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EXPERT OPINION

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Pharmacokinetic and pharmacodynamic considerations for the current chronic constipation treatments

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Introduction: Chronic constipation is a frequent condition often treated pharmacologically. The laxatives available belong to very different pharmacologic groups.

Areas covered: This is a short but comprehensive review of the pharmacology, efficacy and safety of currently available laxatives for chronic constipation. Pertinent publications were retrieved from reference lists of publications and by literature searches via PubMed, lastly performed in November 2012.

Expert opinion: The most relevant laxative groups are the older representatives osmotic salts, sugars and sugar alcohols, macrogol, anthraquinones, diphenolic laxatives or diphenyl methanes (bisacodyl and sodium picosulfate) and the newer compounds prucalopride, lubiprostone and linaclotide. For all of these laxatives efficacy has been shown in controlled trials. Electrolyte losses do not occur when laxatives are given in therapeutic doses (rare exceptions with phosphate salts and salinic laxatives). The older laxatives are also safe regarding teratogenicity, abortion and lactation. For the newer compounds no respective data are available as yet. It is questionable whether the newer compounds offer advantages over the older ones. Unfortunately, comparative trials are lacking.

Keywords: 5-HT, cisapride, constipation, defecation, gastrointestinal motility, gastrointestinal transit, hypomotility, laxatives, prokinetics, prucalopride, quality of life, serotonin, stools

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1. Introduction

Constipation is prevalent all over the world. Many factors, including aging of the population, misconceptions about the normal (and desirable) frequency of bowel movements and fear of the consequences of constipation have resulted in the widespread use of laxatives. On the other hand, concern about potential side effects may result in underuse by patients who would benefit from laxatives for regulation of bowel habits.

The following article will review the pharmacology of the different laxatives. Being a general global overview it does not intend to cover specific drugs in details. A laxative is defined as a compound facilitating defecation irrespective of its mode of action. Though dietary fiber thereby could be subsumed under the term laxative, its chemistry, metabolism and efficacy is beyond the scope of this chapter.

The history of constipation and laxative use is much longer than that of controlled clinical trials and of evidence-based medicine. This is the reason why less randomized controlled trials are available for older than for newer laxatives although the former may work at least as well as the latter.

Pertinent publications were identified by repeated searches via PubMed, lastly performed in November 2012 using the term *laxativ** and the pharmacological

Article highlights.

- Efficacy of the following laxatives has been shown in controlled trials: osmotic salts, sugars and sugar alcohols, macrogol, anthraquinones, diphenyl methanes (bisacodyl and sodium picosulfate (SPS)), prucalopride, lubiprostone and linaclotide.
- When used in recommended doses these drugs are safe with few exceptions regarding phosphate salts and salinic laxatives.
- With the other laxatives, electrolyte problems do not occur when given in recommended doses.
- The older laxatives are also safe regarding teratogenicity, abortion and lactation. For the newer compounds respective data are not available.
- Whether the newer laxatives have advantages over the older ones such as bisacodyl or macrogol has to be shown in comparative trials and by clinical experience.

This box summarizes key points contained in the article.

names of the compounds. Additionally, the reference lists of the relevant papers were screened.

2. General aspects

2.1 Mode of action and classification

Laxation is nearly always associated with both an increased water content of the stools and a shortened transit time. The increase in moisture may be brought about by inhibiting absorption by luminal contents (osmotic laxatives), stimulating secretion or speeding transit (by shortening the time available for water absorption). A faster transit may be obtained by direct pharmacologic stimulation of propulsive motility or by increasing stool bulk eliciting propulsive motility (Figure 1). Hence, stool volume and speed of transit positively affect each other.

2.2 Pharmacokinetics

Under safety aspects a laxative is preferred to act locally not being absorbed. This is fulfilled by the older laxatives with the exception of the osmotic salts but not necessarily for the newer developments (see individual substances for details).

