Functional abdominal pain disorders in children: therapeutic strategies focusing on hypnotherapy
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NONPHARMACOLOGIC TREATMENT OF FUNCTIONAL ABDOMINAL PAIN DISORDERS:
A SYSTEMATIC REVIEW

Juliette M.T.M. Rutten*, Judith J. Korterink*, Leonie M.A.J. Venmans, Marc A. Benninga, Merit M. Tabbers
* both authors contributed equally

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ABSTRACT

Background and objective: Various nonpharmacologic treatments are available for pediatric abdominal pain related functional gastrointestinal disorders (AP-FGIDs). Data on efficacy and safety are scant. The goal of this study was to summarize the evidence regarding nonpharmacologic interventions for pediatric AP-FGIDs: lifestyle interventions, dietary interventions, behavioral-interventions, prebiotics and probiotics, and alternative medicine.

Methods: Searches were conducted of the Medline and Cochrane Library Databases. Systematic reviews and randomized controlled trials (RCTs) concerning nonpharmacologic therapies in children (3-18 years) with AP-FGIDs were included, and data were extracted on participants, interventions, and outcomes. The quality of evidence was assessed by using the GRADE approach.

Results: Twenty-four RCTs were found that included 1390 children. Significant improvement of abdominal pain was reported after hypnotherapy compared with standard care/wait-list approaches and after cognitive behavioral therapy compared with a variety of control treatments/wait-list approaches. Written self-disclosure improved pain frequency at the 6-month follow-up only. Compared with placebo, Lactobacillus rhamnosus GG (LGG) and VSL#3 were associated with significantly more treatment responders (LGG: relative risk 1.31 [95% confidence interval 1.08 to 1.59]; VSL#3: P<0.05). Guar gum significantly improved irritable bowel syndrome symptom frequency; however, no effect was found for other fiber supplements (relative risk 1.17 [95% confidence interval 0.75 to 1.81]) or a lactose-free diet. Functional disability was not significantly decreased after yoga compared with a wait-list approach. No studies were found concerning lifestyle interventions; gluten-, histamine- and carbonic acid-free diets; fluid intake; or prebiotics. No serious adverse effects were reported. The quality of evidence was found to be very low to moderate.

Conclusions: Although high-quality studies are lacking, some evidence shows efficacy of hypnotherapy, cognitive behavioral therapy, T and probiotics (LGG and VSL#3) in pediatric AP-FGIDs. Data on fiber supplements are inconclusive.
INTRODUCTION

Abdominal pain related functional gastrointestinal disorders (AP-FGIDs), diagnosed according to the Rome III criteria, are defined as chronic or recurrent abdominal pain, not explained by underlying organic disorders.\(^1\) AP-FGIDs affect ~20% of children worldwide and include functional dyspepsia, irritable bowel syndrome (IBS), abdominal migraine, functional abdominal pain (FAP) and functional abdominal pain syndrome.\(^1,2\) AP-FGIDs have great impact on children and adolescents’ quality of life, daily activities, and school absenteeism and can have long-term psychological implications.\(^3\) Moreover, patients are at risk for continued symptoms in adulthood, and costs are substantial.\(^4-6\)

Standard medical care consists of reassurance, education and, dietary advice.\(^7\) Despite ongoing efforts to identify causal and contributing factors in AP-FGIDs, successful management is complicated by an incomplete pathophysiological understanding. The biopsychosocial model, based on a complex interplay of genetic, physiological, and psychological factors, is conceptualizing the etiology of FGIDs.\(^7\)

It is hypothesized that pediatric AP-FGIDs are strongly associated with stress and psychological disorders such as anxiety and depression,\(^8\) wherein the coping potentials of children with AP-FGIDs are low compared to those of healthy children.\(^9\) Therefore, interventions such as cognitive behavioral therapy (CBT), hypnotherapy (HT), and yoga are aiming to teach alternative responses to stress.\(^10\) Systematic reviews have concluded that CBT and HT offer beneficial effects for children with AP-FGIDs.\(^11,12\)

The role of food in FGIDs has been revisited recently in the adult literature.\(^13,14\) Food may trigger symptoms in FGID patients who already have physiologic alterations, subsequently making them susceptible for hypersensitivity.\(^13\) However, recognition which specific food components trigger symptoms is difficult and can lead to profusion of investigations and dietary therapies, largely based on expert opinion.\(^14\) Two previous systematic reviews reported that fiber supplements are ineffective in treating AP-FGIDs, whereas conclusions were contradictory regarding probiotics.\(^15,16\)

Treatment of children who have AP-FGIDs can be challenging, especially because high-quality evidence for pharmacologic interventions is lacking.\(^17\) Although several systematic reviews summarizing different nonpharmacologic interventions exist,\(^11,15,18\) the present systematic review provides an up-to-date overview regarding the efficacy and safety of all nonpharmacologic treatments for pediatric AP-FGIDs. Such a comprehensive and recent overview is warranted.

METHODS

Literature search

The Cochrane Library and Medline databases were searched for systematic reviews and randomized controlled trials (RCTs) from inception to October 2013. Search terms used items related to pediatric AP-FGIDs and various nonpharmacologic treatments. To identify additional studies, reference lists of reviews and included studies were searched by hand. The full search...
strategy and keywords are available from the authors.

**Study inclusion**

Two authors (L.M.A.J.V. and M.M.T.) independently assessed eligibility of all abstracts. In case of disagreement, consensus was reached through discussion. Inclusion criteria were: (1) study was a systematic review or RCT; (2) study population comprised children aged 3 to 18 years; (3) diagnosis of recurrent abdominal pain (RAP), FAP, IBS, functional dyspepsia, abdominal migraine, or functional abdominal pain syndrome as defined by authors; (4) interventions were lifestyle advice such as physical exercise, dietary interventions (fiber supplements; lactose-, gluten-, histamine-, and carbonic acid-free diets; and fluid intake), behavioral interventions such as HT, CBT, prebiotics and probiotics and alternative medicine (acupuncture, homeopathy, mind-body therapy, musculoskeletal manipulations such as osteopathic and chiropractic manipulations and spiritual therapies such as yoga); (5) the intervention was compared with placebo, no treatment, any other nonpharmacologic treatment or pharmacologic agent; and (6) outcomes were abdominal pain intensity and/or frequency, quality of life, functional disability (e.g. school absence), and adverse effects. Exclusion criteria were: (1) treatment arm with <10 patients; and (2) language other than English. Potentially relevant studies and studies in which title and abstract provided insufficient information were retrieved as full-text articles.

**Quality assessment and data extraction**

Two authors (L.M.A.J.V. and M.M.T.) independently rated the methodologic quality of the included studies using the Cochrane risk of bias tool. For each outcome, quality of evidence was assessed using the GRADE approach and was categorized as very low, low, moderate, or high.19–21 The same authors extracted data from included studies using structured data extraction forms containing items on participants, study setting, interventions, and outcomes. Disagreements were resolved through consensus or by a third reviewer (M.A.B.).

