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Osmotic and stimulant laxatives for the management of childhood constipation (Review)

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TABLE OF CONTENTS

Evid.-Based Child Health **8:1**: 57–109 (2013)

[Intervention Review]

Osmotic and stimulant laxatives for the management of childhood constipation

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ABSTRACT

Background

Constipation within childhood is an extremely common problem. Despite the widespread use of osmotic and stimulant laxatives by health professionals to manage constipation in children, there has been a long standing paucity of high quality evidence to support this practice.

Objectives

We set out to evaluate the efficacy and safety of osmotic and stimulant laxatives used to treat functional childhood constipation.

Search methods

The search (inception to May 7, 2012) was standardised and not limited by language and included electronic searching (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Group Specialized Trials Register), reference searching of all included studies, personal contacts and drug companies.

Selection criteria

Randomised controlled trials (RCTs) which compared osmotic or stimulant laxatives with either placebo or another intervention, with patients aged 0 to 18 years old were considered for inclusion. The primary outcome was frequency of defecation. Secondary endpoints included faecal incontinence, disimpaction, need for additional therapies and adverse events.

Data collection and analysis

Relevant papers were identified and the authors independently assessed the eligibility of trials. Methodological quality was assessed using the Cochrane risk of bias tool.The Cochrane RevMan software was used for analyses. Patients with final missing outcomes were assumed to have relapsed. For continuous outcomes we calculated a mean difference (MD) and 95% confidence interval (CI) using a fixed-effect model. For dichotomous outcomes we calculated an odds ratio (OR) and 95% confidence intervals (95% CI) using a fixed-effect model. The chi square and I^2 statistics were used to assess statistical heterogeneity. A random-effects model was used in situations of unexplained heterogeneity

Main results

Eighteen RCTs (1643 patients) were included in the review. Nine studies were judged to be at high risk of bias due to lack of blinding, incomplete outcome data and selective reporting. Meta-analysis of two studies (101 patients) comparing polyethylene glycol (PEG) with placebo showed a significantly increased number of stools per week with PEG (MD 2.61 stools per week, 95% CI 1.15 to 4.08). Common adverse events in the placebo-controlled studies included flatulence, abdominal pain, nausea, diarrhoea and headache. Meta-analysis of 4 studies with 338 participants comparing PEG with lactulose showed significantly greater stools per week with PEG (MD 0.95 stools per week, 95% CI 0.46 to 1.44), although follow up was short. Patients who received PEG were significantly less likely to require additional laxative therapies. Eighteen per cent of PEG patients required additional therapies compared to 30% of lactulose patients (OR 0.49, 95% CI 0.27 to 0.89). No serious adverse events were reported with either agent. Common adverse events in these studies included diarrhoea, abdominal pain, nausea, vomiting and pruritis ani. Meta-analysis of 3 studies with 211 participants comparing PEG with milk of magnesia showed that the stools/wk was significantly greater with PEG (MD 0.69 stools per week, 95% CI 0.48 to 0.89). However, the magnitude of this difference is quite small and may not be clinically significant. One child was noted to be allergic to PEG, but there were no other serious adverse events reported. Meta-analysis of 2 studies with 287 patients comparing liquid paraffin (mineral oil) with lactulose revealed a relatively large statistically significant difference in the number of stools per week favouring paraffin (MD 4.94 stools per week, 95% CI 4.28 to 5.61). No serious adverse events were reported. Adverse events included abdominal pain, distention and watery stools. No statistically significant differences in the number of stools per week were found between PEG and enemas (1 study, 90 patients, MD 1.00, 95% CI -1.58 to 3.58), dietary fibre mix and lactulose (1 study, 125 patients, P = 0.481), senna and lactulose (1 study, 21 patients, P > 0.05), lactitol and lactulose (1 study, 51 patients, MD -0.80, 95% CI -2.63 to 1.03), and PEG and liquid paraffin (1 study, 158 patients, MD 0.70, 95% CI -0.38 to 1.78).

Authors' conclusions

The pooled analyses suggest that PEG preparations may be superior to placebo, lactulose and milk of magnesia for childhood constipation. GRADE analyses indicated that the overall quality of the evidence for the primary outcome (number of stools per week) was low or very low due to sparse data, inconsistency (heterogeneity), and high risk of bias in the studies in the pooled analyses. Thus, the results of the pooled analyses should be interpreted with caution because of quality and methodological concerns, as well as clinical heterogeneity, and short follow up. However, PEG appears safe and well tolerated. There is also evidence suggesting the efficacy of liquid paraffin (mineral oil), which was also well tolerated.There is no evidence to demonstrate the superiority of lactulose when compared to the other agents studied, although there is a lack of placebo controlled studies. Further research is needed to investigate the long term use of PEG for childhood constipation, as well as the role of liquid paraffin.

PLAIN LANGUAGE SUMMARY

Laxatives for the management of childhood constipation

Constipation within childhood is an extremely common problem. Despite the widespread use of laxatives by health professionals to manage constipation in children, there has been a long standing lack of evidence to support this practice.This review included eighteen studies with a total of 1643 patients that compared nine different agents to either placebo (inactive medications) or each other. The results of this review suggest that polyethylene glycol preparations may increase the frequency of bowel motions in constipated children. Polyethylene glycol was generally safe, with lower rates of minor side effects compared to other agents. Common side effects included flatulence, abdominal pain, nausea, diarrhoea and headache. There was also some evidence that liquid paraffin (mineral oil) increased the frequency of bowel motions in constipated children and was also safe. Common side effects with liquid paraffin included abdominal pain, distention and watery stools. There was no evidence to suggest that lactulose is superior to the other agents studied, although there were no trials comparing it to placebo. The results of the review should be interpreted with caution due to methodological quality and statistical issues in the included studies. In addition, these studies were relatively short in duration and so it is difficult to assess the long term effectiveness of these agents for the treatment of childhood constipation. Long term effectiveness is important, given the often chronic nature of this problem in children.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

PEG versus placebo for the management of childhood constipation

Patient or population: patients aged 0 to 18 years with a diagnosis of functional constipation
Settings: outpatient
Intervention: PEG versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	PEG versus placebo				
Frequency of defecation (mean number of bowel movements per week)	The mean number of bowel movements ranged across the placebo groups from **1.6 to 2.4** per week	The mean number of bowel movements in the PEG group was on average **2.61 higher** per week (95% CI 1.15 to 4.08)		101 (2 studies)	⊕⊕◯◯ **low**[1,2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Sparse data (101 patients)
[2] Inconsistency (moderate statistical heterogeneity $I^2 = 58\%$)

BACKGROUND

Description of the condition

Constipation within childhood is an extremely common problem (Van den Berg 2006), representing the chief complaint in 3% of visits to general paediatric clinics and as many as 30% of visits to paediatric gastroenterologists (Partin 1992). The term functional constipation is used when no underlying organic cause can be identified for the symptoms. Creating a workable diagnostic classification for functional constipation has proven difficult. Criteria vary, but are mostly based on a variety of symptoms, including decreased frequency of bowel movements, faecal incontinence and a change in consistency of stools (Pijpers 2008).

A team of paediatricians met in 1997 in Rome to standardize the diagnostic criteria for various functional gastroenterological disorders in children. The first paediatric Rome II criteria were published in 1999 (Rasquin-Weber 1999) and were updated during the Rome III process in 2006, producing guidance for functional constipation for neonates, toddlers and children (Hyman 2006; Rasquin 2006).

To diagnose constipation using the Rome III criteria, at least two of the symptoms below must be present for at least one month in infants and children up to age four and at least two months in children over four, with insufficient criteria for the diagnosis of irritable bowel syndrome:

- Two or fewer defecations per week;
- At least one episode per week of incontinence after the acquisition of toileting skills;
- History of retentive posturing or excessive voluntary stool retention (over 4 years) or excessive stool retention (under 4 years);
- History of painful or hard bowel movements;
- Presence of a large faecal mass in the rectum; and
- History of large diameter stools which may obstruct the toilet.

Effective management of childhood functional constipation depends on securing a therapeutic alliance with the parents, particularly through the first years when children cannot accurately report symptoms. Clinicians depend on the reports and interpretations of the parents, who know their child best, and their own training and experience to differentiate between health and illness (Hyman 2006).

Description of the intervention

Laxative therapies are often the mainstay of medical therapy used in children suffering with functional constipation, alongside adjuvant therapies such as dietary and behavioural modification. Osmotic laxatives, such as lactulose, milk of magnesia and polyethylene glycol (PEG), are usually supplied as solutions or powders to be dissolved in water and are therefore relatively easy to administer to young children. Stimulant laxatives, such as Senna and Bisacodyl, come in a variety of forms, including tablets, liquids, and suppositories.

How the intervention might work

Osmotic laxatives are poorly absorbed in the gut. They act as hyperosmolar agents, increasing water content of stool and therefore making stool softer and easier to pass, as well as increasing colonic peristalsis. Stimulant laxatives act on the intestinal mucosa, increasing water and electrolyte secretion. They also stimulate peristaltic action.

Why it is important to do this review

Despite the widespread use of these medications by health professionals to manage constipation in children, there has been a long standing paucity of high quality evidence to support this practice. Previous efforts have been made to produce guidance on this topic (Baker 1999; Anonymous 2006), most recently by the National Institute for Health and Clinical Excellence in the UK (Anonymous 2010).

In recent years, the widespread introduction of PEG to paediatric practice has led to a resurgence in research on paediatric constipation. Some studies have suggested that polyethylene glycol has greater efficacy when compared with placebo (Thomson 2007), as well as when compared to lactulose (Voskujl 2004; Candy 2006). A recently published Cochrane review investigated the specific comparison of PEG versus lactulose (Lee-Robichaud 2010) in children and adults. There currently exists no other systematic review using the Cochrane collaboration format for the use of osmotic laxatives in children. A previous Cochrane review evaluating the effect of stimulant laxatives on constipation in children found no studies of sufficient quality to allow evaluation (Price 2001). An up to date systematic review using the Cochrane Collaboration format is indicated to summarise the current evidence on the use of osmotic and stimulant laxatives for the management of constipation in children.

OBJECTIVES

The primary objectives are to evaluate the efficacy and safety of osmotic and stimulant laxatives used to treat functional childhood constipation.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials were considered for inclusion.

Types of participants

Patients aged 0 to 18 years with a diagnosis of functional constipation, with or without incontinence were considered for inclusion. The diagnosis of constipation was patient self-reported, physician diagnosed, or by consensus criteria (e.g. Rome III). Studies with patients suffering from any underlying pathology, such as thyroid abnormalities, Hirschsprung's disease or having undergone previous bowel surgery at study entry, were excluded.

Types of interventions

Studies comparing osmotic or stimulant laxatives with another intervention or placebo were considered for inclusion. All preparations and dosing regimes were considered. Studies using multiple osmotic or stimulant laxative combinations or combinations of both as their intervention were also considered for inclusion.

Types of outcome measures

Primary outcomes

The primary outcome measure was the frequency of defecation (number of stools per week).

Secondary outcomes

Secondary outcomes included:
1) Faecal incontinence;
2) Disimpaction;
4) Need for additional therapies; and
5) Adverse events.

Search methods for identification of studies

Electronic searches

A. Electronic searching
The following electronic databases were searched for relevant studies:
1. MEDLINE (1966 to May 7, 2012; National Library of Medicine, Bethesda, USA)
2. EMBASE (1984 to May 7, 2012; Elsevier Science, New York, USA)
3. Cochrane Central Register of Controlled Trials
4. Cochrane Inflammatory Bowel Disease and Functional Bowel Disorder Group Specialized Trials Register

The search strategy was not limited by language.
MEDLINE on PUBMED will be searched using the following search strategy:
#1 Constipation
#2 Constipation [MeSH]
#3 faecal impaction OR impaction
#4 delayed bowel movement
#5 obstipation
#6 costiveness
#7 retention
#8 defecation
#9 bowel function*
#10 bowel habit*
#11 bowel movement*
#12 bowel symptom*
#13 bowel motility
#14 colon transit
#15 evacuation
#16 intestinal motility
#17 stool*
#18 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19 Polyethylene glycol*
#20 macrogol*
#21 PEG
#22 polyethylene glycol 3350
#23 polyethylene glycol 4000
#24 Miralax OR Transipeg OR Movicol OR Forlax OR Idrolax OR GoLytely OR PMF-100 OR Golitely OR Nulitely OR Fortans OR TriLyte OR Colyte OR lactulose OR disaccharide OR Apo-Lactulose OR Chronulac OR lactitol OR sorbitol OR Generlac OR Cephulac OR Cholac OR Constilac OR Enulose OR cilac OR Heptalac OR Actilax OR Duphalac OR Kristalose OR milk of magnesia OR magnesium hydroxide OR Magnesium citrate OR citroma OR Osmoprep OR Visicol
#25 senna OR docusate sodium OR Sodium picosulphate OR Bisacodyl OR Cascara OR casanthranol OR Buckthorn OR senokot OR Aloe Vera OR aloin Phenolphthalein OR Dulcolax
#26 laxative*
#27 stimulant
#28 osmotic
#29 #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
#30 For
#31 Treat OR Treatment
#32 Therapy
#33 Efficacy
#34 management OR manage

#35 #30 OR #31 OR #32 OR #33 OR #34
#36 Children OR child
#37 Child [MeSH]
#38 Paediatric
#39 Adolescent
#40 Infant
#41 Neonat*
#42 Toddler
#43 Pediatric
#44 Young
#45 Childhood
#46 #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45
#47 #18 AND #29 AND #35 AND #46
Similar search strategies, but modified appropriately, and using the above keywords were used to search the other electronic databases listed above.
There is some evidence that data from abstracts can be inconsistent with data in published articles (Pitkin 1999), therefore abstract publications were not included in this review.

