EXPERT OPINION

Functional constipation in childhood: current pharmacotherapy and future perspectives

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Introduction: Childhood constipation is a common problem, varying from mild and short-lived to severe and chronic. In the majority of children, no organic cause can be identified and complaints are, thus, referred to as functional constipation. Infrequent painful defecation in combination with fecal incontinence has a significant impact on a child's quality of life. Pharmacological treatment often consists of fecal disimpaction and maintenance therapy. With current treatment options, results are often disappointing.
Areas covered: The aim of this review is to provide an overview of current and future pharmacological therapies for functional constipation in childhood.
Expert opinion: Despite the widespread use of laxatives, there is a paucity of evidence to support this practice. No strong conclusions can be drawn on which laxative to prefer over the other. However, polyethylene glycol appears to be a reasonable first choice for maintenance therapy. Due to advances in our understanding of intestinal (patho)physiology, new classes of drugs have been developed. Data from adult studies are promising; however, pediatric data are lacking. Ongoing and future studies have to determine the efficacy and safety of these new drugs in the treatment of functional constipation in children.

Keywords: child, functional constipation, laxatives, pharmacotherapy

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1. Introduction

Childhood constipation is a worldwide problem with an estimated prevalence varying from 0.7 to 29.6% (median 12%) [1], accounting for ~ 3% of all pediatric office visits [2] and up to 10 to 45% of all pediatric gastroenterology clinic visits [3-6]. Typical symptoms include infrequent painful defecation, large stools, fecal incontinence and abdominal pain. Symptoms vary from mild and short-lived to severe and chronic [6]. The impact of constipation on patient and family life is frequently underestimated. Healthcare providers often assume that constipation will either resolve spontaneously or respond to extra fiber and fluid intake [7]. However, studies clearly show that constipation is associated with an impaired quality of life [8-10], with many children needing long-lasting treatment [11]. Approximately 50% of all children with functional constipation recover and are taken off medication within 6 to 12 months [11], but about one-fourth continues to experience symptoms at adult age [12].

The pathophysiology of constipation is multifactorial and remains incompletely understood [13]. In more than 90% of children with constipation, no organic cause is found [6,] and therefore it is referred to as functional constipation. Strict criteria have been established by experts in the field of pediatric gastroenterology, referred to as the Rome III criteria, to better define pediatric functional gastrointestinal

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Article highlights.

- Functional constipation is a common problem in childhood, varying from mild and short-lived to severe and chronic.
- Pharmacotherapy of functional constipation consists of fecal disimpaction (when fecal impaction is present) and maintenance therapy.
- Several oral and rectal laxatives are available for treating functional constipation.
- Due to a paucity of evidence, current treatment regimens are more experience-based rather than evidence-based and it is impossible to draw firm conclusions on which laxative to prefer over the other.
- Advances in our understanding of intestinal (patho) physiology have lead to the development of new classes of drugs for treating functional constipation. Data from adult studies are promising and studies in children are necessary to determine the efficacy and safety of these new drugs.

This box summarizes key points contained in the article.

diseases. **Table 1** depicts the Rome III criteria for pediatric functional constipation [14].

Although the use of laxatives in clinical practice is widely accepted [15], current treatment guidelines are not evidence-based due to a lack of placebo-controlled trials [16]. Despite the lack of evidence, several guidelines advice that the treatment of functional constipation consists of education, disimpaction (if fecal impaction is present), prevention of reaccumulation of feces and close follow-up [7,17,18].

Non-functional constipation, that is, constipation with an organic etiology (such as Hirschsprung's disease or chronic idiopathic pseudo-obstruction syndrome), often requires management of the specific condition, which is beyond the scope of this review. The management of constipation in infants also requires a specific approach [17], which will not be addressed in this review.

The aim of this review is to provide an overview of the current and future pharmacological therapies for functional constipation in children 1 to 18 years of age.