**Data analysis**

Dichotomous outcomes were analyzed as odds ratios (ORs) or relative risks (RRs) along with 95% confidence intervals (CIs). For continuous outcomes, mean differences (MDs) with 95% CIs were reported. Heterogeneity was quantified by using $\chi^2$ tests and the $I^2$ statistic, which can be interpreted as the percentage of the total variation between studies that is attributable to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas larger values show increasing heterogeneity. If heterogeneity was not revealed, results of the fixed effect model are presented. If there was substantial heterogeneity (>50%), the random effect model was used.
RESULTS

A total of 568 potentially relevant articles and abstracts were identified (Figure 1). After removal of duplicates ($n=316$) and abstracts screening ($n=210$), 42 full-text articles were assessed for eligibility. Twenty-nine articles were excluded because of the following: adult study population ($n=6$), irrelevant outcome measures, such as improvement in rectal sensitivity or gastrointestinal symptoms without abdominal pain ($n=2$), no systematic review or RCT ($n=15$), or inclusion of only trials which were already included by another systematic review ($n=6$). Thirteen articles remained for analysis: 7 systematic reviews$^{11,12,15,16,18,22,23}$ (including 18 RCTs) and 6 RCTs.$^{24-29}$ Two included trials concerned follow-up studies,$^{26,30}$ which will be discussed by their original studies.$^{31,32}$ Two systematic reviews$^{11,12}$ included studies with <10 patients per treatment arm and these studies were therefore excluded.$^{33-35}$

![Flowchart showing results of the literature search and study inclusion](image)

Figure 1. Flowchart showing results of the literature search and study inclusion
Data of 1390 children aged 3 to 18 years were included for analysis. Sample sizes ranged from 21 to 200, and follow-up varied from 2 weeks to 5 years. Four trials investigated fiber supplements compared with placebo,\textsuperscript{24,36–38} and 2 trials studied a lactose-free diet.\textsuperscript{39,40} Four trials investigated probiotics,\textsuperscript{27,41–43} and 3 trials compared HT versus standard care or a wait-list.\textsuperscript{25,32,44} Seven studies compared CBT with standard care, physiotherapy, fiber supplements, biofeedback, and/or parental support.\textsuperscript{28,31,45–49} One trial compared yoga with a wait-list\textsuperscript{50} and 1 trial evaluated written self-disclose (WSD) in addition to standard care.\textsuperscript{29} No studies were included on lifestyle advice or prebiotics. A range of different outcomes were measured, and even if the same outcome was measured, different measurement instruments were used. All trials measured abdominal pain as the primary or secondary outcome.

Nine studies reported disability or school absenteeism,\textsuperscript{25,31,32,38,42,44,47,49,50} Four studies assessed quality of life,\textsuperscript{25,28,29,44} and 8 studies assessed adverse effects.\textsuperscript{24,25,37,38,41–44} Data of 3 studies were used to perform a meta-analysis of the efficacy of fiber supplements,\textsuperscript{36–38} and 3 studies were used to perform a meta-analysis on probiotics.\textsuperscript{41–43} Table 1 presents the characteristics of the included studies.

\textit{Methodological quality}

The overall quality of evidence was very low to moderate. Appendix I shows the GRADE evidence profiles. Concealment of allocation was unclear in 6 studies.\textsuperscript{36,44–46,48,49} Due to the nature of HT, CBT, WSD, and yoga, blinding was not possible for the caregiver or patient.\textsuperscript{25,28,29,31,32,44–50} Dropout was considerable in 4 studies,\textsuperscript{36,40,41,47} or vaguely described in 3 others.\textsuperscript{31,46,50} Two studies excluded patients, due to poor compliance.\textsuperscript{40,41} The method of randomization was unclear in 3 studies.\textsuperscript{27,31,50} Alfvén and Lindstrom\textsuperscript{48} provided no information on outcome blinding or treatment duration. Six trials did not present results with absolute numbers and could therefore not be included in the meta-analysis.\textsuperscript{27,39,40,44,47,48} Analyses for follow-up were uncontrolled for baseline differences by Levy et al.\textsuperscript{31} Because participants were recruited through physician referral and flyers, these patients were therefore seriously motivated, which can cause bias.

\textit{Dietary interventions}

No studies were included evaluating gluten-, histamine- and carbonic acid-free diets or fluid intake.

\textit{Fiber supplements}

Two systematic reviews\textsuperscript{15,16} including 3 RCTs\textsuperscript{36–38} and 1 RCT\textsuperscript{24} evaluated the efficacy of fiber supplements compared with placebo for RAP. A systematic review by Huertas-Ceballos et al\textsuperscript{15} included 2 RCTs, involving 92 children aged 3 to 15 years.\textsuperscript{36,37} Children received fiber supplements for 6 weeks. No information was available regarding daily fiber intake before and/or during intervention weeks. Information about abdominal pain was collected through the use of diaries, but the authors did not clarify how these diaries were analyzed. The systematic review by Horvath et al,\textsuperscript{16} included a third trial with 90 children (aged 7 to 17 years) receiving 4 weeks of glucomannan or identical placebo.\textsuperscript{38} Pain severity was assessed by using the Faces
Pain Scale Revised (6 faces ranging from relaxed to intense pain). School absenteeism and changes in daily activities were self-reported. The primary outcome in all studies was degree of improvement based on abdominal pain frequency or intensity.

After pooling, there was no significant difference between the fiber group in experiencing "no pain" and/or "satisfactory improvement" (52.4%) and the placebo group (43.5%) (RR: 1.17 [95% CI 0.75 to 1.81]). Concerning secondary outcomes, no significant differences for school absenteeism (10% vs 14%; \(P=0.56\)) or daily activities (27% vs 19%; \(P=0.37\)) after glucomannan treatment compared with placebo were found. Romano et al\(^{24}\) enrolled 60 patients (aged 8 to 16 years) comparing 4 weeks of partially hydrolyzed guar gum (PHGG), a water-soluble, dietary fiber, with placebo. Symptoms were assessed by using the Birmingham IBS Symptom Questionnaire, which contains questions on frequency of IBS symptoms (0=none, 5=all the time), and the Wong-Baker FACES Pain Rating Score, which was used to evaluate abdominal pain severity (0=no hurt, 5=hurts worst). The primary outcome was the reduction in frequency and intensity of IBS symptoms. Improvement in the frequency of IBS symptoms was significantly more likely in the PHGG group compared with the control group (43% vs 5% ; \(P=0.025\)) after 8 weeks. Effects on pain intensity were not significant.

Three studies assessed adverse effects. Unknown small numbers of children in both groups reported gas or diarrhea in the trial by Feldman et al\(^{37}\) Horvath et al\(^{38}\) and Romano et al\(^{24}\) reported no adverse effects.

**Lactose-free diet**

Huertas-Ceballos et al\(^{15}\) included 2 trials evaluating a lactose-free diet in RAP. Lebenthal et al\(^{40}\) enrolled 95 participants. After an intestinal biopsy was conducted, those patients with abnormal lactase activity (12-20 U) were excluded: 69 children received 6 weeks of a lactose-containing or lactose-free infant formula. Abdominal pain was documented in diaries by parents. Remarkably, 31 children were excluded due to a lack of compliance; 38 children remained. A lactose tolerance test was performed, the results of which were used to divide children into 2 groups: lactose malabsorbers (\(N=21\)) and lactose absorbers (\(N=17\)). Increased symptoms were described in 48% of the lactose malabsorbers and 24% of lactose absorbers after lactose intake; however, \(P\) values were not reported. Forty of the 69 children continued with a 12-month lactose-free diet. Improvement of abdominal pain after 12 months was similar in both groups (40% vs 38%). Detailed data were not reported, however, and meta-analysis and GRADE evidence profiling were therefore not possible.