2.3 Laxatives and abdominal complaints

Since constipation by itself is often associated with abdominal discomfort, the causative role of a laxative for such symptoms is not always apparent. Compounds digestible by the colonic bacteria (e.g., fiber or lactulose) often produce bloating and flatulence. Some patients experience bloating when treated with macrogol. Diphenyl methanes, anthraquinones and prucalopride due to their mechanism of action may cause cramping abdominal pain.

2.4 Serum electrolytes

In patients abusing laxatives in high doses wasting of potassium and water is not uncommon [1]. This is probably the reason for

warnings about electrolyte losses with laxative treatment. However, prospective therapeutic studies with recommended doses do not show changes in serum electrolyte levels. This holds true for lactulose and macrogol [2], bisacodyl [3,4], sodium picosulfate (SPS) [5], anthraquinones [6,7], lubiprostone [8-10], linaclotide [11] as well as prucalopride [12-14]. Milk of magnesia (magnesium hydroxide) is generally safe but cases with hypermagnesemia have been described [15]. Oral phosphates may cause severe hyperphosphatemia [16]. Particular attention should be paid in patients with renal insufficiency.

2.5 Habituation and tolerance

Long-term use of laxatives is often said to result in habituation (i.e., the reduction or even disappearance of laxative response) and/or tolerance (i.e., the need to increase the laxative dose in order to maintain the desired response). Both could theoretically be induced by damage to the colon or by an adaptive mechanism counteracting the laxative effect on motility or secretion. However, clinical studies do not show a loss of effect of laxatives even if taken over years to decades [4,17]. However, individual patients with slow-transit constipation report the need to increase the laxative dose in order to maintain the desired effect [18].

3. Osmotic laxatives

3.1 Salinic laxatives

These poorly absorbable salts keep water in the colon by osmotic forces. They may be called by their composition or by their trivial name: milk of magnesia ($\text{Mg}(\text{OH})_2$), bitter salt (MgSO_4), Glauber's salt (Na_2SO_4), Karlsbad salt (mixture of Na_2SO_4 , NaHSO_4 and K_2SO_4). Controlled trials with these laxatives are an exception but their efficacy is beyond any doubt [15,19]. The doses required to treat constipation are comparatively large (e.g., 5 g) but smaller amounts may also cause laxation in susceptible individuals, for example, even magnesium containing mineral waters may soften stools. The taste of some of these salts may become problematic on long-term use. Some absorption of the ions may occur [20], potentially causing problems in patients with heart or kidney disease [21]. Otherwise they seem to be safe. Phosphate compounds are used for bowel cleansing for diagnostic purposes [22] as well as for chronic constipation. Though there are no blinded controlled trials in chronic constipation, there is little doubt they do work. The doses required in an open trial were substantial (6 – 12 g/day) [23].

3.2 Sugars and sugar alcohols

The digestive and absorptive capacity of the small intestine for the naturally occurring sugars lactose and fructose, and for the sugar alcohol sorbitol is limited. If this capacity is overrun, the unabsorbed fraction will pass the small intestine unchanged and reach the colon. Lactulose is an indigestible synthetic disaccharide also passing unchanged into the colon. All these saccharides are osmotically active and hence draw water to

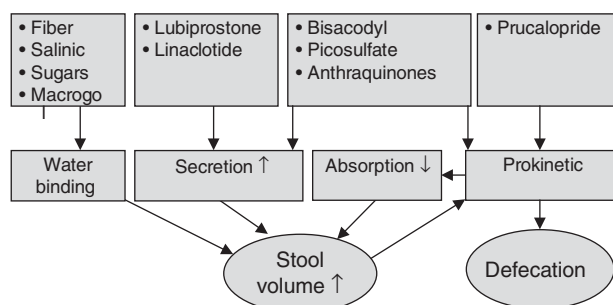


Figure 1. Laxatives, their mode of action and how they promote defecation.