2. Current pharmacotherapy for functional constipation

The medical treatment of functional constipation in children often consists of two steps and each step requires a specific approach. In ~ 50% of constipated children, a large fecaloma can be found upon physical examination [6]. In these patients, the first step of treatment consists of either oral or rectal disimpaction. The second step consists of maintenance treatment, to prevent reaccumulation of feces.

2.1 Disimpaction

Fecal impaction is defined as 'a large fecal mass in either the rectum or the abdomen, which is unlikely to be passed on demand' [19]. It has been shown that children who were treated with some form of disimpaction prior to maintenance therapy are more likely to respond to treatment than children who did not undergo this procedure [20]. Therefore, disimpaction is recommended before initiation of maintenance therapy [17].

Fecal disimpaction may be carried out with either oral or rectal medication. Several studies have shown the effectiveness of oral mineral oil or oral polyethylene glycol (PEG) electrolyte solutions [21-25]. Clearance of fecal impaction was achieved in 55 – 100% of the patients after a mean of 5.7 ± 1.2 days (median 6.0 days, range 3 – 7 days). Both solutions have been shown to be safe for administration, and minor adverse effects, such as diarrhea and abdominal pain, seem to be related to its osmotic laxative effect [13]. Various other oral laxatives are currently used for fecal disimpaction, such as a high dosage of either lactulose or magnesium salts. However, controlled trials evaluating the effect of these compounds regarding disimpaction are lacking [17,26].

For rectal disimpaction, sodium phosphate enemas, saline enemas or mineral oil enemas are widely used and described as effective [6,17]. Phosphate enemas, however, should not be used when Hirschsprung's disease is suspected, because of the risk of hyperphosphatemia.

To date, there have been few studies comparing the effectiveness of oral against rectal disimpaction regimens in children. In one retrospective study, 97% of children treated with PEG were successfully disimpacted compared to 73% of those who received enemas and suppositories ($p < 0.001$) [27]. However, in a prospective trial in which children with fecal impaction were randomly assigned to receive either enemas containing dioctyl sulfosuccinate sodium once daily or PEG (1.5 g/kg/day) for 6 consecutive days, both regimens were equally effective. Fecal incontinence and watery stools were more frequently reported with PEG ($p < 0.01$) [28]. In accordance with these data, a recent randomized controlled trial (RCT) showed that treatment with either one enema or PEG (1.5 g/kg/day) for 3 days was equally effective in children presented with fecal impaction at an emergency department [29]. In addition no significant difference was found in response rate between fecal disimpaction with either oral or rectal mineral oil [30].

Disimpaction with oral laxatives is often preferred, because it is assumed to be less invasive and traumatic [31]. Indeed, the NICE guideline advocates against the use of rectal medications for disimpaction, unless all oral medications had failed [7]. On the other hand, parents should be informed that treatment with an enema may relieve symptoms faster than PEG [29]. Moreover, no difference was found in the amount of reported fearful behavior or struggle to administer the medication, among children who were treated either orally or rectally for fecal impaction [28].

In a recent retrospective chart review, phosphate enemas were compared with milk-and-molasses enemas for treating children with constipation at the emergency department.

Table 1. Diagnostic criteria for functional constipation according to the Rome III consensus.

Must include two or more of the following in a child with a developmental age of at least 4 years with insufficient criteria for diagnosis of irritable bowel syndrome:
Two or fewer defecations in the toilet per week
At least one episode of fecal incontinence per week
History of retentive posturing or excessive volitional stool retention
History of painful or hard bowel movements
Presence of a large fecal mass in the rectum
History of large diameter stools that may obstruct the toilet
Criteria must be fulfilled at least once per week for at least 2 months before diagnosis

Milk-and-molasses is an old home remedy for constipation, consisting of molasses (a by-product of sugar production), water and milk powder. No significant differences were found between the two treatments in terms of efficacy or safety [32]. Although milk-and-molasses is a seemingly benign preparation, its use in children is associated with significant hemodynamic compromise, which can be even lethal [33].

