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Currently recommended treatments of childhood constipation are not evidence based: a systematic literature review on the effect of laxative treatment and dietary measures

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ABSTRACT

Introduction: Constipation is a common complaint in children and early intervention with oral laxatives may improve complete resolution of functional constipation. However, most treatment guidelines are based on reviews of the literature that do not incorporate a quality assessment of the studies.

Objective: To investigate and summarise the quantity and quality of the current evidence for the effect of laxatives and dietary measures on functional childhood constipation.

Methods: The Medline and Embase databases were searched to identify studies evaluating the effect of a medicamentous treatment or dietary intervention on functional constipation. Methodological quality was assessed using a validated list of criteria. Data were statistically pooled, and in case of clinical heterogeneity results were summarised according to a best evidence synthesis.

Results: Of the 736 studies found, 28 met the inclusion criteria. In total 10 studies were of high quality. The included studies were clinically and statistically heterogeneous in design. Most laxatives were not compared to placebo. Compared to all other laxatives, polyethylene glycol (PEG) achieved more treatment success (pooled relative risk (RR): 1.47; 95% CI 1.23 to 1.76). Lactulose was less than or equally effective in increasing the defecation frequency compared to all other laxatives investigated. There was no difference in effect on defecation frequency between fibre and placebo (weighted standardised mean difference 0.35 bowel movements per week in favour of fibre, 95% CI -0.04 to 0.74).

Conclusion: Insufficient evidence exists supporting that laxative treatment is better than placebo in children with constipation. Compared to all other laxatives, PEG achieved more treatment success, but results on defecation frequency were conflicting. Based on the results of this review, we can give no recommendations to support one laxative over the other for childhood constipation.

Functional constipation is a common worldwide complaint in infants and children.¹ The aetiology of constipation is multi-factorial and seldom caused by structural, endocrine or metabolic disease.

Careful history taking and physical examination are usually sufficient to make a diagnosis. Criteria for a definition of functional constipation vary widely and are mostly based on a variety of

What is already known on this topic

- ▶ Constipation is a common worldwide complaint in infants and children which, if not adequately treated, may lead to faecal incontinence and subsequently to psychological problems and social isolation.
- ▶ Guidelines on the treatment of functional constipation in children are authority based rather than evidence based.

What this paper adds

- ▶ Due to a lack of placebo-controlled trials we found insufficient evidence for an effect of any one laxative or dietary treatment of childhood constipation.
- ▶ A uniform definition of functional constipation in children is urgently needed.
- ▶ Well-designed trials on the effectiveness of laxative and dietary treatment of childhood constipation still need to be performed.

symptoms, including decreased frequency of bowel movements, faecal incontinence and a change in consistency of stools.

Traditionally, treatment starts with education of the parents and children. Demystification and understanding of the problem helps to enlist cooperation and to improve compliance.² When not adequately treated, constipation in children may lead to faecal incontinence and, subsequently, to psychological problems and social isolation.³

Most guidelines for the treatment of functional constipation are based on reviews of the literature that do not apply a systematic literature search, do not incorporate quality assessment of studies, or use a language restriction.⁴⁻⁶ On the other hand, a previous Cochrane review evaluating the effect of stimulant laxatives on constipation could not include any study because of the strict inclusion criteria set by the authors.⁷

In this systematic review, we aim to investigate and summarise the quantity and quality of all current evidence for the effect of laxatives and dietary measures on functional childhood

constipation in comparison to placebo, no treatment or alternative treatments.

METHODS

The Medline and Embase databases were searched from inception to December 2007. The keywords used to describe the study population were: “constipation”, “obstipation”, “coprosthesis”, “encopresis”, and “soiling”. These words were combined with keywords referring to the different types of intervention groups that were investigated in the present review.

For the retrieval of controlled trials we used the keywords described in the Cochrane Handbook⁸ and the International Epidemiological Association.⁹ Additional strategies for identifying studies included searching the reference lists of review articles and the included studies. No language restriction was applied. The full search strategy is available from the authors.

STUDY SELECTION

Two reviewers (MP, MYB) independently screened all abstracts of identified published articles for eligibility. For this purpose, three specific criteria were used: (1) the study population consisted of children aged 0–18 years; (2) the study was a randomised controlled trial (ACT), a comparative clinical trial (CCT) or a crossover study; and (3) one of the aims of the study was to evaluate the effect of a medicamentous treatment or dietary intervention on functional constipation with or without faecal incontinence.

All potentially relevant studies, as well as the studies for which the abstracts did not provide sufficient information for inclusion or exclusion, were retrieved as full papers.

Full papers were additionally screened as to whether they fulfilled the following criteria: (4) the intervention consisted of osmotic, bulk-forming, stimulant or emollient laxatives, lubricating agents or dietary measures and were compared to placebo, no treatment or alternative treatment; and (5) outcome measures at least were either establishment of normal bowel habit (increase of defecation frequency and/or decrease of faecal incontinence frequency) or treatment success as defined by the authors of the study.

Excluded were papers concerning children with mental handicaps or psychiatric diseases (eg, eating disorders), as well as studies investigating children with organic causes of

constipation and children with exclusively non-retentive faecal incontinence.

Any disagreements regarding the inclusion of articles were resolved through consensus when possible or by arbitration of a third person (MT).

QUALITY ASSESSMENT

Two reviewers (MP and either MT or MYB) independently rated the methodological quality of the included studies using a standardised list developed for RCTs, the Delphi list¹⁰ (table 1). Disagreement between the two reviewers was resolved by consensus when possible, or a third person (MYB or MT) made the final decision.

DATA EXTRACTION

Two reviewers (MP and either MT or MYB) independently performed a structured data extraction from the original reports. Extracted information included (if available) items referring to study design, setting and participants (diagnosis, age, gender, severity of disease), as well as interventions and outcome measures. Disagreements were resolved by consensus when possible, or a third person (MYB or MT) made the final decision.

DATA ANALYSIS

The inter-assessor reliability on the methodological quality was calculated using Kappa scores.¹¹

In the present review the outcome measure was “treatment success” as defined by the authors of the included study. In addition, the establishment of normal bowel habit defined as an increase of defecation frequency and/or decrease of faecal incontinence frequency was considered as an outcome measure.

When the participants, interventions and outcome measures were sufficiently similar, data were statistically pooled using a random effects model. Heterogeneity was quantified by χ^2 , which can be interpreted as the percentage of the total variation between studies that is attributable to heterogeneity rather than to chance. A p value of less than 0.10 was used as cut-off point to indicate heterogeneity.

As most studies in this systematic review were highly diverse with regard to the participants, interventions and outcome measures, we often refrained from statistically pooling the data and used a best evidence synthesis to summarise the data. Methodological quality scores were calculated as a percentage of the maximum quality score on the Delphi list. High quality is defined as a score of $\geq 60\%$ (ie, ≥ 6 points).

In the best evidence synthesis the level of evidence was ranked^{12 13} (table 2). Studies with a small study sample (<5 children per arm) were excluded, and in this synthesis only significant associations (ie, $p < 0.05$) are considered as associated.

Table 1 The Delphi list

	Yes	No	?
Study population			
D1			
D2			
D3			
D4			
Blinding			
D5			
D6			
D7			
Analysis			
D8			
D9			
D10			

Table 2 Best evidence synthesis

1.	Strong evidence is provided by consistent findings among multiple high-quality studies
2.	Moderate evidence is provided by consistent findings among multiple low-quality studies and/or one high-quality study
3.	Limited evidence is provided by a single low-quality study
4.	Conflicting evidence is provided by inconsistent findings among multiple studies (ie, <75% of the studies reported consistent findings)
5.	No evidence is provided when no studies were found

