotide, use of plecanatide is associated with diarrhoea as the most prevalent side effect (~ 6%). The FDA has approved its use (3 mg) in chronic idiopathic constipation and it is only available in the USA. Finally, efficacy and tolerability of GC-C receptor agonists was similar for linaclotide and plecanatide in patients with chronic idiopathic constipation [106].

Tenapanor inhibits the sodium/hydrogen exchanger isoform 3 (NHE3) in the gastrointestinal tract, thereby reducing the absorption of sodium and phosphate, which improves intestinal fluid, transit and by that stool consistency and the number of bowel movements [107]. In a multicentre, Phase 2, randomised trial, a higher number of patients were CSBM responders with tenapanor 50 mg bid (60.7% vs 33.7%; $p < 0.001$ compared to placebo). Further, more individuals experienced a reduction in abdominal pain (65.5% vs 48.3%; $p < 0.26$ compared to placebo) and a greater composite endpoint response, which is currently used in trials in IBS (50.0% vs 23.6%; $p < 0.001$ compared to placebo). Interestingly for patients with constipation, a mean weekly average ≥ 3 CSBMs was achieved for more than half of the treatment period. Treatment-related adverse events such as diarrhoea, headache, nausea, urinary tract infection and abdominal pain are the most common, ranging in prevalence from ~ 1 to 11% and can be expected in ~ 20% of patients. Tenapanor was approved by the FDA for treatment of IBS-C with constipation in 2019.

5.2.3 Serotonergic Agonists

Prucalopride is an agonist of the 5-HT4 receptor with high-affinity when compared to other drugs of its type such as cisapride and tegaserod. These receptors are present on enteric nervous system neurons and are thereby able, when binded, to stimulate and increase intestinal motility. Positive effects on whole gut transit and bowel movement been shown in small studies [108, 109]. In a meta-analysis of 9 trials [110], a relative risk of 1.63 (1.07–2.49) was found for prucalopride (vs control) to achieve ≥ 3 CSBMs per week. Interestingly, similar response rates were found in patients who were dissatisfied with their earlier laxative treatment [111]. Further, positive effects were seen for the number of CSBMs/week, bowel movement consistency, straining, time to first CSBM and satisfaction with treatment [111, 112]. Also, in a pooled-analysis of 936 women with self-reported inadequate relief of symptoms from laxatives [113], prucalopride 2 mg was able to improve symptoms such as bloating, incomplete bowel movements (large effect), abdominal pain, cramps, straining and painful bowel movements (moderate effect).

Use of prucalopride is associated with expected side effects such as headache, nausea, abdominal pain, and diarrhoea, but these were found to be transient in nature [112]. The 2-mg dose was preferred [111, 112], as use of the 4 mg was not associated with improvement in patient symptoms. Controversially, a smaller trial of 361 patients was unable to show a positive effect of prucalopide 2 mg over placebo during a treatment period of 12 and 24 weeks [114].

Tegaserod, another agonist of the 5-HT4 receptor, has shown positive effects on constipation symptoms in randomised controlled trials [115]. However, the drug had been withdrawn from the market due to concern over putative cardiovascular side effects in 2007. Recently however, it has been re-introduced but only for specific use in adult women, aged < 65 years with a diagnosis of IBS-C subtype constipation, as no increased rates of cardiovascular side effects [116] were found when compared to a control population of premenopausal women.

5.3 Biofeedback Therapy

Biofeedback aims at restoring persistent defaecatory behavioural abnormalities. This treatment approach is based on re-education and retraining of one's defaecation act. Through this approach, a patient is learned to again properly and simultaneously brace the abdominal wall muscles and relax their pelvic floor muscles effectively. Different types of biofeedback therapy exist such as electromyograph biofeedback and balloon sensory biofeedback.

This treatment approach seems effective in patients with dyssynergic defaecation but less in patients with chronic constipation of other aetiologies. Recently, a retrospective analysis [117] has been published reporting a ~ 45% symptom improvement in patients with dyssynergic defaecation. However, earlier trials [13, 118, 119] have reported treatment efficacy rates up to 80%, and have shown that biofeedback therapy is more effective than diazepam, polyethylene glycol, and sham biofeedback. To this date, no clear evidence exists concerning the efficacy of biofeedback in improving rectal sensory perception.