Traditionally, soap suds enemas have been used for fecal disimpaction. However, its use is currently not recommended [17], because of the risk of serious adverse events, such as colitis [34]. Surprisingly, it is still used regularly in primary care [35].

2.2 Maintenance treatment

After the short phase of disimpaction, maintenance treatment should be initiated to prevent reaccumulation of feces. This treatment should consist of dietary interventions, behavioral modifications and laxatives to assure that bowel movements occur at normal intervals with good evacuation [17]. Currently, several oral and rectal laxatives are available for maintenance treatment, which can be categorized into osmotic laxatives, fecal softeners, stimulant laxatives and rectal laxatives (**Table 2**). These laxatives will be discussed below. Non-synthetic laxatives, such as fiber and probiotics, are beyond the scope of this review.

2.2.1 Osmotic laxatives

Osmotic laxatives stimulate retention of water in the intestinal lumen through the luminal accumulation of osmotically active substances. The increased intestinal fluid distends the lumen, which results in stimulation of peristalsis as well as softening and loosening of stools [15]. The laxative effect of these agents depends on the extent to which they remain in the lumen. Absorption by the mucosa, as well as precipitation by other chemicals and metabolism by luminal bacteria, can reduce the osmotic effect [36].

2.2.1.1 Lactulose and lactitol

Lactulose and lactitol are synthetic disaccharides, which are not hydrolyzed by intestinal enzymes in the small intestine. When reaching the colon, these disaccharides are fermented by bacterial enzymes into low molecular weight acids. These acids create an osmotic gradient, resulting in increased luminal fluid, and lower the fecal pH, which stimulates colonic peristalsis.

Although its use is widespread, there have been no placebo-controlled trials evaluating the effect of lactulose or lactitol in children with constipation. In a low-quality [16] crossover trial, Perkin *et al.* compared the effect of lactulose with senna in 21 children with chronic constipation. Treatment with lactulose resulted in a significantly greater improvement of defecation frequency with lesser side effects [37]. Two small, RCTs compared the effect of lactulose and lactitol. No differences were reported in terms of improvement of defecation frequency or stool consistency. Both studies showed a better tolerability and compliance of lactitol [38,39]. In a study by Kokke *et al.*, a fiber mixture and lactulose gave comparable results in children with constipation [40]. Studies comparing the effect of lactulose or lactitol with PEG or mineral oil will be discussed below.

Side effects of lactulose and lactitol are usually mild and transient. Common side effects include bloating, abdominal pain and flatulence. These effects are thought to be related to the intraluminal fermentation of the laxative, which results in the production of gas.

2.2.1.2 Polyethylene glycol

PEG (or macrogol) is a polymer which is not metabolized and minimally absorbed [41] in the intestine and, thus, creates an osmotic gradient in the lumen of the colon. Different PEG formulations have been developed using PEG 3350 and PEG 4000 (with a molecular weight of 3,350 and 4,000 g/mol, respectively), with the addition of electrolytes (iso-osmotic solutions) and without the addition of electrolytes (hypo-osmotic solutions). Both PEG 3350 with electrolytes and PEG 4000 have been proven to be effective in the treatment of adults with constipation [42].

Two RCTs compared the efficacy of PEG with placebo in the treatment of functional constipation in children. Thomson *et al.* performed a high quality [16] placebo-controlled crossover trial, with two 2-week treatment periods separated by a 2-week placebo washout. PEG was found to be significantly more effective than placebo, in terms of number of complete defecations per week ($p < 0.001$), defecation frequency ($p = 0.003$) and pain during defecation ($p = 0.041$) [43]. Nurko *et al.* conducted a randomized, placebo-controlled, dose-ranging study (0.2, 0.4 and 0.8 g/kg/day). The response rate was higher for all PEG doses, compared to placebo ($p < 0.04$) [44]. All different dosages of PEG 3350 significantly increased the stool frequency compared to placebo, but there was no significant difference in response rate among the different PEG dosages.