them but they are also available for degradation by the microbiota. The partially absorbed end products of bacterial degradation are short chain carbonic acids (acetate, propionate, lactate and butyrate). The more the sugars are metabolized by the microbiota the more they lose their osmotic activity. Hence, severely constipated patients are unlikely to benefit from these compounds. In addition, a large amount of gas is produced rendering them poorly tolerated by many patients [2]. The sweet taste (of lactulose) may also be a hindrance since the doses required are considerable (10 – 20 g/day). Randomized controlled trials have been published predominantly for lactulose [2,24,25] but occasionally also for sorbitol and lactose [26,27]. The sugars seem to be equally effective to each other, lactulose being the most expensive. A recent meta-analysis concluded that lactulose is inferior to macrogol with respect to stool frequency per week and relief of abdominal complaints [28]. Lactulose should not be used in the intensive care setting since it carries the risk of Ogilvie's syndrome [29]. Otherwise, the sugars as expected proved to be absolutely safe.

3.3 Macrogol

Polyethylene glycol with a molecular weight of 3500 – 4000 (macrogol) is a macromolecule drawing water to it to maintain isoosmolarity in the lumen of the gut. Only negligible amounts are absorbed [30,31], it is not amenable to bacterial degradation, and therefore gas production does not occur. In usual doses of 10 – 20 g/day it has a slow start of action but there is no loss of effect over time. Macrogol is very well investigated [2,32,33] and more effective than both lactulose [28] and the 5-HT₄ (5-hydroxytryptamine receptor 4) agonist tegaserod [34]. It is very well suited for chronic use with usually daily intake. However, patients may complain of bloating when on macrogol [2]. This is not due to bowel gas but rather to intestinal distension by substantial water binding. Macrogol shares its mode of action as well as its laxative and side effects with calcium polycarbophil [35] and methyl cellulose [36] (otherwise used as an emulgator and as wallpaper glue).

Originally, macrogol preparations were developed for bowel cleansing prior to diagnostic procedures. In this setting, several liters of an isoosmotic solution have to be given. For this purpose, electrolytes must be added in similar concentration as in

the blood in order to avoid an electrolyte shift from serum to bowel lumen. When used as a laxative for chronic constipation however, the required doses are 10- to 20-fold smaller, and diarrhea is not produced. Hence the addition of electrolytes is not necessary. Some trade marks of macrogol contain electrolytes while others do not. Understandably, patients prefer macrogol without electrolytes [37]. Whether containing electrolytes or not, macrogol is safe.

4. Prokinetics: prucalopride

The selective 5-HT₄ receptor agonist prucalopride belongs to the benzofurancarboxamide agonists having high affinity and selectivity for the 5-HT₄ receptor, and tissue-specific agonist activity [38]. The most pronounced effect of prucalopride is stimulation of colonic motility with giant migrating contractions provoking mass movements [39,40]. The oral bioavailability of prucalopride is > 90%, maximal plasma levels are reached after about 2 h. There is no hepatic metabolism with at least 6% of the substance excreted unchanged in feces and about 60% excreted unchanged in urine. The mean terminal half-life is 21 h [39].

Three pivotal trials in patients with chronic constipation over 12 weeks comparing placebo, 2 mg prucalopride once daily (o.m.) and 4 mg prucalopride o.m. have been conducted [12-14]. The main results with 2 mg are shown in Tables 1 – 3. There was no obvious dose-response relation between the two doses. The objective findings are reflected by an improvement of the subjective perception by the patients. These results were confirmed in male and female patients aged ≥ 65 years, treated for 4 weeks [41].

Substance-specific side effects, that is, those occurring significantly more frequently in the prucalopride than in the placebo groups, were headache, nausea, diarrhea and abdominal pain. The majority of adverse events (AEs) occurred within the first 24 h of treatment and proved to be transient. Exclusion of the first day abolished the difference between the prucalopride and the placebo groups.