A thoroughly performed Cochrane systematic review [120] evaluated different findings in 17 studies, ranging from abstracts to randomised controlled trials, in patients with chronic constipation, although not specifically dyssynergic defaecation. Improvements in constipation were evaluated for the number of patients that improved with electromyographic (EMG) biofeedback compared to diazepam [RR 3.00 (1.51–5.98)] and for balloon sensory training compared to surgery [RR 0.43 (0.21–0.89)]. Further, biofeedback led to a lower obstructed defaecation score at 1 year for EMG biofeedback compared to surgery [RR 0.41 (0.26–0.65)], a higher major clinical improvement compared to laxative use [RR 3.65 (2.17–6.13)], and more CSBMs per week [sham 2.8 vs biofeedback 1.8 (1.25–2.35)] at three months. All these were rated from low to very low evidence as further research will probably have an important impact on the effect estimate. In many studies, questions were raised concerning high risk of bias for blinding and other bias, and many studies were possibly underpowered to detect differences between groups. Finally, there are still misconceptions concerning the presence of anatomical abnormalities and clinical symptoms.

5.4 Surgery

Total colectomy with ileorectal anastomosis is considered the most appropriate type of surgical intervention for carefully selected patients with therapy-refractory constipation. Yet, some surgeons may prefer less radical interventions [121].

A systematic review by Knowles et al. [121] describes the total complication rate to be ~ 25%, with high prevalence rates of prolonged post-operative ileus and early adhesive small bowel obstruction, aside from more general prevalent complications (e.g. anastomotic leak, postoperative bleeding, abscess). Further, almost 10% of patients can develop small intestinal bacterial overgrowth [121], which can be clinically challenging due to its recurring nature. Aside from the many methodological limitations, the overall global satisfaction rating was stated to be 85%. However, high numbers of diarrhoea and incontinence (5%–15%), persistent abdominal pain (30%–50%), bloating (10%–40%), and even recurrent constipation (10%–30%) have been reported [121].

Surgery should generally be reserved for patients who do not respond to any of the above treatment options. Despite proper selection of cases, postoperative morbidity of the early and late kind can still be expected. Finally, before considering surgery, a generalised gastrointestinal motility disorder should be excluded [122, 123].

5.5 Discussion of New Therapeutic Targets

Elobixibat (A3309), a selective inhibitor of the ileal bile acid transporter has been proposed as a possible treatment option for chronic idiopathic constipation. Currently, the drug has not been approved by the FDA nor EMA, and is only available for the treatment of chronic idiopathic constipation in Japan. Bile acid diarrhoea is mostly reported in patients after ileocecal resection but also in patients with functional bowel disorders, such as IBS subtype diarrhea [124]. In addition, administration of di-alpha hydroxy bile salt, sodium chenodeoxycholate has shown to accelerate colonic transit in health, stool frequency and consistency, and ease of passage and evacuation [125]. A Phase IIb trial of elobixibat [126] in 190 chronic idiopathic constipation patients was conducted, in which improvements in SBMs (10 mg: 4.0; $p < 0.002$, 15 mg: 5.4; $p < 0.001$, placebo: 1,7), time to first bowel movement, stool consistency and straining were found for the 10 and 15 mg dose. Further, the 15 mg dose improved abdominal bloating, but not pain and abdominal discomfort. In this trial, the 10-mg dose seemed to be the most efficient, according to the higher prevalence of side effects (abdominal pain and diarrhoea) in the 15 mg group. This was later confirmed to be the optimal dose in Japanese patients as well, where the efficacy was confirmed in a 2-week controlled trial and a long-term safety study [127].

During Phase 2 studies in non-alcoholic steatohepatitis and primary biliary cirrhosis, *NGM282*, a recombinant protein identical to the fibroblast growth factor 19, lead to an increased prevalence of diarrhoea. Therefore, a randomised Phase 2 trial [128] to evaluate its effect on colonic transit and bowel function. NGM282 (6 mg) was able to increase the number of bowel movements. In addition, stools were softer and easier to pass normally. Finally, stool weight and faecal fat secretion were normal, although bile acid excretion decreased with a proportional increase in primary bile acids. Further and larger trials are necessary to evaluate the effect of NGM282 on patients' symptoms and bile acid homeostasis.

Velusetrag is another orally administered 5-HT4 receptor agonist, which has shown efficacy in chronic idiopathic constipation. To date, only a small Phase 2 clinical trial has been conducted, with any reporting of current or future Phase 3 trials on ClinicalTrials.gov. In this trial [129], significant improvements in all endpoints were found for velusetrag compared to placebo. Its use led to a mean increase in SBMs/week (all doses: ~ 3.5, placebo: 1.4; $p < 0.0001$), CBMs/week (all doses: ~ 2, placebo: 0.6; $p < 0.0001$) and reduction in time to first bowel movement (velusetrag: 18–21 h, placebo: 47 h; $p < 0.0001$). Velusetrag is currently under evaluation for the treatment of gastroparesis [130].