Since both lactulose and PEG are often considered to be first-line treatment [31,45], several trials studied the efficacy of PEG as against lactulose in children with constipation. Results are not unequivocal; some studies found PEG to be

Table 2. Commonly used laxatives in pediatric constipation.

Laxative class	Mode of action	Laxative agents	Recommended dosage
Osmotic laxatives	Osmotic retention of luminal water	Lactulose	667 mg/mL: 1 – 3 mL/kg/day or b.i.d.
		Lactitol	1 – 6 years: 0.5 – 1.5 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
		PEG	Disimpaction: 1 – 1.5 g/kg/day (maximum of 7 consecutive days) Maintenance: 0.3 – 0.8 g/kg/day
		Magnesium salts	Magnesium oxide: 10 – 17 years: 0.5 – 2 g/day
Fecal softeners	Softening or lubrication of stool	Mineral oil	Maintenance: 2 – 18 years: 1 – 2 mL/kg/day
		Docusate	NA
Stimulant laxatives	Stimulation of colonic peristalsis and secretion	Bisacodyl	3 – 10 years: 5 mg/day at night > 10 years: 5 – 10 mg/day at night
		Picosulfate	4 – 5 years: 3 mg/day > 6 years: 4 – 6 mg/day
		Anthraquinones (senna)	Sennosides A+B: > 6 years: 10 – 20 mg/day
Rectal laxatives	Depending on agent used	Phosphate	Dibasic sodium phosphate/monobasic sodium phosphate 31.8/139.1 mg/mL: 2.5 mL/kg, maximum 133 mL/dose
		Docusate	Sodium docusate/sorbitol 1/250 mg/mL: < 6 years: 60 mL > 6 years: 120 mL
		Citrate/lauryl sulfoacetate	Sodium lauryl sulfoacetate/sodium citrate/sorbitol 9/90/250 mg/mL: 5 mL

Recommended dosage is according to the Dutch Pediatric Association [31].
NA: Not available.

superior, while other studies found no significant differences in stool frequency at the end of follow-up between the two compounds [23,46-50]. Drawing strong conclusions is difficult due to marked heterogeneity of the data. PEG with different molecular weights, with or without electrolytes, has been used in different dosing regimens. Also, different inclusion and exclusion criteria were used. Furthermore, the studies had varying lengths of follow-up. In two recent Cochrane reviews it was concluded that PEG may be superior in treating constipation than lactulose, although the strength of this conclusion was 'extremely limited' [51,52]. Interestingly, Pijpers *et al.* reviewed the same studies to conclude that no recommendation can be made to support the use of one laxative over the other [16]. In a recent study, not included in the previously mentioned reviews, PEG was associated with a significantly higher remission rate compared to lactulose [50].

A recent prospective, randomized, open-label study by Quitadamo *et al.* compared PEG with a fiber-fructose mixture. Both treatments were equally effective (p = 0.788) and safe, but children treated with the fiber-fructose mixture complained significantly more about its taste (p = 0.002) [53].

PEG appears to be safe for both short- and long-term use [54,55]. It is usually well tolerated, with lower rates of minor side effects compared to other agents [52]. Common side effects include flatulence, abdominal pain, nausea and diarrhea and appear to be dose-dependent [44]. Most of these side effects can be attributed to the working mechanism of the drug [13].

2.2.1.3 *Magnesium salts*

Magnesium hydroxide (referred to as 'milk of magnesia' when suspended in water) and other magnesium salts, such as magnesium citrate and magnesium sulfate, are inorganic, poorly absorbed particles. These compounds are thought to exert their laxative effect by either osmosis or the release of prostaglandins or cholecystokinin, resulting in the stimulation of gastrointestinal secretion and colonic motility [17,56,57]. Additionally, magnesium sulfate has recently been associated with an increased expression of aquaporins (proteins that regulate the flow of water molecules), which may contribute to its laxative effect [58]. To our knowledge, there are no placebo-controlled trials evaluating the laxative effect of magnesium salts. Three RCTs have compared the effect of magnesium oxide with PEG [59-61]. Although in two of these studies both substances were equally effective [59,60], a recent Cochrane review found a statistically significant difference favoring PEG. Overall quality of the evidence was low [52].

