Functional abdominal pain disorders in children: therapeutic strategies focusing on hypnotherapy
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CHAPTER 4

PHARMACOLOGIC TREATMENT IN PEDIATRIC FUNCTIONAL ABDOMINAL PAIN DISORDERS: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: To systematically review literature assessing efficacy and safety of pharmacologic treatments in children with abdominal pain related functional gastrointestinal disorders (AP-FGIDs).

Study design: MEDLINE and Cochrane Database were searched for systematic reviews and randomized controlled trials (RCTs) investigating efficacy and safety of pharmacologic agents in children aged 4 to 18 years with AP-FGIDs. Quality of evidence was assessed using Grades of Recommendation, Assessment, Development and Evaluation approach.

Results: We included 6 studies with 275 children (4.5-18 years) evaluating antispasmodic, antidepressant, antireflux, antihistaminic, and laxative agents. Overall quality of evidence was very low. Compared with placebo, some evidence was found for peppermint oil in improving symptoms (OR 3.3 (95% CI 0.9-12.0) and for cyproheptadine in reducing pain frequency (relative risk [RR] 2.43, 95% CI 1.17-5.04) and pain intensity (RR 3.03, 95% CI 1.29-7.11). Compared with placebo, amitriptyline showed 15% improvement in overall quality of life score (P=0.007) and famotidine only provides benefit in global symptom improvement (OR 11.0; 95% CI 1.6-75.5; P=0.02). Polyethylene glycol with tegaserod significantly decreased pain intensity compared with polyethylene glycol only (RR 3.60, 95% CI 1.54-8.40). No serious adverse effects were reported. No studies were found concerning antidiarrheal agents, antibiotics, pain medication, anti-emetics or antimigraine agents.

Conclusions: Because of the lack of high-quality, placebo-controlled trials of pharmacologic treatment for pediatric AP-FGIDs, there is no evidence to support routine use of any pharmacologic therapy. Peppermint oil, cyproheptadine, and famotidine might be potential interventions, but well-designed randomized controlled trials are needed.
INTRODUCTION

When evidence for an organic disorder is not present in children with chronic or recurrent abdominal pain, they are diagnosed with one of the abdominal pain related functional gastrointestinal disorders (AP-FGIDs) defined by the Rome III criteria (Appendix I).1 AP-FGIDs affect approximately 20% of children worldwide and include functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine (AM), functional abdominal pain (FAP) and FAP syndrome.1,2 IBS is most frequently diagnosed in up to 45% of pediatric AP-FGIDs.3–6 AP-FGIDs have a significant impact on families because these children report significantly lower quality of life (QoL),7 increased risks for depressive symptoms, social isolation, and school absenteeism.8 Furthermore, AP-FGIDs have a great impact on health care costs. Average costs of diagnostics are approximately 6000 US dollar per child.9

To date, pathophysiological mechanisms underlying AP-FGIDs are not completely understood. A biopsychosocial model has been postulated, in which genetic, physiological and psychological factors interplay.10 Part of the symptoms in AP-FGIDs are thought to be associated with dysregulation of the brain-gut axis expressed by visceral hypersensitivity and altered gastrointestinal (GI) motility.11 Due to increasing understanding of the brain-gut axis, potential targets for pharmacologic treatment were identified including smooth muscle cells throughout the GI-tract, peripheral receptors, central interneurons, and cortical regions involved in conscious perception of pain.12

However, incomplete pathophysiological understanding still hampers management. Treatment, therefore, remains symptomatic, and 30% of children continue to experience symptoms even in adulthood.13–15 Data on efficacy and safety of pharmacologic therapies in children are scarce. Consequently, a variety of agents are frequently prescribed by pediatricians mainly based on own clinical experiences and results of adults studies, which can be harmful since evidence from adults cannot be directly extrapolated to children. Data on pharmacologic therapies, covering literature published to 2006, concluded that evidence of benefit in children with recurrent abdominal pain was weak.16 Since then, various pharmacologic studies may have been published including new agents. Therefore, our aim is to give an update by systematically reviewing efficacy and safety of different pharmacologic treatments.

METHODS

Cochrane Library and MEDLINE were searched for systematic reviews (SRs) and randomized controlled trials (RCTs) from inception to October 2013. Medical Subject Headings terms used were functional abdominal pain, irritable bowel syndrome, functional dyspepsia, abdominal migraine, child, adolescent, pharmacologic treatment, or therapy. Reference lists of reviews and included studies were searched by hand to identify additional studies. Full search strategy is available from the corresponding author.

Two reviewers independently screened all abstracts for eligibility. In case of disagreement,
consensus was reached by discussion. Inclusion criteria were: (1) study was a SR or RCT; (2) study population consisted of children aged 4-18 years; (3) diagnosis of FAP, FAP syndrome, IBS, FD or AM according to Rome or Apley criteria or other criteria well-defined by the authors; (4) interventions were antispasmodics, antidepressants, antidiarrheal agents, antibiotics, pain medication, antireflux agents, anti-emetics, antimigraine agents, antihistaminic agents, or laxatives; (5) intervention was compared with placebo, no treatment, or any other pharmacologic treatment; and (6) outcome measures were abdominal pain intensity and/or frequency, QoL, functional disability (e.g. school absence) and/or adverse effects. Exclusion criteria were: (1) treatment arm with < 10 patients; and (2) non-English language.