Table 3 Study characteristics

Study, methodological quality score	Setting	Participants	Diagnosis	Interventions	Follow-up (FU) duration (n (%) loss to FU)
Banaszkiewicz <i>et al</i> 2005 ¹⁴ QS 10	Paediatric gastroenterology department	Age 2–16 years. Exclusion: enteric neuromuscular, anatomic, or metabolic diseases (established by medical history, abnormal thyroid hormone level, prior anorectal manometry, barium, or ionogram examination)	Constipation: <3 BM/week for at least 12 weeks	General: 1 ml/kg/day of 70% lactulose (in 2 doses). I: 10 ⁷ colony-forming units of <i>Lactobacillus</i> GG twice daily orally for 12 weeks. n = 43; mean (SD) age: 79 (47) mo.; M/F? C: placebo. n = 41; mean (SD) age: 65 (36) mo.; M/F?	24 weeks. Loss to FU: I: 5 (11.6), C: 3 (7.3)
Bellomo-Brandao <i>et al</i> 2003 ¹⁵ QS 5	General paediatric practice	Age not stated. Exclusion: previous/current disease affecting GI motility; history of GI subocclusive episodes; mechanical obstruction (barium enema); outlet obstruction (defecography)	Constipation: <3 BM/week; diurnal/nocturnal soiling; faecal impaction on palpation/RT; rectal anal inhibitory reflex (manometry)	General: lactulose (667 mg/ml) or magnesium hydroxide (80 mg/ml), daily dose 2 ml/kg, max. 60 ml. When no spontaneous BM after 72 h: saline glycerol enema. I: erythromycin estolate 20 g/kg/day in 4 oral doses every 6 h before meals, max. 1000 mg. n = see notes. C: placebo. n = see notes. Notes: crossover study: Group I (E-P); n = 6; mean (SD) age 9.7 (3.0) yrs; M/F: 5/1 Group II (P-E); n = 8; mean (SD) age 9.6 (3.3) yrs; M/F: 6/2	8 weeks. Loss to FU: 7/14 (50)
Berg <i>et al</i> 1983 ¹⁶ QS 1	General paediatric practice	Age not stated. Children referred to one of the authors with soiling as main complaint. Exclusion: not stated	Uncomplicated functional faecal incontinence indicated by initial assessment and physical examination	General: behavioural treatment. I: Senokot tablets, starting with 1 tablet. If no improvement on the next visit, then increase of dosage to 2 tablets. If still no improvement on the next visit, the dosage was increased to 3 tablets. Tablets were stopped when defecation was regular and there was no soiling. n = 14; age?: M/F?: C1: placebo tablets, see intervention. n = 11; age?: M/F?: C2: no medication. n = 15; age?: M/F?: Notes: mean (SD) total age: 7.9 (2.3) yrs	Variable; up to 12 months. Loss to FU at 12 months: I: 5 (36), C: 2 (18). C2: 6 (40)
Bongers <i>et al</i> 2007 ¹⁷ QS 8	Paediatric gastroenterology department	Age 3–20 weeks. Healthy, receiving at least 2 bottles of milk-based formula a day. Exclusion: Hirschsprung's disease, spinal or anal anomalies, previous colonic surgery, metabolic, cerebral and renal abnormalities, laxative treatment at enrolment	Constipation: at least one of the following: <3 BM/week, painful defecation (crying), or an abdominal or rectal palpable mass	I: new formula with high concentration of sn-2 palmitic acid, a mixture of prebiotic oligosaccharides and partially hydrolysed whey protein (Nutrilon Omneo). n = 18; median age 1.8 (1.1–5.0) mo.; M/F 11/7. C: standard formula (Nutrilon 1). n = 20; median age 1.7 (0.7–3.7) mo.; M/F 8/12. Notes: originally designed as crossover study, but because of large loss to FU, only the first treatment period was analysed	3 weeks. Loss to FU: 3/38 (7.9). Loss to FU after 6 weeks (original crossover concept, see notes): 24/38 (37)
Bu <i>et al</i> 2007 ¹⁹ QS 8	General paediatric practice	Age 0–10 years. Exclusion: children with organic causes of constipation such as Hirschsprung's disease, spina bifida (occulta), hypothyroidism or other metabolic or renal abnormalities, mental retardation, use of drugs influencing GI function other than laxatives	Constipation: <3 BM/week for >2 months and one of the following: anal fissures with bleeding, faecal soiling, passage of large and hard stools	General: lactulose use (1 ml/kg/day in case of no stool passage for 3 days); glycerin enema was used in case of no stool passage for >5 days or abdominal pain due to fecal impaction. I: lactobacillus casei rhamnosus (Lcr35) 8 × 10 ⁷ colony-forming units/day (Antibiophilus 250 mg, 2 capsules, Laboratoires Lyocentre, France). n = 18; mean (SD) age: 36.7 (14.5) mo.; M/F 10/8. C1: magnesium oxide 50 mg/kg/day. n = 18; mean (SD) age: 32.4 (13.9) mo.; M/F 9/9. C2: matching placebo (starch in content). n = 9; mean (SD) age: 35 (14.7) mo.; M/F 4/5	4 weeks. Loss to FU: 4/45 (8.8)

Continued

Table 3 Continued

Study, methodological quality score	Setting	Participants	Diagnosis	Interventions	Follow-up (FU) duration (n (%)) loss to FU
Candy <i>et al</i> 2006 ²⁰ QS 6	Paediatric gastroenterology department	Age 2–11 yrs. Children with intractable constipation that had failed to respond to conventional treatment who were admitted and successfully treated for faecal impaction. Exclusion: contraindication for the use of PEG+E or lactulose	Faecal impaction: definition not stated	General: additional treatment with senna if the response to study treatment was judged inadequate by the investigator. I: PEG+E: starting with half the dosage required for disimpaction per day (13.8 g powder per sachet, dissolved in 125 ml water), n = 28; mean (SD) age 5.8 (2.5) yrs; M/F 17/11. C: lactulose: starting with half the dosage required for disimpaction per day (10 g per sachet, dissolved in 125 ml water), n = 30; mean (SD) age 5.6 (2.8) yrs; M/F 22/8	12 weeks. Loss to FU: I: 1/28 (3). C: 4/30 (13)
Castillejo <i>et al</i> 2006 ²¹ QS 8	Paediatric gastroenterology department	Age 3–10 yrs. Referred for chronic constipation between January 2004 and April 2005. Exclusion: faecal impaction that required enemas in the week before the study, treatment with fibre, laxatives or bulk-forming agents in the 2 weeks prior to the study, organic cause of constipation, renal insufficiency, hypocalcaemia, hyperkalaemia, or metabolic disease at start of the study, long-term use of drugs that affect GI motility, inability to adhere to the study's medication or procedures	Chronic constipation: Rome II criteria	General: standardised toilet training (toilet sitting after each meal, positive motivational reinforcement). I: a cocoa husk supplement (sachet of 5.2 g soluble powder with 4 g cocoa husk and 1 g betafructosans: 3–6 yrs; one sachet before lunch and one before dinner; 7–10 yrs: 2 before lunch and dinner dissolved in 200 ml whole milk), n = 28; mean (SD) age 6.6 (2.3) yrs; M/F 11/17. C: placebo: sachet of 5.2 g soluble powder with glucose, cocoa flavouring and excipients. n = 28; mean (SD) age 6.0 (2.1) yrs; M/F 11/17	4 weeks. Loss to FU: I: 4/28 (14). C: 4/28 (14)
Chao <i>et al</i> 2007 ²² QS 1	Paediatric gastroenterology department	Age 2–6 months. Exclusion: not stated	Constipation: definition not stated	I: magnesium-enriched infant formula (Novafac-IT), n = 47; mean (SD) age 3.9 (1.6) mo.; M/F 24/23. C: 20% strengthened infant formula. n = 46; mean (SD) age 3.8 (1.5) mo.; M/F 23/23	8 weeks. Loss to FU: 0
Dupont <i>et al</i> 2005 ²³ QS 4	Not stated	Age 6 mo. to 3 yrs ambulatory. Exclusion: history of intractable faecaloma or organic GI disease or other neurological, endocrine, metabolic disorders, allergic diseases or allergies	Constipation: <1 BM/day for >1 mo. (age 6–12 mo.); or <3 BM/week for >3 mo. (age 13 mo. to 3 yrs)	General: in case of unsuccessful maximum dose (8 g/day for PEG; 6.66 g/day for lactulose) 1 micro-enema (glycerol) per day was given (max. 3 consecutive days). In case of no defecation, 2 enemas were given in a 48 h interval (max. 2 during the study). I: PEG 4000 4 g/sachet. Starting dose: 1 pair of sachets (1 with PEG 4000 and 1 with placebo). In children 13 mo.–3 years the dose could be doubled if ineffective. If liquid stools are produced for more than 1 day, or more than 2–3 stools/day, the dose could be decreased by 1 pair of sachets/day to a min. of 1 pair every other day and possibly to transitory interruption. n = 51; median age 28 mo.; M/F: 22/29. C: Lactulose 3.33 g/sachet. See above. n = 45; median age 25.8 mo.; M/F: 29/25	84 days. Loss to FU: I: 11 (21.6). C: 9 (20.0)