Extensive experience with magnesium hydroxide has shown its long-term safety [17]. However, it should be used with caution in children with renal impairment, due to the risk of hypermagnesemia [62-64]. Also, severe hypermagnesemia in a 14-year-old girl without renal impairment has been reported [65].

2.2.2 *Fecal softeners*

Fecal softeners are a class of laxatives that mainly soften or lubricate stool. Their effect depends on the strength of their

action on the surface of the stool with a generally modest effect [66].

2.2.2.1 Mineral oil

Mineral oil or liquid paraffin is a liquid composed of hydrocarbons obtained from petroleum. Because it is not absorbed in the intestines, it acts as a local lubricant of feces. It may have an osmotic effect as well, when it is converted to hydroxy fatty acids [67].

No placebo-controlled trials have been conducted with mineral oil in children. There have been few trials comparing mineral oil with other oral laxatives. In a low-quality trial [16], Urganci *et al.* randomized children with constipation to receive either lactulose or mineral oil. Improvement in stool consistency and frequency was significantly higher in the mineral oil group ($p < 0.01$ and $p < 0.05$, respectively). Also, compliance rate with mineral oil was higher (90 vs 60% after 8 weeks of treatment, $p = 0.02$) [68]. In another trial comparing mineral oil with lactulose, treatment with mineral oil gave a significantly higher response rate (85 vs 29% after 8 weeks of treatment, $p < 0.001$) and was associated with lesser side effects [69]. Drawing firm conclusion is hard, because of the low quality of the evidence due to sparse data and a high risk of bias [52].

Rafati *et al.* compared the efficacy of mineral oil with PEG. No difference was found in response rate between the 2 groups [70]. In a low-quality study [16], Sondheimer *et al.* randomized children to receive either mineral oil or a senna concentrate. Treatment with mineral oil resulted in significantly better symptom control in terms of fecal incontinence and defecation frequency [71].

Mineral oil is usually well tolerated and easy to titrate [67]. However, aspiration of mineral oil is associated with lipoid pneumonia, a serious complication [72,73]. Therefore, it should not be used in children who are at risk of aspiration, such as those with neurodevelopmental disorders. Furthermore, the palatability of mineral oil may be an issue and anal leakage of mineral oil may stain clothing and furniture.

2.2.2.2 Docusate

Docusate sodium is a surface-active agent that facilitates the interaction of water with the stool in order to soften the stool, make it more slippery and easier to pass [15]. There are no studies that evaluated the effect of docusate in pediatric constipation [74].

2.2.3 Stimulant laxatives

Stimulant laxatives are a group of laxatives that promote colonic peristalsis and secretion, through stimulation of the enteric nervous system [75]. Most commonly used stimulant laxatives are diphenylmethanes and anthraquinones. Because of concerns regarding structural damage to the enteric nerves and/or the colonic mucosa, physicians are often reluctant to use these medications [76]. However, the suspected damage to the colon is largely derived from uncontrolled observations in humans and from conflicting data in animals [77]. It has not been confirmed in experimental studies or clinical practice [75]. When used at recommended doses, it is unlikely that stimulant laxatives are harmful to the colon [76,77].

Stimulant laxatives are generally well tolerated [75,78,79], although pediatric data is lacking [15]. A common side effect is abdominal pain, which can often be managed by dose titration [75].

2.2.3.1 Diphenylmethanes

Diphenylmethanes include bisacodyl and picosulfate. These are both phenyl methane prodrugs, which are hydrolyzed by colonic bacteria or brush border enzymes to their active metabolite bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM) [75]. BHPM works both as a prokinetic agent [80] and by stimulation of intestinal secretion [81]. Although these drugs are used extensively in the treatment of pediatric constipation [15,35], there is no evidence to support this practice [82]. No adequate trials have been conducted to evaluate their effect [74,82] in children.

2.2.3.2 Anthraquinones

Anthraquinones, such as senna, are metabolized to a pharmacologically active state by intestinal microbiota [83]. These compounds exert their laxative effect through stimulation of colonic motility and inhibition of water absorption from the colon [84,85]. Although there is extensive experience with these agents [17], no placebo-controlled trials for pediatric constipation have been conducted [74,82]. Three low-quality studies compared the effect of senna on pediatric constipation with other laxatives [16]. Studies that compared senna with lactulose or mineral oil are discussed above [37,71]. In a study by Berg *et al.*, children with fecal incontinence and a history of fecal retention were treated with a behavioral approach in combination with either senna, placebo or no medication. There were no significant differences between groups in the number of fecal incontinence episodes per week [86].

2.2.4 Enemas

Enemas can provide both chemical and mechanical stimulation of the colon, as well as lubrication in order to promote defecation. Although rectal laxatives are used as maintenance treatment for pediatric constipation [35], there is little evidence to support this practice [15]. Due to its invasive character, it is often considered to be only appropriate when oral laxative therapy has failed. In a recent prospective controlled trial, children with severe constipation were randomized to either conventional treatment (including oral laxative therapy with PEG) alone or oral laxative therapy in combination with three rectal enemas per week. Although enemas were well tolerated, there were no significant differences between groups in increase in defecation frequency, reduction of fecal incontinence episodes and overall success rates. The authors concluded that there is no place for enemas in the maintenance therapy of severely constipated children [87].

3. Future pharmacotherapy for functional constipation

Because the results of treatment with current laxatives are often disappointing, there is a need for more effective interventions. Increasing insight in the physiology of the intestinal nervous system and epithelium, has led to the development of new classes of drugs for constipation [88]. These drugs often target a specific receptor which is known to affect intestinal function. Based on their mode of action, these drugs can be divided into the classes – serotonin agents, opioid antagonists, chloride channel activators and neurotrophins [89].

3.1 Serotonin agents

Serotonin or 5-hydroxytryptamine (5-HT) plays a key role in mediating peristalsis and stimulating intestinal secretion via 5-HT receptors in the gut wall, and 95% of all serotonin in the body is present within the gastrointestinal tract [88,90,91]. The serotonin receptor subtype 4 (5-HT4) is one of the most thoroughly studied subtypes with regard to gut function [92]. 5-HT4 agonism results in the stimulation of intestinal peristalsis and secretion [91,92]. Multiple 5-HT4 agonists have been developed thus far. A major issue with several of these agents has been the risk of cardiovascular adverse effects, which are thought to be the result of significant affinity of these agents for other proteins, including the hERG-channel which contributes to myocardial electrical activity [93]. Because of this, both cisapride and tegaserod have been withdrawn from the market. The limited available data on the efficacy of these two agents in pediatric constipation are not unequivocal [94-96].

3.1.1 *Prucalopride*

Prucalopride is a 5-HT4 agonist which is a benzofurancarboxamide derivative, and thus belongs to a different class than cisapride and tegaserod [97]. Prucalopride is highly selective for the 5-HT4 receptor and has no measurable affinity for other receptors [97]. It is not associated with serious adverse events or cardiovascular safety concerns [93,98]. In a meta-analysis of studies in adults by Ford and Suares, prucalopride was associated with a significantly higher response rate than placebo. It was concluded that prucalopride is effective for treatment of chronic constipation in adults [98]. Additionally, mechanistic studies have shown stimulation of gastrointestinal motor activity, reduced colonic transit times, increased stool frequency, softer stools and decreased straining [97]. To our knowledge, only one study documented the use of prucalopride in pediatric constipation. In an open-label pilot study, 37 children aged 4 to 12 years with functional fecal retention received prucalopride. After 8 weeks, 55 and 58% of all children were rated as much improved or very much improved by parents and investigators, respectively. Furthermore, a decrease in fecal incontinence rate was observed. In ~ 70% of all patients at least one adverse event was reported, of which headache, abdominal pain and respiratory tract infections were reported most frequently. Most adverse events were mild or moderate and no serious adverse events occurred. Also, no relevant changes in vital parameters or ECG recordings were observed [99]. Currently, prucalopride is studied in a multicenter, Phase III RCT to evaluate its efficacy and safety in pediatric constipation (NCT01330381).