Two reviewers independently rated methodologic quality using the Cochrane risk of bias tool. For each outcome, quality of evidence was assessed by using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.17–19

These reviewers extracted data by using structured data extraction forms which contained items such as author, year of enrollment, participants, study setting, interventions and outcomes. Disagreements of both steps were resolved through consensus, or by a third person (M.B.).

RESULTS

A total of 557 potentially relevant articles and abstracts were identified. After removal of duplicates (n=247) and screening of the abstracts (n=246), 64 full-text articles were assessed for eligibility. Sixty articles did not meet inclusion criteria: adult study population (n=44), irrelevant outcome measures/subject (n=8), and no SR or RCT (n=8). Four articles including 6 studies remained: two SRs16,20 and two RCTs.21,22 One review16 originally included a third study,23 but this study was excluded because of <10 patients per treatment arm (Figure 1).

Compared with placebo, 1 trial investigated antispasmodics,24 2 trials studied antidepressants,25,26 1 trial studied antireflux medication27 and 1 antihistaminic agents.22 One trial evaluated polyethylene glycol 2250 oral solution (PEG 3350) compared to PEG 3350 combined with tegaserod.21 No studies were included on antidiarrheal agents, antibiotics, pain medication, anti-emetics, and antimigraine agents.

Data of 275 children aged 4.5-18 years were included. Sample sizes varied from 25 to 90 children and duration of follow up from 2-13 weeks. See et al stated to have 1-year follow-up without showing data.27 Five studies were conducted in North America21,24–27 and 1 in Asia.22 Five studies were performed at the pediatric gastroenterology department of both secondary and tertiary centers,22,24–27 1 study did not report their setting.21 A range of different outcomes were measured. Even if a same outcome was measured, different measurement instruments were used. All trials measured abdominal pain as primary or secondary outcome. Three studies reported on QoL or overall symptom relief.25–27 Disability was measured in 2 studies.25,26 Adverse effects were reported in all but 1 study.2
Methodologic quality

Overall quality of evidence was very low (Table 1). GRADE evidence profiles are shown in Appendix II. All 6 included studies were RCTs, but details on concealment of allocation were only reported in 2 studies.\textsuperscript{21,22} At baseline, treatment groups were similar with respect to demographic and clinical features in 5 studies.\textsuperscript{21,22,24,26,27} Bahar et al did not present a baseline table.\textsuperscript{25} Risk of performance and detection bias was low in 5 RCTs, because they were double-blind and placebo-controlled.\textsuperscript{22,24-27} Bahar et al did not provide information on how blinding was performed.\textsuperscript{25} Khoshoo et al used no blinding for type of medication. Symptoms were recorded by children and reported by phone twice weekly to the same member of the research team. However, this outcome assessor was

Figure 1. Flowchart showing results of literature search and study inclusion
not blinded.\textsuperscript{21} In 4 studies no patients were lost to follow-up.\textsuperscript{21,22,25,27} Dropout was considerable in the trial by Saps et al, with 7 children not completing the trial (7.8%).\textsuperscript{26} The authors performed intention-to-treat analyses, which reduces risk for attrition bias, but it is not reported whether they imputed missing data.\textsuperscript{26} In Kline et al, attrition bias was considered high, because 16\% of children (n=8) did not complete the study and dropout rates per group were not reported.\textsuperscript{24} Because of heterogeneity of all studies with respect to study population, design and outcomes, we refrained from statistical pooling and the 6 included studies are discussed separately. Characteristics and results are shown in Table 1.

**Antispasmodics**

Kline et al performed a randomized, double-blind controlled trial, including 50 children, aged 8-17 years with IBS according to the Rome or Manning criteria.\textsuperscript{24} Children were assigned to 2 weeks of treatment with 3 times a day pH-dependent, enteric-coated capsules containing peppermint oil or placebo (arachis oil). Peppermint oil and placebo capsules were provided under the same trademark, but further details about differences like taste were not reported. Main outcomes were severity of pain, changes in symptoms, and side effects. A 1-5 scale based on a model derived from prior studies was used by clinicians to rank both severity of pain (1=excellent, 2=good, 3=fair, 4=bad, and 5=terrible) and change in symptoms (1=much better, 2=better, 3=no effect, 4=worse, and 5=much worse). Daily symptom diaries were kept by children and/or parents and the 4-point GI Symptom Rating Scale was measured for 15 GI-symptoms (0=absence of symptom, 3=extreme degree of symptom). After 2 weeks, 76\% of children receiving peppermint oil reported improvement in severity of symptom scale vs 19\% of children receiving placebo (\(P<0.001\)). Mean severity of pain symptoms based on diaries was also mentioned to be significantly lower in the peppermint oil group. However, authors did not clarify how the diaries were analyzed. Significantly more children receiving peppermint oil (71\%) reported improvement on the change of symptom scale compared with placebo (43\%; OR=3.3 [95\% CI 0.9-12.0]; \(P<0.002\)).\textsuperscript{16,24} They also reported no differences on the GI Symptom Rating Scale, but data were not shown. No side effects were reported.

