Expert Opinion on Drug Metabolism & Toxicology

ISSN: 1742-5255 (Print) 1744-7607 (Online) Journal homepage: http://www.tandfonline.com/loi/iemt20

Pharmacokinetic and pharmacodynamic considerations for the current chronic constipation treatments

Stefan Müller-Lissner

To cite this article: Stefan Müller-Lissner (2013) Pharmacokinetic and pharmacodynamic considerations for the current chronic constipation treatments, Expert Opinion on Drug Metabolism & Toxicology, 9:4, 391-401, DOI: 10.1517/17425255.2013.773972

To link to this article: https://doi.org/10.1517/17425255.2013.773972

Published online: 21 Feb 2013.

EXPERT OPINION

Pharmacokinetic and pharmacodynamic considerations for the current chronic constipation treatments

Stefan Müller-Lissner
Park-Klinik Weissensee, Berlin, Germany

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

Expert Opin. Drug Metab. Toxicol. (2013) 9(4):391-401

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

10.1517/17425255.2013.773972 © 2013 Informa UK, Ltd. ISSN 1742-5255, e-ISSN 1744-7607

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 ($Mg(OH)_2$), 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

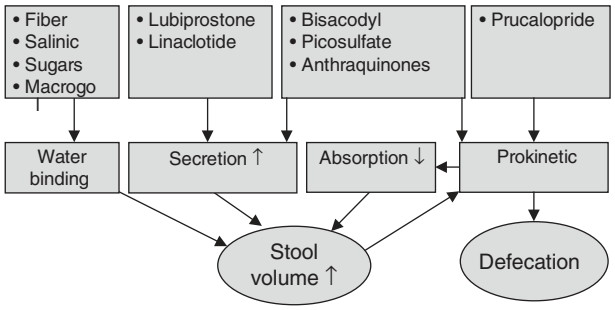

Figure 1. Laxatives, their mode of action and how they promote defecation.

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 loose 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-HT_4 (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-HT_4 receptor agonist prucalopride belongs to the benzofurancarboxamide agonists having high affinity and selectivity for the 5-HT_4 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-HT_4 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-HT_4 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 ≥ 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 ≥ 3 CSBMs/week and an increase ≥ 1 over baseline in 3 of 4 weeks	32.3	7.4	24.9	[54]
Linaclotide (145 μg o.m.)	% of patients with ≥ 3 CSBMs/week and an increase of ≥ 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 ≥ 3 CSBMs/week and an increase of ≥ 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 ≥ 3 CSBMs/week and an increase of ≥ 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 ≥ 3 CSBMs/week and an increase of ≥ 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 ≥ 3 CSBMs/week and an increase of ≥ 1 CSBMs for 9 out of 12 weeks	18.0	5.0	13.0	[58]
Linaclotide (290 μg o.m.)	% of patients with ≥ 3 CSBMs/week and an increase of ≥ 1 CSBMs for 9 out of 12 weeks	19.5	6.3	13.2	[59]
Prucalopride (2 mg o.m.)	% of patients with ≥ 3 CSBMs/week for 12 weeks	30.9	12.0	19.9	[12]
Prucalopride (2 mg o.m.)	% of patients with ≥ 3 CSBMs/week for 12 weeks	24.0	12.0	12.0	[13]
Prucalopride (2 mg o.m.)	% of patients with ≥ 3 CSBMs/week for 12 weeks	19.5	9.6	9.9	[14]
Bisacodyl (5 – 10 mg o.m.)	% of patients with ≥ 3 CSBMs/week for 1 – 4 weeks	67.4	27.4	40.0	[3]
SPS (5 – 10 mg o.m.)	% of patients with ≥ 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 (PGE_2) from macrophages, and that this PG acts as a paracrine factor and decreases aquaphorin 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