Naronapride (ATI-7505), another selective agonist of the 5-HT4 receptor is under development for the treatment of functional gastrointestinal disorders. An abstract [131] reports positive effects of naronapride on the number SBMs and time to first SBM. Further, the company website reports current collaboration with China for drug development; no reports of ongoing or future trials are currently reported on ClinicalTrials.gov. Larger clinical studies are warranted to evaluate its role in the treatment of constipation (Table 2).

6 Stepwise Approach and Combining Treatments in the Difficult Patient

Up to this point, the number of head-to-head trials in functional constipation and constipation in general are lacking. A single-centre randomised double-blind non-inferiority trial [132] was conducted between PEG 3350 (26 mg) and prucalopride (12 mg). This trial was able to show that the most standard used laxative, PEG, was actually non-inferior compared to prucalopride in women in whom laxative use was previously unsatisfactory. The results of this trial strengthen the approach to use PEG as a first-line modality in patients with constipation. Further, no data exist on the combination or augmentation of laxative treatment in functional constipation. Network meta-analysis are an attempt to overcome the limitation in lack of these trials. Although these analyses are associated with an even greater risk of bias assessment, as was described by our group earlier [133]. In chronic idiopathic constipation, similar efficacy was found for all laxatives currently available [88]. However, bisacodyl was thought to possibly lead to more SBMs/week. Certain limitations such as variability in treatment duration, different endpoints, different pain selection, and use of recue medication limit its direct use. The results of this trial strengthen the current stepwise approach.

Patients should first be educated about lifestyle changes as described above. The use of fibres in constipation is limited, nevertheless, associated with little risk [72]. Thereafter, an osmotic laxative should be tried as efficacy with regard to increasing stool frequency and consistency has been shown. Combining stimulant laxatives with fibre, as is often done in clinical practice and clinical trials, could provide relief of symptoms in patients with constipation; there are no placebo-controlled trials to confirm this finding. When stimulant laxative use leads to improvement of symptoms, a dose reduction can help to lessen side effects. As often happens, tolerability and unpredictability go

Table 2 Overview of different treatment modalities

Drug	Trial	Primary endpoint	Dose	Mechanism of action	Side effects
PEG	A randomised, multicentre, placebo-controlled trial of polyethylene glycol laxative for chronic treatment of chronic constipation [49]	Weekly treatment success based on a modification of the ROME criteria	17 g	Osmotic agent	Abdominal distension, diarrhoea, loose stools, flatulence, and nausea
	Comparison of a low-dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation [50]	4-week mean stool frequency	13–39 g		Abdominal pain, bloating, flatus, rumbling
	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 [47]	Complete remission of constipation consisting of ≥ 3 bowel movements/week, no use of laxatives, no straining at defaecation, feeling of complete evacuation, and no hard/pellety stools	250 mL twice daily; PEG 14.6 g twice daily		Nausea, vomiting, anal pain, abdominal pain
Lactulose	Treatment of chronic constipation with lactulose syrup: results of a double-blind study [52]	Maximum use of one other laxative in 21 days	8–30 mL depending on efficacy	Lower pH of stool	Gas formation and intestinal bloating
Bisacodyl	Oral bisacodyl is effective and well-tolerated in patients with chronic constipation [58]	Mean number of CSBMs per week, during the entire 4-week treatment period	5–10 mg	Anti-absorptive-secretory effect and direct prokinetic capabilities	Diarrhoea, abdominal pain, headache
Picosulphate	Multicentre, 4-week, double-blind, randomised, placebo-controlled trial of sodium picosulfate in patients with chronic constipation [57]	Mean number of CSBMs per week during the 4-week treatment phase	9–18 drops	Anti-absorptive-secretory effect and direct prokinetic capabilities	Diarrhoea and abdominal pain
Lubiprostone	Clinical trial: Phase 2 study of lubiprostone for irritable bowel syndrome with constipation [62]	Change from baseline in mean abdominal discomfort/pain score during the first month (28 days) of treatment	8–16–24 μg bid	Chloride channel activation (ClC2)	Nausea, diarrhoea, vomiting, flatulence, abdominal pain and abdominal distension
	Efficacy and Safety of lubiprostone in patients with chronic constipation [63]	Frequency of SBMs during the first week	24 μg bid		Nausea, abdominal pain, headache
Linaclotide	Two randomised trials of linaclotide for chronic constipation [67]	≥ 3 CSBMs per week and an increase of ≥ 1 CSBMs from baseline during ≥ 9 of the 12 weeks	145–290 μg	Secretion of chloride and bicarbonate through the cystic fibrosis transmembrane conductance regulator	Diarrhoea, flatulence, abdominal pain, abdominal distention
	Low-dose linaclotide (72 μg) for chronic idiopathic constipation: a 12-week, randomised, double-blind, placebo-controlled trial [68]	≥ 3 CSBMs per week and an increase of ≥ 1 CSBMs from baseline during ≥ 9 of the 12 weeks	145–72 μg		Diarrhoea, abdominal distention, flatulence
Plecanatide	A randomised Phase III clinical trial of plecanatide, a uroguanylin analogue, in patients with chronic idiopathic constipation [72]	≥ 3 CSBMs per week and an increase of ≥ 1 CSBMs from baseline during ≥ 9 of the 12 weeks	3–6 mg	Secretion of chloride and bicarbonate through the cystic fibrosis transmembrane conductance regulator	Diarrhoea

