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REVIEW ARTICLE

An Update of Pharmacological Management in Children with Functional Constipation

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Abstract

Functional constipation is a common problem in childhood worldwide and has a great impact on social, physical, and emotional functioning of affected children and their caregivers. It is a clinical diagnosis based on the Rome IV criteria. Non-pharmacological treatment involves education, demystification, lifestyle advice, and toilet training. Pharmacological treatment consists of disimpaction, maintenance treatment, and eventually weaning if possible. Polyethylene glycol is considered as the first choice of laxative for both disimpaction and maintenance treatment. Different osmotic laxatives, stimulant laxatives, lubricants, and enemas are available as alternative pharmacological treatment options. Novel drugs are emerging but evidence to support the widespread application of these drugs in the pediatric population is often lacking and more high-quality research is needed in this field. If children remain symptomatic despite optimal pharmacological treatment, botulinum toxin injections in the anal sphincter can be considered as an alternative, more invasive treatment option. This review provides an update on currently available literature concerning the pharmacologic treatment of functional constipation in children.

1 Introduction

Functional constipation (FC) is a common problem in childhood, with a worldwide pooled prevalence of 9.5% [1]. Functional constipation is a clinical diagnosis based on the Rome IV criteria (Table 1) [2]. Children with FC usually present with infrequent painful defecation often accompanied by fecal incontinence and abdominal pain [3]. These symptoms greatly impact social, physical, and emotional functioning of affected children and their caregivers [4, 5]. According to the international guideline from the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN), the first step in the treatment of FC consists of education, demystification, and lifestyle advice [6]. Toilet training with a reward system is added if the child has a developmental age of at least 4 years [6]. If symptoms persist despite non-pharmacological interventions, osmotic laxatives are added to the treatment. Despite medical interventions, a large proportion of patients remain symptomatic. In secondary and tertiary care settings, 40% of treated children have been reported to remain symptomatic after 6–12 months [7]. Furthermore, laxatives may have several side effects, such as fecal incontinence, flatulence, abdominal pain, and nausea [8]. Therefore, new pharmacologic options keep emerging and their efficacy and safety are continuously investigated. Here, we provide an updated review on the currently available literature regarding the pharmacologic treatment of FC in children. Aspects related to the evaluation and non-pharmacological treatment of FC are discussed briefly.

1.1 Definition

The pediatric Rome criteria were first developed in 1999 and enable the diagnosing of functional gastrointestinal disorders according to symptom-based definitions. Since then, the Rome criteria have been revised several times and the last

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Key Points

The osmotic laxative polyethylene glycol is recommended as the drug of first choice for both disimpaction and maintenance treatment of pediatric functional constipation.

Alternative or additional pharmacological treatment options consist of other osmotic laxatives, stimulant laxatives, lubricants, and several types of enemas.

Novel drugs, such as lubiprostone, linaclotide, prucalopride, elobixibat, and pyridostigmine, show promising results in adults. Because of a lack of evidence in the pediatric population, these drugs are not yet included in international guidelines for children with functional constipation.

revision resulted in the current pediatric Rome IV criteria, which were published in 2016 (Table 1) [2]. According to the ESPGHAN/NASPGHAN guideline, intractable constipation is defined as constipation not responding to optimal conventional treatment for at least 3 months [6].

1.2 Pathophysiology

Possible organic causes of constipation include metabolic or endocrine conditions, anatomical anorectal abnormalities, and neuromuscular conditions such as Hirschsprung's disease or spina bifida [9]. However, in approximately 95% of all children with constipation, no organic cause can be found and these children are considered to have FC [10].

The pathophysiology of FC is considered to be multifactorial. In young children, withholding behavior is one of the major contributing factors for developing constipation [11]. This behavior is often initiated after a child has experienced painful defecation due to hard stools [12]. Withholding stools and postponing defecation results in prolonged periods of absorption of water in the colon and rectum. This leads to dry and hard stools that are more difficult to pass and cause pain during defecation, which further stimulates withholding behavior [13]. This often chronic behavior can eventually result in fecal impaction. Fecal impaction is defined as an excessive amount of hard stool in the rectum [6]. Fecal impaction often causes overflow fecal incontinence, which is caused by soft feces that pass the fecal obstruction in the rectum [8]. After prolonged periods of withholding and recurring fecal impaction, the rectal compliance increases and larger volumes of stool are necessary to generate an urge for defecation, leading to an increase of stool retention [13].

Psychological factors and behavioral disorders, such as autism spectrum disorders and attention-deficit/hyperactivity disorder, may also play a role in the pathophysiology of FC [14–16]. Psychological factors include stress, adverse life events, bullying, and anxiety [17, 18]. Other factors that have been suggested to play a role in the development of FC are socioeconomic status, specific parental child-rearing attitudes, genetics, lifestyle, diet, the gut microbiome, and colonic dysmotility [19–21].

2 Evaluation

A thorough clinical evaluation is the most important part in the diagnostic process of FC in children. An extensive clinical history and physical examination can be sufficient to establish the diagnosis if patients meet the diagnostic Rome IV criteria and if symptoms cannot be attributed to an underlying organic cause [2]. Healthcare professionals should always be cautious of alarm signs for underlying organic causes or signs of physical or sexual abuse [6].

Table 1 Rome IV criteria for functional constipation in children [2, 124]

Age	< 4 years	Developmental age of ≥ 4 years
Rome IV criteria	1. < 3 defecations per week 2. History of excessive stool retention 3. History of painful or hard bowel movements 4. History of large-diameter stools 5. Presence of a large fecal mass in the rectum 6. In toilet-trained children, the following additional criteria may be used: ≥ 1 episode of fecal incontinence per week after the acquisition of toileting skills 7. History of large-diameter stools that may obstruct the toilet Must fulfill ≥ 2 criteria for ≥ 1 month prior to diagnosis	1. < 3 defecations in the toilet per week 2. ≥ 1 episode of fecal incontinence per week 3. History of retentive posturing or excessive volitional stool retention 4. History of painful or hard bowel movements 5. Presence of a large fecal mass in the rectum 6. History of large-diameter stools that may obstruct the toilet Must fulfill ≥ 2 criteria at least once per week for ≥ 1 month prior to diagnosis Insufficient criteria for diagnosis of irritable bowel syndrome with constipation

Additional diagnostic testing has a limited role in the evaluation of FC, but may include investigations such as laboratory testing, abdominal radiography, colonic transit time measurement, transabdominal rectal ultrasonography, and anorectal manometry. These additional tests are only indicated when an organic cause is suspected or if children do not respond to treatment, and should not be part of the routine work-up of constipation [6].