Searching other resources

B. Reference searching
The references of all identified studies were inspected for more trials.
C. Personal contacts
Leaders in the field were contacted to try to identify other studies.
D. Drug companies
The manufacturers of osmotic and stimulant laxative agents were contacted for additional data.

Data collection and analysis

All identified abstracts and results from searches were reviewed by two authors (MG and KN). If the reference appeared relevant, a full copy of the study was obtained.

Selection of studies

Two authors (MG and KN), after reading the full texts, independently assessed the eligibility of all trials identified based on the inclusion criteria above. Disagreement among authors was discussed and agreement reached by consensus.

Data extraction and management

A data extraction form was developed and piloted to extract information on relevant features and results of included studies. The two reviewers separately extracted and recorded data on the predefined checklist.
Extracted data included the following items:
a. characteristics of patients: age, sex, duration of symptoms;
b. study methods, total number of patients originally assigned to each treatment group;
c. intervention: preparations, dose, administration regime;
d. control: placebo, other drugs;
e. concurrent medications;
f. outcomes (time of assessment, length of follow up, frequency of defecation, pain on defecation and/or straining, faecal incontinence, stool consistency, need for additional therapies, number and type of adverse events associated with treatment, adverse events); and
g. withdrawals and reasons for withdrawals.

Assessment of risk of bias in included studies

The methodological quality of selected trials was assessed independently by two authors using the Cochrane risk of bias tool (Higgins 2011a). Factors assessed included:

1. sequence generation (i.e. was the allocation sequence adequately generated?);
2. allocation sequence concealment (i.e. was allocation adequately concealed?);
3. blinding (i.e. was knowledge of the allocated intervention adequately prevented during the study?);
4. incomplete outcome data (i.e. were incomplete outcome data adequately addressed?);
5. selective outcome reporting (i.e. are reports of the study free of suggestion of selective outcome reporting?); and
6. other potential sources of bias (i.e. was the study apparently free of other problems that could put it at a high risk of bias?).

A judgement of 'Yes' indicates low risk of bias, 'No' indicates high risk of bias, and 'Unclear' indicates unclear or unknown risk of bias. Disagreements was resolved by consensus. Study authors were contacted for further information when insufficient information was provided to determine the risk of bias.
We used the GRADE approach for rating the overall quality of evidence for the primary outcome. Randomised trials start as high quality evidence, but may be downgraded due to: (1) risk of bias, (2) indirectness of evidence, (3) inconsistency (unexplained heterogeneity), (4) imprecision (sparse data), and (5) reporting bias (publication bias). The overall quality of evidence for each outcome was determined after considering each of these elements, and categorized as high quality (i.e. further research is very unlikely to change our confidence in the estimate of effect); moderate quality (i.e. further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate); low quality (i.e. further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate); or very low quality (i.e. we are very uncertain about the estimate) (Guyatt 2008; Schünemann 2011).

Measures of treatment effect

The primary outcome, frequency of defecation, was assessed using the mean difference (MD) with 95% confidence intervals (CI). The secondary outcomes were assessed by calculating the odds ratio (OR) and 95% CI.

Dealing with missing data

The authors of included studies were contacted to supply any missing data.

Assessment of heterogeneity

Heterogeneity among trial results was assessed by inspection of graphical presentations and by calculating the chi square test of heterogeneity (a P value of 0.10 was regarded as statistically significant). We also used the I^2 statistic to quantity the effect of heterogeneity (Higgins 2003). A random-effects model was used in situations of unexplained heterogeneity. We aimed to further investigate potential sources of heterogeneity.

Assessment of reporting biases

If an appropriate number of studies was found, we aimed to investigate the possibility of a publication bias through the construction of funnel plots (trial effects versus trial size).

Data synthesis

For outcomes that were sufficiently homogenous, meta-analysis was carried out using a fixed-effect model. A random-effects model was used in situations of unexplained heterogeneity.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were to be carried out to further study the effects of a number of variables on the outcomes including:
a. whether patients were being inducted in to 'remission' from constipation or whether this was a study of 'maintenance' therapy;
b. the effect of length of therapy / follow up; and
c. specifically what, if any agents, were initially allowed in the protocol to clear any impaction (such as enemas).

Sensitivity analysis

Sensitivity analyses was conducted based on the following:
a. only including patients' whose outcome is known i.e. number of patients who completed the study used as denominator; and
b. random-effects versus fixed-effect models.

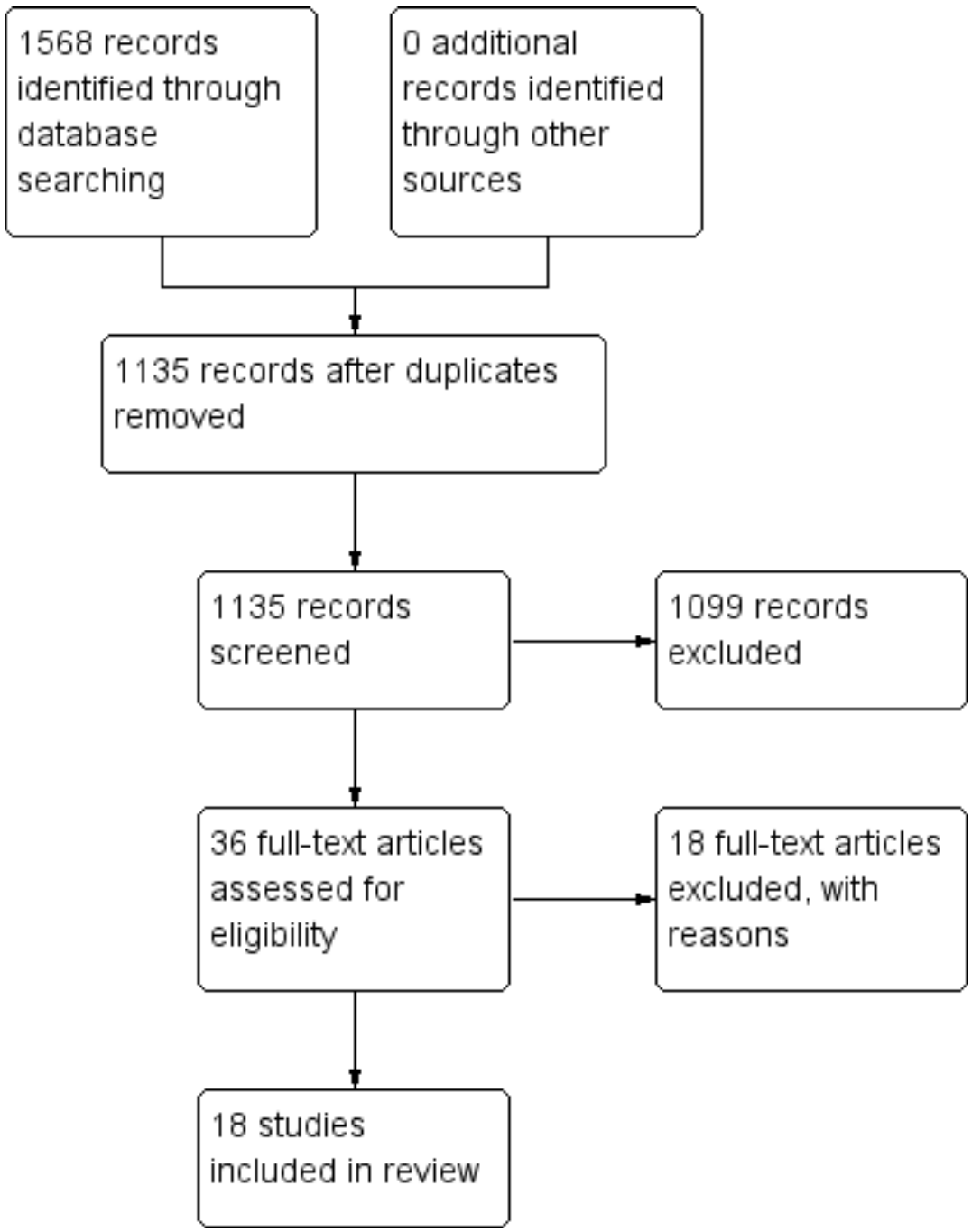
We also planned to consider the effect of:
c. allocation concealment;
d. type of agent;
e. dose of agent; and
f. concurrent medications.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
See:Characteristics of included studies; Characteristics of excluded studies.
The database searches on May 7, 2012, identified 1568 records. No further studies were identified through other sources. After duplicates were removed, 1135 records were screened for inclusion (see Study flow diagram Figure 1). Of these, we identified 36 potentially relevant studies for full text review. Eighteen studies were excluded for various reasons. Six studies were not randomised controlled trials (Moulies 1961; Sonheimer 1982; Tolia 1988; Loening-Baucke 2002; Loening-Baucke 2004; Shevtsov 2005) four studies had no comparison group (Hejl 1990; Youssef 2002; Dupont 2006; Hardikar 2007), two studies concerned adult patients (Ferguson 1999; Corazziari 1996) two were not research articles (Clayden 1978; Kinservik 2004), one study was of children with soiling (Berg 1983), one study was of children with faecal impaction without a diagnosis of functional constipation (Miller 2012); one study was of children with underlying bowel pathology (Kazak 1999) and one study was an abstract publication (Quitadamo 2010).

Figure 1. Study flow diagram.



Eighteen studies were identified which satisfied the inclusion criteria and were included in the review. Two compared PEG with placebo (Thomson 2007; Nurko 2008), five compared PEG with lactulose (Gremse 2002; Voskujl 2004; Dupont 2005; Candy 2006; Wang 2007), three compared PEG with milk of magnesia (magnesium oxide) (Loening-Baucke 2006, Gomes 2011, Ratanamongkol 2009), two compared liquid paraffin with lactulose (Urganci 2005; Farahmand 2007) two compared liquid paraffin with PEG (Tolia 1993; Rafati 2011), one compared PEG with enemas (Bekkali 2009), one compared a dietary fibre mix with lactulose (Kokke 2008), one lactulose with senna (Perkin 1977) and one lactitol with lactulose (Pitzalis 1995).

The total number of participants in the included trials was 1,643. The age range varied from 6 months up to 16 years. The duration of the studies varied from 2 weeks to 12 months. The specific criteria for a diagnosis of constipation also varied between studies, as did the minimum length of symptoms. All studies excluded children with organic causes for their pathology (*see characteristics of included studies*).

Risk of bias in included studies

The risk of bias analysis for the included studies is summarised in Figure 2 and Figure 3.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

