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

Pijpers MA, Tabbers MM, Benninga MA, Berger MY

CRD summary
The review found that there was insufficient evidence to show that laxatives were superior to placebo for treating constipation in children and that no one laxative could be recommended over any other. Although the review was limited in some respects, in particular the failure to address statistical heterogeneity, the authors' cautious conclusions appear justified.

Authors' objectives
To determine the effectiveness of laxatives and dietary interventions for functional childhood constipation.

Searching
MEDLINE and EMBASE were searched from inception to December 2007. Search terms were reported. Reference lists of review articles and eligible studies were checked. The search was not limited by language.

Study selection
Randomised controlled trials (RCTs), comparative clinical trials (CCTs) and crossover studies that compared medications or dietary interventions for functional constipation (with or without faecal incontinence) in children aged 0 to 18 years were eligible for inclusion. The intervention was required to consist of laxatives (osmotic, bulk-forming or emollient), lubricating agents or dietary measures compared with placebo, no treatment or alternative treatment. Required outcomes were establishment of normal bowel habit (more frequent defaecation and/or less frequent faecal incontinence) or treatment success as defined in the study. Studies of children with mental handicaps, psychiatric disorders, organic causes of constipation or exclusively non-retentive faecal incontinence were excluded.

Most of the included studies were conducted in general or gastroenterological paediatric departments in hospitals; only one was set in primary care. Mean age of participants (where stated) ranged from under seven weeks to over 11 years. There was no uniform definition for childhood constipation or for treatment success. Studies differed widely with regard to participants, interventions and outcomes measures. Interventions included laxatives (polyethylene glycol with or without electrolytes, lactulose, mineral oil, senna, liquid paraffin), cisapride (now withdrawn from sale), fibre (cocoa husk, glucomannan), erythromycin estolate, calcium polycarbophil and biofeedback therapy. These were compared with each other or (less commonly) with placebo or no treatment. Some dose-finding studies were also included. Duration of follow-up ranged from three weeks to 12 months.

Two reviewers independently selected the studies. Disagreements were resolved by consensus or by third reviewer.

Assessment of study quality
A published list (Verhagen 1998) was used to evaluate the following components of study validity: randomisation; allocation concealment; baseline group equivalence; reporting of selection criteria; blinding; statistical reporting; use of intention to treat (ITT) analysis; and withdrawal rate. Studies were scored out of a maximum of 10 points; studies that scored six or more points were designated high quality.

Two reviewers independently assessed individual studies. Disagreements were resolved by consensus or by a third reviewer.

Data extraction
Event rates in each group were extracted for dichotomous outcomes, with p values for differences between groups. Mean differences between groups, with standard deviations, were extracted for continuous outcomes.
Two reviewers independently extracted the data. Disagreements were resolved by consensus or by a third reviewer.

**Methods of synthesis**
Where study participants, interventions and outcomes were considered sufficiently similar, a random effects model was used and risk ratios (RRs) and weighted mean differences (WMDs), with 95% confidence intervals (CIs) were calculated. Numbers needed to treat were calculated. Statistical heterogeneity was assessed using the X² test. Studies that were unsuitable for statistical pooling were combined in a narrative synthesis. Studies with fewer than five children per arm were not included in the narrative synthesis.

**Results of the review**
Twenty eight studies were included in the review (n=approximately 2,000, range 14 to 220): 21 RCTs (n=approximately 1,700); one CCT (n=79); and six crossover studies (n=approximately 200). Ten were high quality (scored at least six points). Overall methodological quality was poor. Mean overall quality score was 4.8 points (range one to 10). The most common limitations were lack of allocation concealment, unblinded outcome assessment, lack of intention-to-treat analysis and prognostic differences between groups.

One high quality RCT provided moderate evidence that polyethylene glycol was significantly more effective than placebo at increasing defaecation frequency (WMD 1.64 bowel movements per week, 95% CI 0.99 to 2.28); faecal incontinence rates did not differ significantly.

Polyethylene glycol was significantly more likely than other laxatives to achieve treatment success (RR 1.47, 95% CI 1.23 to 1.76, NNT=4, 95% CI 2.9 to 6; seven studies, two high quality). There was significant heterogeneity (p<0.0001) for this analysis.

Polyethylene glycol was significantly associated with treatment success (or soft/normal stools) when compared with lactulose only (RR 1.63, 1.40 to 1.90, NNT=3.3, 95% CI 2.6 to 4.5; four studies, two high quality). There was significant heterogeneity (p<0.0001) for this analysis.

Overall, there was conflicting evidence on the effectiveness of lactulose (eight studies, three high quality), senna (three low-quality studies) and mineral oil (three low-quality studies) versus comparators. Two studies (one high quality) that compared fibre versus placebo found no significant difference for defaecation frequency. There was moderate evidence (one high-quality study) that infant formula with sn-2 palmitic acid did not differ significantly from standard infant formula for defaecation frequency.

Other results were reported in the review.

**Authors' conclusions**
There was insufficient evidence to show that laxatives were superior to placebo for treating constipation in children. No one laxative could be recommended over any other.

**CRD commentary**
The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies without language restriction. It appeared that no specific attempts were made to retrieve unpublished studies. Publication bias was not formally assessed. Steps were taken to minimise reviewer bias and error by having more than one reviewer independently select studies, assess validity and extract data. However, the tool used for validity assessment was designed for RCTs and of doubtful applicability to other study designs. Characteristics of the included studies were described in adequate detail and study quality was taken into account in interpreting the results. It appeared that appropriate statistical techniques were used to pool data and assess for heterogeneity. However, where significant statistical heterogeneity was detected, it was not explored further and no explanation was proposed. This reduced the credibility of review findings on polyethylene glycol. For most comparisons, the authors appropriately refrained from pooling the data. In some cases, where no statistically significant difference was found between two interventions the authors interpreted this to mean that the interventions were equally effective, but it seemed more plausible that the analyses were underpowered. Although the review was limited in some respects, in particular the failure to address...
statistical heterogeneity, the authors' cautious conclusions appear justified.

Implications of the review for practice and research

**Practice:** The authors stated that despite some evidence of superior treatment success with polyethylene glycol, evidence was inconsistent and no laxative was clearly superior to others. The risk of adverse effects should play a major role in the choice of laxative.

**Research:** The authors stated that there was a need for large well-designed placebo-controlled trials conducted in primary care to evaluate the use of laxatives (especially polyethylene glycol and lactulose) for functional constipation in children; adverse effects should be systematically reported in such studies. Dose-finding studies of laxatives were required. A clear standard definition of childhood constipation was required and should be validated in primary care. Guidelines should make it clear that current recommendations were not evidence-based.

**Funding**
The authors stated that there were no competing interests.

**Bibliographic details**
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): 117-131

**PubMedID**
18713795

**DOI**
10.1136/adc.2007.127233

**Original Paper URL**
<A href="http://adc.bmj.com/content/94/2/117.long"&gt;http://adc.bmj.com/content/94/2/117.long&lt;/A&gt;

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adolescent; Child; Child, Preschool; Constipation /diet therapy /drug therapy; Controlled Clinical Trials as Topic /standards; Evidence-Based Medicine; Humans; Infant; Infant, Newborn; Lactulose /therapeutic use; Laxatives /therapeutic use; Polyethylene Glycols /therapeutic use; Quality Assurance, Health Care

**AccessionNumber**
12009103657

**Date bibliographic record published**
20/05/2009

**Date abstract record published**
27/01/2010

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.