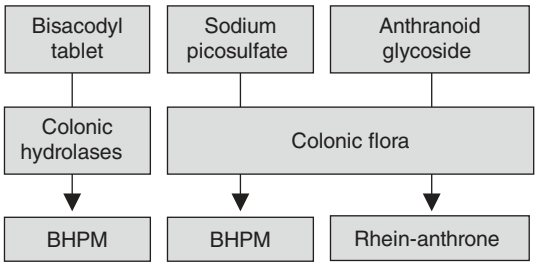

Figure 2. Activation of diphenyl methanes and anthraquinones. They are not systemically absorbed but activated only in the colon. BHPM: *bis*-(*p*-hydroxyphenyl)-pyridyl-2-methane. Only bisacodyl may be given in the form of suppositories.

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.

Melanosis 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]. Melanosis 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]. Gycerol-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.

Bibliography

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

1. Müller-Lissner SA. What has happened to the cathartic colon? Gut 1996;39:486-8
   - **Appearance and disappearance of papers on cathartic colon in comparison with papers on laxative abuse. Cathartic colon was probably produced by the neurotoxin podophyllin.**
2. Attar A, Lémann M, Ferguson A, et al. Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation. Gut 1999;44:226-30
   - **An early randomized controlled trial with macrogol.**
3. Kamm MA, Mueller-Lissner SA, Wald A, et al. Stimulant laxatives are effective in chronic constipation: multi-center, 4-week, double-blind, randomized, placebo-controlled trial of bisacodyl. Clin Gastroenterol Hepatol 2011;9:577-83
   - **The first randomized controlled trial over 4 weeks with bisacodyl.**
4. Ruidisch MH, Hutt H-J, König E. Laxanzien-Langzeittherapie mit Bisacodyl. Wirksamkeit und Verträglichkeit bei Patienten mit Rückenmarkverletzungen. Ärztliche Forschung 1994;41:3-8
5. Müller-Lissner S, Kamm MA, Wald A, et al. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of sodium picosulfate in patients with chronic constipation. Am J Gastroenterol 2010;105:897-903
   - **The first randomized controlled trial over 4 weeks with SPS.**
6. Heiny BM. Langzeitbehandlung mit einem pflanzlichen Laxativum. Serumelektrolyte und Säurenbasenhaushalt. Ärztliche Praxis 1976;28:563-4
7. Rosprich G. Dauerbehandlung mit Laxantien. Therapiewoche 1980;30:5836-7
8. Johanson JF, Ueno R. Lubiprostone, a locally acting chloride channel activator, in adult patients with chronic constipation: a double-blind, placebo-controlled, dose-ranging study to evaluate efficacy and safety. Aliment Pharmacol Ther 2007;25:1351-61
9. Johanson JF, Morton D, Geenen J, Ueno R. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. Am J Gastroenterol 2008;103:170-7
   - **One of the randomized controlled trials with lubiprostone.**
10. Lembo AJ, Johanson JF, Parkman HP, et al. Long-term safety and effectiveness of lubiprostone, a chloride channel (ClC-2) activator, in patients with chronic idiopathic constipation. Dig Dis Sci 2011;56:2639-45
11. Lee N, Wald A. The pharmacokinetics, pharmacodynamics, clinical efficacy, safety and tolerability of linaclotide. Expert Opin Drug Metab Toxicol 2011;7:651-9
    - **Expert review on linaclotide.**
12. Camilleri M, Kerstens R, Rykx A, Vandeplassche L. A placebo-controlled trial of prucalopride for severe chronic constipation. N Engl J Med 2008;358:2344-54
    - **One of the randomized controlled trials with prucalopride.**
13. Quigley EM, Vandeplassche L, Kerstens R, Ausma J. Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation – a 12-week, randomized, double-blind, placebo-controlled study. Aliment Pharmacol Ther 2009;29:315-28
14. Tack J, van Outryve M, Beyens G, et al. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. Gut 2009;58:357-65
15. Kinnunen O, Salokannel J. Constipation in the elderly long-stay patients: its treatment by magnesium hydroxide and bulk laxative. Ann Clin Res 1987;19:321-3
    - **One of the early randomized controlled trials with milk of magnesia.**
16. Aydogan T, Kanbay M, Uz B, et al. Fatal hyperphosphatemia secondary to a phospho-soda bowel preparation in a geriatric patient with normal renal function. J Clin Gastroenterol 2006;40:177
17. Bengtsson M, Ohlsson B. Retrospective study of long-term treatment with sodium picosulfate. Eur J Gastroenterol Hepatol 2004;16:433-4
18. Preston DM, Lennard-Jones JE. Severe chronic constipation of young women: 'idiopathic slow transit constipation'. Gut 1986;27:41-8
19. Kinnunen O, Salokannel J. Comparison of the effects of magnesium hydroxide and a bulk laxative on lipids, carbohydrates, vitamins A and E, and minerals in geriatric hospital patients in the treatment of constipation. J Int Med Res 1989;17:442-54
20. Tatsuki M, Miyazawa R, Tomomasa T, et al. Serum magnesium concentration in children with functional constipation treated with magnesium oxide. World J Gastroenterol 2011;17:779-83
21. Tatsumi H, Masuda Y, Imaizumi H, et al. A case of cardiopulmonary arrest caused by laxatives-induced hypermagnesemia in a patient with anorexia nervosa and chronic renal failure. J Anesth 2011;25:935-8
22. Chen H, Li X, Ge Z. Comparative study on two colonic bowel preparations for patients with chronic constipation. Scand J Gastroenterol 2009;44:375-9
23. Medoff J, Katz S, Malik P, et al. Open-label, dose-ranging pilot study of 4 weeks of low-dose therapy with sodium phosphate tablets in chronically constipated adults. Clin Ther 2004;26:1479-91
24. Kinnunen O, Winblad I, Koistinen P, Solokannel J. Safety and efficacy of a bulk-laxative containing senna versus lactulose in the treatment of chronic constipation in geriatric patients. Pharmacology 1993;47(Suppl 1):253-5
25. Wesselius-De Casparis A, Braadbaart S, et al. Treatment of chronic constipation with lactulose syrup: results of a double-blind study. Gut 1968;9:84-6
26. Lederle FA, Busch DL, Mattox KM, et al. Cost-effective treatment of constipation in the elderly: a randomized double-blind comparison of sorbitol and lactulose. Am J Med 1990;89:597-601
27. Kleessen B, Sykura B, Zunft HJ, Blaut M. Effects of inulin and lactose on fecal microflora, microbial activity, and