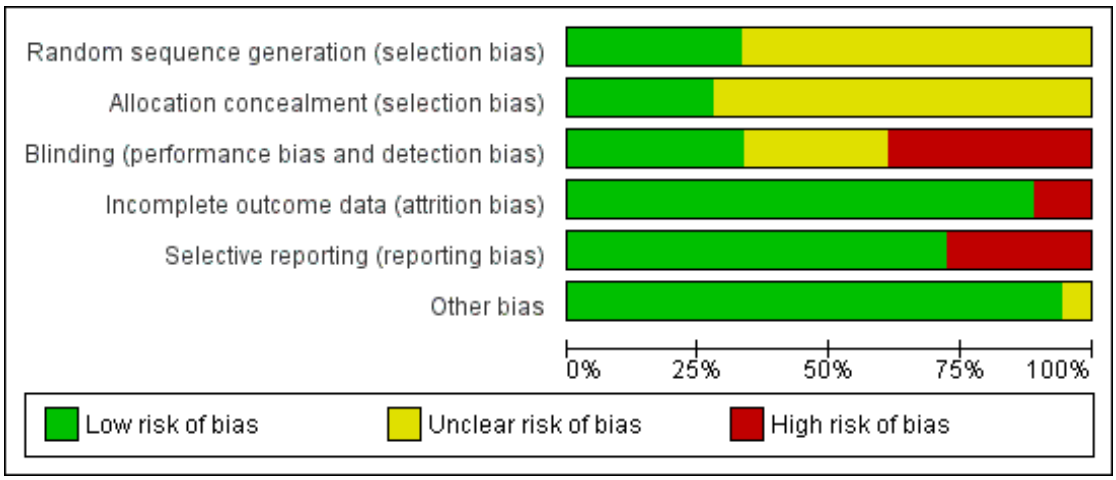
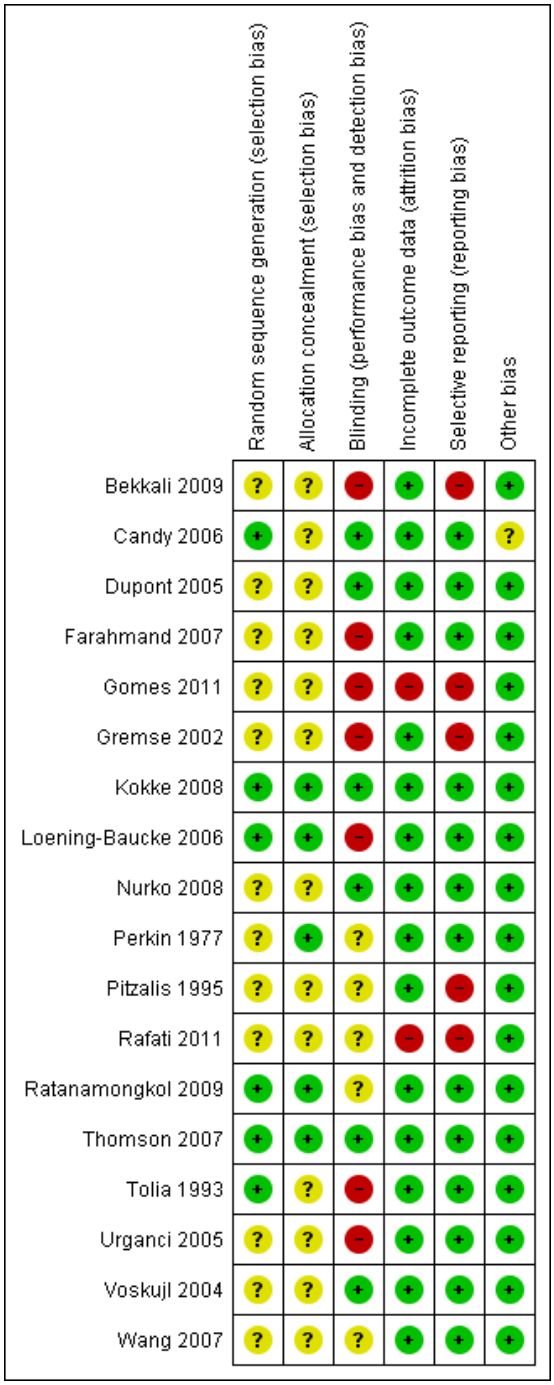


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

In five of the included studies, the method of random allocation of participants to intervention groups was described and was judged as adequate (Tolia 1993; Loening-Baucke 2006; Thomson 2007; Kokke 2008; Ratanamongkol 2009). These studies were rated as low risk for sequence generation. For one study (Candy 2006), the sponsor gave a response to a request for more details and confirmed adequate sequence generation. This study was rated as low risk for sequence generation. Allocation was described as random in the 12 remaining studies, although the method of randomisation was not described. These studies were rated as unclear risk for sequence generation. Allocation concealment was rated as low risk in five studies (Perkin 1977; Loening-Baucke 2006; Thomson 2007; Kokke 2008; Ratanamongkol 2009) and as unclear risk in the other studies.

Blinding

Methods for blinding were described and judged to be adequate in six studies. These studies were rated as low risk for blinding (Voskujl 2004; Dupont 2005; Candy 2006; Thomson 2007; Kokke 2008; Nurko 2008). In five studies, the use of blinding was reported but not described clearly. These studies were rated as unclear risk for blinding (Perkin 1977; Pitzalis 1995; Wang 2007; Ratanamongkol 2009; Rafati 2011). The remaining seven studies were described as open label and were rated as high risk for blinding (Tolia 1993; Gremse 2002; Urganci 2005; Loening-Baucke 2006; Farahmand 2007; Bekkali 2009; Gomes 2011).

Incomplete outcome data

Two studies were judged to be of high risk of bias (Gomes 2011, Rafati 2011). The outcome data was judged as to have been addressed adequately in all the remaining studies.

Selective reporting

In five studies, no details were given of adverse events given and therefore they were judged to be at risk of bias (Pitzalis 1995; Gremse 2002; Bekkali 2009; Gomes 2011; Rafati 2011). The remaining thirteen studies were not clearly free of selective reporting. In these studies there was not enough information available to make a judgement and so they were rated as unclear.

Other potential sources of bias

One study stated that they were supported by a pharmaceutical company, but details of the extent of involvement were unclear. Two studies were sponsored by pharmaceutical companies, but confirmation was received by the authors that industry had no involvement (Thomson 2007; Nurko 2008). Most of the remaining studies did not mention sources of funding and had no other potential sources of bias.

Figure 3 shows the review authors' judgements about each methodological quality item for each included study.

Effects of interventions

See: **Summary of findings for the main comparison** PEG versus placebo for the management of childhood constipation; **Summary of findings 2** PEG versus lactulose for the management of childhood constipation; **Summary of findings 3** PEG versus milk of magnesia (MOM) for the management of childhood constipation; **Summary of findings 4** Liquid paraffin (mineral oil) versus lactulose for the management of childhood constipation

In the analyses, we used as the denominator the total number of patients randomised. In all analyses, the frequency of defecation was measured as stools per week.

PEG versus Placebo

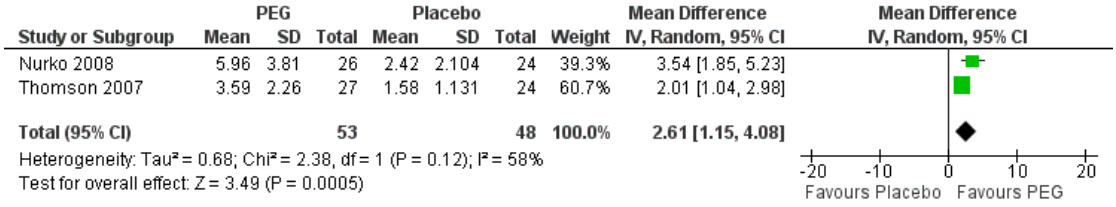
The published results for the two studies concerning 101 patients were inadequate to allow pooling for meta-analysis. The authors were contacted and directed us to the study sponsors who supplied unpublished data to allow analysis for outcomes at 2 weeks. One of the studies (Nurko 2008) used multiple dosing regimens, but data were obtained for the dose of 0.8 g/kg.

Efficacy

Frequency of defecation

Heterogeneity was noted to be moderate (P = 0.12, I^2 = 58%) and using a random-effects model, the mean difference (MD) was 2.61 stools per week (95% CI, 1.15 to 4.08), favouring PEG, see Analysis 1.1 and Figure 4. The GRADE analysis indicated that the overall quality of the evidence for the primary outcome (frequency of defecation) was low due to sparse data (101 patients) and inconsistency (statistical heterogeneity I^2 = 58%) in the pooled analysis (See Summary of findings for the main comparison).

Figure 4. Forest plot of comparison: 1 PEG versus Placebo, outcome: 1.1 Frequency of defecation.



Episodes of faecal incontinence

At 2 weeks, both studies reported higher rates of faecal incontinence in the PEG group. As there was some discrepancy in baseline data between groups in one study (Nurko 2008) and the difference before and after treatment was not reported, meta-analysis for this outcome was not completed.

Safety

Serious adverse events were not reported in the PEG groups in either study, but were seen in the placebo groups (8% of placebo patients experienced a serious adverse event). However, there was no statistically significant difference in the incidence of serious adverse events (OR 0.17, 95% CI 0.02 to 1.48). Minor adverse events were common and included flatulence, abdominal pain, nausea, diarrhoea and headache. However, data were not reported to allow meta-analysis. The studies both stated that no difference in the incidence of adverse events appeared to exist between the groups.

PEG versus Lactulose

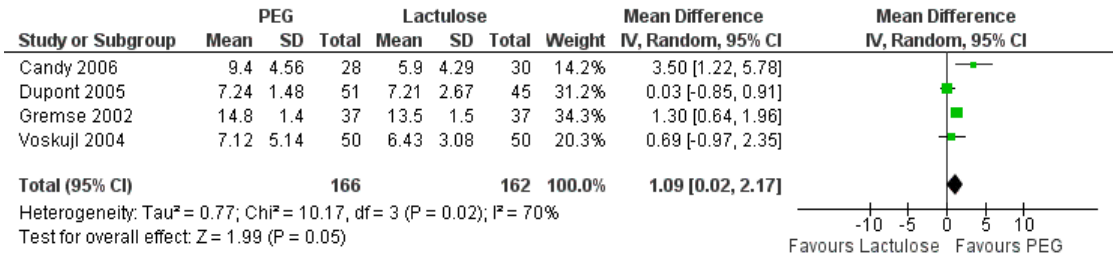
One of the five studies (Wang 2007) did not report data that could be used for meta-analysis. The authors were contacted, but no response was received and so the remaining 4 studies including 328 patients were analysed. One study separated results for babies and toddlers (Dupont 2005). Using the method described in the Cochrane handbook (Higgins 2011b) the mean and standard deviation for the entire sample were calculated.

Efficacy

Frequency of defecation

Heterogeneity was noted to be high (P = 0.02, I^2 = 70%) and using a random-effects model a statistically significant difference in favour of PEG was seen, with a MD of 1.09 stools per week (95% CI, 0.02 to 2.17), see Analysis 2.1 and Figure 5. The GRADE analysis indicated that the overall quality of the evidence for the primary outcome (frequency of defecation) was very low due to sparse data (328 patients), inconsistency (statistical heterogeneity I^2 = 70%), and a high risk of bias (i.e. lack of blinding and selective reporting) in one study in the pooled analysis (See Summary of findings 2).

Figure 5. Forest plot of comparison: 2 PEG versus Lactulose, outcome: 2.1 Frequency of defecation.



Need for additional therapies

Using a fixed-effect model, there was a statistically significant result favouring PEG. For the 3 studies (254 patients) that reported this outcome (Voskujl 2004; Dupont 2005; Candy 2006), 18% of PEG patients required additional therapy compared to 30% of lactulose patients, (OR 0.49, 95% CI 0.27 to 0.89), see Analysis 2.2. When a sensitivity analysis using a random-effects model was calculated the results were no longer statistically significant (OR 0.51, 95% CI 0.19 to 1.38), see Analysis 2.3.

Safety

Serious adverse events were only reported in one study (Candy

2006) and this was a chest infection in a patient in the PEG group, thought to be unrelated to therapy. Minor adverse events were seen in most studies, but were not reported in one study (Gremse 2002). Common adverse events included diarrhoea, abdominal pain, nausea, vomiting and pruritis ani. For the 2 studies (154 patients) that reported data allowing meta-analysis (Dupont 2005; Candy 2006), there was no statistically significant difference in the proportion of patients who experienced at least one adverse event. Twenty-four per cent of PEG patients experienced at least one adverse event compared to 37% of lactulose patients (OR 0.37, 95% CI 0.14 to 1.03), see Analysis 2.4.

PEG versus Milk of Magnesia

Three studies (211 participants) compared PEG to milk of magnesia. One study (Loening-Baucke 2006) reported outcomes at 1 month and 12 months. However, data for outcomes at 4 weeks were used for meta-analysis. Another study (Ratanamongkol 2009) reported median and interquartile ranges for results and these were used to estimate the mean and standard deviation.

Efficacy

Frequency of defecation

Using a fixed-effect model, there was a statistically significant result favouring PEG. The MD was 0.69 stools per week (95% CI, 0.48 to 0.89), see Analysis 3.1. There was no evidence of heterogeneity in the pooled analysis (P = 0.87, I^2 = 0%). The GRADE analysis indicated that the overall quality of the evidence for the primary outcome (frequency of defecation) was low due to sparse data (211 patients) and a high risk of bias (i.e. lack of blinding in one study and lack of blinding, incomplete outcome data and selective reporting in the other study) in two studies in the pooled analysis (See Summary of findings 3).

Safety

A serious adverse event of allergy to PEG was reported in one patient (Loening-Baucke 2006). Minor adverse events data were not reported to allow meta-analysis. One study (Ratanamongkol 2009) noted a statistically significant difference in proportion of patients experiencing diarrhoea. Twenty-eight per cent of patients in the milk of magnesia group experienced diarrhoea compared to 4% of PEG patients (P = 0.002). The final study (Gomes 2011) did not explicitly report adverse event data.

Liquid Paraffin versus Lactulose

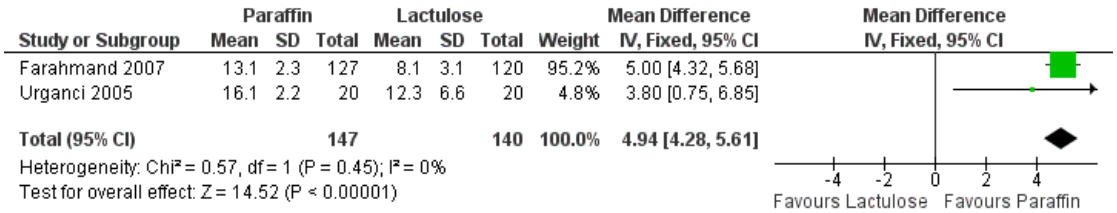
Two studies (Urganci 2005; Farahmand 2007) (287 participants) compared liquid paraffin to lactulose. These studies reported outcomes at 8 weeks.