3 Non-Pharmacological Treatment

Non-pharmacological treatment is the first step in management of FC. The ESPGHAN/NASPGHAN guideline recommends a normal fiber and fluid intake and normal physical activity in combination with education and demystification. Toilet training is added to the treatment for children with a developmental age of at least 4 years [6, 22]. Both patients and parents should be educated about the pathophysiology of FC and the accompanying fecal incontinence.

Several additional non-pharmacological treatment options are available. A recent systematic review and meta-analysis evaluated the available evidence and showed that abdominal electrical stimulation, Cassia Fistula emulsion, and cow's milk exclusion diet may be effective for increasing defecation frequency [23]. Other non-pharmacological treatment options such as prebiotics and probiotics, synbiotics, biofeedback, massage therapy, and alternative medicine have not shown to significantly improve defecation frequency [23].

4 Phases of Pharmacological Treatment

Pharmacological treatment is the next step in the management of FC, when education, demystification, lifestyle and diet advice, and toilet training are not sufficient. Pharmacological treatment consists of three phases: disimpaction, maintenance treatment, and finally, weaning if possible.

4.1 Disimpaction

Fecal disimpaction is the first step in pharmacological treatment and is indicated when a hard fecal mass is identified in the rectum. Disimpaction also improves the response to maintenance treatment [24]. A randomized controlled trial among 90 children with FC compared the effect of high-dose (1–1.5 g/kg/day) oral polyethylene glycol (PEG) and sodium docusate enema for 6 consecutive days on disimpaction, and showed no difference in efficacy between both treatments [25]. High-dose PEG, however, is associated with a higher frequency of fecal incontinence during this treatment phase [25]. Because treatment with rectal enemas is considered to be more invasive than oral PEG, the ESPGHAN/NASPGHAN guideline recommends the use of PEG as a first choice for disimpaction and enemas can be prescribed when PEG is not available [6]. Other oral pharmacological options can be considered for disimpaction if high-dose oral PEG and enemas are not tolerated or ineffective (e.g., lactulose, magnesium citrate, sodium picosulfate). However, evidence regarding the effectiveness and well-established dosages for disimpaction are often lacking for these alternative treatments. For these drugs, studies on disimpaction are discussed in the sections below if evidence is available.

4.2 Maintenance

After successful disimpaction, it is necessary to continue with maintenance treatment. The ESPGHAN/NASPGHAN guideline recommends the use of PEG as a first choice for maintenance treatment, based on the effectiveness concerning defecation frequency when compared with the other laxatives [6, 26]. If PEG is not available, lactulose is recommended as an alternative osmotic laxative. In addition to these two osmotic laxatives, other laxatives are available and are discussed below. No randomized controlled trials (RCTs) have evaluated the optimal duration for maintenance treatment. The recommendations in the ESPGHAN/NASPGHAN guideline state that after 2 weeks of treatment, the effect should be assessed in order to intensify treatment if necessary. Furthermore, treatment should be continued for at least 2 months [6, 8]. Children who are in the process of being toilet trained should continue medication until toilet training is accomplished [27].

Table 2 displays the dosage advice per laxative, based on the ESPGHAN/NASPGHAN guideline and the international clinical resource website: *UpToDate*. It is important to note that advised dosages can change over time and may vary between different guidelines, care centers, and countries.

4.3 Weaning

After a child has been treated for at least 2 months, weaning can be initiated when symptoms are sufficiently reduced or absent for at least 1 month [6]. This means that the child has a defecation frequency of at least three times per week and does not meet the Rome IV criteria for FC anymore. Dosages and dosing frequency should be reduced gradually, in order to prevent relapses [6]. It is important to carefully warn caregivers and children about the risk of relapses.

5 Osmotic Laxatives

Osmotic laxatives are the first-choice medication for maintenance treatment. Osmotic laxatives are poorly absorbed in the gut, which causes an increase in osmolarity, resulting in

the influx of water into the intestinal lumen. The increased amount of water results in the softening and loosening of stools [28]. Additionally, an increase of the intestinal stool volume leads to distention of the lumen, which stimulates peristalsis and helps with the passing of stools [28].

5.1 Polyethylene Glycol

Polyethylene glycol is the first-choice laxative for both disimpaction and maintenance treatment. Polyethylene glycol can be administered orally with or without addition of electrolytes. A recent meta-analysis reported that, for maintenance treatment of FC in children aged 6 months or older, PEG with and without electrolytes are equally effective and both are well tolerated [29]. However, the addition of electrolytes deteriorates the palatability of PEG, and in some children this may negatively affect treatment adherence [29]. A retrospective study in 51 children with FC and fecal impaction also showed no difference in efficacy between PEG with or without electrolytes for disimpaction [30]. However, in contrast to the recent meta-analysis, significantly more adverse events occurred in children receiving PEG with electrolytes compared with PEG without electrolytes; 48% ($n = 11/23$) versus 4% ($n = 1/28$). Adverse events included electrolyte abnormalities, abdominal pain, and nausea and vomiting [30].