bowel habit in elderly constipated persons. Am J Clin Nutr 1997;65(5):1397-402

28. Lee-Robichaud H, Thomas K, Morgan J, Nelson RL. Lactulose versus polyethylene glycol for chronic constipation. Cochrane Database Syst Rev 2010(7):CD007570

29. van der Spoel JI, Oudemans-van Straaten HM, et al. Laxation of critically ill patients with lactulose or polyethylene glycol: a two-center randomized, double-blind, placebo-controlled trial. Crit Care Med 2007;35:2726-31

30. DiPiro JT, Michael KA, Clark BA, et al. Absorption of polyethylene glycol after administration of a PEG-electrolyte lavage solution. Clin Pharmacol 1986;5:153-5

31. Rothfuss KS, Bode JC, Stange EF, Parlesak A. Urinary excretion of polyethylene glycol 3350 during colonoscopy preparation. Z Gastroenterol 2006;44:167-72

32. Corazziari E, Badiali D, Bazzocchi G, et al. Long term efficacy, safety, and tolerability of low daily doses of isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in the treatment of functional chronic constipation. Gut 2000;46:522-6

33. Di Palma JA, Cleveland MV, McGowan J, et al. A randomized, multicenter, placebo-controlled trial of polyethylene glycol laxative for chronic treatment of chronic constipation. Am J Gastroenterol 2007;102:1436-41