3.1.2 *Other 5-HT4 agonists*

The effect and safety of several other 5-HT agonists are being studied for constipation in adults, such as velusetrag and mosapride [100,101]. To date, no pediatric data is available.

3.2 Opioid antagonists

Several peripherally working mu-opioid receptor antagonists are under investigation for the treatment of constipation in adults, such as alvimopan [102]. It has yet to be established whether its use is limited to opioid-induced constipation, or if it is also effective in idiopathic constipation. To our knowledge, no pediatric data for functional constipation is available.

3.3 Chloride channel activators

Activation of chloride channels in the apical membrane of the intestinal epithelium results in increased luminal chloride and water content, which may lead to an accelerated intestinal transit [103].

3.3.1 *Lubiprostone*

Lubiprostone is a prostaglandin E1 derivative, which activates the chloride channel subtype 2 (ClC-2) [104]. In a recent meta-analysis of studies in adults with constipation by Ford and Suares, lubiprostone was associated with a significantly higher response rate than placebo [98]. To our knowledge, one trial has been conducted evaluating the effect of lubiprostone in childhood constipation. Preliminary data suggest that this compound is effective in improving defecation frequency and softening stools in these children [105].

3.3.2 *Linaclotide*

Linaclotide is a synthetic peptide which activates the luminal guanylin receptor on enterocytes. This results in increased secretion of chloride and fluid into the intestinal lumen [75]. It is more effective than placebo in adult constipation [98]. No data is currently available in children.

3.4 Neurotrophins

Neurotrophins comprise a family of proteins that are involved in the growth, development and function of the nervous system. Neurotrophin-3 is thought to play an essential role in the enteric nervous system [106]. In a Phase II RCT, neurotrophin-3 appeared to be a safe and effective agent for the treatment of functional constipation in adults [106]. However, it is currently not being further developed for treatment of chronic constipation [75].

4. Conclusion

Constipation is a common problem in children, which is often treated with laxatives. Despite the widespread use of laxatives, there is a paucity of evidence to support this practice [52]. It is not possible to draw firm conclusions with regard to the efficacy of currently available laxatives, or on which laxative should be preferred over the other. As a consequence, current treatment regimens are more experience-based rather than evidence-based [15,16].

5. Expert opinion

Functional constipation is one of the most common complaints in a daily pediatric practice. Despite the high prevalence and the impaired quality of life of these children and their caretakers, little is known about the pathophysiology of functional constipation and the best way to treat these children. The current treatment of these children is experienced-based, rather than evidence-based. Why is there a lack of evidence in children with functional constipation, why are the studies mainly of low quality and why are the results of the studies not good to compare?

There are several reasons why it is difficult to perform clinical trials in children. Children are considered not to be competent to make decisions with regard to study participation, which makes issues of consent, risks and payment more complex [107]. Furthermore, parents are often reluctant to subject their children to medical research because of fear of side effects and ineffective treatment, mistrust of research and the (expected) inconvenience of study participation [108,109]. Disappointingly, pediatricians themselves often hinder trial participation due to personal treatment preferences, their discomfort of placebo use in children and time constraint [109]. On the other hand, less funding is available to perform such trials in children, because research priorities of governments, industry and funding agencies are often adult-focused because of the greater burden of disease in adults, coupled with financial and marketing considerations [110].

