Pharmacologic Treatment in Pediatric Functional Abdominal Pain Disorders: A Systematic Review

Judith J. Korterink, MD[1,*], Juliette M. T. M. Rutten, MD[1,*], Leonie Venmans, PhD[2], Marc A. Benninga, MD, PhD[1], and Merit M. Tabbers, MD, PhD[1]

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 investigating efficacy and safety of pharmacologic agents in children aged 4-18 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 (aged 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 = .007) and famotidine only provides benefit in global symptom improvement (OR 11.0; 95% CI 1.6-75.5; P = .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. *(J Pediatr 2015;166:424-31)*.

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 1**; available at www.jpeds.com).[1] AP-FGIDs affect approximately 20% of children worldwide and include functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine, 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] Because of 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 into 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 their own clinical experiences and results of adults studies, which can be harmful because evidence from adults cannot be directly

AP-FGID	Abdominal pain-related functional gastrointestinal disorder	IBS	Irritable bowel syndrome
		IBS-C	IBS-constipation predominant
FAP	Functional abdominal pain	PEG 3350	Polyethylene glycol 3350 oral solution
FD	Functional dyspepsia		
GI	Gastrointestinal	QoL	Quality of life
GRADE	Grades of Recommendation, Assessment, Development and Evaluation	RCT	Randomized controlled trial
		RR	Relative risk
		SR	Systematic review

From the [1]Department of Pediatric Gastroenterology and Nutrition, Emma's Children's Hospital Academic Medical Center, Amsterdam, The Netherlands; and [2]Pediatric Association of The Netherlands, Utrecht, The Netherlands

*Contributed equally.

The authors declare no conflicts of interest.

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http://dx.doi.org/10.1016/j.jpeds.2014.09.067

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 syndrome, IBS, FD, or abdominal migraine 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 (eg, 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: 2 SRs[16,20] and 2 RCTs.[21,22] One review[16] originally included a third study,[23] but this study was excluded because of <10 patients per treatment arm (**Figure**).

Compared with placebo, 1 trial investigated antispasmodics,[24] 2 trials studied antidepressants,[25,26] 1 trial studied antireflux medication,[27] and 1 antihistaminic agents.[22] One trial evaluated polyethylene glycol 3350 oral solution (PEG 3350) compared with 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 America[21,24-27] 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.[27]

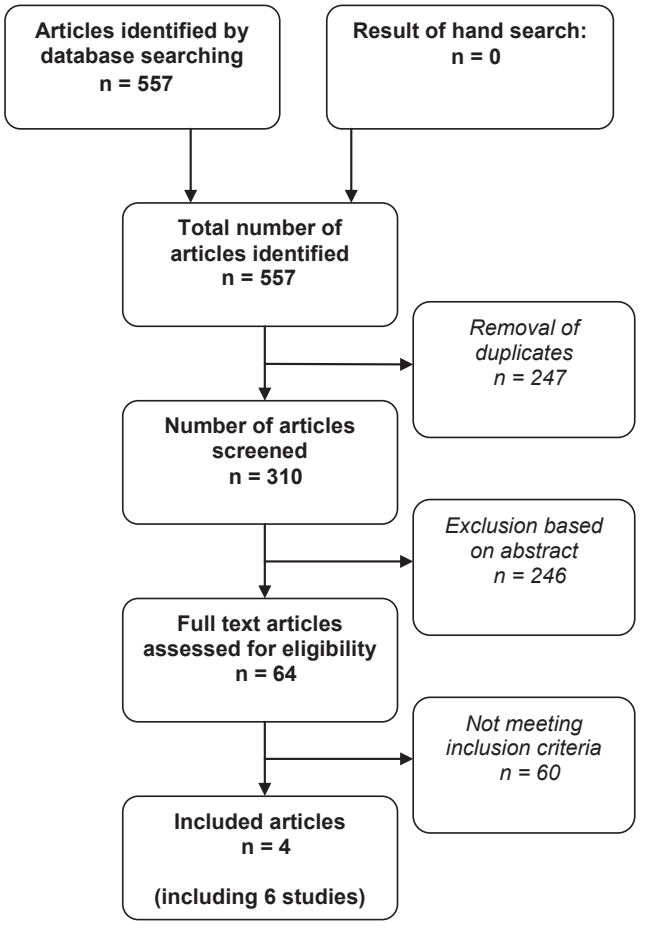

Figure. Flowchart showing results of literature search and study inclusion.

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