Dearlove et al\(^{39}\) included 21 children with RAP in a double-blind, single cross-over study. After 2 weeks of collecting baseline data, all children underwent a 2-week lactose-free diet, followed by another 2 weeks of lactose tonic (2 g/kg) or similarly flavored placebo. Primary and secondary outcomes were not specified. After 3 months, parents were asked whether their child's symptoms (including abdominal pain) were better, worse, or the same. There was no difference in the number of children claiming relief from lactose-free or lactose-containing formula.
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Interventions</th>
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<tbody>
<tr>
<td>Fiber supplements and guar gum</td>
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</tr>
<tr>
<td>Christensen36 (1986)</td>
<td>Children aged 3-14 y (N=40)</td>
<td>Fibers (ispaghula husk) vs placebo</td>
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<tr>
<td>Denmark</td>
<td>RAP (at least 10 episodes of abdominal pain during the last 6 wk, organic causes of pain were excluded)</td>
<td>Dosage: Visiblin 5 mL twice daily; crushed crisp bread with 66% fiber</td>
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<td>Treatment period: 6 wk</td>
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<tr>
<td>Feldman37 (1985) Canada</td>
<td>Children aged 5-15 y (N=52)</td>
<td>Fiber cookies vs placebo</td>
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<td>RAP (organic causes of pain were excluded on the ground of history, examination, and simple laboratory tests)</td>
<td>Dosage: 5 g of corn fiber per cookie; 1 cookie twice daily</td>
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<td>Treatment period: 6 wk</td>
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<tr>
<td>Horvath38 (2013) Poland</td>
<td>Children aged 7-17 y (N=90)</td>
<td>GNN vs placebo</td>
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<tr>
<td></td>
<td>IBS, FAP and functional dyspepsia (Rome III criteria)</td>
<td>Dosage: 2.52 g/d</td>
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<td>Treatment period: 4 wk</td>
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<td>Follow-up: -</td>
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<td>Romano24 (2013) Italy</td>
<td>Children aged 8-16 y (N=60)</td>
<td>PHGG vs placebo</td>
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<td></td>
<td>IBS-C and IBS-D (Rome III criteria)</td>
<td>Dosage: 5g/d</td>
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<td>Treatment period: 4 wk</td>
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<td>Follow-up: 4 wk</td>
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<tr>
<td>Fructose and lactose</td>
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<td>Dearlove39 (1983) United Kingdom</td>
<td>Children aged &gt; 3 y (N=21)</td>
<td>Lactose vs placebo</td>
</tr>
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<td>RAP (&gt; 1/4 d in the last 3 mo)</td>
<td>Dosage: 2 g/kg</td>
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<td>Treatment period: 2 wk</td>
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<td>Follow-up: 3 mo</td>
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<td>Lebenthal40 (1981) United States</td>
<td>Children aged 6-14 y (N=38)</td>
<td>Lactose vs lactose-free formula</td>
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<td>RAP (intermittent episodes of unexplained abdominal pain, in a 4-mo period)</td>
<td>Dosage: 2dd 200mL</td>
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<td>Treatment period: 6 wk</td>
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<td>Follow-up: 12 mo</td>
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<td>Children aged 3-14 y (N = 40)</td>
<td>Fiber supplements and guar gum</td>
<td>Abdominal pain frequency score&lt;br&gt;Improvement: &lt;10 episodes of pain during the study period&lt;br&gt;Instrument: pain diary</td>
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<td>Children aged 5-15 y (N = 52)</td>
<td>Fiber cookies vs placebo</td>
<td>Abdominal pain frequency score&lt;br&gt;Improvement: 50% decrease in frequency of attack&lt;br&gt;Instrument: pain diary</td>
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<td>Children aged 7-17 y (N = 90)</td>
<td>GNN vs placebo</td>
<td>Severity of pain&lt;br&gt;Improvement: no pain or a decrease ≥2/6 points on the FPS-R&lt;br&gt;Instrument: FPS-R&lt;br&gt;School absenteeism&lt;br&gt;Changes in daily activity&lt;br&gt;Instrument: self-reported at baseline and final visit</td>
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<td>Children aged 8-16 y (N = 60)</td>
<td>PHGG vs placebo</td>
<td>IBS symptoms&lt;br&gt;Treatment success: improvement IBS symptoms&lt;br&gt;Instrument: Birmingham IBS Symptom Questionnaire score&lt;br&gt;Intensity of abdominal pain&lt;br&gt;Instrument: Wong-Baker FACES Pain Rating Scale</td>
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<td>Children aged &gt; 3 y (N = 21)</td>
<td>Fructose and lactose</td>
<td>Abdominal pain&lt;br&gt;Instrument: reported at final visit (better, worse, same)</td>
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<td>Children aged 6-14 y (N = 38)</td>
<td>Lactose vs lactose-free formula</td>
<td>Abdominal pain (severity and frequency)&lt;br&gt;Instrument: pain diary</td>
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### Hypnotherapy

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<th>Health Measurement</th>
<th>Follow-up</th>
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<tr>
<td>Gulewitsch(^2)(2013) Germany</td>
<td>Children aged 6-12 y (N=38) FAP and IBS (Rome II criteria)</td>
<td>HT program consist of 4 sessions, 2 children's sessions and 2 parent's sessions in a weekly sequence. Control: wait-list Treatment duration: 4 wk Follow-up: 3 mo</td>
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<td>Van Tilburg(^4)(2009) United States</td>
<td>Children aged 6-15 y (N=34) FAP (abdominal pain at least once a week in the past 3 mo)</td>
<td>Standard care + guided imagery; 3 biweekly sessions, including 1 booster session + 3 daily sessions. Listen to tape with self-exercises ≥ 5 d/wk Control: standard care Treatment period: 2 mo Follow-up: 6 mo</td>
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<td>Vlieger(^10,32)(2007/2012) the Netherlands</td>
<td>Children aged 8-18 y (N=53) FAP and IBS (Rome II criteria)</td>
<td>6 HT sessions Control: Standard medical care + supportive therapy Treatment period: 3 mo Follow-up: 1 y and 5 y</td>
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### Cognitive behavioral therapy

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<td>Duarte(^45)(2006) Brazil</td>
<td>Children aged 5-14 y (N=32) RAP (Apley's criteria)</td>
<td>4 monthly sessions of CBT-family Control: standard care Treatment period: 4 mo Follow-up: -</td>
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<td>Sanders(^46)(1994) Australia</td>
<td>Children aged 7-14 y (N=44) RAP (Apley's criteria)</td>
<td>6-session CBT-family Control: standard care Treatment period: 8 wk Follow-up: 6 and 12 mo</td>
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<td>Robins(^47)(2005) United States</td>
<td>Children aged 6-16 y (N=69) RAP (Apley's criteria)</td>
<td>5-session CBT-family + standard care Control: standard care Treatment period: 10 mo Follow-up: 3 and 6 mo</td>
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<td>6-16 y</td>
<td>RAP</td>
<td>5-session CBT-family + standard care</td>
<td>standard care</td>
<td>10 mo</td>
<td>3 and 6 mo</td>
<td>Abdominal pain, Disability, School absenteeism</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Abdominal pain index**
Clinical remission: > 80% decrease of days of pain, duration, and intensity of abdominal pain
Instrument: abdominal pain dairy

**Quality of life**
Instrument: German KINDL questionnaire

**Disability**
Instrument: Pediatric Pain Disability Index

**School absenteeism**
Instrument: abdominal pain dairy

**Improvement of abdominal pain**
Treatment response: >50% reduction of abdominal pain score
Instrument: Abdominal Pain Index