Two types of PEG are available: PEG 3350 and PEG 4000. The numbers represent the molecular weight of the

Table 2 Pharmacological management of functional constipation in children [6, 8]

	Dosage
Oral laxatives	
PEG 3350/4000	Maintenance: 0.2–0.8 g/kg/day in 1–2 doses Fecal disimpaction: 1–1.5 g/kg/day (maximum 6 days)
Lactulose[a]	0.7–2 g/kg/day, in 1–2 doses
Lactitol	1–6 years: 0.5–1 g/kg/day in 2–3 doses 6–12 years: 10–30 g/day in 2–3 doses 12–18 years: 20–60 g/day in 2–3 doses
Bisacodyl[a]	3–10 years: 5 mg/day, in 1 dose/day (at night) 10–11 years: 5–10 mg/day, in 1 dose/day (at night) 12–18 years: 5–15 mg/day, in 1 dose/day (at night)
Senna[a]	Syrup 8.8 mg sennosides/5 mL or tablets 8.6 mg sennosides/tablet 2–6 years: 2.5–3.75 mL, 1 or 2 doses/day 6–11 years: 5–7.5 mL (or 1–2 tablets), 1 or 2 doses/day 12–18 years: 5-15 mL (or 1–3 tablets), 1 or 2 doses/day
Magnesium hydroxide	2–5 years: 0.4–1.2 g/day, in 1 or more doses 6–11 years: 1.2–2.4 g/day, in 1 or more doses 12–18 years: 2.4–4.8 g/day, in 1 or more doses
Sodium picosulfate	1 month to 4 years: 2.5–10 mg/day, in 1 dose/day 4–18 years: 2.5–20 mg/day, in 1 dose/day
Rectal laxatives/enemas	
Bisacodyl	2–10 years: 5 mg/day, in 1 dose/day (at night) >10 years: 5–10 mg/day, in 1 dose/day (at night)
Sodium lauryl sulfoacetate	1 month to 1 year: 2.5 mL/dose (= 0.5 enema) 1–18 years: 5 mL/dose (= 1 enema)
Sodium docusate[a]	2–11 years: 100 mg/5 mL or 283 mg/5 mL, in 1 dose/day 12–18 years: 283 mg/5 mL, one to three times daily
Sodium phosphate[a]	2–4 years: 29 mL, in 1 dose/day 5–11 years: 59 mL, in 1 dose/day 12–18 years: 118 mL, in 1 dose/day
Lubricants	
Mineral oil/liquid paraffin	Oral: 3–18 years: 1–3 mL/kg/day, 1 or more doses/day (maximum 90 mL/day) Rectal: 2–11 years: 30–60 mL, in 1 dose/day > 11 years: 60–150 mL, in 1 dose/day

PEG polyethylene glycol

[a]Dosages were updated based on the information available on *UpToDate*, 29 November, 2022

molecules at 3.350 and 4.000 g/mol, respectively. Similar efficacy and safety for long-term use of PEG 3350 with electrolytes compared to PEG 4000 without electrolytes in children aged from 6 months to 16 years were reported in a randomized double-blind multicenter study [31].

The use of PEG has been studied intensively over the last decades. In 2016, a Cochrane meta-analysis included studies that compared PEG with placebo, showing a higher frequency of stools per week in children treated with PEG [26]. Several RCTs have compared the efficacy of PEG and lactulose and the same Cochrane meta-analysis reported a significantly higher defecation frequency for PEG [26, 32, 33]. However, these results should be interpreted with caution because of the low quality of the included studies. In addition, the clinical relevance of this difference in defecation frequency is debatable because the mean difference was 0.7 stools per week [26]. The Cochrane meta-analysis also included three studies comparing PEG to magnesium hydroxide, and showed a significantly higher number of defecations in favor of PEG, although the difference was small [26].

The advised dosage for PEG maintenance treatment in children of all ages with FC is 0.2–0.8 g/kg/day, with a starting dose of 0.4 g/kg/day. It can be administered once daily or divided in several doses. Dosages and dosing frequency should be individualized to obtain optimal treatment success. For fecal impaction a dosage of 1–1.5 g/kg/day is advised, with a maximum of 6 consecutive days [6]. A recent systematic review including five studies investigated the optimal dose for children aged younger than 2 years with FC [34]. Children included in these studies were aged 0–24 months, with most children aged 6 months or older. Because of the limited number of included studies and variability in outcome measures for dosages (e.g., mean daily dose, mean initial dose, and median daily effective dose), no definite conclusions could be made regarding the optimal dosage. However, the authors suggest a conservative initial dose to minimize side effects and adjust the dose based on clinical response [34].

Side effects of PEG are generally minor and include flatulence, abdominal pain, nausea, and abdominal bloating [8]. Recent studies regarding the safety of PEG have specifically focused on administration in children under the age of 2 years, reporting only minor side effects for these young pediatric patients [34, 35]. In patients with water and electrolyte balance disturbances (e.g., reduced hepatic or renal functioning, or patients taking diuretics), monitoring of serum electrolytes should be performed and PEG should be prescribed with caution [36].

In recent years, the US Food and Drug Administration has received several reports of neuropsychiatric events in children taking PEG 3350, including tremors, tics, and obsessive compulsive behavior [37]. However, to date, evidence on any relationship between PEG and neuropsychiatric events remains limited to anecdotal reports [36]. In addition, several studies have demonstrated that the administration of PEG does not lead to elevated blood levels of neurotoxins in children and does not lead to anxiety-like behavior in mice [38–40]. The Food and Drug Administration is currently still investigating the long-term safety of PEG in children, but has stated that no changes in current policy are necessary.

5.2 Lactulose and Lactitol

Lactulose and lactitol are synthetic disaccharides of lactose, which are fermented into low-molecular-weight acids in the colon by bacterial enzymes. These acids cause an osmotic effect, resulting in an increase of intraluminal fluids. In addition, the acids result in a lower fecal pH, which stimulates colonic peristalsis [28]. If PEG is not available, lactulose is the second choice of medication for maintenance treatment in children with FC. A Cochrane review included 11 studies investigating lactulose and concluded that lactulose is a safe and effective laxative in children aged from 6 months to 16 years [26]. Adverse events are usually minimal and include abdominal gas, bloating, and cramping [21].

As previously mentioned, evidence has shown that PEG is more effective for the treatment of FC in children than lactulose; however, the difference in defecation frequency is minor (mean difference of 0.7) [26, 32, 33]. The same Cochrane review also compared the efficacy of lactulose with mineral oil (liquid paraffin) and magnesium hydroxide (milk of magnesia), and showed a statistically significant difference in defecation frequency favoring mineral oil and magnesium hydroxide. Mean differences were 1.5 and 4.9 stools per week, respectively [26]. Lactulose also showed no statistically significant differences in defecation frequency compared to lactitol and senna [26]. Lactulose is recommended for maintenance treatment if PEG is not available, as there is more evidence available on the efficacy of lactulose than of mineral oil and magnesium hydroxide and because lactulose is safe for all ages [6].

