Evidence-based guideline development in paediatric gastroenterology

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The effect of placebo in irritable bowel syndrome and functional constipation in children: a systematic review

M.M. Tabbers, A.G.E. Leenders, M.A. Benninga

Abstract

Aim
Placebo effect has an important impact on the interpretation of randomised controlled trials (RCTs) in children with functional gastrointestinal disorders. This article gives an overview of the current evidence for placebo use in the treatment of children with irritable bowel syndrome (IBS) and functional constipation.

Methods
We performed a systematic literature search in Pubmed, Embase, CINAHL and Cochrane Library databases and included systematic reviews and randomised controlled trials concerning placebo treatment in children with IBS and functional constipation.

Results
Two systematic reviews and two subsequent RCTs were found in children with IBS. These studies showed that Lactobacillus GG was more effective than placebo with respect to reduction in pain frequency and decrease in perceived abdominal distension. Compared to placebo, peppermint oil seemed to be more effective in improving symptoms related to IBS. Placebo and amitriptyline were equally effective in response to treatment (child’s assessment of pain relief and sense of improvement) in children with IBS. In a small RCT, however, amitriptyline was more effective compared to placebo in improvement of the overall quality of life score in children with IBS. Only two systematic reviews in children with functional constipation were found, reporting that fibre may be more effective than placebo in improving bowel movements, in improvement stool consistency and in the reduction of abdominal pain. Macrogol was more effective than placebo in increasing number of defecations, reduction of hard stools and in reduction of pain- and straining during defeication.

Conclusion
There is a lack of placebo-controlled trials of high quality in children with IBS and functional constipation. More well designed, large RCTs are necessary to determine and understand the role of placebo in children with these functional gastrointestinal disorders.
Introduction

Many children worldwide suffer from functional gastrointestinal disorders like irritable bowel syndrome (IBS) and functional constipation. (1) A recently published systematic review showed a prevalence up to 19% of IBS during childhood. (2) Whereas a systematic review on paediatric constipation in the general population revealed a prevalence ranging from 0.7% to 29.6%. (3) Both IBS and constipation in childhood carry a considerable cost for society and have a negative effect on the patient’s quality of life (QoL). (3-8) Despite its prevalence and impact on QOL and health expenditures, few therapies have been found to be effective for treating these two conditions. (9,10) The efficacy of therapeutic regimens for paediatric IBS and constipation is undoubtedly impacted by the heterogeneous pathogenesis. Studies in children have shown that the aetiology is most likely multifactorial, due to one or more abnormalities including altered intestinal motility, altered visceral sensation, food intolerance and post-infectious changes. (11-16)

Patients in placebo arms of randomised controlled trials in a variety of disorders often experience considerable clinical improvement. In up to 30-40 percent of adult patients with IBS subjective and objective improvement has been reported. (17) Surprisingly, there is a paucity of large patient sample, placebo-controlled studies of high quality reporting the efficacy of laxative agents in adult patients with constipation. (18)

The aim of this review is to give an overview of the current evidence for placebo use in the treatment of children with irritable bowel syndrome and functional constipation. We will evaluate the effect of placebo, based on trials that randomised patients to a placebo group and to a treatment group.

Materials and methods

To identify published evidence, we searched Pubmed, Embase, CINAHL and Cochrane Library (Clinical trials) databases from inception to November 2009. We used relevant keywords in the area of ‘functional disorders in childhood’ and placebo. There was no restriction on language of publication. One reviewer (MT) screened all abstracts of identified published articles for eligibility. Three specific criteria for inclusion were used: 1. Study population consisted of children 0-18 years, 2. Study was a systematic review or randomised placebo-controlled trial 3. One of the aims of the study was to evaluate the effect of dietary measures, pain medication or laxatives versus placebo or no treatment on IBS and functional constipation. All definitions of IBS and functional constipation were accepted. The Delphi list was used to assess the methodological quality of the included studies. The full search strategy is available from the authors.
Results:

We could not perform a new meta-analysis of all included studies on IBS and functional constipation as most studies were highly diverse with regard to the participants, interventions and outcome measures. We will discuss all studies therefore separately.