34. Di Palma JA, Cleveland MV, McGowan J, Herrera JL. A randomized, multicenter comparison of polyethylene glycol laxative and tegaserod in treatment of patients with chronic constipation. Am J Gastroenterol 2007;102:1964-71

- **One of the rare comparative randomized controlled trials with laxatives, in that case macrogol and tegaserod.**

35. Mamtani R, Cimino JA, Cooperman JM. Comparison of total costs of administering calcium polycarbophil and psyllium mucilloid in an institutional setting. Clin Ther 1990;12:22-4

36. Hamilton JW, Wagner J, Burdick BB, Bass P. Clinical evaluation of methylcellulose as a bulk laxative. Dig Dis Sci 1988;33:993-8

37. Szojda MM, Mulder CJ, Felt-Bersma RJ. Differences in taste between two polyethylene glycol preparations. J Gastrointest Liver Dis 2007;16:379-81

- **Macrogol without electrolytes is preferable when used as a laxative.**

38. De Maeyer JH, Lefebvre RA, Schuurkes JA. 5-HT4 receptor agonists: similar but not the same. Neurogastroenterol Motil 2008;20:99-112

39. Briejer MR, Bosmans JP, Van Daele P, et al. The in vitro pharmacological profile of prucalopride, a novel enterokinetic compound. Eur J Pharmacol 2001;423:71-83

40. Briejer MR, Prins NH, Schuurkes JA. Effects of the enterokinetic prucalopride (R093877) on colonic motility in fasted dogs. Neurogastroenterol Motil 2001;13:465-72

41. Müller-Lissner S, Rykx A, Kerstens R, Vandeplassche L. A double-blind, placebo-controlled study of prucalopride in elderly patients with chronic constipation. Neurogastroenterol Motil 2010;22:991-8

42. Potet F, Bouyssou T, Escande D, Baro I. Gastrointestinal prokinetic drugs have different affinity for the human cardiac human ether-a-gogo K(+) channel. J Pharmacol Exp Ther 2001;299:1007-12

43. Boyce M, Kerstens R, Beyens G, et al. Cardiovascular safety of prucalopride in healthy subjects: results from two randomized, double-blind, placebo-controlled, cross-over trials [abstract]. Gastroenterology 2009;136(Suppl 1):T1265

44. Camilleri M, Beyens G, Kerstens R, et al. Safety assessment of prucalopride in elderly patients with constipation: a double-blind, placebo-controlled study. Neurogastroenterol Motil 2009;21:1256-e117

45. Camilleri M, Bharucha AE, Ueno R, et al. Effect of a selective chloride channel activator, lubiprostone, on gastrointestinal transit, gastric sensory, and motor functions in healthy volunteers. Am J Physiol Gastrointes Liver Physiol 2006;290:G942-7

46. Cuppoletti J, Malinowska DH, Tewari KP, et al. SPI-0211 activates T84 cell chloride transport and recombinant human ClC-2 chloride currents. Am J Physiol Cell Physiol 2004;287:C1178-83

47. Jentsch TJ, Poet M, Fuhrmann JC, Zdebik AA. Physiological functions of ClC Cl- channels gleaned from human genetic disease and mouse models. Annu Rev Physiol 2005;67:779-807

48. Ueno R, Osama H, Habe T, et al. Oral spi-0211 increases intestinal fluid secretion and chloride concentration without altering serum electrolyte levels (abstract). Gastroenterology 2004;126:A-100

49. Barish CF, Drossman D, Johanson JF, Ueno R. Efficacy and safety of lubiprostone in patients with chronic constipation. Dig Dis Sci 2010;55:1090-7

50. Castro J, Martin C, Hughes PA, et al. A novel role of cyclic GMP in colonic sensory neurotransmission in healthy and TNBS-treated mice. Gastroenterology 2011;140:S-538