In the last decade however, pediatric pharmacological research has appeared on the agenda of many countries [111]. By stimulating high quality, ethical research in children, hopefully the availability of authorized medicines for children and the information on the use of medicine in children will increase. Nevertheless, it will probably take decades to significantly narrow the gap between children and adults in availability and access to medicines of comparable quality, efficacy and safety [111]. In general, it is of great importance to conduct research in children. If information is based on results from adult studies, we risk causing harm to children. Children have different pharmacokinetic and pharmacodynamic profiles in comparison with adults, and children can have different and unpredictable responses to medicines [107]. The absence of pediatric dosing information may result in avoidable side effects or inefficacy. Nevertheless, there is still inadequate information on many medicines commonly used in children [112] and up to 80% of all pediatric prescriptions are either unlicensed or used off-label [113].

The lack of well designed placebo-controlled studies was recently highlighted by an excellent Cochrane review by Gordon *et al.* [52]. Their review included 18 RCTs including 1,643 children. Disappointingly, in the 18 studies included in this review, many different definitions for childhood constipation were used, making comparison hardly possible. Experts from different continents in the field of pediatric gastroenterology have reached consensus on which criteria to use for diagnosing functional constipation in children [14]. Uniform use of these criteria will allow better comparison of different studies.

Another limitation of efficacy studies in children with constipation is the overall low to very low quality of data regarding the primary outcome, defecation frequency per week, due to sparse data, inconsistency (heterogeneity) and high risk of bias [52]. Future well-designed, placebo-controlled studies in constipated children, should include i) standardized protocols as suggested by international experts in the field of pediatric functional gastrointestinal disorders, ii) homogeneous patient populations, iii) predefined outcome measures, according to the Rome III criteria for functional childhood constipation, iv) long-term follow-up and v) quality of life assessment and cost-effectiveness analysis. These studies should be executed with greater methodological rigor and should be performed not only in tertiary centers but also in primary and secondary care.

5.1 Treatment recommendations

Based on the present literature and our own large experience in treating children with constipation, we feel that pharmacotherapy should consist of fecal disimpaction and maintenance treatment to prevent the reaccumulation of feces. Successful disimpaction can be achieved through either oral or rectal medications. These two approaches appear to be both equally effective as well as equally distressing for the child. Therefore, the choice of treatment should be made after discussing the advantages and disadvantages of each route with the parents and/or the child. In our institute we advise for oral disimpaction, PEG 1 – 1.5 g/kg/day, for 6 consecutive days, whereas for rectal disimpaction, we advise daily docusate sodium/sorbitol enemas for 3 consecutive days, the latter because of its favorable safety profile.

After disimpaction, maintenance therapy should be initiated. Although there is insufficient data to draw strong conclusions, we recommend oral PEG as the first choice for maintenance therapy. It appears to be equally or more effective when compared to other oral laxatives. This, in combination with its tolerability and safety profile, makes it the first-line treatment. As a starting dose for maintenance therapy, we recommend PEG 0.3 – 0.8 g/kg/day. This dose can be adjusted guided by a combination of defecation frequency, consistency of stools and number of fecal incontinence

episodes. Children with a long-standing history of constipation should be without any complaints for at least 2 months, before laxatives may be tapered gradually.

When children do not have regular stools (≥ 3/week), despite optimal treatment with PEG, the addition of a diphenylmethane can be useful. In the case of failure of these measures, children can be successfully treated with colonic lavage with tap water [114].

Despite treatment with currently available laxatives, a significant proportion of children with functional constipation is not successfully treated and continues to experience symptoms, sometimes even up to adulthood [11,12]. At this time, if the currently available pharmacotherapy fails, patients can require more invasive therapy, such as sacral neuromodulation or surgical interventions such as the creation of a cecostomy for antegrade enemas. Although these therapies are used successfully for severe, refractory constipation [13], they should be considered as a last resort. Due to advances in our understanding of intestinal physiology and pathophysiology, new classes of drugs have emerged for functional constipation, such as serotonin receptor agonists (e.g., prucalopride). Results from adult studies with these new agents are promising. Ongoing and future studies have to determine the efficacy and safety of these new drugs and thus their role in the treatment of functional constipation in children.

Declaration of interest

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