Irritable bowel syndrome (IBS) (see table 1a for study characteristics of the included studies)

We found two systematic reviews. (19, 20) The aim of the first Cochrane review (The Cochrane Library (CENTRAL) 2006 (Issue 4), MEDLINE (1966 to Dec 2006), EMBASE (1980 to Dec 2006), CINAHL (1982 to Dec 2007), ERIC (1966 to Dec 2006), PsycINFO (1872 to Dec 2006), LILACS (1982 to Dec 2006), SIGLE (1980 to March 2005), and JICST (1985 to 06/2000) ) was to determine the effectiveness of dietary interventions for recurrent abdominal pain in school-age children.(19) Selection criteria were randomised or quasi-randomised studies of any dietary treatment versus placebo or no treatment in school-age children with a diagnosis of recurrent abdominal pain (RAP) or functional gastrointestinal disorders based on the Rome II criteria.(21) Two trials were included concerning children with IBS which we will discuss separately.(22,23).

The first RCT compared oral administration of Lactobacillus GG with placebo.(22) Both probiotic and placebo capsules were similar in size, color and taste. The physician recorded pretrial and post-trial measures during an interview using the 15-item Gastrointestinal Symptom Rating Scale (GSRS). The child and family ranked each of the symptoms on a 4-point Likert scale (0 = no or transient symptoms, 1 = occasional symptoms, 2 = frequent symptoms, 3 = severe or continuous symptoms). The study results showed that Lactobacillus GG was not more effective in relieving abdominal pain compared to placebo. The response rate (defined as a decrease in abdominal pain severity of 1 or more levels from baseline to the end of treatment) was 44% (11/25) in the probiotic group versus 40% (10/25) in the placebo group, p=0.77. Furthermore, no significant difference was found in the response rate of diarrhea: 11.8% (2/17) in the probiotic group versus 0% (0/18) in the placebo group, p=0.229, indigestion: 13% (3/23) in the probiotic group versus 4.2% (1/24) in the placebo group, p=0.348 and constipation: 13.6% (3/22) in the probiotic group versus 5% (1/20) in the placebo group, p=0.608. A significant difference was found in perceived abdominal distension (0% in the probiotic group versus 24% in the placebo group, p=0.02). Precise numbers were not given. This RCT included also adult patients between 18 and 20 years. Follow-up was not complete and outcome was only available in 25/32 children in each group. Adverse events were not well reported.

The second trial also compared oral administration of Lactobacillus GG with placebo for a shorter period.(23) The capsules were identical. Since the aim of our study was only to evaluate children with IBS, only data on 37 children with IBS will be discussed. Abdominal
pain diaries were used to measure outcomes. A significant higher success percentage was found in children receiving the probiotic strain LGG (defined as no pain-score of 0 on the faces pain scale- at the end of the intervention) : 33% (6/18) in the probiotic group versus 5 % (1/19) in the placebo group, p=0.04. The self-reported frequency of pain at 4 weeks was significantly reduced in the probiotic group versus placebo: 1.8 versus 3.1, p=0.02. Self-reported severity of pain was not significantly different between both groups at week 4: 2.2 in the probiotic group versus 3.2 in the placebo group, p=0.10. Neither was at 4 weeks improvement of symptoms ( 55% (10/18) in the probiotic group versus 31.6% (6/19) in the placebo group, p=0.19) or use of medication ( 22.2% (4/18) in the probiotic group versus 15.8% (3/19) in the placebo group, p=0.69) or school absenteeism (5.5% (1/18) in the probiotic group versus 0% (0/19) in the placebo group, p=0.49). No adverse effects were reported and LGG was well tolerated.

The aim of the second Cochrane review. The Cochrane Library (CENTRAL) 2006 (Issue 4), MEDLINE (1966 to Dec 2006), EMBASE (1980 to Dec 2006), CINAHL (1982 to Dec 2007), ERIC (1966 to Dec 2006), PsycINFO (1872 to Dec 2006), LILACS (1982 to Dec 2006), SIGLE (1980 to March 2005), and JICST (1985 to 06/2000) was to determine the effectiveness of medication for recurrent abdominal pain in school-age children.(20) Selection criteria were randomised or quasi-randomised studies of a drug treatment versus placebo or no treatment in school-age children with a diagnosis of recurrent abdominal pain (RAP) (Apley or the Rome II criteria for gastrointestinal diseases). The review included only one single trial concerning children with IBS.(24) This trial compared oral administration of peppermint oil with placebo. Pre- and post-trial measurements were recorded by the same investigator during an interview on day 1 and 14 using the 15-item Gastrointestinal Symptom Rating Scale (GSRS). Severity of pain was ranked on a scale of 1 to 5 (1 = excellent, 2 = good, 3 = fair, 4 = bad, and 5 = terrible) on day 1 and day 14 of the trial and also the change in symptoms (1 = much better, 2 = better, 3 = no effect, 4 = worse, and 5 = much worse). Patients filled out a daily abdominal pain diary. A total of 42 children completed the study. The peppermint oil group showed a significant improvement in the change of symptom scale compared to placebo after two weeks: 71% (15/21) in the peppermint oil group versus 19% (9/21) in the placebo group, p< 0.002. OR for improvement was 3.33; 95% CI 0.93, 12.01. Data were not clearly provided. Furthermore, the method of randomisation was not described. No side-effects were reported.