In contrast to other 5-HT₄ receptor agonists, prucalopride does not interact with the hERG channel or 5-HT_{1(b)} receptors, which are considered to be responsible for the adverse cardiovascular effects with other 5-HT₄ receptor agonists [42]. Cardiovascular safety was explicitly evaluated in two crossover studies in healthy volunteers where prucalopride was given at a maximal dose of 10 or 20 mg [43]. No differences in the incidence of prolonged QTc were found between the groups. Cardiovascular safety was confirmed in the clinical trials [12-14,41] and in elderly institutionalized patients (mean age 83 years), most of whom had a prior history of cardiovascular disease [44].

5. Secretory stimulants

5.1 Lubiprostone

Lubiprostone is a member of a new class of compounds called prostones. It activates type-2 chloride channels (ClC-2)

Table 1. Bowel movement variables in randomized controlled trials with laxatives in chronic constipation.

Drug (dose)	Outcome variable	Verum	Placebo	Therapeutic gain	Refs.
Macrogol (17 g o.m.)	CSBMs/week over 6 months	5	2.1	2.9	[33]
Lubiprostone (24 µg b.i.d.)	SBMs in week 1	5.89	3.99	2.9	[49]
Lubiprostone (24 µg b.i.d.)	SBMs in week 1	5.69	3.46	2.23	[9]
Lubiprostone (24 µg b.i.d.)	SBMs in week 1	6.8	3.9	2.9	[8]
Linaclotide (300 µg o.m.)	CSBMs/week over 2 weeks	3.4	0.3	3.1	[53]
Linaclotide (300 µg o.m.)	CSBMs/week over 12 weeks	3.93	1.47	2.46	[57]
Prucalopride (2 mg o.m.)	CSBMs/week over 12 weeks	2.6	1.2	1.4	[12]
Prucalopride (2 mg o.m.)	CSBMs/week over 12 weeks	1.9	1.2	0.7	[13]
Prucalopride (2 mg o.m.)	CSBMs/week over 12 weeks	1.6	1.0	0.6	[14]
Prucalopride (2 mg o.m.)	CSBMs/week over 4 weeks	2.4	1.7	0.7	[41]
Bisacodyl (5 – 10 mg o.m.)	CSBMs/week over 4 weeks	5.2	1.9	3.3	[3]
SPS (5 – 10 mg o.m.)	CSBMs/week over 4 weeks	3.4	1.7	1.7	[5]
Elobixibat (15 mg o.m.)	CSBMs in week 1	4.3	1.1	3.2	[90]

The data are not strictly comparable between the studies since baseline characteristics of the patients, duration of treatment and definition of the outcome variables are not identical. This is reflected by the differences in placebo responses.

b.i.d.: twice daily; CSMB: Complete spontaneous bowel movement; o.m.: Once daily; SBM: Spontaneous bowel movement; SPS: Sodium picosulfate.

Table 2. Outcome variable 'CSBMs/week \geq 3/week' in randomized controlled trials with laxatives in chronic constipation.