Continued

Table 3 Continued

Study, methodological quality score	Setting	Participants	Diagnosis	Interventions	Follow-up (FU) duration (n (%)) loss to FU
Greense <i>et al</i> 2002 ²⁵ OS 2	Paediatric gastroenterology department	Age 2–16 yrs. Referred for subspecialty evaluation of constipation. Exclusion: organic diseases of the large and small intestine; known allergy to PEG or lactulose; previous GI surgery; renal or heart failure; bowel obstruction; ileus; pregnancy; lactation; galactosaemia; diabetes mellitus	Constipation: definition not stated	I: PEG 3350 (Miralax, Braintree Laboratories, Inc, Braintree, Massachusetts) 10 g/m ² /d orally for 2 weeks followed by the other agent for 2 weeks. n = see notes. C: lactulose 1.3 g/kg/day orally for 2 weeks followed by the other agent for 2 weeks. n = see notes. Notes: crossover study. Characteristics of analysed children: n = 37; mean (SD) age 7.8 (3.7) yrs; M/F: 23/14	4 weeks. Loss to FU: 7/44 (15.9)
Halabi <i>et al</i> 1999 ²⁶ OS 5	Paediatric gastroenterology department	Age 4–18 yrs. Children with constipation, adequate documentation, and good patient compliance. Exclusion: small or large bowel organic disease	Constipation: pain, difficulty in defecation, or ≤ 3 BM/week for >3 months	General: clearance of accumulated impacted stool by using lactulose alone or in combination with enema cleansing. I: cisapride syrup 0.3 mg/kg four times a day (Janssen UK) for 8 weeks. Analysed: n = 32; mean (SD) age 8.45 (2.42) yrs; M/F: 18/14. C: placebo (a matching syrup) for 8 weeks. Analysed: n = 32; mean (SD) age 8.26 (2.43) yrs; M/F: 19/13	10 weeks. Loss to FU: 9/79 (11)
Heij <i>et al</i> 1990 ²⁷ OS 5	General paediatric practice	Age not stated. Relatively compact faeces and difficulties at defaecation. Exclusion: not stated	Definition not stated	I: Milk formula "Blue Allomin" with 4% lactulose (5.2 g/l milk) (no other food). n = 109; age: 7.1 wks (1–23); M/F ? C: 2% lactulose (2.6 g/l milk) in the Blue Allomin formula (no other food). n = 111; age: 6.8 (1–26) weeks; M/F? Notes: "dose finding"	2 weeks. Loss to FU: 48/220 (21.8)
Loening-Baucke 2002 ²⁸ OS 3	General paediatric practice	Age ≥ 4 yrs. Referred to and newly evaluated by the author for functional constipation and encopresis. Exclusion: children who refused the toilet for stooling but who had no constipation, children with Hirschsprung's disease, chronic intestinal pseudo-obstruction, or previous surgery of colon or anus	Constipation: delay or difficulty in defecation, and encopresis (≥ 1 /week) for >1 year	I: Miralax (PEG) beverage 17 g dissolved in 240 ml. Initial dose was 0.5 g/kg/day for children with full rectums but no abdominal masses and no history of long intervals between huge BMs. Initial dose was 1 g/kg/day for those with palpable abdominal faecal masses or history of infrequent huge BMs. Large doses were divided in 2 daily doses. Adjustment by 30 ml every 3 days to a dosage that results in 1–2 soft BMs/day and prevents soiling and abdominal pain. n = 28; mean (SD) age 8.7 (3.6) yrs. M/F: 20/8. C: milk of magnesia. Initial dose was 1 ml/kg for children with rectal faecal masses only at initial evaluation or no history of infrequent large BMs. 2.5 ml/kg was given to those who had palpable abdominal faecal masses or history of infrequent huge BMs. Large doses were divided in 2 daily doses. To be adjusted by 7.5 ml every 3 days to a dosage that results in 1–2 soft BMs/day and prevents soiling and abdominal pain. n = 21; mean (SD) age: 7.3 (3.0) yrs; M/F: 17/4. Notes: comparative clinical trial	12 months. Loss to FU: ?

Continued

Table 3 Continued

Study, methodological quality score	Setting	Participants	Diagnosis	Interventions	Follow-up (FU) duration (n (%))	loss to FU
Loening-Baucke <i>et al</i> 2004 ³⁰ QS 5	General paediatric practice	Age >4 yrs. Chronic functional constipation for ≥ 6 mo. with or without encopresis. Exclusion: children with Hirschsprung's disease, hypothyroidism, mental deficiency, chronic debilitating disease or neurological abnormalities or children who had previous surgery of the colon or anus	Constipation: a delay or difficulty in defecation for > 2 weeks, sufficient to cause significant distress to the child, not attributable to organic and anatomic causes or intake of medication	I: Glucosmannan (Dicoform, Rome, Italy), equal to 450 mg of alimentary fibre (4 wks). Given as 100 mg/kg/day (max. 5 g/day), rounded to the nearest 500 mg. Each capsule was either sprinkled on food given with 50 ml of fluid per capsule, or given as a solution (mixed with 50 ml of fluid), or swallowed as a capsule with 50 ml of fluid. n = see notes. C: placebo (maltodextrins) (Dicoform, Rome, Italy). Administration: see above. n = see notes. Notes: crossover study: Group I (P-G): n = 19; age?; M/F?. Group II (G-P): n = 27; age?, M/F?	8 weeks. Loss to FU: 15/46 (32)	
Loening-Baucke <i>et al</i> 2006 ³¹ QS 4	General paediatric practice	Age ≥ 4 yrs. Referred for treatment of functional constipation with faecal incontinence. Exclusion: stool toileting refusal, faecal incontinence without constipation, previous refusal of one of the study medications, children who came from far away for a second opinion, and children with Hirschsprung's disease, chronic intestinal pseudo-obstruction, or previous surgery	Functional constipation: ≥ 2 of the following for at least 8 wks: < 3 BM/wk, > 1 faecal incontinence/wk, large stools in rectum, passing of large stools obstructing the toilet, retentive posturing	General: at first visit disimpaction with 1 or 2 phosphate enemas if necessary. Dosage of study medication was adjusted to reach 1 or 2 stools of milkshake consistency/day. I: 0.7 g/kg body weight PEG daily in 1 solution of 2 g/30 ml. n = 39; mean (SD) age 8.0 (2.8) yrs; M/F 31/8. C: 2 ml/kg body weight milk of magnesia daily. n = 40; mean (SD) age 8.2 (3.1) yrs; M/F 34/6	12 months loss to FU: 5/39 (12.8). C: 19/40 (47.5)	
Ni <i>et al</i> 2001 ³⁴ QS 3	General paediatric practice	Age 1–7 yrs. Exclusion: underlying diseases such as hypothyroidism, hyperparathyroidism, spinal and anal anomalies or mental retardation and those taking medications which might affect the efficacy. Concomitant use of macrolide antibiotics,azole antifungals, HIV protease inhibitors of nefazodone. Patients failing to complete the 4-wk treatment	Constipation: < 2 BM/week for at least 1 mo.	I: MgO (125 mg 3 times/day for patients weighing < 20 kg, or 250 mg 3 times/day for those > 20 kg) plus cisapride syrup (0.2 mg/kg) three times a day. Analysed children: n = 44; mean (SD) age 3.31 (1.68) yrs; M/F: 24/20. C: MgO (125 mg 3 times/day for patients weighing < 20 kg, or 250 mg 3 times/day for those > 20 kg). Analysed children: n = 40; mean (SD) age 3.46 (1.47) yrs; M/F: 27/13	4 weeks. Loss to FU: 128 (31)	