**RCTs published after the systematic reviews:**

One RCT compared amitriptyline, a tricyclic antidepressant, with placebo for 4 weeks after a 1-week baseline observation period. (25) Of all children, 40% in the amitriptyline group were suffering from IBS compared to 62% receiving placebo. The capsules were identical. Pain was assessed daily with self-report abdominal pain diaries. The authors did not report outcomes of the IBS patients separately. Primary outcome measures for the whole group
was overall response to treatment (defined as child’s assessment of pain relief and sense of improvement). Logistic regression did not show any effect of diagnosis in the primary outcome measure within the placebo group (IBS, p=0.42). Therefore, we will discuss the primary outcome measure for the whole group. No significant difference was found in sense of improvement in both groups (63% of patients reported feeling better and 5% feeling worse in the amitriptyline group versus 57.5% feeling better and 2.5% feeling worse in the placebo group, p=0.63), neither in pain relief (excellent in 15% and good in 35% of children in the amitriptyline group versus excellent in 7% and good in 38% in the placebo group, p=0.85). No major side effects were reported.

The second RCT compared amitriptyline with placebo. (26) All patients completed a symptom checklist, a pain rating scale, a visual analog scale and IBS quality of life (QOL) questionnaire at week 2, 6, 10 and at 13 weeks. At baseline, a significant difference in the mean overall QOL scores between both groups was found: 109.4 in the amitriptyline group compared to 127.5 in the placebo group, p=0.05 but not in the mean intensity of pain: 65.9% in the amitriptyline group compared to 64.4% in the placebo group, p=0.9, precise numbers were not given. A significant difference was reported in the primary outcome (improvement in overall QOL-score from baseline), which was in favor of the amitriptyline group: mean overall QOL scores in the amitriptyline group at week 6, 10 and 13 were 127.6, 128.0, 126.2, respectively compared to 132, 129.4, and 129.8 respectively in the placebo group, with p-values of 0.019, 0.004 and 0.013 respectively. Compared with baseline, children receiving amitriptyline were significantly more likely to have at least a 15% improvement in overall QOL score at week 10 (p=0.007) and week 13 (p=0.002) respectively than those receiving placebo. Furthermore there were significant differences found in favor of amitriptyline in improvement in dysphoria at week 10 and 13 (p=0.003 and 0.014, respectively), interference with activities at week 6 and 10 (p=0.03 and p=0.003, respectively), health worry at 10 and 13 weeks (p=0.024 and p=0.0002, respectively), and food avoidance at week 6 and 10 weeks (p=0.008 and p=0.007, respectively). No significant improvement was found for these items or overall score after baseline compared with any other recorded time. Compared with baseline, subjects receiving amitriptyline were significantly more likely to experience a reduction in IBS-associated diarrhea at 6 and 10 weeks (p=0.029 at both intervals) than those receiving placebo. Children receiving amitriptyline were also significantly more likely to experience a reduction in periumbilical abdominal pain at 10 weeks (p=0.018), and in right lower quadrant abdominal pain at 6, 10, and 13 weeks (p=0.014, p=0.039, and p=0.004, respectively. This study has major drawbacks with could have caused bias. Besides the small groups, the method of blinding and randomisation are not clearly described, either the placebo treatment (dosage, taste, color?). Furthermore, the authors do not provide clear information about the intention to treat population. Side effects were not well reported.
Functional constipation (see table 1b for study characteristics of the included studies)

We found two systematic reviews (9,27) The first recent systematic review (MEDLINE and EMBASE databases, search date from inception to December 2007, 28 trials [21 RCTs, 1 comparative clinical trial and 6 crossover studies], 1912 children aged 0–18 years with functional constipation and with or without faecal incontinence) comparing laxatives or dietary measures versus placebo, no treatment, or alternative treatments.(9) We will discuss the included RCTs comparing laxatives or dietary measures versus placebo in children with functional constipation separately.