In a recent open-label randomized study, the use of high-dose lactulose (4–6 mL/kg/day) for fecal impaction as an alternative for to PEG was investigated and promising results were reported [41]. The PEG group showed a faster disimpaction response, but there was no significant difference in achieving disimpaction after the sixth day of treatment. More research is necessary, but these results show that lactulose could perhaps be a good alternative to PEG for fecal impaction if PEG is not available [41].

Lactitol is a lactulose-like derivative with an osmotic effect and it also functions as a lactulose-derived prebiotic. Lactitol showed no significant differences for defecation frequency when compared with lactulose [26]. A study in adults explored the beneficial effects of lactitol on gut

microbial composition and the association with the alleviation of constipation symptoms in 29 patients [42]. The levels of *Bifidobacterium* in the feces increased after administration of lactitol, and this correlated with an improvement of constipation symptoms [42]. These positive results should be interpreted with caution because of the small sample size of the study.

5.3 Magnesium Hydroxide

Magnesium hydroxide (also known as milk of magnesia) and other magnesium salts, such as magnesium sulfate and magnesium citrate, are poorly absorbed particles. The laxative effect is derived from these hyperosmolar agents causing an osmotic gradient [28].

A meta-analysis included three studies comparing PEG with magnesium hydroxide with a follow-up of 4 weeks, and showed a statistically significant higher defecation frequency for PEG (mean difference of 0.69 stools per week) [26]. In contrast to these findings, a recent open-label randomized controlled trial with a follow-up of 12 months reported no difference in treatment success and adverse events between the two laxatives [43]. Treatment success was defined as three bowel movements per week without episodes of fecal incontinence, fecal impaction, or abdominal pain, and no need for another laxative. An additional interesting finding from this study was that magnesium hydroxide was significantly less well tolerated compared with PEG by children aged older than 4 years. A higher number of patients rejected magnesium hydroxide in this group, which could be related to the poor palatability of magnesium hydroxide [43]. The hypothesis that magnesium could positively affect defecation patterns in children is supported by a recent open-label comparator-controlled study evaluating the effect of magnesium-rich formula in 286 infants aged younger than 6 months. Infants receiving magnesium-rich formula were reported to have a significantly softer stool consistency and a significantly higher defecation frequency compared with infants receiving regular formula [44].

Side effects of magnesium hydroxide include diarrhea, abdominal pain, and bloating. Magnesium hydroxide should be used with caution in children with renal insufficiency, owing to the increased chance of hypermagnesemia [28].

Oral magnesium citrate is predominantly used for bowel cleansing prior to colonoscopy in children and little evidence is available for the use in the treatment of FC in children. A retrospective study investigated the use of magnesium citrate for disimpaction in children with constipation compared to PEG via a nasogastric tube and reported similar numbers of successful disimpaction, 90% and 85% respectively [45]. However, 12% of the children were unable to drink the entire dose of magnesium citrate. In this study, the success of disimpaction was assessed on an abdominal radiograph and the dosage of magnesium citrate consisted of one ounce/year of age and was repeated in 3 hours if food-coloring hue liquid stools did not pass [45].

6 Stimulant Laxatives

Stimulant laxatives can be applied as an additional or second-line treatment of FC in children when osmotic laxatives alone are not sufficient. Stimulant laxatives enhance colonic peristalsis and secretion by stimulation of the enteric nervous system [28]. Stimulant laxatives can be subdivided into diphenylmethanes (e.g., bisacodyl and sodium picosulfate) and anthraquinones (e.g., senna). These drugs are often prescribed as additional treatment and are considered to be safe and effective even though there is a shortage of well-designed trials in children [8]. Stimulant laxatives are generally well tolerated, despite the fact that abdominal pain is a common side effect [28].

6.1 Diphenylmethanes

Bisacodyl and sodium picosulfate belong to the group of diphenylmethanes. Diphenylmethanes are hydrolyzed by colonic bacteria or brush border enzymes into their active metabolites, which promote colonic peristalsis and secretion [28]. Bisacodyl can be administered orally or rectally. Oral administration starts with 5 mg once daily for children aged three years or older, and rectal administration starts with 5 mg per day for children aged 2 years or older [6]. Rectal administration is contraindicated in patients with proctitis or anal fissures. Intraluminal administration of bisacodyl is used during colonic manometry for the assessment of the colonic neuromuscular function in children with treatment-refractory constipation. Bisacodyl can elicit high-amplitude propagating contractions and therefore helps to distinguish between patients with normal or impaired colonic propulsion [46, 47]. A recent study including 165 children with treatment-refractory constipation found that in 93% of children intraluminal administration of bisacodyl induced high-amplitude propagating contractions, confirming the stimulating effect of bisacodyl on the colonic peristalsis in children [48]. However, good-quality evidence for the efficacy and safety of bisacodyl in children with FC is lacking [27]. Randomized controlled trials conducted in adults have shown that orally administered bisacodyl is effective and safe in patients with chronic constipation [49, 50]. Promising results for the effectiveness and tolerance of long-term use of bisacodyl were reported by a recent retrospective study in 164 children with FC refractory to conventional treatment [51]. The median number of bowel movements increased from two to four times per week after 4 weeks of treatment and only minor adverse events were reported. However, these

results should be interpreted with caution owing to the retrospective nature of the study.

Sodium picosulfate can only be administered orally and has a similar effect on colonic peristalsis as orally ingested bisacodyl [8]. Evidence for the use of sodium picosulfate for the treatment of FC in children is very scarce. Only the use of sodium picosulfate in combination with a high dose of PEG for disimpaction in children with constipation has been retrospectively studied showing promising results [52, 53]. The highest dosage used for PEG ranged from four to eight sachets per day (13–14.7 g/sachet) and the highest sodium picosulfate dose ranged from 7.5 mg to 10 mg per day [52, 53]. Common adverse effects of bisacodyl and sodium picosulfate include abdominal pain, nausea, and diarrhea [8]. Studies investigating treatment with only sodium picosulfate in children with constipation are lacking.