Continued

Table 3 Continued

Study, methodological quality score	Setting	Participants	Diagnosis	Interventions	Follow-up (FU) duration (n (%)) loss to FU
Nolan <i>et al</i> 1991 ³⁵ OS 4	General paediatric practice	Age 4–16 yrs. Encopresis, evidence of stool on plain abdominal radiograph, attendance at normal school. Exclusion: severe or prolonged constipation necessitating previous hospital admissions for enemas and other treatments; neuromuscular disorders (spina bifida, cerebral palsy, muscular dystrophy); Hirschsprung's disease; use of purgatives for at least 2 wks before baseline assessment	Encopresis: definition not stated	I: laxative therapy: disimpaction: 3-day cycles of 5 ml microlax enemas on day 1, one 5 mg bisacodyl supp after school and one in the evening on day 2, and a 5 mg bisacodyl tablet after school and one in the evening on day 3, up to four cycles; maintenance phase: agarol 5–30 ml once or twice a day, semia granules, and/or bisacodyl tablets (doses were adjusted to maintain at least daily stools); standard paediatric behaviour modification intervention (see below) n = 83; age?; M/F: 55/28. C: standard paediatric behaviour modification intervention: clarification of the postulated underlying physiological basis for encopresis; bowel training programme with possible reinforcement for successful defecation in the toilet and additional reinforcement for every 24 h without soiling; regular sitting programme (5–10 min after each meal); dietary advice, general counseling and support by paediatrician; psychiatric assessment when necessary. n = 86; age?; M/F: 69/17	12 months. Loss to FU: I: 4/83 (4.8). C: 3/86 (3.4)
Nurko <i>et al</i> 2000 ³⁶ OS 6	Paediatric gastroenterology department	Age 2–16 yrs. History of chronic constipation referred for evaluation, and <3 BMs/week. Exclusion: Hirschsprung's disease, congenital abnormalities of the GI tract, pelvic floor dyssynergia	Constipation: <3 BMs/week	General: disimpaction: hypertonic phosphate enemas, semia. I: Cisapride: orally (suspension of 1 mg/ml (Janssen Pharmaceutics, Mexico City)) at 0.2 mg/kg/dose 3 times a day. The dose was increased after 8 wks if there was no clinical response. Max. dose was 10 mg 3 times a day. Analysed: n = 17; mean (SD) age 63 (7.4) mo.; M/F 12/5. C: placebo (see above). Analysed: n = 19; mean (SD) age 75 (9.7) mo.; M/F 12/7	12 weeks Loss to FU: I: 3/20 (15%). C: 1/20 (5%)
Perkin 1977 ³⁷ OS 3	General practice	Age 0–15 yrs. Attending surgery with a history of constipation treated at home for 3 mo. or more; understanding and agreeing to the completion of the patient diary card. Exclusion: requirement of surgical or medical correction (other than laxative)	Constipation: definition not stated	I: lactulose 10–15 ml daily. n = see notes. C: semia syrup 10–20 ml daily. n = see notes. Notes: crossover study: Group I (L-S): n = 11; age?; M/F?: Group II (S-L): n = 9; age?:; M/F?:	3 weeks. Loss to FU: 1/21 (4.7)

Continued

Table 3 Continued

Study, methodological quality score	Setting	Participants	Diagnosis	Interventions	Follow-up (FU) duration (n (%) loss to FU)
Sondheimer <i>et al</i> 1981 ⁴⁰ QS 3	Paediatric gastroenterology department/constipation clinic	Age 3–13 yrs. Referred to a clinic for chronic functional constipation. Exclusion: neurological impairment or faecal soiling in absence of stool retention	Chronic functional constipation: diagnosis based on historical features and a physical exam (dilated rectum, excessive retained stool directly within the anal verge, evidence of perianal soiling)	General: initial catharsis: 5-day course of oral bisacodyl, some combined with a daily enema for 3–5 days. I: mineral oil orally twice daily in doses sufficient to induce loose stools and leakage of oil per rectum. After week 1 the dose was reduced until oil leakage ceased. This dose was maintained for a min. of 3 mo. If symptom control was satisfactory at 3 mo., the daily volume of oil was gradually reduced. n = 19; mean (SD) age 6.3 (2.5) yrs; M/F: 13/6. C: Senokot (tablet or syrup) in doses sufficient to induce at least 1 BM/day during the first 2 wks. After 3 mo. tapering was done by changing from daily to every other day and then every third day. n = 18; mean (SD) age 8.1 (2.6) yrs; M/F: 13/5	6 months. Loss to FU: I: 1/19 (5.2). C: 0%
Thomson <i>et al</i> 2007 ⁴² QS 7	General paediatric practice	Age 2–11 years. Exclusion: current or previous faecal impaction, previous intestinal perforation or obstruction, paralytic ileus, toxic megacolon, Hirschsprung's disease, severe inflammatory conditions, severe gastroesophageal reflux, diabetes, or use of high doses of stimulant laxatives with no effect	Constipation for ≥ 3 months: < 3 BM/week, pain at defecation for $\geq 25\%$ of the days, and $\geq 25\%$ of the BMs with straining and hard or lumpy stools	General: 1 week run-in period, in which previously used laxative treatment was continued. I: PEG+E 6.9 g powder per sachet, dissolved in 62.5 ml tap water (age-specific dose) for 2 weeks. C: matching placebo. Notes: crossover study: Group I (PEG-placebo): n = 27; mean (SD) age 5.3 (2.4) yrs; M/F: 13/14. Group II (placebo-PEG): n = 24; mean (SD) age 5.5 (2.9) yrs; M/F: 9/15	7 weeks (including run-in and washout periods). Loss to FU: 2/51 (4)
Tolia <i>et al</i> 1993 QS 4	Paediatric gastroenterology department	Age > 2 yrs. Normal growth and development. Exclusion: Hirschsprung's disease, history of recurrent vomiting and/or aspiration, central nervous system problems or known history of liver, kidney and heart disease	Constipation: infrequent, large, firm to hard stools, rectal pain or bleeding, small amounts of stool daily, incomplete stool evacuation, periodic passage of large amounts of stool, faecal impaction	I: pineapple-flavoured, balanced oral lavage solution containing PEG 3350 (sweetened with Nutra-sweet) in the dose of 20 ml/kg/h for 4 h once daily on 2 consecutive days (max. amount/h: 1 l), and a single oral dose of metoclopramide (0.1 mg/kg) to prevent nausea and vomiting. n = 19; mean (SD) age 6.44 (2.36) yrs; M/F: 12/7. C: 2–8 tablespoons of mineral oil in two divided doses for 2 days (≈ 30 ml/10 kg bodyweight), blended with 120–180 ml of orange juice. n = 17; mean (SD) age 6.88 (3.26) yrs; M/F: 11/6	2 days. Loss to FU: I: 6/23 (26). C: 6/25 (24)
Urganci <i>et al</i> 2005 ⁴⁴ QS 3	Paediatric gastroenterology department	Age 2–12 yrs. Referred for chronic constipation with evidence of faecal impaction. Exclusion: Hirschsprung's disease, hypothyroidism, mental deficiency, chronic debilitating diseases, neurological abnormalities, previous surgery of colon	Constipation: ≥ 2 of the following for ≥ 3 mo.: hard stools, painful defecation, rectal bleeding, encopresis, < 3 BM/week	General: increase of fibre intake: "age+10" in grams. I: lactulose orally (suspension of 1 ml/kg), twice daily. Dose is adapted by 25% every 3 days as is required to yield two firm loose stools per day. Max. dose is 3 ml/kg/day. n = 20; mean (SD) age 43.7 (31.3) mo.; M/F: 10/10. C: liquid paraffin orally (suspension of 1 ml/kg) twice daily. Adaptation of dose/max. dose: see above. n = 20; mean (SD) age 46.1 (36.4) yrs; M/F: 12/8	8 weeks. Loss to FU: 0

Continued

Table 3 Continued

Study, methodological quality score	Setting	Participants	Diagnosis	Interventions	Follow-up (FU) duration (n (%) loss to FU)
Voskuil <i>et al</i> 2004 ⁴⁶ QS 7	Paediatric gastroenterology department	Age 6 mo–5 yrs. Exclusion: organic causes for defecation disorders, including Hirschsprung's disease, spina bifida occulta, or hypothyroidism	Constipation: ≥ 2 of the following symptoms for the last 3 mo.: < 3 BM/week; encopresis > 1 /week; large amounts of stool every 7–30 days; palpable abdominal or rectal mass on physical examination	General: one enema daily for 3 days to clear any rectal faecal remains (≥ 6 yrs 60 ml Klyx; > 6 yrs 120 ml Klyx). Toilet training after each meal. I: PEG 3350 (6 mo–6 yrs: 1 sachet/day = 2.95 g) (> 6 yrs: 2 sachets/day = 5.9 g). After 1 week the dose was doubled in case of insufficient effect; or halved in case of diarrhoea. n = 50; mean (SD) age 6.5 (3.2) yrs; M/F 27/23. C: lactulose (6 mo–6 yrs: 1 sachet/day = 6 g) (> 6 yrs: 2 sachets/day = 12 g). After 1 week the dose was doubled in case of insufficient effect; or halved in case of diarrhoea. n = 50; mean (SD) age 6.5 (3.4) yrs; M/F 28/22	8 weeks of treatment; 26 weeks of FU. Loss to FU: I: 4/50 (8). C: 5/50 (10)
Wald <i>et al</i> 1987 ⁴⁷ QS 3	General paediatric practice	Age not stated. Encopresis for at least 6 mo. Description of participants in a previous study (Wald 1986). Exclusion: not stated	Encopresis: definition not stated	I: biofeedback: children with an abnormal expulsion pattern were taught a technique to normalise their patterns and they and children with normal expulsion pattern were told to use the technique whenever they attempted to defecate. n = 24; age 8.3 (6–15) yrs; M/F 20/4. C: mineral oil in graded amounts (1–4 tablespoons a day). n = 26; age 8.4 (6–13) yrs; M/F 20/6	I: 12 months. Loss to FU: 10/50 (20)
Wang <i>et al</i> 2007 ⁴⁸ QS 7	General paediatric practice	Age 8–18 years. Children with Bristol stool score I, II or III, informed consent. Exclusion: children with digestive organic diseases or systemic diseases, treatment 1 week previous to inclusion	Constipation: decrease of bowel movement frequency, dry stools, difficult and painful bowel movements, usually with crying and refusal of defecation, affecting appetite and quality of life	I: PEG (Forlax), 20 g/day orally. n = 105; mean (SD) age 11.3 (2.8) yrs; M/F 43/26. C: lactulose 15 g/day in the first 3 days, then 10 ml/day, orally. n = 111; mean (SD) age 11.2 (2.75) yrs; M/F 47/64	2 weeks. Loss to FU: 25/216 (11.6)
Youssef <i>et al</i> 2002 ⁴⁹ QS 7	Paediatric gastroenterology department	Age 3–18 yrs. Evidence of faecal impaction. Exclusion: previous gastrointestinal surgery; allergy/sensitivity to PEG solution or phosphates; signs or symptoms suggestive of obstruction	Faecal impaction: palpable mass in the left lower abdomen and/or a dilated rectum filled with a large amount of hard stool on rectal exam	I1: PEG 3350 in 0.25 g/kg/day. n = 10; mean (SD) age 7.9 (2.5) yrs; M/F 7/3 I2: PEG 3350 in 0.5 g/kg/day. n = 10; mean (SD) age 5.7 (1.7) yrs; M/F 7/3 I3: PEG 3350 in 1.0 g/kg/day. n = 10; mean (SD) age 7.8 (2.9) yrs; M/F 8/2 I4: PEG 3350 in 1.5 g/kg/day. n = 10; mean (SD) age 8.6 (2.9) yrs; M/F 7/3 max. dose: 100 g daily. Notes: "dose finding"	5 days. Loss to FU: 1/41 (2.4)
Zoppi <i>et al</i> 1988 ⁵⁰ QS 3	Not stated	Age not stated. Exclusion: evidence of anatomical disorders; encopresis/soiling; laxative use; pharmacological treatment for 2 mo. prior to entry; presence of infectious diseases	Functional chronic constipation: stool frequency $< 1/48$ h and hard stool consistency	General: balanced diet supplying an amount of energy of 80 kcal/kg/day in accordance with age. I: calcium polycarbophil orally (dosage 0.62/g 3 times/day). n = 14, age?; M/F? C: matching placebo. n = 14; age?; M/F? Notes: mean (SD) total age 9.5 (3.0) yrs; total M/F: 16/12	1 month. Loss to FU: 0%

BM, bowel movement; C, control intervention; GI, gastrointestinal; I, intervention under study; loss to FU, loss to follow-up; M/F, male/female; PEG, polyethylene glycol; QS, quality score; RT, rectal toucher, rectal digital exam.

RESULTS**Study selection**

The search strategy resulted in a total of 736 titles and abstracts. After the eligibility screening, 37 publications met our inclusion criteria. After reading the full-text articles, nine studies were additionally excluded.^{18 24 28 32 33 38 39 41 45}

Table 3 presents the characteristics of the 28 included studies; there were 21 RCTs, 1 CCT²⁶ and 6 crossover studies.^{15 17 25 30 37 42}

All randomised controlled trials and the comparative controlled trial were hospital based, of which nine were conducted at a general paediatric department^{16 19 27 29 31 33 35 47 48} and 11 were conducted in a paediatric gastroenterology department^{14 20-22 26 36 40 43 44 46 49}; two RCTs did not define a setting.^{23 50} Of the crossover studies four were hospital based, of which two were conducted at a general paediatric department^{15 30} and two were conducted in a paediatric gastroenterology department.^{17 25} Only one study was primary care based.³⁷

A total of 1912 children with constipation were included. The sample size of the studies ranged from 14¹⁵ to 220.²⁷

Methodological quality assessment

The reviewers initially agreed on 85% of the quality items. The inter-observer reliability of the methodological quality assessment (0.70) was high.

The most prevalent shortcomings of the studies were: no concealment of treatment allocation (n = 18 (61%)); no similarity between the intervention groups regarding the most important prognostic indicators (ie, age, sex, duration of disease, severity of disease) (n = 20 (71%)); no blinding of outcome assessor (n = 16 (57%)) and no intention-to-treat analysis (n = 21 (75%)). The overall methodological quality had a mean score of 4.8 (range RCTs 1–10; CCT 3; crossover studies 2–8). Only 10 studies (36%) had a score of ≥ 6 points indicating a good methodological quality.

Heterogeneity

Clinical diversity in the studies included with regard to participants, diagnosis, interventions and outcome measures presented, was large. The lack of a uniform outcome measure made a formal meta-analysis impossible. Most studies, however, reported on either treatment success or defecation frequency. Although the definition of treatment success differed substantially between studies, all studies presented treatment success as the percentage of successfully treated children. We therefore statistically pooled results on treatment success for the comparisons between polyethylene glycol (PEG) and any other laxative, and between PEG and lactulose. In case the presentation of the effect on defecation frequency was comparable we pooled the results on the effect on the number of bowel movements (cisapride compared with placebo and fibre compared with placebo). For all other comparisons, a best evidence synthesis was performed to summarise the results.

Laxatives and dietary measures

The results of the included studies that were analysed in the present review and the results of the best evidence synthesis are presented in tables 4 and 5.

PEG compared with placebo

Only one high-quality study⁴² investigated the effect of PEG in comparison with placebo. Compared with placebo, PEG was more effective in increasing defecation frequency (mean treatment difference 1.64 (95% CI 0.99 to 2.28)). For decrease

in faecal incontinence episodes, no significant differences were found (mean treatment difference 0.15 (ns)).

PEG compared with other laxatives

Eight studies comparing PEG to another laxative were included. Of these, one study reported on defecation frequency only.²⁰ The other seven all reported on treatment success^{23 25 29 31 43 46 48} (pooled risk ratio (RR) 1.47 (95% CI 1.23 to 1.76) (χ^2 17.89, $p < 0.0001$)). The number needed to treat (NNT) is 4.0 (95% CI 6.0 to 2.9).

PEG compared with lactulose

Five studies^{20 23 25 46 48} compared the efficacy of PEG with lactulose. Four of these five studies reported on treatment success^{25 46 48} and the number of children with soft or normal stools.²³ All four studies showed that PEG was more effective than lactulose with regard to these outcome measures (pooled RR for treatment success 1.63 (95% CI 1.40 to 1.90) (χ^2 38.95, $p < 0.0001$)). When treating children with constipation 3.3 children need to be treated with PEG in order to get one more treatment success in comparison to treatment with lactulose (95% CI 4.5 to 2.6).

All five studies^{20 23 25 46 48} evaluated the effect on defecation frequency. Three studies scored as high quality.^{20 46 48} One high-quality study²⁰ and one low-quality study²⁵ found PEG to be superior to lactulose in increasing the number of bowel movements. Two high-quality studies^{46 48} and one low-quality study²³ reported no significant difference between PEG and lactulose (conflicting evidence).

Youssef *et al* performed a high-quality, dose-finding study. They compared different doses of PEG (0.25, 0.5, 1.0 and 1.5 g/kg/day) and found that doses of 1.0 and 1.5 g/kg/day were more effective in achieving disimpaction than lower doses.⁴⁵

Lactulose

In addition lactulose was compared to other laxatives in two low-quality studies. Perkin *et al*³⁷ compared lactulose to senna and found no significant difference in defecation frequency between the two treatments (limited evidence). Urganci *et al*⁴⁴ found lactulose to be less effective compared to liquid paraffin in increasing the defecation frequency (limited evidence).