Fibre vs placebo

This review identified two RCTs comparing fibre versus placebo. One small crossover RCT compared fibre (glucomannan) versus placebo. (28) If instituted all children continued the same amount of laxatives during the study period. Patients filled out a daily bowel diary. Remarkably, the initial daily fibre intake was low in 71% (22/31) of all constipated children. Pre-crossover, the RCT found that the proportion of children who had < 3 bowel movements p/week and had abdominal pain was significantly smaller with fibre compared with placebo (< 3 bowel movements/week: 19% with fibre v 52% with placebo; P <0.05; abdominal pain: 10% with fibre v 42% with placebo; P <0.05; absolute numbers not reported for either outcome). Furthermore, the proportion of children who were rated by their physician as having been treated successfully and rated as improved by their parents was significantly larger after treatment with fibre compared with placebo (physician-rated: 45% with fibre v 13% with placebo; P <0.05; parent-rated: 68% with fibre v 13% with placebo; P <0.05; absolute numbers not reported for either comparison). Physician-rated treatment success was defined as > 3 bowel movements/week and ≤ 1 episodes of encopresis every 3 weeks with no abdominal pain. Risk of bias can be caused by the unclear definition of constipation and high loss to follow up rate: 32% (15/46) of children. Although, these rates were comparable in both groups.

The second RCT compared fibre (a cocoa husk supplement) versus placebo.(29) Patients filled out a daily diary. Difference in the mean basal dietary fibre intake was not statistically significant and the mean basal dietary fibre intake was near to that recommended (age + 10 g) in both groups (12.3 g/day with fibre v 13.4 g/day with placebo, p-value not reported). No significant difference was found in the change of the total colon transit time (from 61.4 to 43.6 hours with fibre v 71.5 to 61.5 with placebo, -12.8; 95% CI: -29.7 to 4) nor in the mean defecation frequency per week (6.2 with fibre v 5.1 with placebo, p=0.78). A significant higher number of children (or their parents) reported a subjective improvement in stool consistency (14/24 with fibre v 6/24 with placebo, p< 0.039), but not a subjective improvement in pain (16/24 with fibre v 11/24 with placebo, p=0.109) with fibre compared to placebo. A subanalysis of 12 children with a total basal intestinal transit time > 50th
percentile showed that the change in total intestinal transit time was significantly higher with fibre compared to placebo (-38.1 hour, 95% CI: -67.9 to -8.4; \( p \leq 0.015 \)). Both RCTs reported no adverse effects of fibre.

**Macrogol versus placebo:**

One crossover RCT compared polyethylene glycol 3350 plus electrolytes (PEG+E) versus placebo. (30) Patients filled out a daily bowel diary. Mean number of complete defecations per week was significantly higher in the PEG+E group compared to placebo (3.12 in PEG+E group versus 1.45 in placebo group), with a treatment difference of 1.64 (95% CI 0.99 to 2.28), \( p < 0.001 \). Furthermore a significant difference was found in the mean score “pain on defecation” (0 = none, 1 = mild, 2 = moderate, 3 = severe) in favor of the PEG+E group compared to the placebo group (0.49 in PEG+E group versus 0.77 in the placebo group, \( p = 0.041 \)) and also with respect to straining during defecation (0 = none, 1 = mild, 2 = moderate, 3 = severe): 0.72 in PEG+E group versus 1.37 in the placebo group, \( p < 0.001 \). The percentage of hard stools was also significantly different in favor of PEG: 14.64 in PEG+E group versus 38.19 in placebo group, \( p < 0.001 \). No significant difference was found in the number of mean faecal incontinence episodes between the PEG+E group versus the placebo group (4.70 in PEG+E group versus 4.85 in the placebo group, \( p = 0.685 \)). Similar percentages of adverse events were reported of children receiving PEG+E (31/49, 63%) or placebo (28/49, 57%). Most were gastro-intestinal symptoms, particularly abdominal pain.

**Senna versus placebo:**

One RCT compared senna (Senokot) with placebo and no medication as control interventions in their three-arm study (31) No significant differences were found in effect in decreasing the number of faecal incontinence episodes per week between the groups: senna 55% versus 64% in placebo, \( p = 0.16 \) and 66% in the no treatment group, \( p = 0.81 \). However, the major drawback of this study is that no clear definition was used, whether the children were suffering from functional constipation or from functional non retentive faecal incontinence. Moreover the follow-up in this study was unclear and varied among the patients. Side effects were not well reported.

**Cisapride versus placebo:**

The review identified two RCTs comparing cisapride versus placebo. (9) Cisapride, a prokinetic agent has been withdrawn from the market due to cardiovascular adverse events and will therefore not be discussed in this review.

The second systematic review (PubMed and EMBASE databases, search date not mentioned, [7 RCTs], 594 children aged < 18 years with constipation of > 3 months’ duration in the absence of structural, endocrine or metabolic disease) compared polyethylene glycol (PEG)
versus either placebo or active comparator in children with functional constipation. (27) This review included only one single trial comparing PEG versus placebo which we will discuss separately. In this RCT children received either placebo or 1 of 3 doses of PEG 3350: 0.2 g/kg per day, 0.4 g/kg per day, or 0.8 g/kg per day. (32) Patients filled out a daily bowel diary during the study period. More children in the PEG 3350 group responded to treatment (≥3 BM during the second week of treatment) compared to the placebo group (77%, 74%, and 73% of the 0.2, 0.4, and 0.8 g/kg PEG 3350 groups versus 42% in the placebo group, p=0.026). Furthermore a significant difference was found in the proportion of children with ≥3 bowel movements/week comparing the 0.8 g/kg groups with the placebo group (62% in 0.8 g/kg PEG3350 group versus 29% in the placebo group, p<0.027). The proportion of children responding to treatment without faecal incontinence during the second week was not significantly different between the PEG 3350 group and placebo group: 31% for 0.2 g/kg, 26% for 0.4 g/kg, 31% for 0.8 g/kg and 8% for placebo, (p=0.2). Similar percentages of adverse events were reported among the groups. (14 patients (58.3%) in the placebo group, 9 (34.6%) in 0.2 g/kg, 16 (59.3%) in 0.4 g/kg, and 17 (65.4%) in 0.8 g/kg.) GI-related events, such as flatulence, abdominal pain, nausea, and diarrhea were more frequently reported in the PEG 3350 group compared with placebo. This review has been sponsored by a pharmaceutical agency.

Discussion

The objective of this review was to provide evidence regarding the effect of placebo compared to dietary or drug interventions for the treatment of either irritable bowel syndrome or constipation in children. This study clearly shows that there is a lack of well-designed placebo-controlled trials of high quality in children with irritable bowel syndrome and functional constipation.

With the limited evidence available, compared to placebo significantly more children with IBS were successfully treated with Lactobacillus GG. In a small RCT, amitriptyline was more effective compared to placebo in improvement of the overall quality of life score in children with IBS. In contrast, a more well designed and larger placebo-controlled study showed that amitriptyline was equally effective in reducing pain in children with IBS.

In children with constipation we found some evidence from small trials that fibre may be more effective than placebo in improving both the frequency and consistency of stools and in abdominal pain reduction. Of all currently used laxatives in children with constipation only macrogol was compared to placebo in a well designed manner. These studies showed that macrogol was more effective than placebo in: increasing bowel frequency per week, improving the consistency of stools and reducing pain during defecation. Surprisingly, macrogol was not more effective than placebo in reducing the number of faecal incontinence episodes.
The main question is why well-designed placebo-controlled trials of high quality with large sample sizes are lacking in the most prevalent, frustrating and long-lasting paediatric functional gastrointestinal disorders?\(^{(4,33,34)}\) In the study by Bahar et al. more than half of the eligible adolescents or their guardians refused to participate in their amitriptyline study. The main reason was that guardians did not prefer the potential use of antidepressant medication for their child after the US Food and Drug Administration (FDA) issued formal “black box” warnings regarding the increased potential for suicidality in children using antidepressant medications like amitriptyline. In the study by Saps et al. more than 5 years were necessary to include only 90 patients with abdominal pain by 6 prestigious tertiary referral centres.\(^{(25)}\) This study gives however no information how many patients were invited and what the reasons were of refusal to participate in their trial. Unfortunately, the same information with respect to invitation and refusal of participation are lacking for the 2 placebo-controlled trials in children with constipation.\(^{(30,32)}\) Other general reasons for refusal to participate in a placebo-controlled trials might be the duration of a study, the possibility to receive placebo instead of active drug and the pretreatment period without any “immediate” treatment to relieve complaints.\(^{(26,35)}\).

The response rate of respectively 68% and 40% in the placebo group in the Saps and Nurko trials are surprisingly high and underscores the importance of doing placebo-controlled studies in children with functional gastrointestinal disorders.\(^{(25,32)}\) Saps et al hypothesized that their placebo effect was due to a high level of expectancy of the children and the parents and the frequent contacts between the doctors and the patients.\(^{(25)}\) The study by Nurko et al was too short to draw similar conclusions. They suggested a significant role of behaviour modification including toilet training and special stickers as rewarding. Furthermore, parents were instructed to give praise and positive reinforcement if their child was successful at the toilet. This high placebo rate must challenge clinical researchers to evaluate the effect of placebo compared to new compounds emerging for IBS and constipation such as lubiprostone, prucalopride and linaclotide.\(^{(36-39)}\) Studies in adults with either IBS or constipation using these latter drugs have shown positive results compared to placebo and these findings should now be confirmed in the paediatric population. In the last decade both the FDA and the European Medicines Agency (EMEA) reviewed and updated the legislation on how medicines for children were regulated. These instances aim to stimulate the development of new medicines for children, ensure that medicines used to treat children are subject to high-quality research and ensure that medicines used to treat children are appropriately authorized for use in children. If these agencies believe that a new drug will have significant paediatric use, they obligate manufacturers to carry out paediatric clinical trials before the drug can be marketed.
What are the major drawbacks in the current controlled trials in children? Many of these studies lack a proper design and good methodology. Although all studies included in this review, used the Rome II criteria for IBS or functional constipation, each trial used a different study design with respect to the duration of the study, the number of visits, method of blinding, follow-up and used different outcome measures. One single study included even adult patients. Using homogeneous patient populations and outcome measures lead to more effective comparisons of trials. Indeed, homogeneous patient populations and number of visits are described as potential predictors of the placebo effect in a meta-analysis of IBS trials in adults. Another important issue to consider while developing new studies, is performing adequate double-blinding. Children and guardians who were aware of their treatment assignment could differ from unaware patients in reporting effects to treatment. A RCT in adult IBS patients demonstrated that the patient–practitioner relationship is probably the most robust factor contributing to the placebo effect. On the other hand, investigators aware of treatment assignment may also differ in their assessment of outcomes. Furthermore, most trials do not primarily address the effect of placebo, but evaluate active treatment like L.GG and amitriptyline. These studies can cause bias associated with the interest of the investigators.

In summary, the present review shows a lack of well designed placebo-controlled trials in children with irritable bowel syndrome or constipation. The results of these few, mainly underpowered, studies should be interpreted cautiously given the lack of uniform definitions used for the different functional gastrointestinal disorders investigated, and the methodological limitations of published studies. Future studies are needed, in particular larger studies of longer duration with greater methodological rigor, executed by infrastructures aimed at facilitating international multi-centre, collaborative studies. General practitioners and clinicians of academic and non-academic hospitals should propose interim endpoints for use in paediatric trials of IBS and constipation drugs that are based on clinically valid concepts. The use of probiotics and newer compounds for IBS and functional constipation, such as linoclatide, lubiprostone and prucalopride warrants further study, particularly given the chronic nature of this condition, its major impact on patients’ quality of life, and the shortage of other effective treatments.
Table 1a Study characteristics of included paediatric studies on IBS

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants (number, age, diagnosis, clinical setting)</th>
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<tbody>
<tr>
<td>Bausserman et al.²²</td>
<td>64 children, age 6-20 years with IBS according to Rome II criteria, recruited from a paediatric gastroenterology outpatient clinic in the USA</td>
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<tr>
<td>Gawronska et al.²³</td>
<td>104 children, age 6-16 years, fulfilling Rome II criteria for functional dyspepsia, irritable bowel syndrome (IBS, n=37) or functional abdominal pain, recruited from a tertiary paediatric gastroenterology clinic in Poland</td>
</tr>
<tr>
<td>Kline et al.²⁴</td>
<td>50 children, age 8-17 years with IBS according to Rome II criteria, recruited from three different paediatric gastroenterology outpatient clinics in the USA</td>
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<tr>
<td>Intervention vs control intervention</td>
<td>Study duration</td>
</tr>
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<td>-------------------------------------</td>
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| **Lactobacillus GG (1 capsule twice daily containing 10^10 bacteria)** | 6 weeks         | Response rate of decrease in abdominal pain | I: 44%  
C: 40%  
(p= 0.77) |
| **Placebo**                         |                | Diarrhea       | I: 11.8%  
C: 0%  
(p= 0.229) |
|                                    |                | Indigestion    | I: 13%  
C: 4.2%  
(p=0.348) |
|                                    |                | Constipation   | I: 13.6%  
C: 5%  
(p=0.608) |
|                                    |                | Perceived abdominal distension | I: 0%  
C: 24%  
(p=0.02) |
| **Lactobacillus GG (1 capsule twice daily containing 3x 10^9 colony forming units)** | 4 weeks         | Success percentage | I: 33%  
C: 5%  
(p=0.04) |
| **Placebo**                         |                | Self-reported frequency of pain | I: 1.8  
C: 3.1  
(p=0.02) |
|                                    |                | Self-reported severity of pain | I: 2.2  
C: 3.2  
(p=0.10) |
|                                    |                | Improvement of symptoms | I: 55%  
C: 31.6%  
(p=0.19) |
|                                    |                | Use of medication | I: 22.2%  
C: 15.8%  
(p=0.69) |
|                                    |                | School absenteeism | I: 5.5%  
C: 0%  
(p=0.49) |
| **Peppermint oil, children between 30-45 kg received 1 capsule, children > 45 kg received 2 capsules, three times a day** | 2 weeks         | Improvement in change of symptom scale | I: 71%  
C: 19%  
(p<0.002) |
Table 1a Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants (number, age, diagnosis, clinical setting)</th>
<th>Intervention vs control intervention</th>
<th>Study duration</th>
<th>Outcome measure</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Saps et al.25</td>
<td>90 children, age 8-17 years with functional abdominal pain, functional dyspepsia and IBS according to Rome II criteria, recruited from 6 different tertiary paediatric gastroenterology clinics in the USA. Of all 90 children, 40% in intervention group and 62% in placebo group were diagnosed with IBS.</td>
<td>Amitriptyline, children &lt; 35 kg received 10 mg/day and &gt; 35 kg 20mg/day Placebo</td>
<td>4 weeks</td>
<td>Sense of improvement</td>
<td>I: 63% reported feeling better, 5% feeling worse C: 57,5% reported feeling better, 2.5% feeling worse (p=0.63) Pain relief</td>
</tr>
<tr>
<td>Bahar et al.26</td>
<td>33 children, age 12-18 years, with newly diagnosed IBS according to Rome II criteria, recruited from a outpatient private-practice paediatric gastroenterology clinic in the USA.</td>
<td>Amitriptyline, children 30-50 kg received 10 mg/day between 50-80 kg 20mg/day and &gt; 80 kg 30 mg/day Placebo</td>
<td>13 weeks Mean overall QOL scores I: 127.6 (week 6), 128.0 (week 10), 126.2 (week 13) C: 132 (week 6), 129.4 (week 10), 129.8 (week 13) (p= 0.019 week 6, p=0.004 week 10 p=0.013 week 13)</td>
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### Table 1a

<table>
<thead>
<tr>
<th>Intervention vs control intervention</th>
<th>Study duration</th>
<th>Outcome measure</th>
<th>Results</th>
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</table>
| **Amitriptyline, children < 35 kg received 10 mg/day and > 35 kg 20mg/day** | 4 weeks | Sense of improvement | I: 63% reported feeling better, 5% feeling worse  
C: 57.5% reported feeling better, 2.5% feeling worse  
(p=0.63) |
| **Placebo** | | Pain relief | I: 15% reported excellent, 35% good  
C: 7% reported excellent, 38% good  
(p=0.85) |
| **Amitriptyline, children 30-50 kg received 10 mg/day between 50-80 kg 20mg/day and > 80 kg 30 mg/day** | 13 weeks | Mean overall QOL scores | I: 127.6 (week 6), 128.0 (week 10), 126.2 (week 13)  
C: 132 (week 6), 129.4 (week 10), 129.8 (week 13)  
(p= 0.019 week 6, p=0.004 week 10 p=0.013 week 13) |
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants (number, age, diagnosis, clinical setting)</th>
<th>Intervention vs control intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loening-Baucke et al. 27</td>
<td>31 children, age 4.5–11.7 years, with constipation for 6 months or longer, recruited from a tertiary paediatric gastroenterology clinic in the USA</td>
<td>Glucomannan (fibre), 100 mg/kg/day, up to 5 g/day Placebo (maltodextrins), 4 weeks</td>
</tr>
<tr>
<td>Castillejo et al. 28</td>
<td>56 children, age 3-10 years with chronic idiopathic constipation according to the Rome II criteria recruited from a tertiary paediatric gastroenterology clinic in Spain</td>
<td>Cocoa husk supplement (fibre), 3–6 yrs: 10.4 g/day; 7–10 yrs: 20.8 g/day Placebo</td>
</tr>
<tr>
<td>Thomson et al. 29</td>
<td>51 children, age 2-11 years with chronic constipation (lasting ≥3 months, defined as ≤2 complete bowel movements per week and one of the following: pain on defecation on 25% of days; ≥25% of bowel movements with straining; ≥25% of bowel movements with hard/lumpy stools, recruited from six general paediatric practices in the UK</td>
<td>PEG+E, starting dose: &lt;7 yrs 6.9 g/day, 7–11 yrs 13.8 g/day Placebo</td>
</tr>
</tbody>
</table>
## Study characteristics of included paediatric studies on constipation