Efficacy

Frequency of defecation

Using a fixed-effect model, there was a statistically significant result favouring paraffin. The MD was 4.94 stools per week (95% CI 4.28 to 5.61) see Analysis 4.1 and Figure 6. There was no evidence of heterogeneity in the pooled analysis (P = 0.45, I^2 = 0%). The GRADE analysis indicated that the overall quality of the evidence for the primary outcome (frequency of defecation) was low due to sparse data (287 patients) and a high risk of bias (i.e. lack of blinding in both studies) in two studies in the pooled analysis (See Summary of findings 4).

Figure 6. Forest plot of comparison: 4 Paraffin versus Lactulose, outcome: 4.1 Frequency of defecation.



Safety

No serious adverse events were reported in either study. Minor adverse events such as abdominal pain, distention and watery stools were reported with both agents, but data were not presented in a manor to allow meta-analysis.

PEG versus Enemas

One study (Bekkali 2009) compared PEG to enemas (90 participants), This study reported outcomes at 4 weeks.

Efficacy

Frequency of defecation

There was no statistically significant difference in the frequency of defecation between PEG and enema groups. The MD was 1.00 stools per week (95% CI -1.58 to 3.58).

Succesful disimpaction
Successful disimpaction was reported in 80% of enema patients compared to 68% of PEG patients. However, the difference was not statistically significant (OR 0.52, 95% CI 0.20 to 1.37).
Safety
Adverse event data were not explicitly reported within this study, although the authors reported significantly higher rates of faecal incontinence and watery stools with PEG.

Dietary fibre mix versus Lactulose

One study (Kokke 2008) compared dietary fibre with lactulose (125 participants). This study reported outcomes at 8 weeks.
Efficacy
Frequency of defecation
Kokke 2008 reported that there was no statistically significant difference in the frequency of defecation between the two agents at eight weeks (mean 7 stools per week in the fibre group versus 6 stools per week in the lactulose group; P = 0.481).
Safety
The authors reported no serious or significant adverse effects. There were three cases of diarrhoea (one in the fibre mixture group and two in the lactulose group).

Senna versus Lactulose

One crossover study (Perkin 1977) compared senna with lactulose (21 participants),
Efficacy
Passage of stool
There was no statistically significant difference between the two agents in the number of patients passing stools of any kind each day.
Safety
No serious or significant adverse effects were reported in the 2 study groups. Minor adverse events such as colic or diarrhoea, were more commonly seen in the senna group.

Lactitol versus Lactulose

One study (Pitzalis 1995) compared lactitol to lactulose (51 participants), This study reported outcomes at 30 days.
Efficacy
Frequency of defecation
There was no statistically significant difference in the frequency of defecation between the two agents. The MD was -0.80 stools per week (95% CI -2.63 to 1.03).
Safety
Adverse events were not reported.

PEG versus Liquid paraffin

Two studies (196 participants) compared PEG to liquid paraffin (Tolia 1993; Rafati 2011). The studies had varying lengths of follow up (2 days versus assessments at 7 to 120 days). The two studies were not pooled for meta-analysis because the primary outcomes were not similar enough to allow pooling.
Efficacy
Frequency of defecation
Rafati 2011 found no statistically significant difference in the frequency of defecation between PEG and liquid paraffin. The MD was 0.70 stools per week (95% CI -0.38 to 1.78). Tolia 1993 reported on the frequency of bowel movements after treatment (scored as > 5, 1 to 5 or none). The authors reported that PEG patients had more frequent bowel movements after treatment than liquid paraffin patients (P < 0.005).
Safety
No serious adverse events were reported. Tolia 1993 reported significantly more vomiting in the PEG group compared to liquid paraffin (P < 0.005)..

Subgroup and sensitivity analyses

GIven the heterogenous nature of the included studies, further subgroup or sensitivity analyses were not completed.

Publication Bias

Publication bias was not investigated as there were not enough studies to construct a reliable funnel plot.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

PEG versus lactulose for the management of childhood constipation

Patient or population: patients aged 0 to 18 years with a diagnosis of functional constipation
Settings: outpatient
Intervention: PEG versus lactulose

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	PEG versus lactulose				
Frequency of defecation (mean number of bowel movements per week)	The mean number of bowel movements ranged across the lactulose groups from **5.9 to 13.5** per week	The mean number of bowel movements in the PEG group was on average **1.09 higher** per week (95% CI 0.02 to 2.17)		328 (4 studies)	⊕○○○ **very low**[1,2,3]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Sparse data (328 patients)
[2] Inconsistency (high statistical heterogeneity $I^2 = 70\%$; $P = 0.02$)
[3] High risk of bias in one study in pooled analysis due to lack of blinding and selective reporting

PEG versus milk of magnesia (MOM) for the management of childhood constipation

Patient or population: patients aged 0 to 18 years with a diagnosis of functional constipation
Settings: outpatient
Intervention: PEG versus MOM

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	PEG versus lactulose				
Frequency of defecation (mean number of bowel movements per week)	The mean number of bowel movements ranged across the MOM groups from **4.3 to 9.7** per week	The mean number of bowel movements in the PEG group was on average **0.69 higher** per week (95% CI 0.48 to 0.89)		211 (3 studies)	⊕⊕◯◯ **low**[1,2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Sparse data (211 patients)
[2] High risk of bias in two studies in pooled analysis due to lack of blinding in one study and lack of blinding, incomplete outcome data and selective reporting in the other study

Liquid paraffin (mineral oil) versus lactulose for the management of childhood constipation

Patient or population: patients aged 0 to 18 years with a diagnosis of functional constipation
Settings: outpatient
Intervention: Liquid paraffin (mineral oil) versus lactulose

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	PEG versus lactulose				
Frequency of defecation (mean number of bowel movements per week)	The mean number of bowel movements ranged across the lactulose groups from **8.1 to 12.3** per week	The mean number of bowel movements in the PEG group was on average **4.94 higher** per week (95% CI 4.28 to 5.61)		287 (2 studies)	⊕⊕◯◯ **low**[1,2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Sparse data (287 patients)
[2] High risk of bias in two studies in pooled analysis due to lack of blinding in both studies

DISCUSSION

Summary of main results

Lactulose was the most studied agent. Despite the many agents that it was compared to, no trial found superiority of lactulose in terms of efficacy. All but one trial found lactulose was inferior to other agents. Although, it is worth noting that there were no studies comparing lactulose with placebo. In addition, the occurrence of minor adverse events, such abdominal cramps and flatus, were more common in the lactulose groups.

PEG was also frequently studied, with trials comparing its efficacy for constipation with lactulose, milk of magnesia and placebo. All the results showed a statistically significant benefit favouring PEG. However, the effect size was modest in these analyses, particularly for the pooled analysis of PEG versus milk of magnesia. Although PEG was superior to milk of magnesia the magnitude of this difference is quite small and may not be clinically significant. With the exception of 1 case of allergy to PEG, no significant adverse events were associated with the use of PEG and the limited evidence reported suggests that minor adverse events occur with a similar or reduced frequency. There was one study that found that PEG was of similar efficacy to rectal enemas for treating faecal impaction.

The largest treatment effect seen within this review, in terms of the frequency of defecation (i.e. number of stools per week), was seen with liquid paraffin (mineral oil) when compared to lactulose. While a number of case reports have been made that raise safety concerns about liquid paraffin in terms of the risk of aspiration pneumonia (Zanetti 2007), no cases of this or any serious adverse events were noted in the trials in this review.

Overall completeness and applicability of evidence

While there are a large number of studies included in this review, it is clear that these studies are extremely heterogenous, with nine different study agents and a variety of specific treatment regimens reported. As such, despite the common nature of the problem, it is difficult to draw particularly strong conclusions for any of the investigated agents. The scope of this study was osmotic and stimulant laxatives, but the vast majority of studies investigated osmotic laxatives.

If we consider PEG, while this was the most studied agent in 10 different trials, with a total of 1161 participants, these studies compared PEG to 5 different agents, as well as its use for constipation or faecal impaction. In addition, there was wide variation in study length and the time at which outcomes were assessed. Clearly, given the modest effect sizes and small sample sizes, coupled with these variations in treatment protocols (time of outcome assessment, use of additional therapies, specific form of interventional laxative used), the ability to use these findings to inform clinical practice is modest at best. These factors have certainly contributed to the statistical evidence of heterogeneity in intervention effects observed in meta-analyses comparing PEG to placebo or lactulose. As constipation is a chronic problem, outcomes really need to be assessed in the medium to long term. However, only one study assessed outcomes beyond three months and half of the studies measured outcomes at 1 month or less. If management of chronic constipation is considered in terms of induction (disimpaction) and maintenance of remission, the limitation in the application of these results becomes apparent. It is difficult to comment on the ability of PEG or lactulose to maintain a child's normal bowel habits over the long term, when the studies have such short follow up periods. In addition, outcomes such as frequency of defecation are inherently limited in relation to the realities of clinical practice. While there may be a statistically significant increase in rates of defecation between study groups, this does not give any information as to whether the patient or their parents feel that there has been a functional improvement.

Quality of the evidence

There were no studies that were judged to be fully free of risk of bias. While the majority of studies described themselves as randomised, only six studies provided enough detail to be judged as at low risk of bias. The other studies were rated as unclear for random sequencer. This was also the case for allocation concealment, again with the majority of studies giving insufficient detail to be judged as low risk of bias. Seven studies were open label (high risk of bias) or reported insufficient information to be judged at low risk of bias. Four studies were judged to be at high risk of bias for selective reporting and two studies were judged to be at high risk of bias due to selective reporting. This has to be considered when judging the conclusions of this review. Furthermore, GRADE analyses indicated that the overall quality of the evidence for the primary outcome (number of stools per week) was low or very low due to sparse data, inconsistency (heterogeneity), and high risk of bias in the studies in the pooled analyses. Thus, given these concerns the results of the pooled analyses should be interpreted with caution.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence base suggests that PEG is moderately effective at improving the frequency of defecation in children with chronic constipation when compared to placebo and more effective than other agents, such as lactulose, milk of magnesia or liquid paraffin (mineral oil). It also appears to have a good safety profile, with minor adverse events common, but less so than with these other agents. The strength of this evidence is limited by sparse data, inconsistency (clinical and statistical heterogeneity) and a high risk

of bias in some studies included in the pooled analyses. It is also difficult to comment on the use of PEG for the long term management of childhood constipation as most studies only measured short term outcomes. While only two studies investigated liquid paraffin in comparison with lactulose, they found a reasonable effect size supporting the use of liquid paraffin. There was no evidence found to suggest lactulose is more effective than the other agents studied, but there was a lack of placebo controlled trials.

Implications for research

The evidence base for this extremely prevalent problem is small and published papers are generally of sub optimal quality, as well as having problems with methodological, statistical and clinical heterogeneity. As such, the strength of our conclusions is extremely limited and more research is needed. Key questions that need addressing include the safety of liquid paraffin, given its apparent effectiveness, but limited investigation. In particular, future research should compare liquid paraffin with PEG. The role of PEG for the long term management of chronic constipation also needs further investigation to allow research to better inform actual clinical practice. There is a lack of studies comparing lactulose with placebo.

Future research should be clear at the outset as to whether it seeks to investigate the use of agents for the induction of remission from severe constipation, or whether it will investigate maintenance of normal bowel habits. Studies should be reported in sufficient detail to allow the methodology to be assessed and replicated by other researchers.

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REFERENCES

References to studies included in this review

Bekkali 2009 ***{published data only}***
Bekkali NL, van den Berg MM, Dijkgraaf MG, van Wijk MP, Bongers ME, Liem O, et al.Rectal fecal impaction treatment in childhood constipation: enemas versus high doses oral PEG. *Pediatrics* 2009;**124**(6):e1108–15.

Candy 2006 ***{published data only}***
Candy DC, Edwards D, Geraint M. Treatment of faecal impaction with polyethylene glycol plus electrolytes (PGE + E) followed by a double-blind comparison of PEG + E versus lactulose as maintenance therapy. *Journal of Pediatric Gastroenterology and Nutrition* 2006;**43**(1):65–70.

Dupont 2005 ***{published data only}***
Dupont C, Leluyer B, Maamri N, Morali A, Joye J, Fiorini J, et al.Double-blind randomized evaluation of clinical and biological tolerance of polyethylene glycol 4000 versus lactulose in constipated children. *Journal of Pediatric Gastroenterology and Nutrition* 2005;**41**(5):625–33.

Farahmand 2007 ***{published data only}***
Farahmand F. A randomised trial of liquid paraffin versus lactulose in the treatment of chronic functional constipation in children. *Acta Medica Iranica* 2007;**45**:183–8.

Gomes 2011 ***{published data only}***
Gomes PB, Duarte MA, Melo Mdo C. Comparison of the effectiveness of polyethylene glycol 4000 without electrolytes and magnesium hydroxide in the treatment of chronic functional constipation in children. *Jornal de Pediatria* 2011;**87**(1):24–8.

Gremse 2002 ***{published data only}***
Gremse DA, Hixon J, Crutchfield A. Comparison of polyethylene glycol 3350 and lactulose for treatment of chronic constipation in children. *Clinical Pediatrics* 2002; **41**(4):225–9.