**Quality of life**
Instrument: Peds QL

**Disability**
Instrument: Functional Disability Inventory

**School absenteeism**
Instrument: abdominal pain dairy

**Abdominal pain score**
Clinical remission: > 80% decrease of intensity and frequency of abdominal pain
Instrument: abdominal pain dairy

**Abdominal pain intensity**
Instrument: red and white VAS

**Abdominal pain frequency**
Instrument: daily numbers of pain in pain dairy

**Abdominal pain intensity**
Instrument: VAS

**Abdominal pain**
Instrument: Abdominal Pain Index.

**Disability**
Instrument: Functional Disability Inventory

**School absenteeism**
Instrument: Record of school attendance

- **Low**
- **Very low**
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Treatment Period</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levy26,31 (2010/2013) United States</td>
<td>Children aged 7-17 y (N=200) RAP (≥3 episodes of abdominal pain during a 3-mo period)</td>
<td>3-session social learning + CBT-family Control: education + support intervention</td>
<td>Treatment period: 3 wk</td>
<td>Follow-up: 12 mo</td>
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<tr>
<td>Alfvén and Lindstrom45 (2007) Sweden</td>
<td>Children aged 6-18 y (N=48) RAP (Apley's criteria)</td>
<td>Psychological + psychotherapy Control: physiotherapy</td>
<td>Treatment period: at least 2 sessions, according to the expressed needs</td>
<td>Follow-up: 12 mo</td>
</tr>
<tr>
<td>Humphreys and Gevirtz49 (1998) United States</td>
<td>Children aged 4-18 y (N=64) RAP</td>
<td>4 groups: 1. Fiber + biofeedback + CBT + parental support 2. Fiber + biofeedback + CBT 3. Fiber + biofeedback 4. Fiber Treatment period: 8-session CBT Dosage: 10+ g/d fiber cookies or bars</td>
<td>Follow-up: -</td>
<td></td>
</tr>
<tr>
<td>Groß and Warschburger28 (2013) Germany</td>
<td>Children aged 6-12 y (N=29) CAP (Rome III criteria)</td>
<td>6-session CBT (group sessions) + listen to CD with self-exercises Control: wait-list Treatment period: 2 mo</td>
<td>Follow-up: 3 mo</td>
<td></td>
</tr>
<tr>
<td>Wallander29 (2011) USA</td>
<td>Children aged 11-17 y (N=63) RAP (Apley's criteria)</td>
<td>WSD + standard care: 3 20-min writing sessions Control: standard care Treatment period: 5 d Follow-up: 6 m</td>
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<tr>
<td>Probiotics</td>
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<tr>
<td>Bausserman and Michail41 (2005) USA</td>
<td>Children aged 6-17 y (N=64) IBS (Rome II criteria)</td>
<td>LGG vs placebo Dosage: 10^10 CFU, twice daily Treatment period: 6 wk Follow-up: -</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Francavilla43 (2010) Italy</td>
<td>Children aged 5-14 y (N=141) IBS and FAP (Rome II criteria)</td>
<td>LGG vs placebo Dosage: 3×10^9 CFU, twice daily Treatment period: 8 wk Follow-up: 8 wk</td>
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</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Age Group</td>
<td>RAP Criteria</td>
<td>Intervention</td>
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<tr>
<td>Levy</td>
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<td>RAP (≥3 episodes of abdominal pain during a 3-mo period)</td>
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</tr>
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<td>Sweden</td>
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<td>RAP (Apley’s criteria)</td>
<td>Psychological + psychotherapy</td>
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<td>Children aged 4-18 y (N = 64)</td>
<td>RAP</td>
<td>4 groups: 1. Fiber + biofeedback + CBT + parental support 2. Fiber + biofeedback 3. Fiber 4. Fiber</td>
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<td>Germany</td>
<td>Children aged 6-12 y (N = 29)</td>
<td>CAP (Rome III criteria)</td>
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<td>Bausserman</td>
<td>USA</td>
<td>Children aged 6-17 y (N = 64)</td>
<td>IBS (Rome II criteria)</td>
<td>LGG vs placebo</td>
</tr>
<tr>
<td>Francavilla</td>
<td>Italy</td>
<td>Children aged 5-14 y (N = 141)</td>
<td>IBS and FAP (Rome II criteria)</td>
<td>LGG vs placebo</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Age Group</td>
<td>Diagnosis</td>
<td>Intervention</td>
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<tr>
<td>Gawrónska²⁶ (2007) Poland</td>
<td>Children aged 6-16 y (N=104)</td>
<td>LGG vs placebo</td>
<td>Dosage: $3 \times 10^9$ CFU, twice daily</td>
<td>Treatment period: 4 wk</td>
</tr>
<tr>
<td>Guandalini²⁷ (2010) Italy and India</td>
<td>Children aged 4-18 y (N=59)</td>
<td>VSL#3 vs placebo</td>
<td>Dosage: 4-11y: 1 sachet, 12-18y: 2 sachets</td>
<td>Treatment period: 6 wk</td>
</tr>
<tr>
<td>Kuttner⁵⁰ (2006) Canada</td>
<td>Children aged 11-18 y (N=25)</td>
<td>Yoga intervention for 1 hour followed by daily home practice guided by a video</td>
<td>Control: wait-list</td>
<td>Treatment period: 4 wk</td>
</tr>
</tbody>
</table>

CAP=chronic abdominal pain; CFU=colony-formic units; FPS-R=faces pain scale-revised; GNN=glucomannan; IBS-C=irritable bowel syndrome constipation predominant; IBS-D=irritable bowel syndrome diarrhea predominant; N/A=not available; PedsQL=Pediatric Quality of Life Inventory; VAS=visual analog scale
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Age Group</th>
<th>Diagnosis (Rome II criteria)</th>
<th>Intervention</th>
<th>Dosage</th>
<th>Treatment Period</th>
<th>Follow-up</th>
<th>Abdominal Pain Intensity</th>
<th>Improvement</th>
<th>Instrument</th>
<th>Disability</th>
<th>Instrument</th>
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</thead>
<tbody>
<tr>
<td>Gawronska</td>
<td>Poland</td>
<td>6-16 y (N=104)</td>
<td>FAP, functional dyspepsia, and IBS (Rome II criteria)</td>
<td>LGG vs placebo</td>
<td>3x10⁹ CFU, twice daily</td>
<td>4 wk</td>
<td>-</td>
<td>Abdominal pain intensity, School absenteeism</td>
<td>Improvement: no pain or a change in the FPS-R by at least 2 faces</td>
<td>FPS-R, Record of school attendance</td>
<td></td>
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<tr>
<td>Guandalini</td>
<td>Italy and India</td>
<td>4-18 y (N=59)</td>
<td>IBS (Rome II criteria)</td>
<td>VSL#3 vs placebo</td>
<td>4-11y: 1 sachet, 12-18y: 2 sachets</td>
<td>6 wk</td>
<td>-</td>
<td>Abdominal pain score (frequency and intensity)</td>
<td>Responders: decreased pain score of ≥1 point</td>
<td>Self-administered questionnaire</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuttner</td>
<td>Canada</td>
<td>11-18 y (N=25)</td>
<td>IBS (Rome I criteria)</td>
<td>Yoga intervention for 1 hour followed by daily home practice guided by a video</td>
<td></td>
<td>4 wk</td>
<td>-</td>
<td>Abdominal pain intensity, Disability</td>
<td></td>
<td>Numeric rating scale, Functional Disability Inventory</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CAP=chronic abdominal pain; CFU=colony-formic units; FPS-R=faces pain scale-revised; GNN=glucomannan; IBS-C=irritable bowel syndrome constipation predominant; IBS-D=irritable bowel syndrome diarrhea predominant; N/A=not available; PedsQL=Pediatric Quality of Life Inventory; VAS=visual analog scale.
**Hypnotherapy**

One systematic review\(^{11}\) (including 2 RCTs\(^{32,44}\)) and 1 RCT\(^{25}\) evaluated the effects of HT for FAP and IBS. Two studies examined HT by therapists \(^{25,32}\) and 1 examined HT with self-exercises on CD.\(^{44}\) All studies used diaries to assess pain intensity and frequency. Gulewitsch et al\(^{25}\) recalculated pain scores into an abdominal pain index. The abdominal pain index, disability and school absenteeism were the primary outcomes. Clinical remission was defined as > 80% decrease on the abdominal pain index: 55% (11 of 20) of children showed clinical remission after HT, compared to 5.6% (1 of 18) of wait-list control subjects (RR 9.90 [95% CI 1.14 to 69.28]).

Vlieger et al\(^{30,32}\) included 53 children in their research. Clinical remission, defined as a >80% reduction of abdominal pain scores, was the primary outcome. After 3 months of HT, 59% showed clinical remission compared to 12% receiving standard care (\(P<0.001\)). Differences persisted after 1 (85% vs 25%; \(P<0.001\)) and 5 years (68% vs 20%; \(P=0.005\)).\(^{30,32}\) Van Tilburg et al\(^{44}\) compared 19 children receiving 2 months of standard care plus HT through self-exercises on CD with 15 children receiving standard care. Primary or secondary outcomes were not specified. Efficacy was based on an abdominal pain index,\(^{44}\) with higher scores indicating more abdominal pain (range 0-40). After treatment, children receiving HT reached an improvement of 9.7 points vs 3.1 points in control subjects (\(P=0.02\)). Significantly more children responded to HT compared to controls (63% vs 27%, \(P=0.03\)). At 6 months follow-up, beneficial effects persisted in 62.5% of the HT-group.

Two trials assessed quality of life, but results were conflicting.\(^{25,44}\) To evaluate this secondary outcome, Gulewitsch et al\(^{25}\) used the validated German KINDL questionnaire. No significant effects were reported by children (\(P=0.120\)) or parents (\(P=0.678\)) compared with control subjects. Van Tilburg et al\(^{44}\) demonstrated a significant quality of life improvement compared to standard care (\(P=0.049\), measured by using the validated Pediatric Quality of Life Inventory. Two studies reported significant improvement of disability.\(^{25,44}\) Gulewitsch et al used Pediatric Pain Disability Index to assess impairment in 12 daily activities. HT had a significant beneficial effect on the self-reported disability compared to control subjects (MD -9.14 [95% CI -14.41 to -3.87]).\(^{25}\) Van Tilburg et al used the Functional Disability Inventory.\(^{44}\) Children receiving HT exhibited a significant reduction of disability compared to control subjects (\(P=0.01\)).

Two studies did not describe differences in school absenteeism between either treatment group.\(^{32,44}\) In 1 trial, school absenteeism was seldom reported, and therefore no calculation was performed.\(^{25}\) One child dropped out because of transient headaches after listening to the CD.\(^{44}\) Gulewitsch et al\(^{25}\) reported no side effects.

**Cognitive Behavioral Therapy**

Two systematic reviews\(^{12,22}\) (including 6 RCTs\(^{31,45-49}\)) and 1 RCT\(^{28}\) were included in the assessment of the various CBT-methods. Four trials evaluated the efficacy of family-focused cognitive behavioral therapy (CBT-family).\(^{31,45-47}\) A visual analog scale (VAS)\(^{45,46}\) and Faces Pain Scale-Revised\(^{31}\) were used to assess pain intensity. Robins et al\(^{47}\) used the Abdominal Pain Index...
for assessments.\textsuperscript{47} Only Levy et al\textsuperscript{31} specified primary outcomes, which were abdominal pain intensity and disability scores. A significantly higher proportion of children in the trial by Sanders et al\textsuperscript{46} were pain free after CBT-family compared with standard care (MD -3.61 [95\% CI -5.76 to -1.46]); these changes persisted at 6 months (P=0.02), but disappeared at the 12-month follow-up. Duarte et al\textsuperscript{45} reported significantly decreased abdominal pain frequency at 3 months follow-up (P=0.001), but no effect was seen for pain intensity. In the study by Robins et al,\textsuperscript{47} CBT-family added to standard care resulted in a significantly lower Abdominal Pain Index compared with standard care alone (P<0.05), with continuing effects at 6 and 12 months follow-up. Levy et al\textsuperscript{31} compared CBT-family with education and support intervention in 200 children. A significant reduction in pain intensity as indicated by parents was reported after 3 sessions of CBT-family (P<0.01). This reduction persisted for 12 months but was not significant when reported by children.\textsuperscript{26} There was no beneficial effect of CBT-family for disability,\textsuperscript{31,47} but a significant improvement in school absenteeism was reported after CBT-family plus standard care (P=0.047).\textsuperscript{47}

Two studies evaluated the effects of individual CBT.\textsuperscript{48,49} Alfvén and Lindstrom\textsuperscript{48} randomized children to undergo CBT plus physiotherapy (N=25) or physiotherapy alone (N=23). Pain intensity score (1-3), frequency score (1-3), and duration score (1-3) were summed into individual pain scores ranging from 3 to 9. Pain score reduction at the 1-year follow-up was not significantly different between groups (46\% vs 44\%; P-value not reported). Humphreys and Gevirtz\textsuperscript{49} divided 64 patients (aged 4-18 years) into 4 groups to compare CBT, fiber supplements, biofeedback, and parental support in different combinations. Children kept diaries and reported pain intensity using a VAS; the primary outcome was the number of self-reported pain free days. Results of the first 3 groups (CBT, biofeedback, and parental support) were combined and compared with a group receiving fiber supplements. After treatment, 33 (72\%) of 46 children in the intervention groups were pain free compared to 1 (7.1\%) of 14 children taking fiber supplements only (OR 33.0 [95\% CI 3.9 to 278.5]).\textsuperscript{22} Humphreys and Gevirtz\textsuperscript{49} investigated school absenteeism and reported significant effects favoring CBT.

Groß and Warschburger\textsuperscript{28} compared CBT group sessions (N=15) versus wait-list control subjects (N=14).\textsuperscript{28} Pain intensity was assessed using a VAS. Although primary outcomes on pain intensity (P=0.001), frequency (P=0.003) and duration (P=0.002) significantly improved after CBT, only pain duration was still significant at 3 months follow-up (P=0.014). Quality of life was measured as a secondary outcome, using the Pediatric Quality of Life Inventory. A significant improvement favoring CBT was reported on physical functioning (P<0.001), psychological functioning (P=0.003), social functioning (P=0.044), and school functioning (P=0.012). However, results disappeared after 3 months of follow-up.

**Written self-disclosure (WSD)**

Wallander et al\textsuperscript{29} evaluated WSD in addition to standard care in 63 children (aged 11-18 years) with RAP. In three 20-minute sessions, patients were asked to write about their “deepest thoughts and feelings about the most distressing experience in their life”. Primary and secondary
outcomes were not specified. Seven patients were lost to follow-up and excluded from analyses. Abdominal pain frequency was rated using a 6-point scale. Although there were no differences at 3 months, pain frequency was significantly less after WSD and standard care at 6-month follow-up compared with standard care alone ($F_{[1,51]} = 6.50, P=0.014, \text{Cohen’s } d = 0.61$). Physical and psychosocial quality of life was measured by using the Pediatric Quality of Life Inventory, and no significant differences were reported.

**Pre- or probiotics**

One systematic review$^{18}$ (including 3 RCTs$^{41-43}$) evaluated the effects of *Lactobacillus rhamnosus* GG (LGG) compared with placebo. Data were pooled by Horvath et al for treatment responders and treatment success, which were secondary outcomes. Baussermann and Michail$^{41}$ classified children as responders if abdominal pain severity decreased ≥1 points on a 4-point Likert scale. Francavilla et al$^{42}$ used a VAS and defined treatment success as a decrease of >50% of pain episodes and intensity. Gawronńska et al$^{43}$ defined treatment success as no pain or change in Faces Pain Scale-Revised by ≥2 faces. LGG supplementation was associated with significantly more treatment responders (67%) compared with placebo (51%) ($N=290$; RR 1.31 [95% CI 1.08 to 1.59]; number needed to treat 7 [95% CI 4 to 22]).$^{18}$ Subgroup analysis showed results being mainly applicable for IBS ($N=167$; RR 1.70 [95% CI 1.27 to 2.27]; number needed to treat 4 [95% CI 3 to 8]). Guandalini et al$^{27}$ conducted a crossover trial, comparing 6 weeks of VSL#3 versus placebo in 59 children with IBS. VSL#3 is a probiotic mixture comprising 8 different strains of *Bifidobacterium, Lactobacillus, and Streptococcus*. After a 2-week washout period, each patient switched to the other group for another 6 weeks of treatment. Abdominal pain was measured as secondary outcome: frequency and intensity were rated on a 5-point Likert scale. After treatment, a significant reduction in the abdominal pain score of 1.0±0.2 was reported in the VSL#3 group versus 0.5±0.2 in control subjects ($P<0.05$). One study evaluated school absenteeism, but no significant difference was found.$^{42}$ No adverse effects of LGG were reported, although it was unclear in 2 studies how adverse effects were assessed.$^{41,42}$ No studies were included on prebiotics.

**Alternative medicine**

One study of the systematic review by Birdee et al$^{23}$ was included regarding alternative therapy. Kuttner et al$^{50}$ compared 14 children receiving yoga to 11 wait-list control subjects. After 4 weeks, questionnaires were completed, and control subjects received 4 weeks of yoga and completed additional questionnaires. Pain intensity was measured on a numeric scale of 1 to 10. Results before the crossover phase were not reported because of baseline differences. Functional disability decreased after yoga, but increased in control subjects (MD -9.60 [95% CI -19.66 to 0.46]). Primary or secondary outcomes were not specified. No studies were included evaluating acupuncture, homeopathy, mind-body therapy, musculoskeletal manipulations such as osteopathic and chiropractic manipulations.
DISCUSSION

This systematic review includes 24 studies with very low to moderate methodologic quality. Some evidence was found indicating beneficial effects of PHGG, HT, CBT and probiotics (LGG and VSL#3). No beneficial effects were reported for fiber supplementation other than PHGG and a lactose-restricted diet. No studies were included on life-style advice, other dietary advice, or prebiotics. No serious adverse effects were reported.

Dietary interventions are frequently used in AP-FGIDs, because many patients and some physicians consider symptoms to be meal related. Fiber supplementation is believed to be helpful because it softens stools and enhances colonic transit. However, studies in children and adolescents evaluating ispaghula husk and glucomannan found no favorable effects. Improvement in abdominal pain frequency was reported after administration of corn fiber, but questions were raised whether statistical analyses were adequate. Re-analyses by Huertas-Ceballos et al failed to replicate the findings. Adult studies produced conflicting results and a meta-analysis reported only beneficial effects for ispaghula husk. The main component of PHGG is galactomannan, which softens stool, improves fecal output and increases bulk capacities. PHGG treatment in IBS children found a reduced frequency in IBS symptoms, but pain intensity was not decreased. Results of an open PHGG trial in adult patients with IBS produced significant improvements in gastrointestinal symptoms, quality of life, and psychological distress, but the effects tended to fade out after the 12-week treatment period.

Malabsorption and intolerance to carbohydrates such as fructose and lactose are believed to cause symptoms such as bloating, diarrhea and abdominal pain. However, neither lactose nor fructose intolerance was established as a cause of pain in 220 children with RAP in a recent study, and lactose restriction did not improve symptoms in pediatric trials. Recently, diets of low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) have been extensively studied in adults. FODMAPs are poorly absorbed short-chain carbohydrates, which may cause gas production, bloating, and abdominal pain. A low FODMAP diet seems beneficial in adult IBS trials, but due to heterogeneity in study design and outcomes and because of unknown long-term safety and efficacy, definitive conclusions cannot be drawn. Recently, a randomized, double blind, crossover trial in 33 IBS children reported improvement in abdominal pain after receiving a 48-hour low FODMAP diet. Although these results seem promising, more long-term studies are needed to further assess the efficacy and safety of a low FODMAP diet in children and adolescents.

In HT, suggestions toward control and normalization of gut functioning, ego-strengthening, and stress reduction are conveyed to patients after inducing a hypnotic state. Results of studies in children and adolescents found significantly lower abdominal pain levels and symptom scores after HT, either through individual or group sessions with therapists or with self-exercises on a CD. Effects persist up to 5 years after treatment. Results are in accordance with adult IBS trials showing that HT is superior to a variety of control treatments, with long-lasting effects. Working mechanisms of HT are still poorly understood, but outcomes of adult studies hypothesize that HT affects both physiological processes, such as colonic motility and pain processing brain
regions, and psychological factors such as stress and dysfunctional cognitions. CBT aims to change attitudes, cognitions and behavior that may play a role in generating or maintaining symptoms and is effective in improving pain and other IBS symptoms in adults. Trials in children and adolescents also indicate beneficial effects of CBT, especially CBT-family, in improving pain and disability and effects appear to be long-lasting. Results of the trial by Levy et al trial are of particular interest since it includes 200 children and adolescents. A RCT on individual CBT published shortly after the literature search of the present systematic review, showed improvement in 60% of children with FAP after CBT, but results did not differ compared to standard care (including 6 supportive sessions with the pediatric gastroenterologist). However, children receiving CBT reported significantly less symptoms of anxiety or depression compared to children receiving standard care.

WSD targets psychosocial stress and may work through changing expression and increasing insight about emotions. It is reportedly effective in a wide variety of adult organic and functional disorders. WSD in addition to standard care significantly reduced pain frequency after 6 months in pediatric RAP but not after 3 months. Although further research is needed, WSD may be a useful adjunct to other treatment regimens because it can be easily integrated, requires little training, and has low costs.

Probiotics are beneficial species of bacteria that may improve AP-FGID symptoms by preventing overgrowth of potentially pathogenic bacteria, maintaining integrity of gut mucosa and/or altering intestinal inflammatory responses. RCTs in children and adolescents evaluating LGG and VSL#3 in FAP, IBS and functional dyspepsia indicate beneficial effects over placebo, but probiotics seem mostly effective in IBS. Probiotics also seem effective in adults with AP-FGIDs, but future research must clarify which probiotic strains are most effective. Although >40% of children with IBS and FAP use complementary and alternative medicine, data are lacking on the efficacy and safety of almost all forms of this treatment in these children and adolescents. Yoga may address psychosocial factors and decrease stress. Kuttnner et al reported significantly lower levels of functional disability and gastrointestinal symptoms after yoga, but it is noteworthy that P values <0.1 were considered reflective of statistical trends worthy of interpretation. However, a pilot study in children and adolescents aged 8 to 18 years with IBS and FAP also showed significant short-term improvement in abdominal pain frequency and intensity. It thus seems worthwhile to further explore efficacy of yoga. Because treatment protocols in CBT, HT, and yoga all incorporate relaxation exercises, one might hypothesize that relaxation training alone can also be beneficial in AP-FGIDs. This therapeutic approach may be interesting to address in future research because it has been shown to be effective in children and adolescents with recurrent headaches as well.

The methodologic quality of the included studies varied from very low to moderate, and the results should therefore be interpreted cautiously. The low quality was mainly due to small sample sizes, lack of adequate follow-up, substantial dropout rates, or considerable risk of bias. However, it should be taken into account that blinding of patients and caregivers is not possible in psychological therapies such as HT or CBT. By using validated diagnostic
criteria for AP-FGIDs, applicability of results is increased, which strengthens the results. Due to considerable heterogeneity of studies, meta-analysis could only be conducted for fiber supplementation and probiotics. Other possible limitations of this systematic review include the possibility of publication bias and language restriction to English. However, by conducting a comprehensive and contemporaneous literature search, we attempted to minimize the risk of missing relevant studies. Use of a wide variety of definitions for clinical improvement also hampers the interpretation of results. Clinical relevance of a 1-point reduction on a 4-point Likert scale may be questioned, while an 80% reduction in abdominal pain frequency and intensity scores seems overly conservative. Unfortunately, a standard definition of improvement for therapeutic studies on AP-FGIDs is lacking. Consensus on a standard definition is necessary because it increases homogeneity of future trials and allows better comparison of results. In addition, performing analyses on number needed to treat and RR is often restricted because most RCTs fail to report on numbers or percentages of patients experiencing significant improvement.

A limited number of RCTs (n=8) reported on adverse effects, thereby hindering interpretation of results on safety. However, in those studies, no serious adverse effects were shown, apart from a small number of children reporting gas or diarrhea. In interpreting FGID trials, the placebo effect may play an important role. Placebo responses in trials of adults with IBS vary from 16.0% to 71.4%, and high placebo rates up to 53% were reported in RCTs on children and adolescents. High placebo responses may also display natural course of FGIDs with fluctuating symptoms. Improving the patient-practitioner relationship and active listening approaches are essential in mediating placebo responses, which may be especially important in nonpharmacologic therapies in which contact with therapists is mostly frequent.

CONCLUSIONS

To date, high-quality studies on nonpharmacologic treatments in pediatric AP-FGIDs are lacking, and the need for these studies is evident. However, available evidence indicates beneficial effects of HT, CBT and probiotics (LGG and VSL#3) in some children. Data on fiber supplementation for children and adolescents with AP-FGIDs is inconclusive, but PHGG may be an option. No serious adverse effects were reported.

Since symptoms may resolve without active treatment in a significant proportion of children, the first step in management may consist of physician reassurance and education. However, approximately one-third of children continue to experience symptoms. Clinicians may consider HT, CBT or probiotics (LGG and VSL#3), especially in children with persisting symptoms. Additional high-quality studies are required in children with mild symptoms as well as severe symptoms to further assess the effectiveness of nonpharmacologic therapies and to identify factors predicting response, with the goal of optimizing and tailoring individual treatment. Because abdominal pain is the key symptom in AP-FGIDs and to decrease heterogeneity, we emphasized the importance of including abdominal pain severity, frequency, and/or intensity as
a primary outcome measure in trials evaluating (non)pharmacologic treatments for AP-FGIDs. In addition, adverse effects need to be reported systematically to better assess safety.
REFERENCES


17. Huertas-Ceballos A, Logan S, Bennett C, et al. Pharmacological interventions for recurrent abdominal pain (RAP) and irritable


APPENDIX I. 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 Dietary advice**

**Question:** Should fiber supplements vs placebo be used for recurrent abdominal pain?

**Settings:** private practices, hospital

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Risk of bias</td>
</tr>
<tr>
<td>3</td>
<td>randomized trials</td>
<td>serious&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> Christensen: >20% was lost to follow-up.

<sup>2</sup> Moderate: I=40%

<sup>3</sup> 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.
**Question:** Should guar gom vs placebo be used for chronic abdominal pain and irritable bowel syndrome?

**Settings:** Gastroenterology unit university hospital

<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 studies</strong></td>
<td><strong>Design</strong></td>
<td><strong>Risk of</strong></td>
<td><strong>Inconsistency</strong></td>
<td><strong>Indirectness</strong></td>
</tr>
<tr>
<td>1</td>
<td>randomized trials</td>
<td>no serious risk of bias</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
</tbody>
</table>

1 One study only.
2 Low sample size (<400).

**GRADE evidence profile Hypnotherapy**

**Question:** Should hypnotherapy vs standard care / wait-list be used for functional abdominal pain or irritable bowel syndrome?

**Settings:** diverse

<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 studies</strong></td>
<td><strong>Design</strong></td>
<td><strong>Risk of</strong></td>
<td><strong>Inconsistency</strong></td>
<td><strong>Indirectness</strong></td>
</tr>
<tr>
<td>1</td>
<td>randomized trials</td>
<td>serious</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
</tbody>
</table>

1 Gulewitsch (2013)
2 A wait-list design does not control for attention or expectation of a future symptom improvement.
3 One study only.
4 Low sample size.
5 Van Tilburg (2009)
6 Concealment of allocation unclear. Intervention unblinded.
7 In the article not sufficient data are given to present (complete) results.
8 Vlieger (2007)
9 Intervention unblinded.
<table>
<thead>
<tr>
<th>Question</th>
<th>Settings</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality Importance</th>
<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>
</tr>
</thead>
<tbody>
<tr>
<td>Should guar gum vs placebo be used for chronic abdominal pain and irritable bowel syndrome?</td>
<td>Gastroenterology unit university hospital</td>
<td>24</td>
<td>-</td>
<td></td>
<td>2</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>none</td>
<td>19</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>Quality of life(^5,10) (measured with: question; Better indicated by lower values)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no serious indirectness</td>
<td>no serious indirectness</td>
<td>none</td>
<td>19</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>School absence(^9) (follow-up 5 years; assessed with: question)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no serious indirectness</td>
<td>no serious indirectness</td>
<td>none</td>
<td>7/22</td>
<td>3/27</td>
<td>RR 0.35 (0.10 - 1.19)</td>
</tr>
<tr>
<td>Disability score(^1) (follow-up 2 weeks; measured with: questionnaire; Better indicated by higher values)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no serious indirectness</td>
<td>no serious indirectness</td>
<td>none</td>
<td>20</td>
<td>18</td>
<td>-</td>
</tr>
</tbody>
</table>

1 Gulewitsch (2013)
2 A wait-list design does not control for attention or expectation of a future symptom improvement.
3 One study only.
4 Low sample size.
5 Van Tilburg (2009)
6 Concealment of allocation unclear; intervention unblinded.
7 In the article not sufficient data are given to present (complete) results.
8 Vlieger (2007)
9 Intervention unblinded.
**GRADE evidence profile Cognitive behavioral therapy**[^28,^31,^45-^49]

**Question:** Should cognitive-behavioral family therapy vs standard pediatric care be used for recurrent abdominal pain?

**Settings:** diverse[^45-^47]

<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>Pain intensity (follow-up 6 months; Better indicated by lower values)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median frequency of episodes of pain (Better indicated by lower values)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Abdominal pain index (Better indicated by lower values)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[^1]: Concealment of allocation was unclear. Outcome was assessed by parents and children who could not be blinded. In total 38/44 participants completed the study but we were unable to ascertain the numbers by group to which they were allocated.

[^2]: One study only.

[^3]: Low sample size.

[^4]: Concealment of allocation was unclear.

[^5]: In the article not sufficient data are given to present (complete) results.

[^6]: There is significant differential loss to follow-up in this study with outcome data are available for 40/46 patients in the intervention group and 29/40 in the control group.
**Question:** Should cognitive-behavioral interventions and dietary fiber vs dietary fiber alone be used for recurrent abdominal pain?

**Settings:** community hospital

<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>Cognitive-behavioral interventions and dietary fiber</th>
<th>Dietary fiber alone</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>randomized trials</td>
<td>serious¹</td>
<td>no serious inconsistency²</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>33/46 (71.7%)</td>
<td>1/14 (7.1%)</td>
<td>OR 33.0 (3.9 - 278.5)</td>
<td>646 more per 1000 (from 159-884 more)</td>
<td>MODERATE</td>
<td>CRITICAL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Concealment of allocation was unclear.
2. One study only.
**Question:** Should psychological treatment and physiotherapy vs physiotherapy only be used for recurrent abdominal pain?
**Settings:** primarily, secondarily and tertiary referred children

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Risk of bias</td>
</tr>
<tr>
<td>1</td>
<td>randomized trials</td>
<td>very serious</td>
</tr>
</tbody>
</table>

1 Concealment of allocation and blinding of outcomes was unclear. Duration of treatment has not been described.
2 One study only.
3 Low sample size (N=48).
4 In the article not sufficient data are given to present (complete) results.
**Question:** Should cognitive behavioral therapy vs education be used for functional abdominal pain?

**Settings:** secondary and tertiary hospitals

<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>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
</tr>
<tr>
<td>1 randomized trials</td>
<td>very serious¹</td>
<td>no serious inconsistency²</td>
<td>serious³</td>
<td>no serious imprecision</td>
</tr>
<tr>
<td>Pain reported by parents (follow-up 12 months; measured with: faces pain scale; Better indicated by lower values)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 randomized trials</td>
<td>very serious¹</td>
<td>no serious inconsistency²</td>
<td>serious³</td>
<td>no serious imprecision</td>
</tr>
<tr>
<td>Functional disability reported by parents (follow-up 12 months; measured with: functional disability inventory; Better indicated by lower values)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 randomized trials</td>
<td>very serious¹</td>
<td>no serious inconsistency²</td>
<td>serious³</td>
<td>no serious imprecision</td>
</tr>
<tr>
<td>Pain reported by child (follow-up 12 months; measured with: faces pain scale; Better indicated by lower values)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ Attrition is described, significant differences between completers and non-completers are not reported. Randomization unclear. Baseline differences.

² One study only.

³ Participants were a volunteer group who had been referred by providers or responded to notices regarding the study. Consequently, they may not be representative of the larger population of families and children with FAP.
**Question:** Should cognitive behavioral group therapy vs wait-list be used for functional abdominal pain?

**Settings:** not reported

<table>
<thead>
<tr>
<th></th>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quality</td>
<td>Importance</td>
<td>No of studies</td>
<td>Design</td>
<td>Risk of bias</td>
</tr>
<tr>
<td>Pain intensity (follow-up 3 months; measured with: VAS scale; Better indicated by lower values)</td>
<td>1 randomized trials</td>
<td>serious¹</td>
<td>no serious inconsistency¹</td>
<td>no serious indirectness</td>
<td>serious³</td>
</tr>
<tr>
<td>Pain frequency (follow-up 3 months; times per day measured with pain diary; Better indicated by lower values)</td>
<td>1 randomized trials</td>
<td>serious¹</td>
<td>no serious inconsistency¹</td>
<td>no serious indirectness</td>
<td>serious³</td>
</tr>
<tr>
<td>Pain duration (follow-up 3 months; hours per day measured with pain diary; Better indicated by lower values)</td>
<td>1 randomized trials</td>
<td>serious¹</td>
<td>no serious inconsistency¹</td>
<td>no serious indirectness</td>
<td>serious³</td>
</tr>
<tr>
<td>Quality of life (follow-up 3 months; measured with PedsQL; Better indicated by higher values)</td>
<td>1 randomized trials</td>
<td>serious¹</td>
<td>no serious inconsistency¹</td>
<td>no serious indirectness</td>
<td>serious³</td>
</tr>
</tbody>
</table>

¹ No blinding.
² One study only.
³ Low sample size.
GRADE evidence profile Written self-disclosure²⁹

**Question:** Should written self-disclose + standard care vs standard care be used for functional abdominal pain?

**Settings:** Gastrointestinal clinic

<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>Pain frequency</strong> (follow-up 6 months; measured with Abdominal Pain Frequency Rating; Better indicated by lower values)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 randomized trials</td>
<td>serious¹</td>
<td>no serious inconsistency²</td>
<td>no serious indirectness</td>
<td>serious³</td>
</tr>
<tr>
<td><strong>Quality of life</strong> (follow-up 6 months; measured with PedsQL; Better indicated by higher values)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 randomized trials</td>
<td>serious¹</td>
<td>no serious inconsistency²</td>
<td>no serious indirectness</td>
<td>serious³</td>
</tr>
</tbody>
</table>

¹ No blinding.
² One study only.
³ Low sample size.
**GRADE evidence profile: Probiotics**

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

**Settings:** secondary and tertiary centers

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of studies</strong></td>
<td><strong>Design</strong></td>
<td><strong>Risk of bias</strong></td>
</tr>
<tr>
<td>3</td>
<td>randomized trials</td>
<td>serious</td>
</tr>
</tbody>
</table>

1 In Bausserman the lost-to-follow up was >20%.
**Question:** Should VSL#3 vs placebo be used for IBS (ROME II)?

**Settings:** 5 pediatric tertiary care centers

<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></td>
<td>VSL#3</td>
<td>Placebo</td>
<td>Relative (95% CI)</td>
<td>Absolute</td>
</tr>
<tr>
<td>Abdominal pain (follow-up 6 weeks)</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>serious³</td>
</tr>
</tbody>
</table>

¹ No details about randomization mentioned.
² One study only.
³ Only children with IBS have been included.
⁴ Low sample size.
⁵ In the article not sufficient data are given to present (complete) results.
**GRADE evidence profile Alternative medicine**

**Question:** Should yoga vs wait-list be used for IBS?

**Settings:** gastroenterology clinic at the local children’s hospital

<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>No of studies</td>
<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>1 randomized trials</td>
<td>serious¹</td>
<td>no serious inconsistency²</td>
<td>serious³</td>
<td>serious⁴</td>
</tr>
</tbody>
</table>

¹ No details about randomization. No description of the reasons for lost to follow-up.

² One study only.

³ Children aged 11-18 years with IBS.