Based on all the studies on lactulose, we found conflicting evidence for an effect of lactulose on defecation frequency in comparison with PEG, liquid paraffin, and senna with lactulose being less than or equally effective.

In a low-quality, dose-finding study on lactulose, Hejl *et al*²⁷ investigated the effect of a milk formula with either 4% or 2% lactulose. They reported no significant differences between the two doses regarding all outcome measures.

Cisapride

Cisapride, a prokinetic agent, has been withdrawn from the market because of cardiovascular adverse events. Nevertheless, we found two studies comparing the effect on defecation frequency of cisapride with placebo.^{26 36} Nurko *et al* performed a high-quality study and reported no significant difference between cisapride and placebo.³⁶ In a low-quality study Halabi *et al* found cisapride to be more effective compared to placebo.²⁶

Pooling the data resulted in a weighted, standardised mean difference of 4.0 bowel movements per week in favour of cisapride (95% CI 0.38 to 7.64) (χ^2 4.69, $p < 0.05$).

Table 4 Results of the included studies used in our review

Study (quality)	Intervention	Control intervention	Outcome measure	Results	Efficacy
a: PEG compared to placebo					
Thomson <i>et al</i> 2007 ⁴² (HQ)	PEG+E, starting dose: <7 yrs 6.9 g/day, 7–11 yrs 13.8 g/day	Placebo	Mean defecation frequency/week	Mean (SD) I: 3.12 (2.05). Mean (SD) C: 1.45 (1.2) (p<0.001)	More effective ns
			Faecal incontinence	Mean (SD) I: 4.70 (6.3). Mean (SD) C: 4.85 (7.9)	
b: PEG compared to lactulose					
Candy <i>et al</i> 2006 ²⁰ (HQ)	PEG+E, starting with half the dosage required for disimpaction/day	Lactulose, starting with half the dosage required for disimpaction/day	Mean defecation frequency/week	Mean (SD) I: 9.4 (4.6). Mean (SD) C: 5.9 (4.3) (p = 0.007)	More effective
Voskuil <i>et al</i> 2004 ⁴⁶ (HQ)	PEG 3350, starting dose <6 yrs 2.95 g/day, >6 yrs 5.9 g/day	Lactulose, starting dose <6 yrs 6 g/day, >6 yrs 12 g/day	Mean defecation frequency/week	Mean (SD) I: 7.1 (5.1). Mean (SD) C: 6.4 (5.2) (p = 0.505)	ns
Dupont <i>et al</i> 2005 ²³ (LQ)	PEG 4000, starting dose 4 g/day	Lactulose, starting dose 3.33 g/day	Treatment success (≥3 BMs/week and no soiling)	I: 31/50 (63%). C: 23/50 (47%) (p = 0.013)	More effective
			Median defecation frequency/week	I: 8.5 (range 7.5–12.5) in babies, 7 (5–8) in toddlers. C: 11.5 (9–13) in babies, 6 (4–7) in toddlers	ns
			Children with soft/normal stools	I: 44/47 (93.6%). C: 29/40 (72.5%) (p = 0.008)	More effective
Gremse <i>et al</i> 2002 ²⁵ (LQ)	PEG 3350, 10 g/m ² /day	Lactulose, 1.3 g/kg/day	Mean defecation frequency/2 weeks	Mean (SD) I: 14.8 (1.4). Mean (SD) C: 13.5 (1.5) (p<0.05)	More effective
			Global assessment of treatment success	I: 31/37 (84%). C: 17/37 (45.9%) (p = 0.002)	More effective
Wang <i>et al</i> 2007 ⁴⁸ (HQ)	PEG 4000, 20 g/day	Lactulose, 15 g/day	Median defecation frequency/week	I: 7. C: 6. I: 76/105 (72%)	ns
			Children in clinical remission of constipation	C: 45/111 (41%) (p<0.01)	More effective
c: PEG compared to other laxatives					
Tolia <i>et al</i> 1993 ⁴³ (LQ)	PEG 3350, 20 ml/kg/h	Mineral oil, 30 ml/10 kg	Children with >1 BM after treatment	I: 17/19 (89%). C: 12/17 (71%) (p<0.005)	More effective
Loening-Baucke 2002 ²⁹ (LQ)	PEG 3350, starting dose 0.5 or 1 g/kg/day	Milk of magnesia, starting dose 1 or 2.5 ml/kg/day	Treatment success (≥3 BMs/week and ≤2 soiling episodes per month)	I: 17/28 (61%). C: 14/21 (67%) (p = 0.67)	ns
Loening-Baucke <i>et al</i> 2006 ³¹ (LQ)	PEG 3350, 0.7 g/kg body weight PEG daily	Milk of magnesia, 2 ml/kg body weight daily	Improvement (≥3 BMs/week and ≤2 soiling episodes/month; no abdominal pain)	I: 24/39 (62%). C: 17/40 (43%) (p = 0.086)	ns
d: Lactulose compared to other laxatives					
Perkin 1977 ³⁷ (LQ)	Lactulose, 10–15 ml/day	Senna, 10–20 ml/day	Mean defecation frequency/week	Mean (SD) I: 18.1 (2.0). Mean (SD) C: 17.1 (1.5) (p = 0.075)	ns
Urganci <i>et al</i> 2005 ⁴⁴ (LQ)	Lactulose, starting dose 1 ml/kg twice/day	Liquid paraffin, starting dose 1 ml/kg twice/day	Mean defecation frequency/week	Mean (SD) I: 12.3 (6.6). Mean (SD) C: 16.1 (2.2) (p<0.05)	less effective
e: Cisapride					
Halabi <i>et al</i> 1999 ²⁶ (LQ)	Cisapride	Placebo	Mean defecation frequency/week	Mean (SD) I: 6.7 (0.9). Mean (SD) C: 1.3 (0.9) (p<0.0001)	More effective
Ni <i>et al</i> 2001 ³⁴ (LQ)	Cisapride, 0.2 mg/kg 3 dd + MgO 125 or 250 mg 3 times/day	Magnesium oxide, 125 or 250 mg 3 times/day	Children with ≥3 BMs/week	I: 40/44 (91%). C: 27/40 (67%) (p = 0.013)	More effective
Nurko <i>et al</i> 2000 ³⁶ (HQ)	Cisapride, 0.2 mg/kg/dose 3 times/day	Placebo	Mean defecation frequency/week	Mean (SD) I: 4.1 (1.1). Mean (SD) C: 2.2 (0.6) (p>0.05)	ns
f: Senna					
Berg <i>et al</i> 1983 ¹⁸ (LQ)	Senna, starting dose one tablet	Placebo (C1), starting dose one tablet. No medication (C2)	Relief of soiling (on a 4-point scale indicating frequency of soiling)	I: 5/14 (55%). C1: 7/11 (64%) p = 0.16. C2: 6/15 (66%) (p = 0.81)	ns
Perkin 1977 ³⁷ (LQ)	Senna, 10–20 ml/day	Lactulose, 10–15 ml/day	Mean defecation frequency/week	Mean (SD) I: 17.1 (1.5). Mean (SD) C: 18.1 (2.0) (p = 0.075)	ns
Sondheimer <i>et al</i> 1981 ⁴⁰ (LQ)	Senna, in doses sufficient to induce 1 BM/day	Mineral oil, twice/day in doses sufficient to induce loose stools rectal oil leakage	Children with daily BMs	I: 9/18 (50%). C: 16/19 (89%) (p<0.05)	Less effective

Continued

Table 4 Continued

Study (quality)	Intervention	Control intervention	Outcome measure	Results	Efficacy
g: Mineral oil					
Sondheimer <i>et al</i> 1981 ⁴⁰ (LQ)	Mineral oil, twice/day in doses sufficient to induce loose stools rectal oil leakage	Senna, in doses sufficient to induce 1 BM/day	Children with daily BMs	I: 16/19 (89%). C: 9/18 (50%) (p<0.05)	More effective
Tolia <i>et al</i> 1993 ⁴³ (LQ)	Mineral oil, 30 ml/10 kg	PEG 3350, 20 ml/kg/h	Children with >1 BM after treatment	I: 12/17 (71%). C: 17/19 (89%) (p<0.005)	Less effective
Wald <i>et al</i> 1987 ⁴⁷ (LQ)	Mineral oil 1–4 tablespoons/day	Biofeedback	Children with <1 soiling episode/week	I: 13/26 (50%). C: 14/24 (60%) (p = 0.47)	ns
h: Fibre					
Castillejo <i>et al</i> 2006 ²¹ (HQ)	Cocoa husk supplement (fibre), 3–6 yrs: two sachets (= 8 mg)/day; 7–10 yrs: four sachets (= 16 mg)/day	Placebo, 3–6 yrs: two sachets/day; 7–10 yrs: four sachets/day	Mean defecation frequency/week	Mean (SD) I: 6.2 (3.3). Mean (SD) C: 5.1 (2.1) (p = 0.78)	ns
Loening-Baucke <i>et al</i> 2004 ³⁰ (LQ)	Glucomanan (fibre), 100 mg/kg/day	Placebo (maltodextrins), 100 mg/kg/day	Mean defecation frequency/week	Mean (SD) I: 4.5 (2.3). Mean (SD) C: 3.8 (2.2) (p = 0.139)	ns
i: Laxatives investigated in one single study					
Banaszkiewicz <i>et al</i> 2005 ¹⁴ (HQ)	Lactobacillus GG, 10 ⁹ colony-forming units twice/day +70% lactulose 1 ml/kg/day	Placebo +70% lactulose, 1 ml/kg/day	Mean defecation frequency/week at 12 weeks	Mean (SD) I: 6.1 (1.8). Mean (SD) C: 6.8 (3.1) (p = 0.5)	ns
Bellomo-Brandao <i>et al</i> 2003 ¹⁵ (LQ)	Erythromycine estolate, 20 g/kg/day	Placebo	Improvement of constipation (based on stool frequency, soiling, faecal impaction, faecal consistency and pain at stool passage)	End phase 1: mean (SD) E-P: 2.2 (1.0). Mean (SD) P-E: 2.9 (2.8). End phase 2: mean (SD) E-P: 4.3 (2.3). Mean (SD) P-E: 2.4 (2.1) (E vs P: p = 0.006)	More effective
Bongers <i>et al</i> 2007 ¹⁷ (HQ)	New formula with high concentration of sn-2 palmitic acid, a mixture of prebiotic oligosaccharides and partially hydrolysed whey protein (Nutrilon Omneo)	Standard formula (Nutrilon 1)	Mean defecation frequency/week	Mean (SD) I: 5.6 (2.8). Mean (SD) C: 4.9 (2.5) (p = 0.36)	ns
			Improvement of hard to soft stools	Mean (SD) I: 9/10 (90%). Mean (SD) C: 5/10 (50%) (p = 0.14)	ns
Bu <i>et al</i> 2007 ¹⁹ (HQ)	<i>Lactobacillus casei rhamnosus</i> (Lcr35), 8 × 10 ⁹ colony-forming units/day	Magnesium oxide (C1), 50 mg/kg/day. Placebo (C2)	Mean defecation frequency/day	Mean (SD) I: 0.6 (0.2). Mean (SD) C1: 0.5 (0.1) (p = 0.77). Mean (SD) C2: 0.4 (0.1) (p = 0.006)	ns
Chao <i>et al</i> 2007 ²² (LQ)	Magnesium-enriched infant formula (Novalac-IT)	20%-strengthened infant formula	Improvement of constipation (based on stool consistency, frequency and volume, and defecation difficulties)	I: 42/47 (89%). C: 25/46 (54%) (p<0.001)	More effective
Nolan <i>et al</i> 1991 ³⁵ (LQ)	Senna and/or bisacodyl and/or agarol	Standard paediatric behaviour modification	Treatment success	I: 42/83 (51%). C: 31/86 (36%) (p = 0.079)	ns
Zoppi <i>et al</i> 1998 ⁵⁰ (LQ)	Calcium polycarboxophil, 0.62/g 3 times/day	Placebo	Children with disappearance of constipation (1 BM/day, soft stools)	I: 6/14 (43%). C: 0/14 (0%) (p ≤ 0.01)	More effective

BM, bowel movement; C, control intervention; HQ, high methodological quality; I, intervention under study; LQ, low methodological quality; ns, not significant.

One low-quality study that investigated cisapride added to magnesium oxide found this combination to be more effective than magnesium oxide alone (limited evidence).³⁴

Senna

In total, three low-quality studies reported on the effect of senna on constipation. Sondheimer *et al* compared senna with mineral oil and found senna to be less effective in increasing daily bowel movements (limited evidence).⁴⁰

Berg *et al* compared senna to placebo and no medication. They found no significant differences in effect in decreasing the number of faecal incontinence episodes per week between the groups (limited evidence).¹⁶

Perkin *et al* used lactulose as comparison and reported no significant differences in effect on defecation frequency (limited evidence).³⁷

In conclusion, based on all the included studies on senna, we found conflicting evidence for the effect of senna compared to placebo, no medication, mineral oil or lactulose, with senna being less than or equally effective.

Mineral oil

Three low-quality studies reported on the effect of mineral oil on the number of bowel movements and episodes of faecal incontinence.^{40 43 47} Of these, two used a different laxative as control intervention, that is, PEG⁴³ and senna,⁴⁰ and one study used biofeedback therapy as control intervention.⁴⁷ Wald *et al* found no significant difference in the number of children with <1 faecal incontinence episode per week, between mineral oil and biofeedback therapy (limited evidence).⁴⁷

Sondheimer *et al* reported that mineral oil resulted in more children with daily bowel movements compared with senna

Table 5 Best evidence syntheses of comparisons made by more than one of the included studies

Intervention	Control intervention	Outcome measure	Study	Methodological quality	Results	Evidence*
PEG	Placebo	Defecation frequency	Thomson ⁴²	HQ	More effective	Moderate evidence Conflicting evidence
		Defecation frequency	Voskuiji ⁴⁶ Candy ²⁰	HQ HQ	ns More effective	
	Lactulose	Defecation frequency	Wang ⁴⁸	HQ	ns	
			Dupont ²³	LQ	ns	
			Gremse ²⁵	LQ	More effective	
Lactulose	Senna	Defecation frequency	Perkin ³⁷	LQ	ns	Conflicting evidence
	Liquid paraffin	Defecation frequency	Urganci ⁴⁴	LQ	Less effective	
Senna	Lactulose	Defecation frequency	Perkin ³⁷	LQ	ns	Conflicting evidence
	Mineral oil	Defecation frequency	Sondheimer ⁴⁰	LQ	Less effective	
	Placebo and no medication	Faecal incontinence frequency	Berg ¹⁶	LQ	ns	
Mineral oil	Biofeedback therapy	Faecal incontinence frequency	Wald ⁴⁷	LQ	ns	Conflicting evidence
	Senna	Defecation frequency	Sondheimer ⁴⁰	LQ	More effective	
	PEG	Defecation frequency	Tolia ⁴³	LQ	Less effective	

*Evidence for an effect of the intervention under study compared to all control interventions.

HQ, high methodological quality; LQ, low methodological quality; ns, not significant polyethylene glycol.

(limited evidence),⁴⁰ and Tolia *et al* found mineral oil to be less effective compared with PEG for children having more than one bowel movement per day after treatment (limited evidence).⁴⁵

Based on all studies on mineral oil, we found conflicting evidence for the effect of mineral oil compared to PEG, senna or biofeedback therapy, with mineral oil being less than, more or equally effective.

Erythromycin estolate

Bellomo-Brandao *et al* compared the effect of erythromycin estolate with the effect of placebo in a low-quality study. They found erythromycin estolate to be more effective than placebo in improving constipation (limited evidence).¹⁵

Calcium polycarbophil

Zoppi *et al* performed a low-quality study and found calcium polycarbophil to be more effective than placebo in clearing constipation in children (limited evidence).⁵⁰

Laxative therapy

In a low-quality study Nolan *et al*⁵⁵ compared laxative therapy (ie, Microlax and senna and/or bisacodyl and/or agarol) with standard paediatric behaviour modification. They reported no significant differences between the two treatment groups with regard to a decrease in stool retention (limited evidence).