Kokke 2008 ***{published data only}***
Kokke FT, Scholtens PA, Alles MS, Decates TS, Fiselier TJ, Tolboom JJ, et al.A dietary fiber mixture versus lactulose in the treatment of childhood constipation: a double-blind randomized controlled trial. *Journal of Pediatric Gastroenterology and Nutrition* 2008;**47**(5):592–7.

Loening-Baucke 2006 ***{published data only}***
Loening-Baucke V, Pashankar D. A randomized, prospective, comparison study of polyethylene glycol 3350 without electrolytes and milk of magnesia for children with constipation and fecal incontinence. *Pediatrics* 2006;**118** (2):528–35.

Nurko 2008 ***{published and unpublished data}***
Nurko S, Youssef NN, Sabri M, Langseder A, McGowan J, Cleveland M, et al.PEG3350 in the treatment of childhood constipation: a multicenter, double-blinded, placebo-controlled trial. *Journal of Pediatrics* 2008;**153**(2):254–61.

Perkin 1977 ***{published data only}***
Perkin JM. Constipation in childhood: a controlled comparison between lactulose and standardized senna. *Current Medical Research and Opinion* 1977;**4**(8):540–3.

Pitzalis 1995 *{published data only}*
Pitzalis G, Deganello F, Mariani P, Chiarini-Testa MB, Virgilii F, Gasparri R, Calvani L, Bonamico M. Lactitol in chronic idiopathic constipation in children. *Pediatria Medica e Chirurgica* 1995;**17**(3):223–6.

Rafati 2011 *{published data only}*
Rafati MR, 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**(2):154–8.

Ratanamongkol 2009 *{published data only}*
Ratanamongkola P, Lertmaharitb S, Jongpiputvanichc S. Polyethylene glycol 4000 without electrolytes versus milk of magnesia for the treatment of functional constipation in infants and young children: A randomized controlled trial. *Asian Biomedicine* 2009;**3**(4):391–9.

Thomson 2007 *{published and unpublished data}*
Thomson MA, Jenkins HR, Bisset WM, Heuschkel R, Kalra DS, Green MR, et al.Polyethylene glycol 3350 plus electrolytes for chronic constipation in children: a double blind, placebo controlled, crossover study. *Archives of Disease in Childhood* 2007;**92**(11):996–1000.

Tolia 1993 *{published data only}*
Tolia V, Lin CH, Elitsur Y. A prospective randomized study with mineral oil and oral lavage solution for treatment of faecal impaction in children. *Alimentary Pharmacology and Therapeutics* 1993;**7**(5):523–9.

Urganci 2005 *{published data only}*
Urganci N, Akyildiz B, Polat TB. A comparative study: the efficacy of liquid paraffin and lactulose in management of chronic functional constipation. *Pediatrics International* 2005;**47**(1):15–9.

Voskujl 2004 *{published data only}*
Voskuijl W, de Lorijn F, Verwijs W, Hogeman P, Heijmans J, Mäkel W, et al.PEG 3350 (Transipeg) versus lactulose in the treatment of childhood functional constipation: a double blind, randomised, controlled, multicentre trial. *Gut* 2004;**53**(11):1590–4.

Wang 2007 *{published data only}*
Wang BX, Wang MG, Jiang MZ, Xu CD, Shao CH, Jia LY, et al.Forlax in the treatment of childhood constipation: a randomized, controlled, multicenter clinical study. *Zhongguo Dang Dai Er Ke Za Zhi* 2007;**9**(5):429–32.

References to studies excluded from this review

Berg 1983 *{published data only}*
Berg I, Forsythe I, Holt P, Watts J. A controlled trial of 'Senokot' in faecal soiling treated by behavioural methods. *Journal of Child Psychology and Psychiatry and Allied Disciplines* 1983;**24**(4):543–9.

Clayden 1978 *{published data only}*
Clayden GS. Dioctyl sodium sulphosuccinate in constipation. *Lancet* 1978;**2**(8093):787.

Corazziari 1996 *{published data only}*
Corazziari E, Badiali D, Habib FI, Reboa G, Pitto G, Mazzacca G, et al.Small volume isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in treatment of chronic nonorganic constipation. *Digestive Diseases and Sciences* 1996;**41**(8):1636–40.

Dupont 2006 *{published data only}*
Dupont C, Leluyer B, Amar F, Kalach N, Benhamou PH, Mouterde O, et al.A dose determination study of polyethylene glycol 4000 in constipated children: factors influencing the maintenance dose. *Journal of Pediatric Gastroenterology and Nutrition* 2006;**42**(2):178–85.

Ferguson 1999 *{published data only}*
Ferguson A, Culbert P, Gillett H, Barras N. New polyethylene glycol electrolyte solution for the treatment of constipation and faecal impaction. *Italian Journal of Gastroenterology and Hepatology* 1999;**31 Supp 3**:S249–52.

Hardikar 2007 *{published data only}*
Hardikar W, Cranswick N, Heine RG. Macrogol 3350 plus electrolytes for chronic constipation in children: a single-centre, open-label study. *Journal of Paediatrics and Child Health* 2007;**43**(7-8):527–31.

Hejl 1990 *{published data only}*
Hejl M, Kamper J, Ebbesen F, Hansted C. Infantile constipation and Allomin-lactulose. Treatment of infantile obstipation in infants fed with breast milk substitutes. A controlled clinical trial of 2 per cent and 4 per cent Allomin-lactulose. *Ugeskrift for Laeger* 1990;**152**(25):1819–22.

Kazak 1999 *{published data only}*
Kazak SS, Beketova HV, Voronina SS, Amanbaieva HT. Forlax in the treatment of the constipation syndrome in children with combined digestive organ pathology. *Likarska Sprava* 1999, (7-8):142–7.

Kinservik 2004 *{published data only}*
Kinservik MA, Friedhoff MM. The efficacy and safety of polyethylene glycol 3350 in the treatment of constipation in children. *Pediatric Nursing* 2004;**30**(3):232–7.

Loening-Baucke 2002 *{published data only}*
Loening-Baucke V. Polyethylene glycol without electrolytes for children with constipation and encopresis. *Journal of Pediatric Gastroenterology and Nutrition* 2002;**34**(4):372–7.

Loening-Baucke 2004 *{published data only}*
Loening-Baucke V, Krishna R, Pashankar DS. Polyethylene glycol 3350 without electrolytes for the treatment of functional constipation in infants and toddlers. *Journal of Pediatric Gastroenterology and Nutrition* 2004;**39**(5):536–9.

Miller 2012 *{published data only}*
Miller MK, Dowd MD, Friesen CA, Walsh-Kelly CM. A randomized trial of enema versus polyethylene glycol 3350 for fecal disimpaction in children presenting to an emergency department. *Pediatric Emergency Care* 2012;**28**(2):115–9.

Moulies 1961 *{published data only}*
Moulies A. The treatment of constipation in the child: results obtained with a new medicinal agent prepared from

the pericarp of senna follicles. *Gazette Medicale de France* 1961;**68**:239–44.

Quitadamo 2010 ***{published data only}***
Quitadamo P, Coccorullo P, Del Giudice E, Mallardo S, Ferra V, Poli E, et al.Prospective, randomized, controlled, multicenter study on the effectiveness of polyethylene glycol 3350 with electrolytes versus a mixture of acacia fiber, psyllium fiber and fructose in the treatment of chronic functional constipation in childhood. *Digestive and Liver Disease* 2010;**42**:S355.

Shevtsov 2005 ***{published data only}***
Shevtsov SA. Clinical efficacy of duphalac in the treatment of functional constipations. Ë *ksperimental'naia i Klinicheskaia Gastroë nterologiia* 2005, (6):58–60.

Sonheimer 1982 ***{published data only}***
Sondheimer JM, Gervaise EP. Lubricant versus laxative in the treatment of chronic functional constipation of children: a comparative study. *Journal of Pediatric Gastroenterology and Nutrition* 1982;**1**(2):223–6.

Tolia 1988 ***{published data only}***
Tolia V. Use of a balanced lavage solution in the treatment of fecal impaction. *Journal of Pediatric Gastroenterology and Nutrition* 1988;**7**(2):299–301.

Youssef 2002 ***{published data only}***
Youssef NN, Peters JM, Henderson W, Shultz-Peters S, Lockhart DK, Di Lorenzo C. Dose response of PEG 3350 for the treatment of childhood fecal impaction. *Journal of Pediatrics* 2002;**141**(3):410–4.

Additional references

Anonymous 2006
Anonymous. Evaluation and treatment of constipation in children: summary of updated recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *Journal of Pediatric Gastroenterology and Nutrition* 2006;**43**(3):405–7.

Anonymous 2010
Anonymous. Constipation in children and young people: diagnosis and management of idiopathic childhood constipation in primary and secondary care. Available from http://www.nice.org.uk/nicemedia/live/12993/48721/48721.pdf [Accessed 13th July 2010]. Published by the RCOG Press at the Royal College of Obstetricians and Gynaecologists, London, UK, 2010.

Baker 1999
Baker SS, Liptak GS, Colletti RB, Croffie JM, Di Lorenzo C, Ector W, et al.Constipation in infants and children: evaluation and treatment. A medical position statement of the North American Society for Pediatric Gastroenterology and Nutrition. *Journal of Pediatric Gastroenterology and Nutrition* 1999;**29**(5):612–26.

Guyatt 2008
Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al.GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924–6.

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–560.

Higgins 2011a
Hggins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011)*. The Cochrane Collaboration, 2011. Available from www.cochrane–handbook.org.

Higgins 2011b
Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011)*. The Cochrane Collaboration, 2011. Available from www.cochrane–handbook.org.

Hyman 2006
Hyman PE, Milla PJ, Marc A. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* 2006;**130**(5):1519–26.

Lee-Robichaud 2010
Lee-Robichaud H, Thomas K, Morgan J, Nelson RL. Lactulose versus polyethylene glycol for chronic constipation. *Cochrane Database of Systematic Reviews* 2010, Issue 7. [DOI: 10.1002/14651858.CD007570.pub2]

Partin 1992
Partin JC, Hamill SK, Fischel JE, Partin JS. Painful defecation and fecal soiling in children. *Pediatrics* 1992;**89** (6 Pt 1):1007–9.

Pijpers 2008
Pijpers MA, Tabbers MM, Benninga MA, Berger MY. Currently recommended treatments of childhood constipation are not evidence based: a systematic literature review on the effect of laxative treatment and dietary measures. *Archives of Disease in Childhood* 2009;**94**(2): 117–31.

Pitkin 1999
Pitkin RM, Branagan MA, Burmeister LF. Accuracy of data in abstracts of published research articles. *JAMA* 1999;**281** (12):1110–1.

Price 2001
Price KJ, Elliot TM. Stimulant laxatives for constipation and soiling in children. *Cochrane Database of Systematic Reviews* 2001, Issue 3. [DOI: 10.1002/14651858.CD002040]

Rasquin 2006
Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams J, Staiano A, et al.Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology* 2006;**130**(5): 1527–37.

Rasquin-Weber 1999

Rasquin-Weber A, Hyman PE, Cucchiara S, Fleisher DR, Hyams JS, Milla PJ, et al.Childhood functional gastrointestinal disorders. *Gut* 1999;**45 (Suppl 2)**:1160–8.

Schünemann 2011

Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al.Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011)*. The Cochrane Collaboration, 2011. Available from www.cochrane–handbook.org.

Van den Berg 2006

Van den Berg MM, Benninga MA, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. *American Journal of Gastroenterology* 2006;**101**(10): 2401–9.