Drug (dose)	Outcome variable	Verum	Placebo	Therapeutic gain	Refs.
Linaclotide (300 µg o.m.)	% of patients with \geq 3 CSBMs/week and an increase \geq 1 over baseline in 3 of 4 weeks	32.3	7.4	24.9	[54]
Linaclotide (145 µg o.m.)	% of patients with \geq 3 CSBMs/week and an increase of \geq 1 CSBMs for 9 out of 12 weeks	21.2	3.3	17.9	[55] (trial 303)
Linaclotide (290 µg o.m.)	% of patients with \geq 3 CSBMs/week and an increase of \geq 1 CSBMs for 9 out of 12 weeks	19.4	3.3	16.1	[55] (trial 303)
Linaclotide (145 µg o.m.)	% of patients with \geq 3 CSBMs/week and an increase of \geq 1 CSBMs for 9 out of 12 weeks	16.0	6.0	10.0	[55] (trial 01)
Linaclotide (290 µg o.m.)	% of patients with \geq 3 CSBMs/week and an increase of \geq 1 CSBMs for 9 out of 12 weeks	21.3	6.0	15.3	[55] (trial 01)
Linaclotide (290 µg o.m.)	% of patients with \geq 3 CSBMs/week and an increase of \geq 1 CSBMs for 9 out of 12 weeks	18.0	5.0	13.0	[58]
Linaclotide (290 µg o.m.)	% of patients with \geq 3 CSBMs/week and an increase of \geq 1 CSBMs for 9 out of 12 weeks	19.5	6.3	13.2	[59]
Prucalopride (2 mg o.m.)	% of patients with \geq 3 CSBMs/week for 12 weeks	30.9	12.0	19.9	[12]
Prucalopride (2 mg o.m.)	% of patients with \geq 3 CSBMs/week for 12 weeks	24.0	12.0	12.0	[13]
Prucalopride (2 mg o.m.)	% of patients with \geq 3 CSBMs/week for 12 weeks	19.5	9.6	9.9	[14]
Bisacodyl (5 – 10 mg o.m.)	% of patients with \geq 3 CSBMs/week for 1 – 4 weeks	67.4	27.4	40.0	[3]
SPS (5 – 10 mg o.m.)	% of patients with \geq 3 CSBMs/week for 1 – 4 weeks	51.1	18.0	33.1	[5]

The data are not strictly comparable between the studies since baseline characteristics of the patients, duration of treatment and definition of the outcome variables are not identical. This is reflected by the differences in placebo responses.

CSMB: Complete spontaneous bowel movement; o.m.: Once daily; SPS: Sodium picosulfate.

increasing chloride concentration in intestinal fluid with associated passive transport of sodium and water across the mucosa, causing an increased fluid secretion into the intestinal lumen and thereby promoting intestinal transit. Lubiprostone is rapidly and extensively metabolized within the gastrointestinal (GI) tract and therefore has very low bioavailability following oral administration. Consequently, it cannot be detected in plasma, urine or stool. A substance called M3

seems to be the active metabolite of lubiprostone, its half-life being around 1 h. About 60% of M3 is excreted in the urine and 30% in the feces [45–48].

Clinical studies of 4 weeks duration have demonstrated lubiprostone's efficacy in the short-term treatment of chronic idiopathic constipation (Table 1) [8,9,49]. To assess safety, lubiprostone 24 µg twice daily (b.i.d.) was given as needed for 48 weeks to constipated patients [10]. The most characteristic

Table 3. Outcome variable ‘increase ≥ 1 in mean number of CSBMs/week’ in randomized controlled trials with laxatives in chronic constipation.

Drug (dose)	Outcome variable	Verum	Placebo	Therapeutic gain	Refs.
Linaclotide (145 μg o.m.)	≥ 3 CSBMs/week and increase of ≥ 1 CSBMs for 9 out of 12 weeks	21.2	3.3	17.9	[55] (trial 303)
Linaclotide (290 μg o.m.)	≥ 3 CSBMs/week and increase of ≥ 1 CSBMs for 9 out of 12 weeks	19.4	3.3	16.1	[55] (trial 303)
Linaclotide (145 μg o.m.)	≥ 3 CSBMs/week and increase of ≥ 1 CSBMs for 9 out of 12 weeks	16.0	6.0	10.0	[55] (trial 01)
Linaclotide (290 μg o.m.)	≥ 3 CSBMs/week and increase of ≥ 1 CSBMs for 9 out of 12 weeks	21.3	6.0	15.3	[55] (trial 01)
Linaclotide (290 μg o.m.)	≥ 3 CSBMs and an increase of ≥ 1 CSBM from baseline (at least 9 of 12 weeks)	18.0	5.0	13.0	[58]
Linaclotide (290 μg o.m.)	≥ 3 CSBMs and an increase of ≥ 1 CSBM from baseline (at least 9 of 12 weeks)	19.5	6.3	13.2	[59]
Prucalopride (2 mg o.m.)	% of patients with an increase ≥ 1 of CSBMs/week week 1–12	47.3	25.8	21.5	[12]
Prucalopride (2 mg o.m.)	% of patients with an increase ≥ 1 of CSBMs/week for 1 – 12 weeks	43.0	28.0	15.0	[13]
Prucalopride (2 mg o.m.)	% of patients with an increase ≥ 1 of CSBMs/week for 1 – 12 weeks	38.1	20.9	17.2	[14]
Bisacodyl (5 – 10 mg o.m.)	% of patients with an increase ≥ 1 of CSBMs/week for 1 – 4 weeks	82.0	40.4	41.6	[3]
SPS (5 – 10 mg o.m.)	% of patients with an increase ≥ 1 of CSBMs/week for 1 – 4 weeks	65.5	32.2	33.3	[5]