Table 2 (continued)

Drug	Trial	Primary endpoint	Dose	Mechanism of action	Side effects
Prucalopride	A placebo-controlled trial of prucalopride for severe chronic constipation [79]	Proportion of patients ≥ 3 CSBMs, averaged over 12 weeks	2–4 mg	5-HT4 receptor agonist with enterokinetic capabilities	Headache, nausea, abdominal pain, diarrhoea
	Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives [78]	Proportion of patients ≥ 3 CSBMs, averaged over 12 weeks	2–4 mg		Headache, nausea, abdominal pain, diarrhoea, flatulence, viral infection

hand-in-hand with their use and hamper patient enthusiasm. When the above-mentioned treatments do not resolve the patients' symptoms sufficiently, then further treatment should be decided based on associated symptoms.

When abdominal pain is present, preference should be given to the use of linaclotide, plecanatide or tenapanor. The positive effects of linaclotide on abdominal bloating and its good clinical efficiency are important factors in patient treatment. When patients experience linaclotide-associated diarrhoea, a dose reduction can help achieve satisfactory results. Prucalopride is a good alternative option when pain is less predominant, although moderately positive effects on pain can be expected, as described above. Trials with prucalopride were conducted mainly in patients who did not achieve treatment satisfaction with earlier available treatments, and this may warrant a more advanced position in the treatment sequence. On the other hand, as a motility agent, prucalopride is the only treatment option that may address the often co-existing upper gastrointestinal hypomotility in these patients. Moreover, prucalopride has been shown to be effective in patients with idiopathic gastroparesis [134], leading to improvements in the Gastrointestinal Cardinal Symptom index and symptoms such as fullness/satiety, nausea/vomiting, and bloating/distention. Lubiprostone is another alternative, but side effect of nausea has been reported, although a lower starting dose and postprandial intake could reduce its occurrence. When the use of these drugs does not lead to the expected changes, reconsideration of the diagnosis and evaluation of the different constipation subtypes is in place. A recent network meta-analysis [135] has shown superiority of all drugs compared to placebo. At 12 weeks of treatment, prucalopride 2 mg or 4 mg once daily ranked first compared to the other evaluated drugs. For shorter-term treatment, diphenyl methane laxatives were deemed superior [88, 135]. These results should be interpreted with caution for daily clinical practice [133]. In case of a defaecatory disorder, biofeedback therapy should be the mainstay treatment. In case of functional constipation or STC, different combinations of treatments could be tried, although there is no controlled trial evidence and this is mostly based on expert opinion. Next to head-to-head trials, there is a need for differentiation of the different constipation subtypes in future trials, as in all current trials, this is unknown. Finally, good patient-doctor relationship and communication is essential in the treatment and long-term follow-up of these chronic symptoms.

Compliance with Ethical Standards

Conflict of interest Jan Tack has given Scientific advice to AlfaWassermann, Allergan, Christian Hansen, Danone, Grünenthal, Ironwood, Janssen, Kiowa Kirin, Menarini, Mylan, Neutec, Novartis, Noventure,

Nutricia, Shionogi, Shire, Takeda, Theravance, Tramedico, Truvion, Tsumura, Zealand and Zeria pharmaceuticals, has received research support from Shire, Sofar and Tsumura, and has served on the Speaker bureau for Abbott, Allergan, AstraZeneca, Janssen, Kyowa Kirin, Menarini, Mylan, Novartis, Shire, Takeda, Truvion and Zeria. Imke Masuy and Jasper Pannemans have no competing interests to declare.

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