Zanetti 2007

Zanetti G, Marchiori E, Gasparetto TD, Escuissato DL, Soares Souza A Jr. Lipoid pneumonia in children following aspiration of mineral oil used in the treatment of constipation: high-resolution CT findings in 17 patients. *Pediatric Radiology* 2007;**37**(11):1135–9.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bekkali 2009

Methods	Randomised controlled open label trial of polyethylene glycol (PEG) + electrolytes versus enemas for faecal impaction
Participants	90 children between 4 and 16 years of age and demonstrated evidence of faecal impaction on rectal examination. to fulfill > 1 of the other Rome III criteria for functional constipation present for 8 weeks, that is, (1) defecation frequency of 3 times per week, (2) > 1 faecal incontinence episode per week, (3) history of retentive posturing or excessive volitional stool retention, (4) history of painful or hard defecation, and (5) history of large-diameter stools that may obstruct the toilet. Patients with a history of colorectal surgery or an organic cause for constipation were excluded
Interventions	Peg 3350 + electrolytes (Movicolon, Norgine, Amsterdam),1.5 g/kg per day) for 6 consecutive days. Then maintenance (0.5 g/kg per day) for 2 weeks. Dioctylsulfosuccinate sodium enemas (Klyx, Pharmachemie, Haarlem, The Netherlands).Once daily for 6 consecutive days (60 mL for children < 6 years of age and 120 mL for children > 6 years of age)
Outcomes	The primary outcome was successful disimpaction. Secondary outcome measures of defecation and faecal incontinence frequency, abdominal pain, watery stools, CTT values, and child's behavior scores were calculated for children who completed the study protocol. Follow up for 2 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full details reported
Selective reporting (reporting bias)	High risk	No adverse event data reported
Other bias	Low risk	None apparent

Candy 2006

Methods	Open label treatment of faecal impaction with PEG + electrolytes followed by a randomised double blind controlled trial of PEG + electrolytes versus lactulose. Only data from second phase of the trial were analysed
Participants	Children aged 2 to 11 years could be enrolled in the study if they had intractable constipation that had failed to respond to conventional treatment and would require hospital admission for disimpaction. 58 children were enrolled. All patients included had successfully been disimpacted in phase 1 of the trial. Children were excluded if they had any condition contraindicating the use of PEG + E or lactulose or pre-existing organic pathology
Interventions	PEG 3350 + electrolytes (Movicol, Norgine, UK) 1 sachet per day (mean) versus lactulose (10 g lactulose powder dissolved in at least 125 mL water), 2.5 sachets per day (mean). Concomitant use of senna allowed
Outcomes	The primary outcome was the mean number of defecations per week. Secondary outcomes included amount of stool, problems on defaecation (pain, straining, abdominal pain, rectal bleeding or soiling). Follow up for 12 weeks
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Study sponsor contacted and confirmed they generated a computerised randomisation list
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Similar appearance of products, identical packaging
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full details reported
Selective reporting (reporting bias)	Low risk	Data reported appropriately
Other bias	Unclear risk	Supported by Norgine. Extent of involvement unclear

Dupont 2005

Methods	Randomised double blind controlled trial of PEG 4000 versus lactulose
Participants	96 children aged 6 months to 3 years with constipation despite the usual dietary treatment for at least 1 month. Children were ineligible if they had a history of intractable fecaloma or organic gastrointestinal disease such as Hirschsprung disease
Interventions	PEG 4000 1 sachet (4 g/sachet) versus Lactulose 1 sachet /(3.33grames/sachet). The dose could be doubled if ineffective. If the maximum authorized dose was unsuccessful, one micro-enema (glycerol) per day could be prescribed for a maximum of 3 consecutive days. If the child produced no stools after treatment two enemas could be administered at a 48-hour interval
Outcomes	The primary endpoint was biological tolerance,. Secondary endpoints included clinical efficacy measured by stool frequency and consistency, disappearance of abdominal pain and bloating, Follow up was up to 12 weeks
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Described and appropriate
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full details reported
Selective reporting (reporting bias)	Low risk	Data reported appropriately
Other bias	Low risk	None apparent

Farahmand 2007

Methods	Randomised controlled open label trial comparing liquid paraffin versus lactulose
Participants	247 children aged 1 month to 12 years with diagnosis of functional constipation. Children with organic causes for defecation disorders were excluded from the study
Interventions	Liquid paraffin or lactulose, 1-2 ml/kg twice daily for each drug, for 8 weeks, increase or decrease of volume of each drug allowed by 25% every 3 days as required, to yield, 1 or 2, firm to loose stools. Patients received one or two enemas daily for two days to clear any rectal impaction at study entry

Farahmand 2007 (*Continued*)

Outcomes	Primary outcome was the number of successful bowel movements per week, with treatment success defined as three or more episodes per week. Secondary outcomes were the incidence and severity of adverse events.Follow up was for 8 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full details reported
Selective reporting (reporting bias)	Low risk	Data reported appropriately
Other bias	Low risk	None apparent

Gomes 2011

Methods	Randomised controlled open label trial comparing PEG versus magnesium hydroxide
Participants	38 children aged 1 to 15 years old with functional constipation according to the Rome III criteria. Children with excluded organic causes, neurological problems or previous surgery to the digestive system were excluded
Interventions	1 mL/kg/day for magnesium hydroxide (maximum dose 3 mL/kg/day, up to 60 mL/day) and 0.5 g/kg/day for PEG (maximum dose 1.5 g/kg/day, up to 48 g/day)
Outcomes	Outcomes included: Stool characteristics (Bristol),5 frequency of bowel movements (number of movements per week), abdominal pain, straining, faecal incontinence, and acceptance of medication. Therapeutic interventions were considered failures when there was lack of acceptance, vomiting upon administration or absence of improvement in frequency of bowel movements and/or ongoing Bristol types 1, 2 or with use of maximum doses of the medication from the moment of the first return appointment
Notes	

Risk of bias

Gomes 2011 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	High risk	No details regarding dropouts reported
Selective reporting (reporting bias)	High risk	No details regarding adverse events reported
Other bias	Low risk	None apparent

Gremse 2002

Methods	Randomised controlled open label crossover trial of PEG versus lactulose
Participants	37 children aged 2 to 16 years of age who were referred for subspecialty evaluation of constipation completed the study.Those with organic disease were excluded
Interventions	PEG 3350 (Miralax, Braintree Laboratories, Inc, Braintree,MA) 10 g/m2/day or lactulose 1.3 g/kg/day both for two weeks and then patients switched agents for a further two weeks
Outcomes	Primary outcome was number of defecations per week. Secondary outcomes included stool form, ease of passage and global assessments by parents. 4 week follow up
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Open label

Gremse 2002 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Full details reported
Selective reporting (reporting bias)	High risk	Details not reported - no response from author
Other bias	Low risk	None apparent

Kokke 2008

Methods	Randomised double blind controlled trial of a dietary fibre mix versus lactulose
Participants	135 children ages 1 to 13 years were included. Children with organic causes of defecation disorders were excluded
Interventions	Patients received either a yogurt drink containing lactulose (10 g/125 mL, Duphalac Lactulose, Solvay, the Netherlands).or a mixed dietary fibres (10 g/125 mL). The fibre mixture yogurt contained 3.0 g transgalacto-oligosaccharides (Vivinal GOS Elixor Sirup, Friesland Foods Domo, Zwolle, the Netherlands), 3.0 g inulin (Frutafit TEX, Cosun, Roosendaal, the Netherlands), 1.6 g soy fibre (Fibrim 2000, J. Rettenmaier & Sohne, Ellwangen, Germany), and 0.33 g resistant starch 3 (Novelose 330, National Starch& Chemical GmbH, Neustadt, Germany) per 100 mL
Outcomes	The primary outcome parameter was defecation frequency per week. Secondary outcome parameters included faecal incontinence each day stool consistency and flatulence. Follow up was for 12 weeks
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated list
Allocation concealment (selection bias)	Low risk	Sequence allocation coordinated by external research organisation
Blinding (performance bias and detection bias) All outcomes	Low risk	Bottles with yogurt were prepared and packed by Numico Research (Wageningen, the Netherlands). Storage and delivery were supervised by the local hospital pharmacist. The treatment products could not be distinguished from each other with respect to colour, taste, or consistency

Kokke 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Full details reported
Selective reporting (reporting bias)	Low risk	Data reported appropriately
Other bias	Low risk	None apparent

Loening-Baucke 2006

Methods	Randomised controlled open label trial comparing PEG 3350 without electrolytes with milk of magnesia
Participants	79 children aged > 4 years and presence of functional constipation with faecal incontinence. Exclusion criteria included organic causes for symptoms, toileting refusal or medication refusal
Interventions	PEG 0.7 g/kg body weight daily or Milk of magnesia 2 mL/kg body weight daily. Instructions were given to parents on how to vary doses to achieve acceptable stools. Children were disimpacted with 1 or 2 phosphate enemas in the clinic on the day of the visit, if necessary, and started laxative therapy that evening. Senna was allowed
Outcomes	Primary outcome was Improvement defined as 3 bowel movements per week, 2 episodes of faecal incontinence per month, and no abdominal pain, with or without laxative therapy. Secondary outcomes included (1) improvement in stool frequency per week, improvement in episodes of faecal incontinence per week, and resolution of abdominal pain; (2) safety profile; and (3) patient's acceptance and compliance. Follow up was for 12 months
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Drawing lots
Allocation concealment (selection bias)	Low risk	Assignments in sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full details reported
Selective reporting (reporting bias)	Low risk	Data reported appropriately

Loening-Baucke 2006 (*Continued*)

Other bias	Low risk	None apparent

Nurko 2008

Methods	Randomised, multicenter, double-blind trial comparing PEG 3350 with placebo
Participants	103 children 4 to 16 years of age. Patients who were taking other laxatives were included only if they had > 3 bowel movements per week while taking the laxative, and all laxatives were stopped at least 2 days before the run-in period started. Exclusion criteria included children with organic causes of constipation
Interventions	PEG3350, (MiraLax, Braintree Laboratories, Inc; Braintree, MA) at doses of 0.2, 0.4, 0.6 or 0.8 grams per kilogram per day or placebo. (CrystalLight, Proctor and Gamble; Cincinnati, OH). All received behavioural modification
Outcomes	The primary outcome was the proportion of patients who responded to treatment. Response to treatment was defined as >3 BM during the second week of treatment. Secondary efficacy variables included the weekly number of BM and faecal incontinence episodes and changes in the scores of stool consistency, straining, and abdominal cramping. 2 weeks follow up
Notes	Additional Mean and Standard deviation data regarding the frequency of defecations were obtained from Braintree Labs Inc

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Identically labelled bottles that were reconstituted with water to 4,000 mL by study personnel in the pharmacy. There was no difference in the colour, appearance, or taste among the different doses
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full details reported
Selective reporting (reporting bias)	Low risk	Data reported appropriately
Other bias	Low risk	Supported by Braintree Labs Inc. They confirmed they had no involvement in the running of the study or the writing of the published manuscript

Perkin 1977

Methods	Randomises controlled crossover trial of lactulose versus senna
Participants	21 children under 15 years of age with a history of greater than 3 weeks constipation. Children with other organic causes of constipation were excluded
Interventions	Lactulose 10-15 mL per day or Senna 10-20 mL per day for 1 week, then1 week with no treatment and then patients switched to received the other treatment
Outcomes	Stool consistency, number of stools per day and adverse events. Follow up for 3 weeks
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random number list, but method of creation not described
Allocation concealment (selection bias)	Low risk	Assignments in sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Although author describes that identical bottles with no identification were used, further detail to confirm blinding are not given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full details reported
Selective reporting (reporting bias)	Low risk	Data reported appropriately
Other bias	Low risk	None apparent

Pitzalis 1995

Methods	Randomised controlled trial comparing lactitol with lactulose
Participants	42 children aged 8 months - 16 years old with less than 3.5 stools per week. Patients with other organic pathology were excluded
Interventions	Lacitol (Portolac zyma) 250 mg/kg/day single dose, Can be increased to 400mg/kg/day. Lactulose (Epalfen zambon) 500 mg/kg/day single dose, Can be increased to 750 mg/kg/day
Outcomes	Primary outcome measure was the frequency of defecation and secondary measures included palatability and colonic transit time. Follow up was for 1 month

Pitzalis 1995 (*Continued*)

Notes	Italian publication	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full details reported
Selective reporting (reporting bias)	High risk	No adverse events mentioned
Other bias	Low risk	None apparent

Rafati 2011

Methods	Randomised controlled trial comparing PEG with liquid paraffin	
Participants	158 children aged 2 to 12 years with a history of functional constipation	
Interventions	1.0-1.5 g/kg/day PEG 3350 or 1.0-1.5 ml/kg/day liquid paraffin orally for 4 months. PEG 3350 powder was prepared as a 40% solution to trust reliable to apply the paediatric dosing and to increase compliance and liquid paraffin was provided from a pharmaceutical factory. For rectal disimpaction, bisacodyl suppositories were applied at the beginning of the study	
Outcomes	Primary outcomes were stool and encopresis frequency per week	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Rafati 2011 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts are not explained
Selective reporting (reporting bias)	High risk	No adverse event data reported
Other bias	Low risk	None apparent

Ratanamongkol 2009

Methods	Randomised controlled trial comparing PEG 4000 without electrolytes to milk of magnesia
Participants	94 infants and children aged one-four years. Patients were organic causes for their constipation or renal insufficiency were excluded
Interventions	PEG400 without electrolytes, 0.5 g/kg/day, maximal does 1 g/kg/day or milk of magnesia suspension, 400 mg/5mL, 0.5 mL/kg/day, maximal does 3 mL/kg/day
Outcomes	The primary outcome measure was the improvement rate, defined as the proportion of patients who had > three bowel movements per week, < two episodes of faecal incontinence per month, and no painful defecation, with or without laxative therapy. Other outcome studies were: 1) improvement in stool frequency per week; 2) the proportion of the patients who had any adverse effects; and 3) the compliance rate, defined as the proportion of patients who received more than 80% of the medication. Follow up was for 4 weeks
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated random number list
Allocation concealment (selection bias)	Low risk	Sealed opaque assignment envelopes sequentially opened
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not clear whether this was a blinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full details reported

Ratanamongkol 2009 (*Continued*)

Selective reporting (reporting bias)	Low risk	Data reported appropriately
Other bias	Low risk	None apparent