The data are not strictly comparable between the studies since baseline characteristics of the patients, duration of treatment and definition of the outcome variables are not identical. This is reflected by the differences in placebo responses.

CSMB: Complete spontaneous bowel movement; o.m.: Once daily; SPS: Sodium picosulfate.

treatment-related AE was nausea (19.8%) also being a prominent feature in the other trials.

5.2 Linaclotide

Linaclotide is a minimally absorbed peptide agonist of the guanylate cyclase-C receptor on the luminal surface of the intestinal epithelium that stimulates intestinal fluid secretion. The generation of cyclic guanosine monophosphate (cGMP) within intestinal epithelial cells triggers a signal transduction cascade causing chloride and bicarbonate secretion into the lumen, resulting in an acceleration of intestinal transit. Interestingly, cGMP also seems to affect visceral pain perception. It reduced the firing of afferent pain fibers in mice with experimental visceral hypersensitivity [50]. Accordingly, linaclotide not only accelerated GI transit but also reduced visceral nociception in several animal models [51,52]. The drug has recently been reviewed in this Journal [11].

Following two dose-finding studies in chronic constipation [53,54], two large 12-week placebo-controlled studies were conducted with 145 or 290 μg linaclotide o.m. proving its efficacy (Tables 1 – 3) [55]. No relevant side effects were observed.

The drug was also investigated in constipation-predominant irritable bowel syndrome (C-IBS). Apart from improving variables of constipation, linaclotide also had a significant effect on pain [56–59].

6. Laxatives with a dual mode of action

The naturally occurring anthraquinones belong to the oldest drugs ever used by mankind while the diphenyl methanes (bisacodyl and its derivative SPS) have been synthesized in the 50s (Figure 2). This is the reason why their mode of action was explored late after their discovery and clinical trials of current standard are absent in the case of the anthraquinones and very recent in the case of the diphenyl methanes (refer to Section 6.2). The prokinetic effect of the members of these groups of laxatives has been described in the late 60s [60,61] and has later been confirmed [62,63]. Their anti-absorptive and secretagogue action was found in the mid-70s [64,65]. The receptors for these effects have not been identified. Recently, it has been proposed that bisacodyl increases the secretion of prostaglandin E₂ (PGE₂) from macrophages, and that this PG acts as a paracrine factor and decreases aquaporin AQP3 expression in colon mucosal epithelial cells [66].

6.1 Anthraquinones

The anthraquinones comprise the sennosides A and B and other less well-investigated members of the group such as aloe and cascara. The anthraquinones naturally occur as glycosides and pass unchanged through the small intestine. They are then split by the colonic microbiota into the active

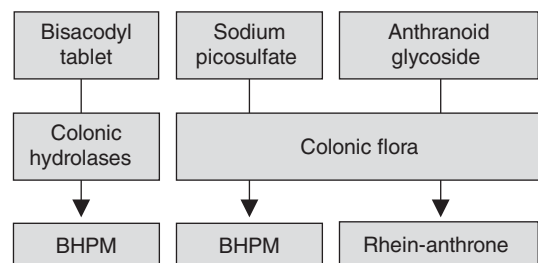


Figure 2. Activation of diphenyl methanes and anthraquinones. They are not systemically absorbed but activated only in the colon. BHPM: *bis-(p-hydroxyphenyl)-pyridyl-2-methane*. Only bisacodyl may be given in the form of suppositories.