51. Bryant AP, Busby RW, Bartolini WP, et al. Linaclotide is a potent and selective guanylate cyclase C agonist that elicits pharmacological effects locally in the gastrointestinal tract. Life Sci 2010;8:19-20

52. Eutamene H, Bradesi S, Larauche M, et al. Guanylate cyclase C-mediated antinociceptive effects of linaclotide in rodent models of visceral pain. Neurogastroenterol Motil 2010;22:312-22

53. Johnston JM, Kurtz CB, Drossman DA, et al. Pilot study on the effect of linaclotide in patients with chronic constipation. Am J Gastroenterol 2009;104:125-32

54. Lembo AJ, Kurtz CB, Macdougall JE, et al. Efficacy of linaclotide for patients with chronic constipation. Gastroenterology 2010;138:886-95

55. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med 2011;365:527-36

- **Two of the randomized controlled trials with linaclotide.**

56. Andresen V, Camilleri M, Busciglio IA, et al. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. Gastroenterology 2007;133:761-8

57. Johnston JM, Kurtz CB, Macdougall JE, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. Gastroenterology 2010;139:1877-86

58. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol 2012;107:1702-12

59. Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol 2012;107:1714-24

60. Hardcastle JD, Mann CV. Study of large bowel peristalsis. Gut 1968;9:512-20

•• **A very nice early experimental study in colonic motility elucidating the prokinetic effect of bisacodyl.**

61. Hardcastle JD, Wilkins JL. The action of sennosides and related compounds on human colon and rectum. Gut 1970;11:1038-42

62. Materia E, Corraziari E, Bausano G, et al. Effect of bisacodyl on motor activity of sigmoid colon. Ital J Gastroenterol 1988;20:246-9

63. Rodriguez L, Siddiqui A, Nurko S. Internal anal sphincter relaxation associated with bisacodyl-induced colonic high amplitude propagating contractions in children with constipation: a colo-anal reflex? Neurogastroenterol Motil 2012;24:1023-e545

64. Binder HJ, Donowitz M. A new look at laxative action. Gastroenterology 1975;69:1001-5

65. Ewe K, Hölker B. The effect of a diphenolic laxative (Bisacodyl) on water- and electrolyte transport in the human colon. Klin Wochenschr 1974;52:827-33

66. Ikarashi N, Baba K, Ushiki T, et al. The laxative effect of bisacodyl is attributable to decreased aquaporin-3 expression in the colon induced by increased PGE2 secretion from macrophages. Am J Physiol Gastrointest Liver Physiol 2011;301:G887-95

67. Lemli M. Metabolism of sennosides – an overview. Pharmacology 1988;36(Suppl 1):126-8

68. Marlett JA, Li BUK, Patrow CJ, Bass P. Comparative laxation of psyllium with and without senna in an ambulatory constipated population. Am J Gastroenterol 1987;82:333-7

69. Passmore AP, Wilson-Davies K, Stoker C, Scott ME. Chronic constipation in long-stay elderly patients: a comparison of lactulose and a senna-fibre combination. BMJ 1993;307:769-71

• **One of the randomized controlled trials with senna.**

70. Kinnunen O, Salokannel J. The carry-over effect on the bowel habit in elderly long-term patients of long-term bulk-forming products containing stimulant laxative. Acta Med Scand 1987;222:477-9

71. Maclennan WJ, Pooler AF. A comparison of sodium picosulphate with standardized senna in geriatric patients. Curr Med Res 1975;2:641-7

72. Willems M, van Buuren HR, de Krijger R. Anthranoid self-medication causing rapid development of melanosis coli. Neth J Med 2003;61:22-4

73. Speare GS. Melanosis coli. Experimental observations on its production and elimination in twenty-tree cases. Am J Surg 1951;82:631-7

•• **Early observations on the development and disappearance of melanosis coli.**