Infant formula with sn-2 palmitic acid

In their high-quality study Bongers *et al* found no difference in the defecation frequency of children treated with a new infant formula with a high concentration of sn-2 palmitic acid, a mixture of prebiotic oligosaccharides and partially hydrolysed whey protein (Nutrilon Omneo), and children treated with a standard infant formula (moderate evidence).¹⁷

Fibre

In one high-quality study²¹ the effect of a cocoa husk supplement on the defecation frequency was investigated, and in a low-quality study³⁰ the effect of glucomannan was investigated. In both studies fibre was compared to placebo, and both found no statistical significant difference in defecation frequency between the treatment groups. The pooled weighted standardised mean difference was 0.35 bowel movements per week in favour of fibre (95% CI -0.04 to 0.74) (χ^2 3.11, $p < 0.10$), which is neither significant, nor clinically relevant.

DISCUSSION

Laxatives used in daily clinical practice are insufficiently tested against placebo in the case of children. This may be because laxatives have already proven to be effective in adults, or because it may be considered unethical to conduct placebo-controlled studies among children. However, these arguments do not hold, when considering that constipation usually has a different aetiology in adults compared with children, and it should be considered unethical to treat children without prior evidence for a beneficial effect of this treatment.

Compared to all other laxatives, the percentage treatment success was higher in children treated with PEG (pooled RR 1.47 (95% CI 1.23 to 1.76) (χ^2 17.89, $p < 0.0001$)).

Clinical and statistical heterogeneity between studies was large and the overall methodological quality of the 28 included studies was poor. Only 10 studies were of high methodological quality.

The major drawback of these studies is the lack of a uniform definition of childhood constipation and treatment success, making the results difficult to compare. In addition, the definition of functional constipation varies over time and between authors. Only defecation frequency was consistently

reported in all studies; however, we are fully aware that it is not sufficient to quantify constipation only in terms of number of stools per week. How outcome can affect the results of our review is illustrated by the case of PEG; whereas PEG was found to be more effective on "treatment success" when compared with lactulose, this could not be demonstrated for an effect on the number of bowel movements.

In order to perform proper studies on the effect of an intervention for childhood constipation, a uniform definition is urgently needed. In 1999 experts in the field of paediatric gastroenterology reached the first consensus on defining childhood constipation.⁵³ In 2006 the definition for childhood constipation was redefined since several studies showed that the earlier criteria were too restrictive and excluded several groups of children with constipation.^{51 52} All these definitions are based on constipation seen in referred children. However, because most children with constipation are seen in primary care, the definitions also need to be validated in primary care.

STUDY LIMITATIONS

As in every systematic review, there is a risk that not all relevant studies are included. To minimise this risk, we performed a sensitive literature search without language restrictions.

A large number of outcome measures have been analysed in the included studies. Because it was not feasible to present all these results, we have analysed and presented those outcomes only that enabled a comparison between the studies. In a best evidence synthesis, bias may occur due to misclassification of the methodological quality of the studies. However, because the quality scores of the individual studies were low, that misclassification of an item would not have changed the classification into a high or a low methodological quality.

Only significant effects were assumed to be effective in our best evidence synthesis; this assumption may misclassify the results of studies with a small sample size. Most comparisons were evaluated in only one study, and the methodological quality was low; consequently the level of evidence for the effect of an intervention was low.

The chi-squared test used to detect statistical heterogeneity is of limited value since there are very few studies in the meta-analyses, which imply a low power of this test. For this reason, a p value of less than 0.10 is used to indicate heterogeneity rather than the conventional cut-off point of 0.05.

COMPARISON WITH PREVIOUS REVIEWS

Only Price *et al*⁷ performed a systematic review of the literature; they aimed to investigate the effect of stimulant laxative treatment in children with chronic constipation, however, none of the studies found complied with their strict criteria. Although most guidelines provide a review of available studies, none of these reviews provide a summary of the quantity and quality of all current evidence based on a systematic search of the literature. Guidelines on the treatment of functional constipation in children are therefore authority based rather than evidence based.

IMPLICATIONS FOR PRACTICE

There is insufficient evidence to support that laxative treatment of childhood constipation is better than placebo. In comparison to other laxatives, however, PEG is more effective in achieving treatment success. Because of the heterogeneity between the included studies this result should be interpreted with caution. Based on the results of this review we cannot give a

recommendation to support one laxative over the other for childhood constipation. Given the lack of evidence for differences in effect of laxatives, adverse effects play an important role in the choice of a laxative.

Two guidelines on the management of childhood constipation were recently published.^{4 5 6} The main shortcoming of these guidelines was the lack of a systematic review of the available evidence.⁵⁴ Therefore it remains unclear whether the recommendations of the guidelines are based on personal conviction of the guideline committee or on scientific evidence. Our systematic review of the literature reveals that there is insufficient evidence to recommend one laxative above the other. In future guidelines this can be stated. This will make it clear that recommendations will be based on personal experience and consensus rather than scientific evidence. In addition it will be evident that all available experience should be consulted; this includes experience from primary care. In the guideline committees thus far primary care was under represented.

FUTURE RECOMMENDATIONS

For future research we recommend large, well-designed, placebo-controlled, randomised trials that evaluate the effect of laxatives (especially PEG and lactulose) on functional constipation in children. Since most children with constipation will first consult their general practitioner, these studies should also be performed in general practice. A well-defined and uniform definition of functional constipation is urgently needed. Dose-finding studies in children are needed in case of the introduction of new laxatives and, since adverse effects may play an important role in the choice of a laxative, it is also necessary to investigate their side effects.

CONCLUSION

Due to a lack of placebo-controlled trials we found insufficient evidence for an effect of any one laxative or dietary treatment of childhood constipation. Although, PEG achieved more treatment success compared to all other laxatives, the results on defecation frequency were conflicting. Based on the results of this review we cannot give a recommendation to support one laxative over the other for childhood constipation.

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respectively.³ Hospital admissions during the same time period totalled approximately 350 and 530 for varicella and zoster, respectively; hospitalisation was most common for those aged <4 years old.³

Of the mothers interviewed, just over 30% (61/200) were aware of the availability of an effective vaccine. Women of childbearing age are an at-risk population and should be a target group for immunisation. Also, the vaccine is available in Ireland upon request and parents may choose to administer to their child. This information needs to be disseminated to parents principally via public health clinics and general practitioner practices.

Mothers interviewed were from a cross-section of Irish society (table 1). Education level varied, the majority agreeing to partake had completed at least secondary level education, 70% had completed some form of third-level education. Willingness to comply with vaccination policies varied according to social grouping. It is generally accepted that women of a higher educational background are more questioning of vaccination policies while those of lower income tend to be more trusting of health-care providers.⁴ The majority of mothers (91%) would have agreed to have their child vaccinated were universal recommendations in place despite socioeconomic or educational grouping, with most willing to pay independently of insurance status.

The most useful information obtained from this study was that if the varicella vaccine were introduced, according to the figures obtained from this study, 91% of mothers interviewed would vaccinate their child, with the possibility of another 4% (table 3). Despite the small numbers interviewed, there was a cross-section of society sampled, and if given the option, the majority would have been happy for their child to be immunised with this safe and effective vaccine.

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CORRECTION

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Pijpers MAM, Tabbers M, Benninga MA, *et al*. Currently recommended treatments of childhood constipation are not evidence based. A systematic literature review on the effect of laxative treatment and dietary measures. *Arch Dis Child* 2009;**94**: 117–31.

Two errors were noticed by the authors in their systematic review of the literature on treatment of childhood constipation. These errors did not affect the study's conclusions. Here is the corrected data. Corrections are in *italics*.

Table 4b PEG compared to lactulose

Study (quality)	Intervention	Controlle intervention	Outcome measure	Results	Efficacy
Gremse <i>et al</i> ²³ , 2002 (LQ)	PEG 3350, 10 g/m ² /day	Lactulose, 1.3 g/kg/day	Mean defecation frequency/2 weeks	I: 14.8 ± 1.4 C: 13.5 ± 1.5 (p < 0.05)	More effective
			Global assessment of treatment succes	I: 31/37 (84%) C: 17/37 (45.9%) (p = 0.002)	More effective

Table 4i Laxatives investigated in one single study

Study (quality)	Intervention	Controlle intervention	Outcome measure	Results	Efficacy
Bongers <i>et al</i> ¹⁵ , 2007 (HQ)	New formula with high concentration of sn-2 palmitic acid, a mixture of prebiotic oligosaccharides and partially hydrolysed whey protein (Nutrilon Omneo)	Standard formula (Nutrilon 1)	Mean defecation frequency/week	I: 5.6 ± 2.8 C: 9 ± 2.5 (p = 0.36)	Not significant
			Improvement of hard to soft stools	I: 9/10 (90%) C: 5/10 (50%) (p = 0.14)	Not significant