<table>
<thead>
<tr>
<th>Study duration</th>
<th>Outcome measure</th>
<th>Results</th>
</tr>
</thead>
</table>
| 4 weeks        | Children with def. frequency < 3 p/week | I: 19%  
C: 52%  
(p< 0.05) |
|                | Abdominal pain | I: 45%  
C: 13%  
(p< 0.05) |
|                | "Improved" (physician-rated) | I: 45%  
C: 13%  
(p< 0.05) |
|                | "Improved" (parent rating) | I: 68%  
C: 13%  
(p< 0.05) |
| 4 weeks        | Change in colonic transit time (hours) | I: 6.2  
C: 5.1  
(p=0.78) |
|                | Mean defecation frequency/week | I: 61.4 → 43.6  
C: 71.5 → 61.5  
(ns) |
|                | Nr of patients with subjective improvement in stool consistency | I:14  
C:6  
(p=0.039) |
|                | Nr of patients with subjective improvement in pain | I:16  
C:11  
(p=0.109) |
| 2 weeks        | Mean defecation frequency/week | I: 3.12  
C: 1.45  
(p<0.001)  
I: 0.49 |
|                | Mean score "pain on defecation" | C: 0.77  
(p=0.041) |
|                | Straining during defecation | I: 0.72  
C: 1.37  
(p<0.001) |
|                | % hard stools | I: 14.64  
C:38.19  
(p<0.001) |
|                | Mean number of faecal incontinence episodes | I: 4.70  
C: 4.85  
(p=0.685) |
### Table 1b Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants (number, age, diagnosis, clinical setting)</th>
<th>Intervention vs control intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berg et al.⁵⁰</td>
<td>40 children, age not stated, children with uncomplicated functional faecal incontinence, recruited from a general paediatric practice in the UK</td>
<td>Senna, starting dose 1 tablet (increase to 2 or 3 if there was no improvement)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo (C1), starting dose 1 tablet or No medication (C2)</td>
</tr>
<tr>
<td>Nurko et al.⁵¹</td>
<td>103 children, age 4-16 years with chronic constipation (lasting ≥3 months, &lt;3 spontaneous bowel movements p/week and 1 or more symptoms of straining, hard stools, sensation of incomplete evacuation, large bowel movements or painful defecation), recruited from tertiary centres in the USA</td>
<td>PEG 3350 0.2 g/kg/day</td>
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<tr>
<td></td>
<td></td>
<td>PEG 3350 0.4 g/kg/day or PEG 3350 0.8g/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>Study duration</td>
<td>Outcome measure</td>
<td>Results</td>
</tr>
<tr>
<td>-----------------------</td>
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<td>--------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Variable, up to 12 months | Relief of soiling                 | I: 5/14 (55%)  
C1: 7/11 (64%)  
(p=0.16)  
C2: 6/15 (66%)  
(p=0.81) |
| 14 days               | Response to treatment              | I: 77%, 74%, and 73% of the 0.2, 0.4, and 0.8 g/kg PEG 3350  
C: 42%  
(p= 0.026)  
|                       | % of children with ≥ 3 bowel movements/week | I: 62% in 0.8 g/kg PEG3350  
C: 29%  
(p=0.027) |
|                       | % of children responding to treatment without faecal incontinence during the second week | I:31%, 26% and 31% of the 0.2, 0.4, and 0.8 g/kg PEG 3350  
C: 8%  
(p=0.2) |
References


191