74. Ghadially FN, Parry EW. An electron-microscope and histochemical study of melanosis coli. J Path Bact 1966;92:313-17

75. Scott RS. Management of constipation in obstetrics: a clinical report on 592 cases. Western Med 1965;6:342-4

76. Wager HP, Melosh WD. The management of constipation in pregnancy. Quart Rev Surg 1958;15:30-4

77. Heidemann A, Miltenburger HG, Mengs U. The genotoxicity status of senna. Pharmacology 1993;47(Suppl 1):178-86

78. Cameron BD, Phillips MWA, Fenerty CA. Milk transfer of rhein in the rhesus monkey. Pharmacology 1988;36:221-5

79. Faber P, Strenge-Hesse A. Relevance of rhein excretion into breast milk. Pharmacology 1988;36(Suppl 1):212-20

80. Werthmann MW Jr, Krees S. Quantitative excretion of senokot in human breast milk. Med Am Dist Columbia 1973;42:4-5

81. Roth W. Pharmakokinetik und laxierende Wirkung von Bisacodyl nach Gabe verschiedener Zubereitungsformen. Arzneim Forsch Drug Res 1988;38:570-4

82. Kienzle-Horn S, Vix JM, Schuijt C, et al. Efficacy and safety of bisacodyl in the acute treatment of constipation: a double-blind, randomized, placebo-controlled study. Aliment Pharmacol Ther 2006;23:1479-88

83. Kienzle-Horn S, Vix JM, Schuijt C, et al. Comparison of bisacodyl and sodium picosulfate in the treatment of chronic constipation. Curr Med Res Opin 2007;23:891-9

84. Wulkow R, Vix JM, Schuijt C, et al. Randomised, placebo-controlled, double-blind study to investigate the efficacy and safety of the acute use of sodium picosulphate in patients with chronic constipation. Int J Clin Pract 2007;61:944-50

85. Nishimura M, Kast A, Tsunenari Y. Reproduction studies of sodium picosulphate. Pharmacometrics 1976;12:67-78

86. Friedrich C, Richter E, Trommeshauser D, et al. Lack of excretion of the active moiety of bisacodyl and sodium picosulfate into human breast milk: an open-label, parallel group, multiple dose study in healthy lactating women. Drug Metab Pharmacokinet 2011;26:458-64

87. Hofmann AF, Poley JR. Role of bile acid malabsorption in pathogenesis of diarrhea and steatorrhea in patients with ileal resection. I. Response to cholestyramine or replacement of dietary long chain triglyceride by medium chain triglyceride. Gastroenterology 1972;62:918-34

88. Mekjian HS, Phillips SF, Hofmann AF. Colonic secretion of water and electrolytes induced by bile acids: perfusion studies in man. J Clin Invest 1971;50:1569-77

89. Coremans G, Tack J, Vantrappen G, et al. Is the irritable bowel really irritable? Ital J Gastroenterol 1991;23(8 Suppl 1):39-40

90. Chey WD, Camilleri M, Chang L, et al. A randomized placebo-controlled phase IIb trial of A3309, a bile acid transporter

inhibitor, for chronic idiopathic constipation. Am J Gastroenterol 2011;106:1803-12

• **One of the randomized controlled trials with elobixibat.**

91. Simren M, Bajor A, Gillberg PG, et al. Randomised clinical trial: the ileal bile acid transporter inhibitor A3309 vs. placebo in patients with chronic idiopathic constipation. Aliment Pharmacol Ther 2011;34:41-50

92. Wong BS, Camilleri M, McKinzie S, et al. Effects of A3309, an ileal bile acid transporter inhibitor, on colonic transit and symptoms in females with functional constipation. Am J Gastroenterol 2011;106:2154-64

93. Rafati M, Karami H, Salehifar E, Karimzadeh A. Clinical efficacy and safety of polyethylene glycol 3350 versus liquid paraffin in the treatment of pediatric functional constipation. Daru 2011;19:154-8