Thomson 2007

Methods	Randomised controlled double blind crossover trial comparing PEG 3350 with electrolytes versus placebo
Participants	51 children aged 24 months to 11 years were eligible for enrolment. Constipation was defined according to the Rome criteria. Children were excluded from the study if they had current or previous faecal impaction or organic pathology causing their constipation Also, if they were currently receiving doses of stimulant laxatives considered by local observers to be at the higher end of their own dose spectrum (senna or sodium picosulphate) with no effect, having assessed to their clinical satisfaction adequate compliance
Interventions	Placebo or PEG 3350 with electrolytes (Movicol, Norgine Pharnaceuticals, UK). The dosing regimen was based on age and clinical response. Participants received 2 weeks of therapy, followed by a 2 week washout period and then a further 2 weeks with the alternate therapy
Outcomes	The primary efficacy variable was the mean number of complete defaecations per week. Secondary efficacy variables included the total number of complete and incomplete defaecations per week, pain on defaecation, straining on defaecation, faecal incontinence, stool consistency, and a global assessment of treatment by the investigator and by the child or his or her parent or guardian, as well as recording of adverse events. Follow up for 6 weeks
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated random number list
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes used
Blinding (performance bias and detection bias) All outcomes	Low risk	Described and appropriate
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full details reported
Selective reporting (reporting bias)	Low risk	Data reported appropriately

Thomson 2007 (*Continued*)

Other bias	Low risk	Sponsored by Norgine Pharmaceuticals. The author confirmed that they had no involvement in the writing of the final manuscript

Tolia 1993

Methods	Randomised controlled open trial comparing PEG 3350 with mineral oil (liquid paraffin) for the treatment of faecal impaction
Participants	36 children older than 2 years in age with constipation were potentially acceptable for the study. Patients were excluded if they had any other organic cause for their impaction. physical examination by the presence of firm to hard faecal impaction in the anal canal and rectal ampulla on an otherwise normal complete initial physical examination
Interventions	PEG 3350 (Colyte, 20 mL/kg/hour for 4 hours) on two days or 30 mL/10kg of mineral oil twice a day for two days. Those receiving PEG had a single dose of metoclopramide
Outcomes	Outcomes included time to first stool, frequency of stool movements, consistency, distention, cramps, nausea and vomiting, as well as side effects.Follow up were after two days
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated random number list
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full details reported
Selective reporting (reporting bias)	Low risk	Data reported appropriately
Other bias	Low risk	None apparent

Urganci 2005

Methods	Randomised open label trial of Liquid paraffin versus lactulose
Participants	40 children 2 to 12 years old with constipation with evidence of faecal impaction were enrolled in the study.Those with organic pathology were excluded
Interventions	Liquid paraffin or lactulose 1 ml/kg, twice daily for each drug. For determination of the best dose for each child, parents were asked to increase or decrease the volume of each drug by 25% every 3 days as required, to yield two firm-loose stools per day. The maximum dose used throughout the study was 3 mL/kg per day for each drug. All participants received behavioural advice and saw a nutritionist
Outcomes	Primary outcome was effective treatment, defined as clearance of the impaction (more than three bowel movements per week and improvement in stool consistency). Secondary outcomes included stool frequency and stool consistency in first 4 weeks and last 4 weeks, as well as adverse events. Follow up was for 8 weeks
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full details reported
Selective reporting (reporting bias)	Low risk	Data reported appropriately
Other bias	Low risk	None apparent

Voskujl 2004

Methods	Randomised double blind trial comparing PEG 3350 with Lactulose
Participants	100 children aged six month to 15 years were included in this study. Children with an organic cause for their constipation were excluded
Interventions	Patients had a 1 week run in and then received daily rectal enemas for 3 days (<6 years of age received 60 ml Klyx (sodium dioctylsulfosuccinate and sorbitol) while those >6 years of age received 120 ml Klyx). Lactulose (6 g (sachet)) versus PEG 3350 (2.95 g (sachet)

Voskujl 2004 (*Continued*)

	) 1 sachet per day under 6 starting, 2 over 6. Reassed at 1 week and either increase by 1 sachet or decreased by 50%
Outcomes	The primary outcomes were frequency of stools, frequency of encopresis, and overall treatment success at eight weeks. An increase in defecation frequency was considered to have improved if it rose to three or more times a week while encopresis had to decrease to an incidence of one episode or less every two weeks. The incidence of adverse events was also documented. Follow up was for 8 weeks
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical sachets, released by central pharmacy
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full details reported
Selective reporting (reporting bias)	Low risk	Data reported appropriately
Other bias	Low risk	None apparent

Wang 2007

Methods	Randomised controlled multi-centre trial comparing PEG 4000 with lactulose
Participants	216 children from 8-18 years old. Those with other organic disease were excluded
Interventions	Patients received either PEG 4000 (Forlax, 2 sachets x 20g/day) versus lactulose (15 mL/day, then drop to 10 mL after 3 days)
Outcomes	Primary outcome was frequency of bowel movements. Secondary outcomes included stool consistency, abdominal symptoms and safety. Follow up was for 2 weeks
Notes	Chinese publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Wang 2007 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full details reported
Selective reporting (reporting bias)	Low risk	Data reported appropriately
Other bias	Low risk	None apparent

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Berg 1983	Study does not include patients with functional constipation, but those diagnosed with functional soiling
Clayden 1978	Not a RCT, Letter
Corazziari 1996	Not a Paediatric study
Dupont 2006	Not a RCT, no comparison group
Ferguson 1999	Not a Paediatric study
Hardikar 2007	Not a RCT, no comparison group
Hejl 1990	Not a RCT, no comparison group
Kazak 1999	Meets exclusion criteria, children have underlying pathology
Kinservik 2004	Review article
Loening-Baucke 2002	Not a RCT
Loening-Baucke 2004	Not a RCT, retrospective chart review
Miller 2012	The trial focused on the treatment of faecal impaction rather than treatment of constipation
Moulies 1961	Not a RCT

(*Continued)*

Quitadamo 2010	Abstract publication
Shevtsov 2005	Not a RCT
Sonheimer 1982	Not a RCT
Tolia 1988	Not a RCT
Youssef 2002	Not a RCT, no comparison group

DATA AND ANALYSES

Comparison 1. PEG versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of defecation	2	101	Mean Difference (IV, Random, 95% CI)	2.61 [1.15, 4.08]
2 Serious adverse events	2	101	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.48]

Comparison 2. PEG versus Lactulose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of defecation	4	328	Mean Difference (IV, Random, 95% CI)	1.09 [0.02, 2.17]
2 Need for additional therapies	3	254	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.27, 0.89]
3 Need for additional therapies (sensitivity analysis)	3	254	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.19, 1.38]
4 Adverse events	2	154	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.14, 1.03]

Comparison 3. PEG versus Milk of Magnesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of defecation	3	211	Mean Difference (IV, Fixed, 95% CI)	0.69 [0.48, 0.89]
2 Frequency of defecation (sensitivity analysis)	3	211	Mean Difference (IV, Random, 95% CI)	0.69 [0.48, 0.89]

Comparison 4. Paraffin versus Lactulose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of defecation	2	287	Mean Difference (IV, Fixed, 95% CI)	4.94 [4.28, 5.61]

Comparison 5. PEG versus Enema

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of defecation	1	80	Mean Difference (IV, Fixed, 95% CI)	1.00 [-1.58, 3.58]
2 Successful disimpaction	1	90	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.20, 1.37]

Comparison 6. Lactulose versus Lactitol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of defecation	1	42	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-2.63, 1.03]

Comparison 7. PEG versus Paraffin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of defecation	1	158	Mean Difference (IV, Fixed, 95% CI)	0.70 [-0.38, 1.78]

Analysis 1.1. Comparison 1 PEG versus Placebo, Outcome 1 Frequency of defecation.

Review: Osmotic and stimulant laxatives for the management of childhood constipation

Comparison: 1 PEG versus Placebo

Outcome: 1 Frequency of defecation

Study or subgroup	PEG N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Nurko 2008	26	5.96 (3.81)	24	2.42 (2.104)		39.3 %	3.54 [1.85, 5.23]
Thomson 2007	27	3.59 (2.26)	24	1.58 (1.131)		60.7 %	2.01 [1.04, 2.98]
Total (95% CI)	**53**		**48**			**100.0 %**	**2.61 [1.15, 4.08]**

Heterogeneity: Tau^2 = 0.68; Chi^2 = 2.38, df = 1 (P = 0.12); I^2 =58%

Test for overall effect: Z = 3.49 (P = 0.00048)

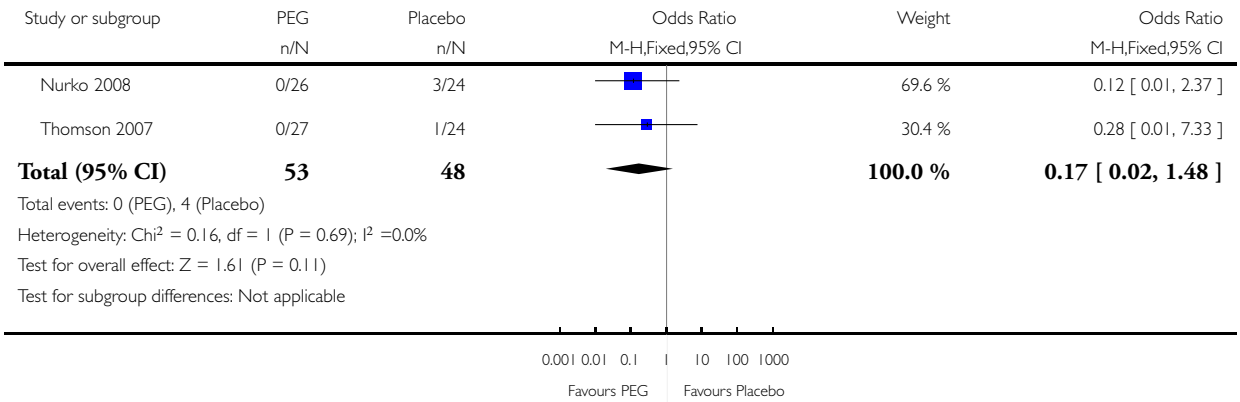
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 PEG versus Placebo, Outcome 2 Serious adverse events.

Review: Osmotic and stimulant laxatives for the management of childhood constipation

Comparison: 1 PEG versus Placebo

Outcome: 2 Serious adverse events



Analysis 2.1. Comparison 2 PEG versus Lactulose, Outcome 1 Frequency of defecation.

Review: Osmotic and stimulant laxatives for the management of childhood constipation

Comparison: 2 PEG versus Lactulose

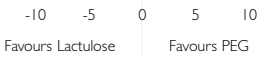
Outcome: 1 Frequency of defecation

Study or subgroup	PEG N	Mean(SD)	Lactulose N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Candy 2006	28	9.4 (4.56)	30	5.9 (4.29)		14.2 %	3.50 [1.22, 5.78]
Dupont 2005	51	7.24 (1.48)	45	7.21 (2.67)		31.2 %	0.03 [-0.85, 0.91]
Gremse 2002	37	14.8 (1.4)	37	13.5 (1.5)		34.3 %	1.30 [0.64, 1.96]
Voskujl 2004	50	7.12 (5.14)	50	6.43 (3.08)		20.3 %	0.69 [-0.97, 2.35]
Total (95% CI)	**166**		**162**			**100.0 %**	**1.09 [0.02, 2.17]**

Heterogeneity: $Tau^2 = 0.77$; $Chi^2 = 10.17$, df = 3 (P = 0.02); $I^2 = 70\%$

Test for overall effect: Z = 1.99 (P = 0.047)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 PEG versus Lactulose, Outcome 2 Need for additional therapies.

Review: Osmotic and stimulant laxatives for the management of childhood constipation

Comparison: 2 PEG versus Lactulose

Outcome: 2 Need for additional therapies

Study or subgroup	PEG n/N	Lactulose n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Candy 2006	0/28	8/30		26.1 %	0.05 [0.00, 0.85]
Dupont 2005	14/51	19/45		47.4 %	0.52 [0.22, 1.22]
Voskujl 2004	9/50	10/50		26.5 %	0.88 [0.32, 2.39]
Total (95% CI)	**129**	**125**		**100.0 %**	**0.49 [0.27, 0.89]**

Total events: 23 (PEG), 37 (Lactulose)

Heterogeneity: $Chi^2 = 3.85$, df = 2 (P = 0.15); $I^2 = 48\%$

Test for overall effect: Z = 2.32 (P = 0.020)

Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 PEG versus Lactulose, Outcome 3 Need for additional therapies (sensitivity analysis).

Review: Osmotic and stimulant laxatives for the management of childhood constipation

Comparison: 2 PEG versus Lactulose

Outcome: 3 Need for additional therapies (sensitivity analysis)

Study or subgroup	PEG n/N	Lactulose n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Candy 2006	0/28	8/30		10.3 %	0.05 [0.00, 0.85]
Dupont 2005	14/51	19/45		47.6 %	0.52 [0.22, 1.22]
Voskujl 2004	9/50	10/50		42.2 %	0.88 [0.32, 2.39]
Total (95% CI)	**129**	**125**		**100.0 %**	**0.51 [0.19, 1.38]**

Total events: 23 (PEG), 37 (Lactulose)

Heterogeneity: $Tau^2 = 0.36$; $Chi^2 = 3.85$, df = 2 (P = 0.15); $I^2 = 48\%$

Test for overall effect: Z = 1.33 (P = 0.18)

Test for subgroup differences: Not applicable

Analysis 2.4. Comparison 2 PEG versus Lactulose, Outcome 4 Adverse events.