6.2 Anthraquinones

Senna contains various anthraquinones, which are metabolized by intestinal bacteria into their pharmacological active metabolites. These active metabolites stimulate colonic motility and prevent the reabsorption of water from the colon [28]. Senna can only be administered orally. Little evidence is available regarding the efficacy of senna for the treatment of FC in children. Only one randomized controlled trial with a small sample size ($n = 37$) compared the differences in outcome after treatment with senna or mineral oil in children with chronic FC. Senna showed poorer results with respect to defection frequency and fecal incontinence after 3 months of follow-up [54]. Another crossover study compared senna to lactulose in children with constipation aged younger than 15 years, but showed no significant difference in the number of patients passing stools per day [55]. Senna was administered in a dosage of 10–20 mL daily and lactulose at 10–15 mL daily [55]. Common side effects are diarrhea, abdominal pain, nausea, and flatulence and young children are at risk of diaper rash, blisters, and peeling skin [8, 56]. A literature review on the side effects of senna for children with constipation identified eight publications, consisting of case reports and case series, reporting perineal blisters and severe perineal rash [57]. In addition, a retrospective review of 796 children with FC or constipation, due to various organic diseases, investigated senna-related side effects. In 2.2% of this population, blisters and rash were reported, a correlation was found with higher doses of senna (median of 60 mg/day) and with children who were in diapers [57]. However, because of the retrospective design of this study and the high risk of bias, these results should be interpreted with caution.

7 Lubricants

Lubricants exert their laxative effect by softening or lubricating stools. Mineral oil, also known as liquid paraffin, is one of the most commonly used lubricants. It is an orally administered oily liquid comprising hydrocarbons obtained from petroleum and is not absorbed by the colon or small bowel [28, 58].

A small number of RCTs have compared mineral oil with other laxatives such as PEG, lactulose, and senna. A Cochrane systematic review included two studies comparing PEG and mineral oil, and showed no significant difference in the increase of defecation frequency after 1 month of treatment [26]. However, the quality of the studies was very low because of sparse data and a high risk of bias [26, 59, 60]. However, mineral oil is suggested to be more effective than lactulose and senna for the treatment of FC in children [26]. Two RCTs comparing mineral oil with lactulose were included in the Cochrane review and showed a significant difference in stools per week (mean difference of 4.94) favoring mineral oil, but again the quality of evidence was low because of the small sample size and risk of bias [26, 61, 62]. One randomized controlled trial with a small sample size reported a higher defecation frequency and less fecal incontinence for mineral oil compared with senna [54].

Mineral oil is considered to be safe for the treatment of FC in children and the most common side effects, such as abdominal pain, nausea, vomiting, diarrhea, and flatulence, are generally mild [26]. Another adverse event is the leakage of mineral oil out of the anus, which can result in irritated skin around the anus and cause stains on clothes [8]. Over the years, multiple cases of severe adverse events, such as granulomas of the intestinal tract and lipoid pneumonia, have been reported [58, 63, 64]. Therefore, the Committee on Safety of Medicines advises that mineral oil should not be administered to children aged under 3 years. In addition, children with swallowing difficulties should also not receive mineral oil because they are at a greater risk of aspiration and developing lipoid pneumonia. Mineral oil is best avoided in children with coagulation disorders because there is a theoretic concern that long-term use of mineral oil reduces the absorption of fat-soluble vitamins [58, 65].

8 Enemas

Enemas are rectally administered fluids containing ingredients that can cause an increase in gut motility or intestinal fluid secretion. Some enemas contain multiple ingredients and combine both mechanisms of action [8]. The effect usually occurs within minutes after administration. Enemas are predominantly used for fecal impaction and are not the first

choice for maintenance treatment of children with FC [6]. Several different enemas solutions are currently used in practice for the treatment of FC in children. Sodium docusate is a surface-active agent that stimulates the retention of water in the stools, which softens the stools and exerts the lubricating effect [28]. Reported side effects include abdominal pain and anal discomfort [21]. Sodium lauryl sulfoacetate softens the feces by redistributing the water that is bound to hard feces. This enema does not exert an osmotic effect and is predominantly prescribed in infants [8]. Sodium phosphate enemas contain a hyperosmolar phosphate solution and are contraindicated for patients with or suspected of Hirschsprung's disease or renal insufficiency. These patients are at a greater risk of developing hyperphosphatemia [8]. Other adverse events are mostly minor and include abdominal pain, emesis, and diarrhea [66]. Some enemas contain a combination of ingredients, for example, an enema consisting of docusate, magnesium citrate, mineral oil, and sodium phosphate [67].

The effect of enemas on disimpaction has been investigated by a limited number of studies. A systematic review included two studies comparing the effect of oral PEG to enemas (dioctyl sulfosuccinate sodium and milk and molasses) for disimpaction in children aged 1–17 years with FC [68]. The primary outcome was treatment success, defined as the absence of fecaloma in one study and no need to visit the emergency department in the other study [68]. A meta-analysis of the two studies showed a significantly reduced success rate for PEG; however, the difference was minor (risk ratio of 0.83) and therefore not clinically relevant. Secondary outcomes reported a higher defecation frequency for PEG, but also an increased risk of watery stools and fecal incontinence [68]. The results of this systematic review, however, should be interpreted with caution because of the high risk of bias of the included studies and the sparse data. Recently, the short-term efficacy and safety of promelaxin microenemas compared to PEG in infants and toddlers with FC were explored in a randomized controlled non-inferiority trial [69]. In accordance with previous studies, both treatments were considered equally effective. The primary outcome was the response rate, defined as three or more stools per week and an average increase of one stool per week if the baseline frequency was already three bowel movements per week. The study reported 183 adverse events, but concluded that these were all unrelated to both treatment arms. However, no further information nor explanation about these adverse events and their relation with the treatments was given [69].