compound rhein-anthrone [67]. Clinical trials are sparse but prove their efficacy as measured by stool frequency and consistency. Senna worked better than placebo [68] and lactulose [24,69], and similar to magnesium hydroxide [70] and SPS [71]. The required dose is around 20 – 40 mg of pure sennosides.

Melanosia coli is a dark-brown discoloration of the colon mucosa occurring within weeks to months of regular anthraquinone intake [72]. It disappears over weeks to months when anthraquinone intake is discontinued [73]. The pigmentation is due to cell debris after apoptosis of colonic epithelia stained by the anthraquinone and then phagocytosed by submucosal macrophages [74]. Melanosia does not appear to have any functional significance.

When taken in recommended doses, sennosides are safe, do not produce diarrhea and do not cause electrolyte disturbances [6,7,24]. There is apparently no fetotoxicity when sennosides are taken by pregnant women [75,76] nor are there respective concerns from animal experiments (Table 4) [77]. Sennosides are in agreement with their unabsorbable nature not excreted in breast milk [78-80].

6.2 Diphenolic laxatives (diphenyl methanes)

The diphenyl methane laxatives consist of bisacodyl and its ester SPS. Free bisacodyl will be absorbed in the small intestine and perform an enterohepatic circulation [81]. In order to avoid this it is given in tablets dissolving in the lower gut. By contrast, SPS passes the small intestine unchanged and unabsorbed, and hence may be administered as drops. It is bacterially activated in the colon.

The efficacy of both drugs was already obvious before recently high quality placebo-controlled trials were published. This is reflected by the use of bisacodyl as a rescue medication in most of the trials with the newer laxatives. The trials with the diphenyl methanes lasted for either 3 days [82-84] or 4 weeks [3,5]. In the latter trials, the patients were allowed to adjust the starting dose of 10 mg o.m. About half of them were satisfied with 5 mg/day, the others continued to take 10 mg/day (Tables 1 – 3).

Like the sennosides, the diphenyl methanes are safe without affecting electrolyte levels [3-5,82]. Since they are not absorbed, this holds also true for pregnancy and lactation (Table 4) [85,86].

6.3 Elobixibat

This drug is in clinical trial Phase II of development and is shortly mentioned here since it shows a completely novel mode of action. It inhibits ileal bile salt absorption leading to an increased spill over of bile salts into the colon. In the colon, bile salts stimulate secretion [87,88] and motility [89]. Clinical efficacy of elobixibat starts from a daily dose of 15 mg onward (Table 1) [90-92].

7. Miscellaneous

7.1 Liquid paraffin

Oral paraffin is mainly used in the pediatric setting as a 'stool softener'. In children, it was found to be nearly as effective as macrogol but caused more AEs [93]. In another study it proved to be superior to lactulose [94]. There are concerns about malabsorption of fat-soluble vitamins when used chronically and about lipid pneumonia in case of aspiration [95].

7.2 Docusate

Though docusate seems to be commonly used in some countries to treat constipation, there is apparently no evidence at all that it is better than placebo. One trial is flawed since placebo responders were excluded [96], in a second trial docusate has been shown to be inferior to psyllium [97], in a third it did not improve the effect of senna [98]. This is not astonishing since in animal experiments it does not affect water content of the digesta in any segment of the gut [99].

8. Rectally administered laxatives

8.1 Enemas

There are several osmotically active preparations in enema-form on the market containing, for example, phosphates, citrates or sorbitol. Though no clinical trials could be found, their acute effect is obvious. With phosphate enemas severe hyperphosphatemia and with magnesium sulfate enema magnesium toxicity has been reported [100-102]. Rectal paraffin for fecal impaction seems to be safe [103].

8.2 Suppositories

Bisacodyl may be applied in the form of suppositories where it acts locally [104] and is accepted by the medical community also in the absence of controlled trials since it is the most frequently used rescue medication in trials with oral laxatives (e.g., [9,12,13,14,33,57,58]). Defecation will occur about 20 min after administration [81]. Glycerol-containing suppositories are used in practice [105] but controlled trials in constipation are lacking. They are inferior to a phosphate enema for preparing the bowel for sigmoidoscopy [106].

Table 4. Evidence for safety of laxatives in pregnancy and lactation.

Drug or class	Pregnancy		Lactation	
	Evidence	Recommendation	Evidence	Recommendation
Salinic laxatives	Long experience but no data	Not recommended	Long experience but no data	Not recommended
Sugars and sugar alcohols	Not absorbed	No objection	Not absorbed	No objection
Phosphate salts	No data	Not recommended	No data	Not recommended
Macrogol	Minimal absorption	No objection	Minimal absorption	No objection
Lubiprostone	No data	Contraindicated	No data	Not recommended
Linaclotide	No data	Contraindicated	No data	Not recommended
Prucalopride	No data	Contraindicated	No data	Not recommended
Sennosides	Long experience, animal data, clinical reports	No objection	No excretion in breast milk	No objection
Bisacodyl & SPS	Long experience, animal data, clinical reports	No objection	No excretion in breast milk	No objection

Data from [2,24,25,30,31,75,76,78-80,85,86,110,111].

SPS: Sodium picosulfate.

9. Expert opinion

‘Constipation’ should only be treated when the patient is suffering but not to ‘normalize’ stool frequency in the absence of complaints. Dietary fiber is unfortunately neither very effective nor very well tolerated. Likewise, changes in life style such as increasing physical activity and increasing fluid intake – if ever accepted by the patient – have not been proved to be effective in relieving constipation [107]. In many cases therefore a laxative will be required. It is a prejudice that regular use of a laxative may lead to electrolyte imbalance and/or to tolerance if taken in recommended doses. The available laxatives may be considered to be safe with the usual restrictions for pregnancy (Table 4).

Comparing the efficacy of the different laxatives is difficult for at least two reasons. First, head-to-head comparative trials would clearly be interesting but pharmaceutical companies tend to avoid these. However, Tables 1 – 3 show that the recently developed compounds do not appear to be superior to the older and hence much cheaper diphenyl methanes. Second, not all patients are satisfied with a single laxative [108,109]. It may be necessary to try two or three of them to find the best choice. Macrogol, bisacodyl or SPS is a good start.

In contrast to the other laxatives, prucalopride is expected to also act on higher segments of the GI tract, namely

esophagus, stomach and small intestine. This gives hope that the drug could help in reflux disease, gastroparesis and intestinal pseudo-obstruction. In other words, a patient complaining of a sense of abdominal fullness, distension or bloating would be a good candidate to try prucalopride. Prucalopride is currently only approved for women in whom laxatives fail to provide adequate relief. However, the trials showed numerically similar results in women and in men. The low proportion of men in the samples resulted in a borderline statistical significance. This was the reason to not approve the drug for men. Such a restrictive policy by the regulatory authorities will not serve the benefit of the patients and will further increase the costs of drug development.

It will be interesting whether linaclotide will prove to be clinically useful to simultaneously treat pain and constipation in IBS.

Declaration of interest

S Müller-Lissner has served as a speaker, a consultant, an investigator or an advisory board member for Almirall, Axcan, Boehringer Ingelheim, Falk Foundation, Janssen Pharmaceuticals, Movetis, Menarini Farmaceutica, Mundipharma GmbH, Novartis, Pfizer Inc., Procter & Gamble, Shire-Movetis, Sucampo Pharma and Zeria Pharma.

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