94. Urganci N, Akyildiz B, Polat TB. A comparative study: the efficacy of liquid paraffin and lactulose in management of chronic functional constipation. Pediatr Int 2005;47:15-19

95. Gondouin A, Manzoni P, Ranfaing E, et al. Exogenous lipid pneumonia: a retrospective multicentre study of 44 cases in France. Eur Respir J 1996;9:1463-9

96. Hawley PH, Byeon JJ. A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. J Palliat Med 2008;11:575-81

97. McRorie JW, Daggy BP, Morel JG, et al. Psyllium is superior to docusate sodium for treatment of chronic constipation. Aliment Pharmacol Ther 1998;12:491-7

98. Tarumi Y, Wilson MP, Szafran O, Spooner GR. Randomized, double-blind, placebo-controlled trial of oral docusate in the management of constipation in hospice patients. J Pain Symptom Manage 2013;45(1):2-13

99. McRorie J, Pepple S, Rudolph C. Effects of fiber laxatives and calcium docusate on regional water content and viscosity of digesta in the large intestine of the pig. Dig Dis Sci 1998;43:738-45

100. Ashton MR, Sutton D, Nielsen M. Severe magnesium toxicity after magnesium sulphate enema in a chronically constipated child. BMJ 1990;300(6723):541

101. Hsu HJ, Wu MS. Extreme hyperphosphatemia and hypocalcemic coma associated with phosphate enema. Intern Med 2008;47:643-6

102. Mendoza J, Legido J, Rubio S, Gisbert JP. Systematic review: the adverse effects of sodium phosphate enema. Aliment Pharmacol Ther 2007;26:9-20

103. Farahmand F, Eftekhari K, Modarresi V, et al. Comparing oral route paraffin oil versus rectal route for disimpaction in children with chronic constipation; a randomized control trial. Iran J Pediatr 2010;20:291-6

104. Flig E, Hermann TW, Zabel M. Is bisacodyl absorbed at all from suppositories in man? Int J Pharm 2000;196:11-20

105. Shafe ACE, Lee S, Dalrymple JSO, Whorwell PJ. The LUCK study: laxative usage in patients with GP-diagnosed constipation in the UK, within the general population and in pregnancy. An epidemiological study using the General Practice Research Database (GPRD). Therap Adv Gastroenterol 2011;4:343-63

106. Underwood D, Makar RR, Gidwani AL, et al. A prospective randomized single blind trial of Fleet phosphate enema versus glycerin suppositories as preparation for flexible sigmoidoscopy. Ir J Med Sci 2010;179:113-18

107. Müller-Lissner SA, Kamm MA, Scarpignato C, Wald A. Myths and misconceptions about chronic constipation. Am J Gastroenterol 2005;100:232-42

•• **A thorough discussion of a series of prejudices about chronic constipation and its treatment with laxatives and other measures.**

108. Müller-Lissner S, Pehl C. Laxantiengebrauch und Zufriedenheit chronisch obstipierter Frauen – eine Umfrage bei Patientinnen und Gastroenterologen in Deutschland. Z Gastroenterol 2012;50:573-7

109. Müller-Lissner S, Tack J, Feng Y, et al. Levels of satisfaction with current chronic constipation treatment options in Europe – an internet survey. Aliment Pharmacol Ther 2012;doi: 10.1111/apt.12124; Epub ahead of print

110. Tytgat GN, Heading RC, Müller-Lissner S, et al. Contemporary understanding and management of reflux and constipation in the general population and pregnancy: a consensus meeting. Aliment Pharmacol Ther 2003;18:291-301

111. Anonymous. Prucalopride. In chronic constipation: poorly documented risks. Prescrire Int 2011;20:117-20

Affiliation

Stefan Müller-Lissner
Professor,
Park-Klinik Weissensee,
Schönstrasse 80,
13086 Berlin, Germany
Tel: +4930 96283600; Fax: +4930 96283605;
E-mail: mueli@park-klinik.com