The efficacy of different enema solutions used in pediatric emergency departments was investigated by a retrospective study in 768 children with constipation with and without underlying anatomical disorders [67]. The enema solutions included sodium phosphate, pink lady, and soap suds, and the study reported that there was no significant association between stool output (small, medium, or large) and enema solution. In addition, a low rate of side effects was reported for all enemas, side effects were minor and consisted mostly of abdominal pain and vomiting [67]. It is worth mentioning that soap suds are widely used in emergency departments; however, little evidence is available supporting their efficacy and safety [70]. In the past, several case reports have mentioned soap-induced colitis, raising safety concerns regarding the treatment of constipation with soap suds [71, 72]. It is recommended to use other, more extensively studied treatments for disimpaction, such as those mentioned above [72]. A recent retrospective case series report from Japan explored the use of olive oil enemas as adjunctive treatment in 118 children with severe chronic constipation, with and without underlying medical disorders [73]. The authors reported that the use of olive oil enemas in combination with glycerin was effective in 79.6% of children with FC. Effectiveness was defined as achieving fecal disimpaction within several visits to the outpatient department, in which the absence of previous symptoms was considered as fecal disimpaction [73].

The long-term use of enemas has only been investigated by one randomized controlled trial. The study explored the regular use of enemas as an addition to conventional maintenance treatment in 100 severely constipated children (aged 8–18 years) with a follow-up of 52 weeks [74]. Conventional treatment consisted of education, behavioral strategies, and PEG. The study showed no additional positive effect for defecation frequency, fecal incontinence frequency, and overall treatment success and suggested that enemas should not be used for maintenance treatment.

9 Novel Therapies

In recent years, several new pharmacological treatment options have been investigated for childhood FC. For most of these medications, trials were first performed in adults and subsequently in the pediatric population. Applying knowledge obtained from adult studies to the pediatric population requires great care because of the differences in physiology and pharmacokinetics between children and adults [21]. As previously mentioned, psychological and behavioral factors play a major role in the pathophysiology of FC in children. Withholding behavior is considered to be the most contributing factor in the development of constipation in children, whereas this barely plays a role in the pathophysiology of FC in adults. Hence, it is important that studies evaluating the efficacy and safety of new drugs for the treatment of FC are conducted in the pediatric population. International recommendations for trials in children with FC recommend to conduct randomized, double-blind, placebo-controlled clinical trials with a parallel group [75]. Furthermore, FC should be defined per

the Rome IV criteria, the follow-up period should at least be 8 weeks, and treatment success should be defined as no longer fulfilling the Rome IV criteria [75].

9.1 Prosecretory Agents

Lubiprostone, linaclotide, and plecanatide are prosecretory agents that modulate epithelial channels in the intestine, stimulating the secretion of fluids into the intestinal lumen and increasing stool volume, aiming to accelerate colonic transit [21]. Lubiprostone activates the type 2 chloride channels on enterocytes, which leads to an increased intestinal fluid secretion [76]. Multiple RCTs have been performed in adults with FC, and have shown that lubiprostone is safe and increases spontaneous bowel movements in adults [77–80]. Less evidence is available in the pediatric population. An open-label study including 127 children aged 3–17 years and ≥ 12 kg in weight suggested that lubiprostone is efficacious and safe for children with FC [81]. However, this study did not include a control group and therefore carried a risk of a placebo effect. In a recent large, multicenter, double-blind RCT, the effectiveness and safety of lubiprostone in 606 children with FC aged 6–17 years was investigated [82]. The authors concluded that lubiprostone can be considered safe for children aged 6 years or older, but the drug showed no significant difference in the improvement of spontaneous bowel movements compared to placebo after 9 weeks of treatment [82]. Another multicenter open-label trial investigated the safety of lubiprostone in children with FC aged 6–17 years (mean age 10.3 years). In line with the other trials, the drug was well tolerated in children [83]. Side effects of lubiprostone are generally minor and include nausea, vomiting, abdominal pain, and diarrhea [82]. All three studies mentioned above performed a subgroup analysis for efficacy and safety based on the administered dose. Children were allocated to a dosage of 12 µg once a day, 12 µg twice a day, or 24 µg once a day, depending on their weight. None of the studies reported any difference between the dosages for efficacy and safety [81–83].

Linaclotide increases the intestinal fluid secretion by activating the guanylate cyclase C receptor [21]. Linaclotide has been proven to be safe and efficient for the treatment of FC and irritable bowel syndrome with constipation in adults [84, 85]. Thus far, only one retrospective non-controlled trial evaluated the use of linaclotide for the treatment of FC in 60 children with a median age of 13.9 years [86]. The study showed a positive clinical response based on the physician's assessment in 45% of children with FC (n = 60/93) after 2.5 months of follow-up. However, 20% of all children (n = 19/93), including children with irritable bowel syndrome with constipation, stopped using linaclotide because of side effects [86]. The occurrence of the most commonly reported adverse events, such as diarrhea and abdominal pain, was analyzed per dose: 72 µg or 145 µg. In the subgroup receiving 72 µg, 60% (n = 6/10) of the patients reported an adverse event compared with 28% (n = 14/50) in the subgroup receiving 145 µg. The safety and efficacy of different dosages of linaclotide in children aged 6–17 years with FC were evaluated in a multicenter, randomized, double-blind, placebo-controlled trial; however, the study has not yet been published (NCT02559570). Another phase III study is currently recruiting patients and will also investigate linaclotide in children with FC (aged 6–17 years) [NCT04026113]. In addition, there is an ongoing phase II study that investigates the effect of linaclotide in younger children with FC (aged 2–5 years) [NCT04110145].

Plecanatide is a new guanylate cyclase C receptor agonist, which is considered safe and effective in adults with chronic idiopathic constipation [87–89]. However, to date, no studies on the use of plecanatide in the pediatric population have been published. More evidence will become available soon, as two ongoing phase II studies in the pediatric population are registered. These studies evaluate the efficacy and safety of plecanatide in adolescents with chronic idiopathic constipation based on the Rome III criteria (NCT03120520) and in children (aged 6–18 years) with irritable bowel syndrome with constipation (NCT03596905).

9.2 Serotonergic Agents

Serotonin or 5-hydroxytryptamine (5-HT) is a central and enteric neurotransmitter that binds to the 5-HT4 receptors in the intestine. This results in the increase of fluid secretion and gut motility, which promotes the passage of stool [21]. Multiple 5-HT4 agonists have been developed, including prucalopride, velusetrag, and naronapride.

Prucalopride is a selective, high-affinity 5-HT4 receptor agonist. A meta-analysis of 16 studies has shown that the drug is well tolerated and effective for adults with constipation [90]. Prucalopride increases the frequency of spontaneous bowel movements per week and the side effects are acceptable and minor [90]. Two studies in the pediatric population have been published. An open-label phase I study in 37 children, who all received a single dose of 0.03 mg/kg of prucalopride, suggested that prucalopride was well tolerated in children (aged 4–12 years) with FC [91]. The authors also suggested that the drug could potentially be clinically effective, based upon positive findings for defecation frequency, stool consistency, and fecal incontinence frequency [91]. However, a subsequent multicenter, randomized, placebo-controlled, double-blind, phase III trial assessing the safety and efficacy of prucalopride in 213 children with FC concluded that prucalopride was no more effective than placebo [92]. Children with a body weight under 50 kg received 0.04

mg/kg of prucalopride once daily, and children weighing > 50 kg received 2 mg of prucalopride once daily, no differences between both subgroups were found. At present, an ongoing phase III clinical trial is investigating the efficacy and long-term safety of prucalopride in 255 children with FC (NCT04759833).

Velusetrag and naronapride are also 5-HT4 receptor agonists and phase II trials in adults with chronic constipation show positive results on bowel movement frequency [93, 94]. No studies have been performed in the pediatric population yet and there are no future studies planned.

9.2.1 Differences Between Adults and Children

The difference in the effect of lubiprostone and prucalorpide compared with the adult population can possibly be related to the fact that withholding behavior plays a major role in the pathophysiology of FC in children. Pharmacological treatment may soften the stool and improve gut motility, but it is not expected to overcome withholding behavior [92]. This raises questions regarding the preferred study design for future trials in children with FC. It could be suggested to exclude children with withholding behavior in future studies investigating specific drugs that have been proven effective in adults but not yet in children, in order to assess whether children without withholding behavior do improve after treatment. However, this would also exclude a proportion of children fulfilling the Rome IV criteria for FC and this would severely limit the generalizability of these study results. Another factor that should be considered when comparing pediatric and adult studies are the differences in diagnostic criteria and the primary outcome measures used in these studies [95].

9.3 Bile Acids

Endogenous deconjugated bile salts increase intraluminal fluid secretion and colonic motility by activating bile acid receptors in enteric neurons [21, 96]. Bile salts comprise free bile acids. Chenodeoxycholic acid is a primary bile acid that improves colonic transit times and increases the number of bowel movement in adults [97, 98]. Fecal bile acid composition was determined in 165 children with and without FC in an observational study [99]. The study showed that a small subset of children with FC ($n = 6/73$) had an altered metabolism of chenodeoxycholic acid, suggesting that bile acids may play a role in childhood FC [99]. No studies have been performed in the pediatric population exploring the use of bile acids for treatment of FC. Elobixibat is a novel drug that affects bile salt metabolism by inhibiting ileal bile acid transporters. Normally, most bile salts are bound to the bile acid transporters in the ileum and only a small concentration continues to the colon. Elobixibat inhibits the reabsorption of bile acids in the small intestine, resulting in higher concentrations of bile acids in the colon. A recent systematic review and meta-analysis in Japanese adults with chronic idiopathic constipation according to the Rome criteria included three RCTs and showed a significant improvement in weekly spontaneous bowel movements compared with placebo [100]. Two other RCTs, which were not included in the systematic review also showed that elobixibat increased colonic transit and softened stool consistency [101, 102]. Currently, no pediatric studies on the use of elobixibat for FC have been performed nor are these currently being conducted.

9.4 Cholinesterase Inhibitors

Pyridostigmine is an acetylcholinesterase inhibitor that increases the availability of acetylcholine in the neuromuscular junctions. This results in an improvement of transmission of impulses and thereby stimulates the gastrointestinal motility [21, 103]. A small number of studies regarding the efficacy and safety of pyridostigmine for the treatment of FC are available, and even less for FC in the pediatric population. An observational case series of 13 adults with slow-transit constipation ($n = 6$) or intestinal pseudo-obstruction ($n = 7$) investigated the effect of pyridostigmine on constipation symptoms. Patients with slow-transit constipation showed no improvement in symptoms, in contrast to the group with recurrent pseudo-obstruction that did show an improvement in symptoms [104]. Similar results for improvement in defecation frequency and stool consistency were found in a randomized double-blind controlled study comparing pyridostigmine and bisacodyl in 68 adults with refractory chronic constipation [103]. A case series of four children with gastrointestinal motility disorders reported decreased abdominal distention, increased defection frequency, improved enteral feeding tolerance, and minor side effects after treatment with pyridostigmine [105]. At present, no further studies investigating the efficacy and safety of this drug are being performed in children with constipation.

10 Botulinum Toxin Injection (Botox®)

If patients do not respond to optimal conservative treatment, one of the last treatment options is the botulinum toxin injection (BTI), also known as Botox®, in the anal sphincter [6]. Botulinum toxins inhibit the release of acetylcholine from neurons, resulting in partial chemical paralysis of the muscle and thereby relaxation of the injected anal sphincter muscles. A BTI is usually administered under general anesthesia. It is generally injected into the internal anal sphincter, dividing the total dose over four to eight injections each in different sites of the muscle [106]. The pharmacological effect of

botulinum toxin is transient because over time new neuromuscular junctions may develop and the function of the original neural endplate is restored [107]. The relaxing effect lasts 3–6 months; therefore, patients often require one or more subsequent injections [108]. Botox® dosages used in studies investigating BTI in children with defecation disorders vary widely, with a range from 12 to 200 U in total, but 100 U seems to be a commonly used dosage [109]. In addition, the number of injections and the specific sites of the injections in the anal sphincter also differ between studies. Currently, there are no guidelines available that provide advice for the dosage of BTI in children with FC.

A BTI has been shown to be effective and safe for the treatment of children with impaired rectal evacuation due to Hirschsprung's disease or internal anal sphincter achalasia [109–112]. These data, however, cannot simply be applied to children with FC, who have a normal rectoanal inhibitory reflex. Nevertheless, a BTI could help in breaking through the vicious cycle of stool withholding in children with FC. Because of the temporary paralysis of the anal sphincter, withholding stools is not possible and stool consistency becomes softer, which results in less pain during defecation. A BTI is used in clinical practice as a treatment of last resort; however there is a lack of RCTs providing evidence for the efficacy of BTI in children with FC. A recent prospective cohort study investigated the effect of BTI on constipation symptoms in children with FC ($n = 17$).

[106] After 2 months of follow-up, 47% of the caregivers of the children ($n = 7/15$) reported that the BTI had an overall positive effect and the outcome measures of abdominal pain severity and constipation severity improved significantly compared with baseline. After 4 months, 60% of the caregivers ($n = 6/10$) reported an overall positive effect. Three children with FC received an additional injection between 2 and 4 months follow-up and were analyzed separately [106]. This was a non-randomized non-controlled study with a small FC population ($n = 17$), so these results should be interpreted with great care. A recent randomized controlled study included 40 pediatric patients with FC (according to Rome IV criteria) with obstruction defecation syndrome (according to the National Institute for Health and Care Excellence definition) [113]. The study explored the role of a BTI as an addition to conventional treatment for FC, which consisted of a modified diet, toilet training, and stimulant laxatives. The authors concluded that the addition of a BTI did not result in significant improvement of defecatory problems assessed by the Rintala score [113]. However, it should be considered that the Rintala score is established to evaluate fecal continence and it does not necessarily reflect constipation severity.

11 Prognosis and Follow-Up

A large proportion of children with FC respond well to treatment with acceptable side effects and will recover within a year [7]. The prognosis and prognostic factors of FC in children were investigated in a systematic review, including 14 heterogeneous prospective follow-up studies with a total of 1752 children [7]. This systematic review reported that half of the children treated for FC were recovered and taken off laxatives after 6–12 months of follow-up. An additional 10% were symptom free, but still being treated with laxatives. After a follow-up of 1–2 years and 5–10 years, the recovery rate was 58% and 56%, respectively [7]. Children treated in a pediatric gastroenterology department showed a higher recovery rate than children treated in general pediatric departments [7]. In contrast to the large group of children that will recover, a sizable group remains symptomatic regardless of treatment and can remain symptomatic into adolescence or adulthood [114–116].

Research on factors influencing the clinical course of FC in children is limited [6]. A systematic review attempted to perform a meta-analysis on prognostic factors, but because of the large variations in prognostic factors between studies this was not possible [7]. Some studies have suggested that a longer period of time between the age of onset and the first presentation is negatively related to recovery [116, 117]. There is strong evidence that demographics such as sex and a positive family history have no prognostic value [6]. A recent prospective study in 122 children with FC (defined by the Rome III criteria) explored the association between self-efficacy, the belief that one has the skill to succeed at a goal, and treatment success [118]. Treatment success was defined as having at least three bowel movements and no fecal incontinence episodes in the third week of treatment. Patients who were successfully treated, scored higher on the self-efficacy questionnaire before the clinic visit, immediately after, and at a follow-up of 3 weeks than the group that did not respond to treatment [118]. This study showed that self-efficacy is associated with treatment success of FC in children after a short-term follow-up and the authors suggest that enhancing self-efficacy in children with FC may be a good addition to improve treatment outcome [118]. Another factor that is crucial for treatment success is treatment adherence. Poor adherence to pharmacological maintenance treatment is common in children and is considered to play an important role in poor outcomes [119–121]. Taste and palatability of orally administered drugs can be a great problem for the tolerability of children for medications and should be considered when deciding on treatment options [122]. Evidence on treatment adherence in children with FC is limited. In a recent cross-sectional survey study including 115 children with FC, as defined by the Rome IV criteria,

adherence to PEG treatment was evaluated and associated factors were identified [123]. This study showed that poor treatment adherence is common in children with FC, as only 37% of all children were adherent to the treatment with PEG. Treatment inconvenience, dissatisfaction with treatment, and the emotional impact of a child's constipation symptoms were identified as factors that may have a negative effect on treatment adherence [123].

12 Conclusions

Pediatric FC is a common problem. Diagnosis is made based on the Rome IV criteria after evaluation of a thorough clinical history and physical examination. Additional diagnostic testing is only indicated when an organic cause is suspected or if children do not respond to treatment despite optimal treatment. The pathophysiology of FC is considered to be multifactorial, and withholding behavior plays a major role. The first step in treating FC involves education, demystification, lifestyle advice, and toilet training (when developmental age is at least 4 years). Pharmacological treatment with laxatives consists of three steps: disimpaction, maintenance treatment, and ultimately weaning if possible. Polyethylene glycol is considered as the first choice of laxative for both disimpaction and maintenance treatment. For disimpaction, high-dose PEG is recommended and if PEG is not available enemas are second choice. The osmotic laxative lactulose is the second option for maintenance treatment. Stimulant laxatives (bisacodyl or senna) or lubricants (mineral oil) can be considered as alternative or additional treatment options if children are not responsive to the initial treatment. A large proportion of children remains symptomatic after 6–12 months of treatment; therefore, it is necessary that new pharmacological options are being developed and investigated. Novel drugs, such as lubiprostone, linaclotide, prucalopride, elobixibat, and pyridostigmine, show promising results. However, high-quality randomized controlled clinical trials in the pediatric population are needed to establish the efficacy and safety for these new treatment options, including the investigation of optimal dosages. Pharmacological pediatric trials should consider the different pathophysiology, definition of FC, and primary outcomes for the pediatric population compared to adults when setting up the study design. If children remain symptomatic despite optimal conservative treatment, BTIs in the anal sphincter can be considered as an alternative treatment option.

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