**Antidepressants**

Two double-blind randomized placebo-controlled trials including 123 children evaluated amitriptyline.\textsuperscript{25,26} Bahar et al included 33 adolescents aged 12-18 years, while Saps et al included 90 children aged 8-17 years. Duration of treatment in the Bahar et al study was 8 weeks, in Saps et al 4 weeks. Placebo capsules were identical to amitriptyline capsules in the Saps trial, and details about the appearance of the placebo were not reported by Bahar et al. Improvement in overall QoL score was primary outcome measure in the Bahar study.\textsuperscript{25} A 34-item IBS-QoL questionnaire, validated in adults, was used, but 2 questions on sexual activity were omitted. Items were scored on a 1-5 scale (1=not at all, 5=extremely). Minimum and maximum scores on this IBS-QoL questionnaire were not reported. In addition, a symptoms checklist, pain-rating scale, and visual analog scale were used for assessing associated IBS-symptoms, interference
with daily life, and pain frequency and intensity. At baseline, differences in mean QoL scores between the amitriptyline and placebo group were borderline significant (109.4 vs 127.5; \( P=0.05 \)). Reported mean overall QoL scores at week 6, 10 and 13 were 127.6, 128.0, and 126.2 in the amitriptyline group and 132, 129.4, and 129.8 in the placebo-group, respectively, without reporting \( P \) values. Improvement in overall QoL scores, children receiving amitriptyline reported significantly greater improvements at all 3 moments (\( P=0.019 \), \( P=0.004 \) and \( P=0.013 \), respectively). However, absolute change in overall QoL scores was not reported, but only displayed in a figure. Immediately and 3 weeks after treatment, significantly more children in the amitriptyline group reported at least 15% of improvement in QoL (\( P=0.007 \) and \( P=0.002 \) respectively). Again, no absolute percentages were reported. Authors did not clarify on the ratio for this cut-off value of 15%. Scores on almost all associated IBS-symptoms, interference with daily life, and pain frequency and intensity did not differ between groups. No adverse effects were reported.

Saps et al used overall assessment of satisfactory relief and satisfaction with treatment as primary outcome.\(^26\) Two questions regarding the subject’s overall status (better, same, or worse) and sense of improvement (excellent, good, fair, poor, or failed) were used. Secondary outcomes included effects on disability. Validated, self-reported, and age-appropriate questionnaires were used. At end of treatment, 59% of children in the amitriptyline group compared with 53% in the placebo group reported to feel better (relative risk [RR] 1.12 [95% CI 0.77-1.63; \( P=0.54 \)]).\(^20\) Significant abdominal pain reduction compared with baseline was reported in both groups (\( P<0.0001 \)), but there was no significant difference (\( P=0.18 \)). Absolute numbers, however, were not reported. No significant differences were shown with regards to disability. Mild adverse events occurred in first 2 weeks of treatment, but how adverse effects were assessed was not reported. Two children in the amitriptyline group dropped out because of fatigue, rash and headaches, and 1 child in the placebo group discontinued the study because of dizziness. The proportion of patients experiencing at least 1 adverse event did not differ between groups (RR 1.91, 95% CI 0.18-20.35; \( P=0.59 \)).\(^20\)
Table 1. Study characteristics and results from included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants &amp; Diagnosis</th>
<th>Interventions</th>
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<tbody>
<tr>
<td><strong>Kline et al (2001)</strong></td>
<td>Children 8-17 years (N=50) IBS (Rome/Manning criteria)</td>
<td>Peppermint oil vs placebo&lt;br&gt;Dosage: 0.1 or 0.2 ml 3 times daily&lt;br&gt;Treatment period: 2 weeks</td>
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<td><strong>Bahar et al (2008)</strong></td>
<td>Children 12-18 years (N=33) IBS (Rome II criteria)</td>
<td>Amitriptyline vs placebo&lt;br&gt;Dosage: 10 mg/day (30-50 kg), 20 mg/day (50-80 kg), 30 mg/day (&gt;80 kg)&lt;br&gt;Treatment period: 8 weeks</td>
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<td><strong>Saps et al (2009)</strong></td>
<td>Children 8-17 years (N=90) IBS, FAP and FD (Rome II criteria)</td>
<td>Amitriptyline vs placebo&lt;br&gt;Dosage: 10 mg/day (&lt;35 kg), 20 mg/day (&gt;35 kg)&lt;br&gt;Treatment period: 4 weeks</td>
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<td><strong>See et al (2001)</strong></td>
<td>Children 5-18 years (N=25) FD (Apley criteria)</td>
<td>Famotidine vs placebo&lt;br&gt;Dosage: 0.5 mg/kg/dose 2 times daily (max. 40 mg/day)&lt;br&gt;Treatment period: 3+3 weeks (cross-over)</td>
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Table 1. Study characteristics and results from included trials

<table>
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<tr>
<th>Study Participants &amp; Diagnosis</th>
<th>Interventions</th>
<th>Outcome measures &amp; instruments</th>
<th>Results</th>
<th>Overall quality (GRADE)</th>
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<tr>
<td>Children 8-17 years (N=50)</td>
<td>IBS (Rome/Manning criteria)</td>
<td>Peppermint oil vs placebo.Dosage: 0.1 or 0.2 ml 3 times daily.Treatment period: 2 weeks</td>
<td>Significantly more children in peppermint oil group reported improvement in symptoms 71% vs 43%; P&lt;0.002 (OR=3.3 (95% CI 0.9-12.0). No significant differences in GSRS</td>
<td>Very low</td>
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<td>IBS-QoL questionnaire</td>
<td>Severity of pain and change in symptoms.Instruments: pain and symptom scales (5-point scale), symptom diaries, Gastrointestinal Symptom Rating Scale (GSRS)</td>
<td>Adverse effects.Instrument: recorded by investigator and patient</td>
<td>No adverse effects reported</td>
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<td>Improvement in overall QoL.Instrument: IBS-QoL questionnaire</td>
<td>Amitriptyline vs placebo. Dosage: 10 mg/day (30-50 kg), 20 mg/day (50-80 kg), 30 mg/day (&gt;80 kg).Treatment period: 8 weeks</td>
<td>Frequency and intensity of abdominal pain.Instrument: Visual analog scale (0-10).Interference with daily life.Instrument: Pain-rating scale (0-6)</td>
<td>Amitriptyline group significantly greater improvements overall QoL during and after treatment (P=0.019, P=0.004 and P=0.013)No significant differences (P&gt;0.05)No significant differences (P&gt;0.05)</td>
<td>Very low</td>
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<td>No adverse effects reported</td>
<td>Overall satisfactory relief + satisfaction with treatment.Instrument: 2 questions about overall status and sense of improvement.Disability.Instrument: Pediatric Functional Disability Inventory (PFDI)</td>
<td>Level of abdominal pain.Instrument: pain diaries scoring pain frequency, intensity and peptic index.Global improvement of symptoms.Instrument: question feeling better, not better, worse</td>
<td>No significant difference (P=0.81) in percentage of children feeling better: 59% vs 53% (RR 1.12; 95% CI 0.77-1.63).No significant differences in PFDI (P=0.31)Mild adverse effects reported (RR 1.91; 95% CI 0.18-20.35)</td>
<td>Very low</td>
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<td>No significant differences in level of abdominal pain, regardless of order of drugs</td>
<td>Significantly more children receiving famotidine improved: 66.7% vs 15.4% (P=0.015) (OR 11.0; 95% CI 1.6-75.5)</td>
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| Sadeghian et al (2008) | Children 4.5-16 years (N=29) FAP (Rome II criteria) | Cyproheptadine vs placebo  
Dosage: 0.25-0.5 mg/kg/day (max 12 mg/day children 2-6 yr; max. 16 mg/day children 7-14 yr)  
Treatment period: 2 weeks |
| Khoshoo et al (2006) | Children 13-18 years (N=48) IBS-C (Rome II criteria) | PEG 3350 vs PEG 3350 + tegaserod  
Dosage: 17 gr/day PEG 3350, Tegaserod 6 mg 2 times daily  
Treatment period: 4 weeks |

CI=confidence interval; FAP=functional abdominal pain; FD=functional dyspepsia; GSRS=Gastrointestinal Symptom Rating Scale; IBS=irritable bowel syndrome; IBS-C=irritable bowel syndrome constipation predominant; OR=odds ratio; PEG 3350= polyethylene glycol 3350 oral solution; PFDI=Pediatric Functional Disability Inventory; QoL=quality of life; RR=relative risk
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<tr>
<td>Children 4.5-16 years (N=29)</td>
<td>Cyproheptadine vs placebo</td>
<td>Frequency and intensity of abdominal pain</td>
<td>Significantly more children in the cyproheptadine group improved/resolved with respect to abdominal pain frequency (P=0.002) with RR 2.43 (95% CI 1.17-5.04) and pain intensity (P=0.001) with RR 3.03 (95% CI 1.29-7.11)</td>
<td>Very low</td>
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<td>FAP (Rome II criteria)</td>
<td>Dosage: 0.25-0.5 mg/kg/day (max 12 mg/day children 2-6 yr; max. 16 mg/day children 7-14 yr)</td>
<td>Global improvement of symptoms</td>
<td>Significantly more children globally improved in cyproheptadine group (86.7% vs 35.7%; P=0.005)</td>
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<td></td>
<td>Treatment period: 2 weeks</td>
<td>Adverse events</td>
<td>No adverse effects reported</td>
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<td>Instrument: self-reported diary (scale 1-6)</td>
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<td>Instrument: self-reported diary (scale 1-4)</td>
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<td>Adverse events</td>
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<td>Instrument: recorded by research nurse</td>
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<td>Children 13-18 years (N=48)</td>
<td>PEG 3350 vs PEG 3350 + tegaserod</td>
<td>Adequate reduction of abdominal pain</td>
<td>Significantly more children receiving PEG 3350 + tegaserod adequate pain reduction (66.7% vs 18.5%; P&lt;0.05) (RR 3.60: 95% CI 1.54-8.40)</td>
<td>Very low</td>
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<td>IBS-C (Rome II criteria)</td>
<td>Dosage: 17 gr/day PEG 3350, Tegaserod 6 mg 2 times daily</td>
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<td></td>
<td>Treatment period: 4 weeks</td>
<td>Adverse effects</td>
<td>No adverse effects reported</td>
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<td>Instrument: daily pain diaries (scale 0-10); adequate pain reduction: ≥3 points</td>
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<td>Adverse effects</td>
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<td>Instrument: not reported</td>
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Antireflux agents
See et al included 25 children aged 5-18 years with recurrent abdominal pain according to Apley criteria and dyspeptic symptoms, such as epigastric pain, pain before and after eating, chest pain, nausea, vomiting, and loss of appetite. Children were randomly assigned to treatment with twice daily famotidine or placebo during 3 weeks (treatment period 1). In case of persisting symptoms after treatment period 1, crossover occurred directly afterwards and continued for another 3 weeks (treatment period 2). In patients demonstrating improvement after treatment period 1, crossover occurred only if symptoms recurred and persisted for 3 weeks. Placebo was prepared with sugar suspension matching the famotidine suspension, and both famotidine and placebo were inserted in a white opaque gelatin capsule. Abdominal pain was assessed using abdominal pain score, which combined pain frequency, pain severity (affective facial scale) and a peptic index (amount of experienced peptic symptoms). In addition, global improvement (better, not better, or worse) was assessed. No significant difference in abdominal pain score was shown between both groups. When analyzing global improvement, 66.7% of children improved on famotidine, compared to 15.4% on placebo (OR 11.0; 95% CI 1.6-75.5; P=0.015).

Antihistaminic agents
Sadeghian et al studied cyproheptadine in a double blind placebo-controlled trial including 4.5- to 12-year-old children with FAP according to Rome II criteria (N=29). Children were randomized to either cyproheptadine or placebo. Placebo was prepared in similar bottles as cyproheptadine syrup. Primary outcome was self-reported change in frequency and intensity of abdominal pain using a 6-point scale (1=complete resolved, 2=very much improved, 3=improved, 4=no change, 5=become worse, and 6=become much worse). In addition, global assessment of improvement was measured using a 4-point scale (1=no pain, 2=become better, 3=no change, 4=become worse). Questionnaires used were not validated. After 2 weeks of treatment, 86.7% of children in the cyproheptadine group vs 35.7% receiving placebo reported improvement/resolution with respect to pain frequency (RR 2.43 [95% CI 1.17-5.04]; P=0.002). Significantly more children in the cyproheptadine group reported improvement/resolution with respect to pain intensity (86.7% vs 28.6%; RR 3.03 [95% CI 1.29-7.11]; P=0.001). Global assessment of improvement reported by children was significantly better in the cyproheptadine group (86.7% vs 35.7%; P=0.005). No serious adverse effects were reported.

Laxatives
Khoshoo et al performed a trial in 48 children aged 13-18 years with constipation predominant IBS according to Rome II criteria. Patients were randomly allocated to PEG 3350 oral solution or combination therapy consisting of PEG 3350 and tegaserod. All patients received same dosage of laxatives. Daily diaries were kept to assess abdominal pain using standard pain rating scale (0= no pain, 10=worst possible pain) and frequency of bowel movements. Adequate pain reduction was defined as reduction of ≥ 3 points on pain rating scale. After 4 weeks of treatment, significantly more children receiving the combination of laxatives reported adequate
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Pain reduction, compared to children receiving PEG 3350 alone (66.7% vs 18.5%; RR 3.60 [95% CI 1.54-8.40]; \( P < 0.05 \)). No adverse effects were reported, but again it was unclear how adverse effects were assessed.

**DISCUSSION**

This SR clearly reveals a lack of adequately powered, high-quality, placebo-controlled drug trials in children with AP-FGIDs. Weak evidence was found that treatment with peppermint oil or cyproheptadine or combination of 2 laxatives is effective in children with IBS and FAP for some outcome measures. Famotidine did not show significant improvement of abdominal pain, however, when analyzing global symptom improvement, famotidine was more effective compared to placebo among children with recurrent abdominal pain and dyspepsia. Amitriptyline seems to improve QoL, but no effect in reduction of abdominal pain was demonstrated compared with placebo.

Kline et al reported beneficial effect of peppermint oil for children with IBS.\(^{24}\) It is unknown whether taste of placebo was similar to peppermint oil. It is likely that recognizable taste of peppermint influences effect in favor of this drug. Peppermint oil has shown its efficacy and safety in adult IBS patients.\(^{28-30}\) The menthol component is known to block Ca\(^{2+}\) channels,\(^{31,32}\) which may lead to reduction of colonic spasms.\(^{33}\) It is noteworthy that trials evaluating effects of another widely used antispasmodic, mebeverine, are lacking. Pediatric use of this compound is based on adult trials, where it is considered clinically effective. Two meta-analyses, however, report inconsistent data regarding efficacy of mebeverine.\(^{34,35}\) More importantly, evidence on efficacy in adults cannot be directly extrapolated to children.

**Tricyclic antidepressants**, such as amitriptyline and selective serotonin reuptake inhibitors, are antidepressants, both used in treating AP-FGIDs.\(^{36}\) Low dose of amitriptyline is believed to work primarily by inducing pain tolerance through peripheral or central antinociceptive properties and anticholinergic effects\(^{25,37}\) and has been demonstrated to have beneficial effect in treatment of adults with IBS and FD.\(^{37-41}\) These effects were not confirmed in pediatric AP-FGIDs, when comparing amitriptyline to placebo.\(^{25,26}\) However, Bahar concluded that amitriptyline significantly improved QoL, after they measured greater improvement of scores in the intervention-group.\(^{25}\) Because baseline scores were already substantially higher in the placebo group, greater improvement of absolute scores is needed to reach the 15% margin, therefore, these results were limited. Furthermore, absolute mean QoL scores after treatment did not differ significantly. It is conceivable that the dose used in children (10-30mg) was too low compared to 75mg used in adults with IBS.\(^{37}\) Higher placebo success rate in children (53%) compared to adults (40%) with IBS may explain the lack of statistical difference in favor of amitriptyline.\(^{42}\)

Significant benefit of famotidine was only found when assessing global symptom improvement in children with recurrent abdominal pain and dyspepsia, whereas no significant decrease in abdominal pain was demonstrated.\(^{27}\) Famotidine inhibits gastric acid secretion\(^{43}\) and is therefore promising in patients with dyspeptic symptoms. Among adult patients with dyspeptic symptoms,
H2-receptor antagonist demonstrated statistically significant improvement in dyspeptic symptoms,\textsuperscript{44,45} and famotidine showed significant improvement in belching, heartburn, and feeling of acid regurgitation compared with placebo.\textsuperscript{46} Cyproheptadine is an antihistaminic agent and has been successfully applied for migraine.\textsuperscript{47} Mechanism of action is probably due to Ca2+ channel blocking or antiserotonin effect.\textsuperscript{47-50} Because of the antiserotonin effect, cyproheptadine was hypothesized to be effective in pediatric AP-FGIDs. Sadeghian reported significant effect of cyproheptadine on frequency and severity of FAP, without serious side effects.\textsuperscript{22} Again, results should be cautiously interpreted because of very low methodologic quality, usage of nonvalidated questionnaires, and limited follow-up of 2 weeks. Recent retrospective trials showed some effect for children with abdominal migraine\textsuperscript{51} and functional dyspepsia.\textsuperscript{52} Just 1 study evaluated efficacy of laxatives in children with AP-FGIDs. Khoshoo showed that tegaserod in addition to PEG 3350 significantly reduced abdominal pain in IBS-constipation predominant (IBS-C), compared to PEG 3350 alone.\textsuperscript{21} Tegaserod acts upon 5-hydroxytryptamine4 GI-receptors, which play a key role in motility and moderate visceral sensitivity.\textsuperscript{53} Adult studies also show promising results in IBS-C for relief of abdominal pain, bloating and constipation.\textsuperscript{53,54} Nevertheless, tegaserod has been associated with serious cardiovascular ischemic events and was therefore withdrawn from the market on order of the Food and Drug Administration.\textsuperscript{55} In the last decade new laxatives as prucalopride, lubiprostone, and linaclotide have been shown effective in treating adult IBS-C.\textsuperscript{39} However, these compounds have not been evaluated in children with IBS-C.

Results in this review should be interpreted cautiously, given the very low quality of all studies. This was often due to small sample sizes, poorly reported side effects, lack of follow-up or because of considerable risk of bias. Performing placebo-controlled studies on children is complicated because ethical considerations must balance protection of individual children with the importance of allowing research needed to improve pediatric medicine, but also because parents often refuse to have their child participating in placebo-controlled trials because of “risk” of being assigned to the placebo arm.\textsuperscript{56} Interpretation of results was also hampered by heterogeneity of study population, a wide range of different outcomes, and differences in instruments used to measure these outcomes. Furthermore, it is important to realize that 2 studies were funded by pharmaceutical industry.\textsuperscript{24,25} One of the limitations of this SR concerns possible publication bias, that is, statistical significant positive results being more likely to be published. Furthermore, our search was restricted to English language. To minimize risk of not including all relevant studies, we carried out a comprehensive and contemporaneous literature search. GRADE approach aims to prevent heterogeneity of included studies as much as possible. As a consequence, however, possible interesting studies that do not exactly fulfill predefined outcome measures, must be excluded. The RCT of Collins et al on rifaximin in children with chronic abdominal pain, for example, was therefore excluded.\textsuperscript{57} Another limitation includes the possibility of bias in reporting outcomes, because children aged 4-18 years are included and (part of) outcomes may be reported by parents. Sadeghian reported outcomes recorded by children and caregivers separately and both reported similar answers with respect to treatment.
response. But all other studies did not report whether children completed questionnaires themselves or with help of their caregivers. They did use age-appropriate questionnaires, but the possibility of bias due to reporting by children vs caregivers cannot be excluded. All studies used well-defined inclusion criteria. One study used Apley criteria and although these criteria are not validated and possibly arbitrary, they are well-defined and were widely used for decades because validated criteria were lacking prior to the introduction of the Rome criteria. However, the remaining 5 studies used Rome and Rome II criteria which are validated, thereby increasing applicability of outcomes of this review.4

High success rates for placebo were often reported for pediatric patients with FGIDs,22,24,58–60 up to 53% in the study by Saps et al.26 It is known that an active listening approach and encouraging attitude toward treatment help improve subjects’ responses to both therapeutic attempts and placebo.58,61 Furthermore, high placebo response might point towards natural course of disease or fluctuations in symptoms.

In the last decade, several nonpharmacologic therapies (e.g. hypnotherapy62,63 and cognitive behavioral therapy64–67) have shown their efficacy in treating children with AP-FGIDs, with success rates up to 85%.68,69 Moreover, these therapies are not hampered by severe side effects. Evidence for pharmacologic treatment in children with AP-FGIDs is low. It is not possible to recommend any specific pharmacologic treatment. Clinicians may choose to prescribe drugs in children in whom symptoms are severe and have not responded to physician reassurance, time, or simple dietary interventions. Peppermint oil, cyproheptadine, or famotidine may be considered in treating children with either FAP or IBS, but well-designed trials with long-term follow-up are needed to confirm data presented in this review.

This review clearly demonstrated that more research is needed to investigate pharmacologic therapies in these children.70 We recommend, while designing new studies, to take into account use of homogeneous outcome measures, use of validated instruments to measure abdominal pain, anxiety, depression, adequate relief and QoL, placebo arm, sufficient sample size, and long-term follow-up.
REFERENCES


54. Kellow J, Lee OY, Chang FY, et al. An Asia-Pacific, double blind, placebo controlled, randomised study to evaluate the efficacy, safety, and tolerability of tegaserod in...


APPENDIX I. Rome III criteria for AP-FGIDs

**Functional dyspepsia (FD)**

1. Persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus)
2. Not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not IBS)
3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms

*Criteria fulfilled at least once per week for at least 2 months before diagnosis*

**Irritable bowel syndrome (IBS)**

1. Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time:
   a. Improved with defecation
   b. Onset associated with a change in frequency of stool
   c. Onset associated with a change in form (appearance) of stool
2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms

*Criteria fulfilled at least once per week for at least 2 months before diagnosis*

**Abdominal migraine (AM)**

1. Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 hour or more
2. Intervening periods of usual health lasting weeks to months
3. The pain interferes with normal activities
4. The pain is associated with 2 or more of the following:
   a. Anorexia
   b. Nausea
   c. Vomiting
   d. Headache
   e. Photophobia
   f. Pallor
5. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms

*Criteria fulfilled 2 or more times in the preceding 12 months*

**Functional abdominal pain (FAP)**

1. Episodic or continuous abdominal pain
2. Insufficient criteria for other FGIDs
3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms

*Criteria fulfilled at least once per week for at least 2 months before diagnosis*

**Functional abdominal pain syndrome (FAPS)**

Must include childhood functional abdominal pain at least 25% of the time and 1 or more of the following:

1. Some loss of daily functioning
2. Additional somatic symptoms such as headache, limb pain, or difficulty sleeping.

*Criteria fulfilled at least once per week for at least 2 months before diagnosis*
APPENDIX II. GRADE evidence profiles

GRADE approach, was categorized as follows:

- **Very low**: Any estimate of effect is uncertain.
- **Low**: Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Moderate**: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **High**: Further research is unlikely to change our confidence in the estimate of effect.
GRADE evidence profile peppermint oil\(^{24}\)

**Question:** Should peppermint oil vs placebo (arachis oil) be used for IBS according to the Rome criteria?

**Settings:** 2 university hospitals, 1 private clinic United States of America (USA)

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
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<td>Improvement in symptoms (follow-up 2 weeks; assessed with: scales recording severity and change of symptoms and a symptom dairy)</td>
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<tr>
<td>1</td>
<td>randomized trials</td>
<td>very serious(^1)</td>
<td>no serious inconsistency(^2)</td>
<td>no serious indirectness</td>
<td>serious(^3)</td>
<td>none</td>
<td></td>
<td></td>
<td>15/21 (71.4%)</td>
<td>9/21 (42.9%)</td>
<td>OR 3.33 (0.93 - 12.01)</td>
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<td></td>
<td>Adverse events (follow-up 2 weeks)</td>
<td></td>
<td>0/21 (0%)</td>
<td>0/21 (0%)</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>randomized trials</td>
<td>very serious(^1)</td>
<td>no serious inconsistency(^2)</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td></td>
<td></td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

\(^1\) Concealment of allocation was unclear. Eight patients withdrew and it was not clear from which group.

\(^2\) One study only.

\(^3\) Total number of events is less than 300 and 95% CI around the pooled estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm.
**GRADE evidence profile amitriptyline**<sup>25,26</sup>

**Question:** Should amitriptyline vs placebo be used for abdominal pain related functional gastrointestinal disorders?

**Settings:** Private clinic USA<sup>25</sup>; six hospitals USA<sup>26</sup>

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Amitriptyline</td>
<td>Placebo (95% CI)</td>
</tr>
<tr>
<td>Feeling better (Saps) (follow-up 4 weeks; assessed with: question)</td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>random-ized trials</td>
<td>very serious&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Quality of life (Bahar) (follow-up 13 weeks; measured with: IBS quality of life questionnaire; Better indicated by lower values)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>random-ized trials</td>
<td>very serious&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abdominal pain reduction (Saps) – insufficient data for GRADE profiling
### Disablity (Saps) - insufficient data for GRADE profiling

### Adverse events (Saps: unclear how the adverse events were assessed)

<table>
<thead>
<tr>
<th></th>
<th>randomized trials</th>
<th>very serious</th>
<th>no serious inconsistency</th>
<th>serious</th>
<th>no serious imprecision</th>
<th>none</th>
<th>3/46 (6.5%)</th>
<th>1/44 (2.3%)</th>
<th>RR 1.91 (0.18 - 20.35)</th>
<th>20 more per 1000 (from 19 fewer - 299 more)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 random trial</td>
<td>very serious</td>
<td>no serious inconsistency</td>
<td>serious</td>
<td>no serious imprecision</td>
<td>none</td>
<td>3/46 (6.5%)</td>
<td>1/44 (2.3%)</td>
<td>RR 1.91 (0.18 - 20.35)</td>
<td>20 more per 1000 (from 19 fewer - 299 more)</td>
</tr>
</tbody>
</table>

### School attendance (Saps) - insufficient data for GRADE profiling

1 Conceilment of allocation unclear. Seven patients were lost to follow-up.
2 One study only.
3 Only tertiary care patients.
4 Total number of events is less than 300 and 95% CI around the pooled estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm.
5 Concealment of allocation was unclear. The baseline table was not presented.
6 The sample size is very low (N=33).
7 Concealment of allocation unclear and it was unclear how adverse events were assessed.
**GRADE evidence profile famotidine**

**Question:** Should famotidine vs placebo be used for Apley criteria for recurrent abdominal pain?

**Settings:** 1 secondary center USA

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Famotidine</th>
<th>Placebo</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
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</thead>
<tbody>
<tr>
<td>Global improvement in symptoms (follow-up 14 days; assessed with: question: do you feel better, not better, worse)</td>
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</tr>
<tr>
<td>1 randomized trials</td>
<td>very serious</td>
<td>no serious inconsistency</td>
<td>serious</td>
<td>serious</td>
<td>none</td>
<td>8/12 (66.7%)</td>
<td>2/13 (15.4%)</td>
<td>OR 11.00 (1.6 - 75.5)</td>
<td>1000 more per 1000 (from 92 more - 1000 more)</td>
<td>VERY LOW</td>
<td>CRITICAL</td>
</tr>
<tr>
<td>1</td>
<td>randomized trials</td>
<td>very serious</td>
<td>no serious inconsistency</td>
<td>serious</td>
<td>serious</td>
<td>none</td>
<td>8/12 (66.7%)</td>
<td>2/13 (15.4%)</td>
<td>OR 11.00 (1.6 - 75.5)</td>
<td>1000 more per 1000 (from 92 more - 1000 more)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

1. No detail of the generation of the randomization sequence is provided. Results are taken from the first period of the trial, before the crossover.
2. One study only.
3. The outcome is a global assessment of pain only.
4. Total number of events is less than 300 and 95% CI around the pooled estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm.
GRADE evidence profile cyproheptadine

**Question:** Should cyproheptadine vs placebo be used for functional abdominal pain?

**Settings:** University hospital Iran

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of</strong></td>
<td><strong>Design</strong></td>
<td><strong>Risk of bias</strong></td>
<td><strong>Inconsistency</strong></td>
<td><strong>Indirectness</strong></td>
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<tr>
<td>studies</td>
<td>randomized trials</td>
<td>serious¹</td>
<td>no serious inconsistency²</td>
<td>serious</td>
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<tr>
<td><strong>Intensity abdominal pain (follow-up 2 weeks)</strong></td>
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<tr>
<td>1</td>
<td>randomized trials</td>
<td>serious¹</td>
<td>no serious inconsistency²</td>
<td>serious</td>
</tr>
<tr>
<td><strong>Adverse events (follow-up 2 weeks)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomized trials</td>
<td>serious¹</td>
<td>no serious inconsistency²</td>
<td>serious</td>
</tr>
</tbody>
</table>

¹ Short follow-up (two weeks only).
² One study only.
³ Total numbers of events is less than 300 and 95% CI around the pooled estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm.
**GRADE evidence profile laxative with tegaserod**

**Question:** Should laxative with tegaserod vs laxative be used for adolescents with constipation dominated IBS?

**Settings:** 1 secondary center USA

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
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<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Adequate pain reduction (follow-up 4 weeks; assessed with: scale 0-10)</td>
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<tr>
<td>1</td>
<td>randomized trials</td>
<td>serious¹</td>
<td>no serious inconsistency²</td>
<td>serious³</td>
</tr>
<tr>
<td>Adverse events (follow-up 4 weeks)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>randomized trials</td>
<td>serious¹</td>
<td>no serious inconsistency²</td>
<td>serious³</td>
</tr>
</tbody>
</table>

¹ There was no blinding for type of medication.
² One study only.
³ The study was not placebo controlled.
⁴ Very low sample size (N=48).