Review: Osmotic and stimulant laxatives for the management of childhood constipation

Comparison: 2 PEG versus Lactulose

Outcome: 4 Adverse events

Study or subgroup	PEG n/N	Lactulose n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Candy 2006	17/28	25/30		75.6 %	0.31 [0.09, 1.05]
Dupont 2005	2/51	3/45		24.4 %	0.57 [0.09, 3.58]
Total (95% CI)	**79**	**75**		**100.0 %**	**0.37 [0.14, 1.03]**

Total events: 19 (PEG), 28 (Lactulose)

Heterogeneity: $Chi^2 = 0.30$, df = 1 (P = 0.59); $I^2 = 0.0\%$

Test for overall effect: Z = 1.91 (P = 0.057)

Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 PEG versus Milk of Magnesia, Outcome 1 Frequency of defecation.

Review: Osmotic and stimulant laxatives for the management of childhood constipation

Comparison: 3 PEG versus Milk of Magnesia

Outcome: 1 Frequency of defecation

Study or subgroup	PEG N	Mean(SD)	MOM N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Gomes 2011	17	5 (1.56)	21	4.31 (1.89)		3.4 %	0.69 [-0.41, 1.79]
Loening-Baucke 2006	39	9.7 (5.6)	40	9.7 (6)		0.6 %	0.0 [-2.56, 2.56]
Ratanamongkol 2009	47	5.94 (0.652)	47	5.25 (0.32)		95.9 %	0.69 [0.48, 0.90]
Total (95% CI)	**103**		**108**			**100.0 %**	**0.69 [0.48, 0.89]**

Heterogeneity: $Chi^2 = 0.28$, df = 2 (P = 0.87); $I^2 = 0.0\%$

Test for overall effect: Z = 6.61 (P < 0.00001)

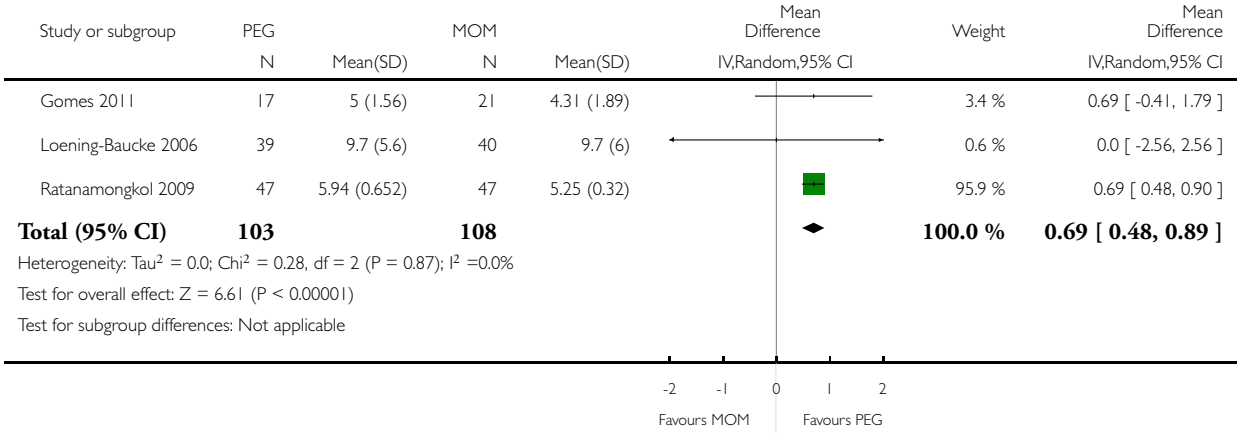
Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 PEG versus Milk of Magnesia, Outcome 2 Frequency of defecation (sensitivity analysis).

Review: Osmotic and stimulant laxatives for the management of childhood constipation

Comparison: 3 PEG versus Milk of Magnesia

Outcome: 2 Frequency of defecation (sensitivity analysis)

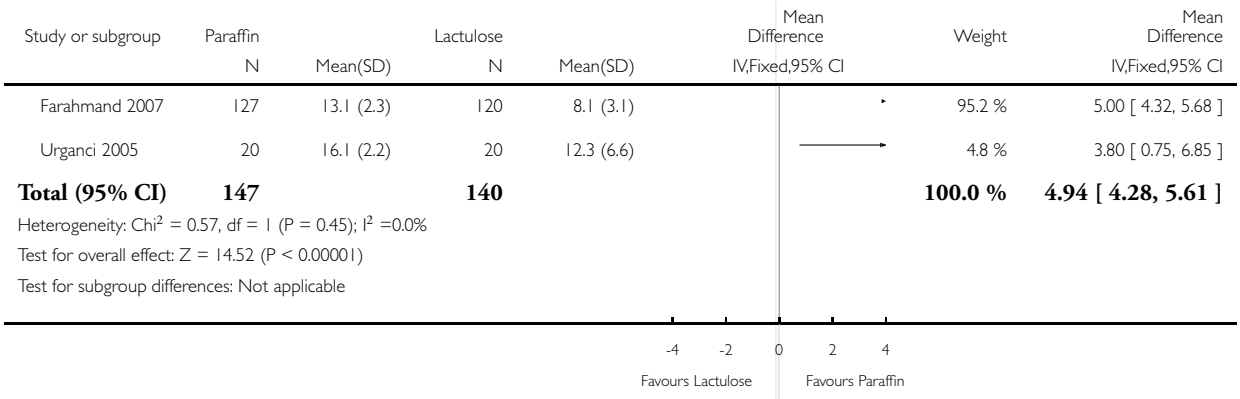


Analysis 4.1. Comparison 4 Paraffin versus Lactulose, Outcome 1 Frequency of defecation.

Review: Osmotic and stimulant laxatives for the management of childhood constipation

Comparison: 4 Paraffin versus Lactulose

Outcome: 1 Frequency of defecation



Analysis 5.1. Comparison 5 PEG versus Enema, Outcome 1 Frequency of defecation.

Review: Osmotic and stimulant laxatives for the management of childhood constipation

Comparison: 5 PEG versus Enema

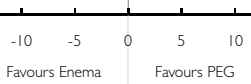
Outcome: 1 Frequency of defecation

Study or subgroup	PEG N	Mean(SD)	Enema N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bekkali 2009	39	8.7 (6.4)	41	7.7 (5.3)		100.0 %	1.00 [-1.58, 3.58]
Total (95% CI)	**39**		**41**			**100.0 %**	**1.00 [-1.58, 3.58]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.76 (P = 0.45)

Test for subgroup differences: Not applicable

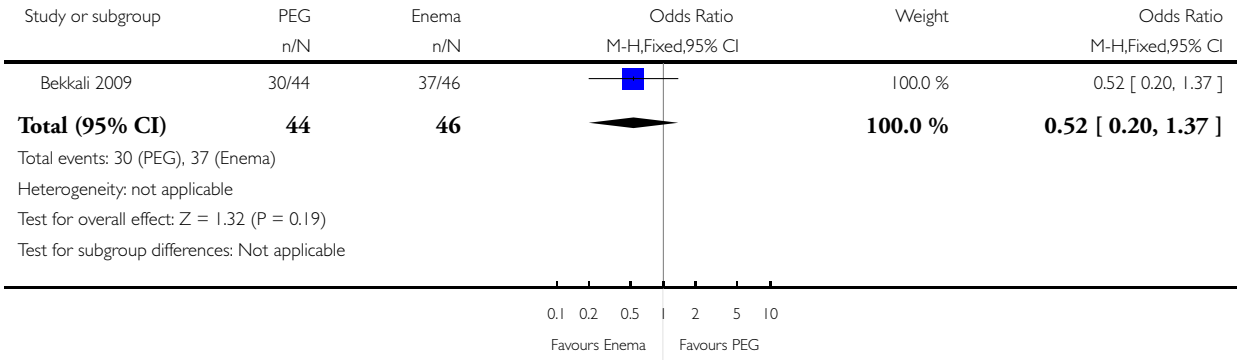


Analysis 5.2. Comparison 5 PEG versus Enema, Outcome 2 Successful disimpaction.

Review: Osmotic and stimulant laxatives for the management of childhood constipation

Comparison: 5 PEG versus Enema

Outcome: 2 Successful disimpaction

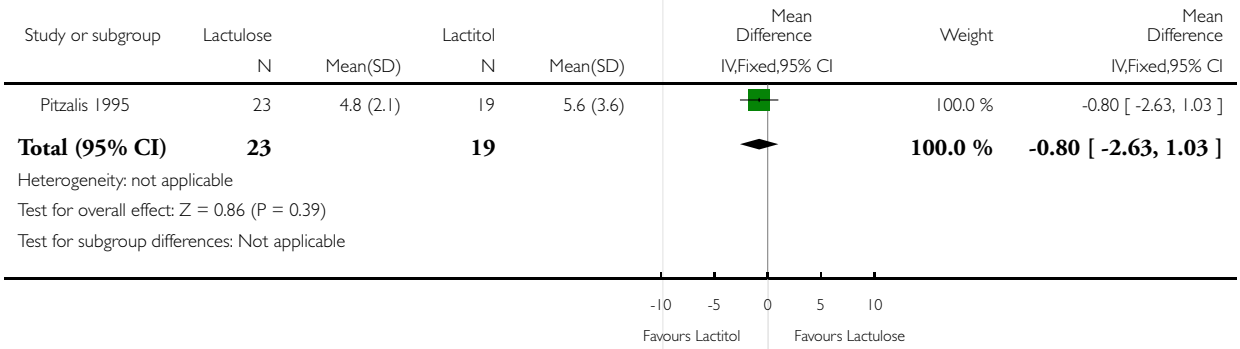


Analysis 6.1. Comparison 6 Lactulose versus Lactitol, Outcome 1 Frequency of defecation.

Review: Osmotic and stimulant laxatives for the management of childhood constipation

Comparison: 6 Lactulose versus Lactitol

Outcome: 1 Frequency of defecation

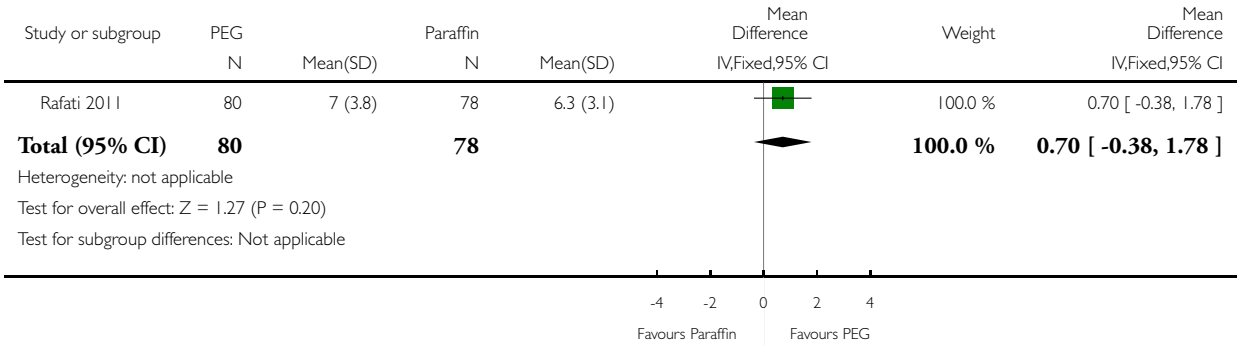


Analysis 7.1. Comparison 7 PEG versus Paraffin, Outcome 1 Frequency of defecation.

Review: Osmotic and stimulant laxatives for the management of childhood constipation

Comparison: 7 PEG versus Paraffin

Outcome: 1 Frequency of defecation



HISTORY

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CONTRIBUTIONS OF AUTHORS

Morris Gordon conceived the review, carried out the search, data extraction and analysis and led the writing of the manuscript. Khimara Naidoo also conducted the search, data extraction and assisted with the analysis, as well as commenting on drafts of the manuscript. Anthony Akobeng and Adrian Thomas assisted with the analysis and contributed towards the writing and commented on drafts of the review.

DECLARATIONS OF INTEREST

Morris Gordon received a travel grant from Norgine Pharmaceuticals to present the results of this review at Digestive Disease Week in Chicago, May 2011. Norgine had no input in the design, execution or write up of the study. Additionally, Morris Gordon has received travel grants since completing this review from Cassen Fleet Pharmaceuticals and Ferring Pharmaceuticals to attend Digestive Disease Week 2012, but again they have had no involvement in this or any other research works completed.

INDEX TERMS

Medical Subject Headings (MeSH)

Constipation [*drug therapy]; Defecation [drug effects; physiology]; Dietary Fiber [adverse effects; therapeutic use]; Lactulose [adverse effects; therapeutic use]; Laxatives [adverse effects; *therapeutic use]; Magnesium Hydroxide [adverse effects; therapeutic use]; Mineral Oil [adverse effects; therapeutic use]; Osmosis; Polyethylene Glycols [adverse effects; therapeutic use]; Randomized Controlled Trials as Topic; Sugar Alcohols [adverse effects; therapeutic use]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant