Pediatric functional abdominal pain disorders

From diagnosis to management - a clinical approach

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CHAPTER 6

Pharmacologic Treatment in Functional Abdominal Pain Disorders in Children: a systematic review

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ABSTRACT

Context: Functional abdominal pain disorders (FAPDs) are common in childhood, impacting quality of life and school attendance. There are several compounds available for the treatment of pediatric FAPDs, but their efficacy and safety are unclear because of a lack of head-to-head randomized controlled trials (RCTs).

Objective: To systematically review the efficacy and safety of the pharmacologic treatments available for pediatric FAPDs.

Data Sources: Electronic databases were searched from inception to February 2021.

Study Selection: RCTs or systematic reviews were included if the researchers investigated a study population of children (4-18 years) in whom FAPDs were treated with pharmacologic interventions and compared with placebo, no treatment or any other agent.

Data Extraction: Two reviewers independently performed data extraction and assessed their quality. Any interresearcher disagreements in the assessments were resolved by a third investigator.

Results: Seventeen articles representing 1197 children with an FAPD were included. Trials investigating antispasmodics, antidepressants, antibiotics, antihistaminic, antiemetic, histamine-2-receptor antagonist, 5-HT4-receptor agonist, melatonin, and buspirone were included. No studies were found on treatment with laxatives, antidiarrheals, analgesics, antimigraines and serotonergics.

Limitations: The overall quality of evidence on the basis of the Grading of Recommendations, Assessment, Development and Evaluations system was very low to low.

Conclusion: On the basis of current evidence, it is not possible to recommend any specific pharmacologic agent for the treatment of pediatric FAPDs. However, agents such as antispasmodics or antidepressants can be discussed in daily practice because of their favorable treatment outcomes and the lack of important side effects. High-quality RCTs are necessary to provide adequate pharmacologic treatment. For future intervention trials, we recommend using homogenous outcome measures and instruments, a large sample size, and long-term follow-up.

BACKGROUND

Functional abdominal pain disorders (FAPDs) are common in childhood and include functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine (AM), and functional abdominal pain–not otherwise specified (FAP-NOS) (**Supplemental Table 5**).[1,2] They are associated with a reduced quality of life, higher risks of anxiety and depression disorders, and high rates of school absenteeism, leading to a substantial impact on health costs.[3–7] A large proportion of children continue to experience FAPD-related symptoms in adulthood highlighting the necessity of adequate treatment in pediatric FAPDs.[8–11]

To date, the pathophysiological mechanisms of FAPDs are not completely understood. The hypothesis is that FAPDs are caused by a biopsychosocial model, in which genetic, physiologic, psychological, and socioenvironmental factors interplay and symptoms are thought to be caused by dysregulation of the brain-gut axis. This results in disturbances in the gastrointestinal tract and the central nervous system possibly leading to visceral hypersensitivity and abnormal gastrointestinal motility.[12,13] Current available treatment options for pediatric patients with FAPDs consist of education, reassurance, lifestyle interventions, nonpharmacologic (ie, hypnotherapy and cognitive-behavioral therapy), and pharmacologic treatment regimes. However, management remains mostly symptom based because no gold standard of treatment exists.[14]

In 2015 a systematic review, which included 6 studies with 275 children with FAPDs, reported a lack of high-quality, placebo-controlled pharmacologic trials for treatment of pediatric FAPDs and found no evidence to support routine use of any pharmacologic therapy.[15] However, since then more intervention studies have been published that include new pharmacologic agents that may comprise future treatment recommendations. Therefore, our aim is to give an update by systematically reviewing the efficacy and safety of pharmacologic treatment in children with FAPDs.

METHODS

Literature Search

PubMed, Medline, Embase, PsycINFO, and Cochrane Library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect, and Cochrane Central Register of Controlled Trials) were searched from inception to February 2021. To identify unpublished or ongoing studies, the ClinicalTrials.gov register, the World Health Organization International Clinical Trials Registry Platform Search Portal, and the Current Controlled Trials metaRegister of Controlled Trials active registers were searched. To identify relevant articles and reviews missed by the search strategies, the reference lists from reviewed articles were searched by hand. The full search strategies are available on request. The protocol was registered at the International Prospective Register of Systematic Reviews (identifier CRD42020159847).

Study Inclusion

Two researchers (R.R. and C.M.A.B.) independently reviewed the titles and abstracts yielded by the search using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Duplicated records were removed. In case of interresearcher disagreements, a third investigator (M.G.) was consulted. Inclusion and exclusion criteria are presented in **Table 1**. Outcome measures were identified according to the core outcome set (COS) for FAPDs.[16] There were no language restrictions. All potentially relevant studies were retrieved in full.

Table 1. Eligibility Criteria

Inclusion criteria
Study was a systematic review or RCT.
Study population consisted of children aged 4–18 y.
FAPDs were diagnosed or treated, or its course followed. FAPDs included: • IBS • FD • AM • FAP-NOS
FAPDs in alignment with Rome criteria, other international criteria, or a precise definition by the author.
Interventions were: • Antispasmodics (peppermint oil, hyoscine butylbromide, mebeverine) • Antidepressants (amitriptyline) • Laxatives – Osmotic laxatives (polyethylene glycol, lactulose, lactitol) – Stimulant laxatives (bisacodyl) – Lubricants (mineral oil or liquid paraffin) – Enemas • Antidiarrheal agents (loperamide) • Antibiotics • Analgesics (paracetamol, NSAID, tramadol) • Antireflux agents (PPI, H_2-receptor antagonists, prokinetics) • Antiemetic agents (ondansetron) • Antimigraine agents (sumatriptan, propranolol) • Antihistaminic agents (cyproheptadine) • Serotonergic agents
Outcomes measures[a] (assessed before and after start with pharmacological treatment) were: • Treatment success as defined by the authors (to be reported) • Pain frequency or change in frequency of pain • Pain intensity or change in pain intensity • Withdrawal due to adverse events • Quality of life or change in quality life measured by using any validated defined measurement tool • Anxiety and/or depression determined by using any validated defined measurement tool • Serious adverse events • Adverse events • Stool consistency (disease-specific [IBS-C or IBS-D]) as defined by the authors (Bristol stool or similar) at study end • Frequency of defecation at study end • Adequate relief (as reported by the patient or parent) • School attendance or change in school attendance or performance
Exclusion criteria
Studies including children with: • Hirschsprung disease • Previous bowel surgery • Complex congenital disorders
If the range of children's age was wider than 4-18 y, the authors were requested for separate data of the children aged 4–18 y. If such data were not available or no response was given, the study was excluded.
Quasi-randomized, no randomization, cohort, case control, animal studies, editorial, commentary, case reports.
Abstracts were considered if they met the inclusion criteria; if not enough data to judge were presented, the authors were contacted, and if no response was received within 2 wk, abstracts were excluded.
If inclusion could not be decided on the basis of the full text, the authors were contacted. If no response was received within 2 wk, the study was excluded.

H_2, histamine 2; IBS-D, irritable bowel syndrome with diarrhea; NSAID, nonsteroidal antiinflammatory drug; PPI, proton pump inhibitor.

[a]*outcome measures were identified according to the COS for FAPDs.*

Quality Assessment and Data Extraction

Two review authors (R.R. and C.M.A.B.) independently performed data extraction from all included studies, using a predesigned data extraction form containing items on study details (author, publication year, country), participants (subjects, age, sex, disease and definition), inclusion and exclusion criteria of the study, intervention characteristics (type and dose of pharmacologic treatment), control characteristics (no intervention, placebo, or other pharmacologic interventions, including dose and details), total number of patients originally assigned to each intervention group (*N* patients/controls), outcome measures, instruments and results (type of outcome measures used, time of assessment, and length of follow-up), and adverse events.

The risk of bias of all included studies was independently assessed by the same authors by using the Cochrane risk-of-bias tool.[17] Bias was assessed as a judgment (high, low, or unclear) for individual elements from 5 domains (selection, performance, attrition, reporting, and other). For each outcome, the overall quality of evidence was assessed by using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (**Supplemental Tables 6–15)**.[18,19] Any interresearcher disagreements in the assessments were resolved by a third investigator (M.G.).

Data Analysis

Dichotomous outcomes were reported as odds ratios or relative risks (RRs) along with 95% confidence intervals (CIs). Continuous outcomes were reported as mean differences (MDs) with 95% CIs. In case of crossover trials, only data from the first phase of the study (ie, before the crossover occurred) were extracted.

RESULTS

A total of 1989 potentially relevant articles and abstracts were identified (Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 flow diagram, **Fig 1**). After removal of duplicates (n = 196) and screening of titles and abstracts, 55 full-text articles were assessed for eligibility. In total, 25 articles did not meet inclusion criteria and were excluded for various reasons. We identified 11 systematic reviews[15,20–29] and 6 ongoing trials. Authors of the ongoing trials were contacted. We identified 3 additional relevant articles by searching by

hand reference lists from these systematic reviews.[30–32] In total, 17 articles were included for analysis.[30–46] Details of excluded studies are shown in **Supplemental Tables 16–18**.

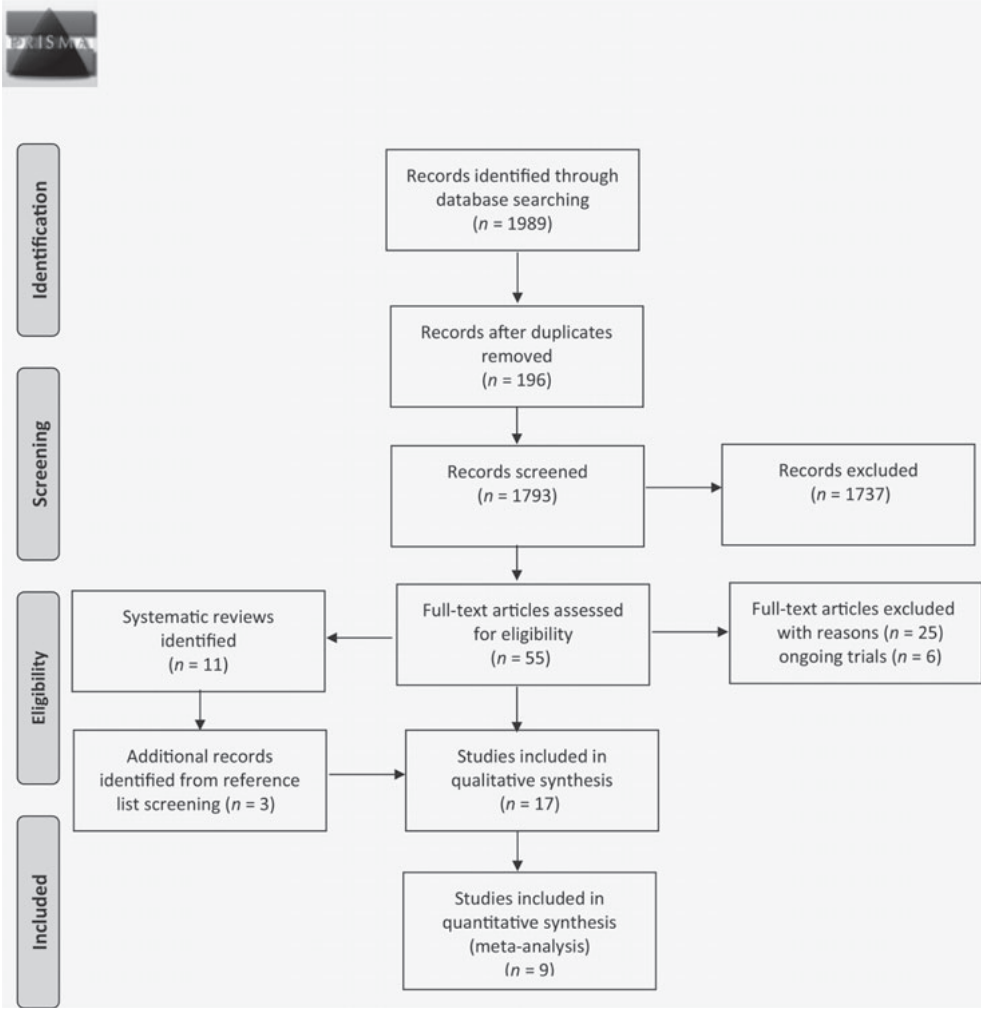

***Figure 1**. PRISMA 2009 flow diagram.*
Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 flow diagram. For more information, visit www.prisma-statement.org. Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7):e1000097.

Studies reporting 1197 children aged 3 to 18 years of age were included for analysis. Sample sizes ranged from 14 to 132 patients, and follow-up ranged from 2 weeks to 1 year. In 5 trials, researchers investigated antispasmodics compared with placebo[30,32,33,35,40]; in 3 trials, researchers evaluated treatment with antidepressants[34,37,42]; in 2 trials, researchers studied antibiotics[43,44]; and in 2 trials, researchers compared antihistaminic treatment versus placebo.[36,39] In the remaining studies, researchers evaluated treatment with 5-HT4-receptor agonist (tegaserod),[46] H_2-receptor antagonist (famotidine),[38] antiemetic (domperidone),[45] melatonine,[31] and buspirone.[41] No studies were included with laxatives, antidiarrheal agents, analgesics, antimigraine agents, and serotonergic agents as treatment.

In the majority of randomized controlled trials (RCTs), researchers did not present results with absolute numbers; these studies could not be included in the meta-analysis. Because of heterogeneity and limited reporting, no further meta-analysis was possible. The characteristics of the included studies are presented in **Table 2**.

Table 2. Study Characteristics of Included Studies

Author; Location	Participants	Intervention	Outcome Measures and Instruments	Quality
Antidepressants				
Roohafza et al[34] (2014), Iran	Children aged 6–18 y (N = 115) FAP (Rome III criteria)	Citalopram versus placebo Dosage: 10 mg/day in the first wk, increasing to 20 mg/day for remaining 3 wks Treatment period: 4wks	Treatment success Improvement: 2-point reduction Instrument: WBFPRS, score 0–5 Depression Instrument: CDI Anxiety Instrument: RCMAS Adverse events reported Instrument: checklist including common side effects of citalopram	Very Low
Saps et al[37] (2009), United States	Children 8–17 y (N = 90) FAP, FD, IBS (Rome II criteria)	Amitriptyline versus placebo Dosage: 10 mg/d in patients <35 kg or 20 mg/d in patients >35 kg Treatment period: 4 wk	Treatment success Improvement: child's assessment of satisfactory relief and satisfaction with treatment with "good" or "excellent" Instrument: assessed by the following 2 questions "Overall, how do you feel your problem is?" and "How did the medication relieve your pain?" Pain intensity Instrument: World Graph Rating Scale Depression Instrument: CDI Anxiety Instrument: State-Trait Anxiety Inventory for Children Adverse events reported	Very Low
Bahar et al[42] (2008), United States	Children 12–18 y (N=33) IBS (Rome II criteria)	Amitriptyline versus placebo Dosage: patients 30–50 kg: 10 mg/d; patients 50–80 kg: 20 mg/d; and patients > 80 kg: 30 mg/d Treatment period: 8 wk	Treatment success Improvement: ≥15% improvement in overall quality of life score Instrument: IBS-QoL questionnaire. Pain (frequency and intensity) Instrument: VAS Adverse events reported	Very Low

Author; Location	Participants	Intervention	Outcome Measures and Instruments	Quality
Antispasmodics				
Asgarshirazi et al[40] (2015), Iran	Children 4–13 y (N = 120) FGIDs (Rome III criteria)	Peppermint oil versus: Folic acid tablet (group 1) Lactol tablets (group 2) Dosage: 187–374 mg 3 times daily Treatment period: 4 wk	Pain intensity Instrument: rating scale 0 to 10 Pain frequency Instrument: episodes per week, all assessed on patient's or their parents' reports Side effects monitored	Very Low
Karabulut et al[32] (2013), Turkey	Children 4–18 y (N = 78) IBS (Rome III criteria)	Trimebutine versus usual care Dosage: 3 mg/kg per d 3 times daily Treatment period: 3 wk	Treatment success Improvement: treatment responders by 'Adequate relief' Instrument: parental reporting of pain relief ("Yes or No")	Very Low
Kline et al[33] (2001), United States	Children 8–17 y (N = 42) IBS (Rome I/Manning criteria)	Peppermint oil versus placebo Dosage: 0.1 mL 3 times daily (30- 45 kg), 0.2 mL 3 times daily (>45 kg) Treatment period: 2 wk	Treatment success Improvement: defined as "better" or "much better" Instrument: pain and symptom scales (5-point scale) Pain intensity Improvement: severity of pain and change in symptoms Instruments: pain and symptom scales (5-point scale), symptom diaries, GSRS Adverse effects Instrument: recorded by investigator and patient	Very Low
Narang et al[30] (2015), India	Children 4–12 y (N = 132) RAP (Apley Criteria)	Drotaverine Hydrochloride versus placebo Dosage: 10 mL orally 3 times daily (4–6 y), 40 mg 3 times daily (>6 y) Treatment period: 4 wk	Pain frequency Improvement: number of episodes of pain in 4 weeks, number of pain-free days in 4 weeks Instruments: patient dairy for assessment by parents including a visual analogue scale and FACES Pain Scale School attendance Improvement: number of school days missed in 4 weeks Instrument: parent report Adequate relief Instrument: parental reporting of their perception of child's mood, activity, alertness, oral intake, and comfort, Likert scale (5-point scale) Adverse events reported	Very Low

Author; Location	Participants	Intervention	Outcome Measures and Instruments	Quality
Pourmoghaddas et al[35] (2014), Iran	Children 6–18 y (N = 115) FAP (Rome III criteria)	Mebeverine versus placebo Dosage: 135 mg 2 times daily Treatment period: 4 wk	Treatment success Improvement: 2-point reduction Instrument: WBFPRS (scale 1 to 6) or report of "no pain" Adverse events Instruments: after 2 weeks by telephone interview and at 4-week visit using a checklist with common side effects of mebeverine	Very Low
Antibiotics				
Collins et al[43] (2011), United States	Children 8–18 y (N = 75) CAP (Rome II criteria)	Rifaximin versus placebo Dosage: 550 mg 3 times daily Treatment period: 10 d	Pain (frequency and intensity) Instrument: VAS (0 to 10) Adverse events reported	Very Low
Heyland et al[44] (2011), Austria	Children 3–16 y (N = 40) RAP was defined according to the definition of Apley and Naish in children positive for *Blastocystis hominis*	TMP/SMX versus placebo Dosage: TMP 6 mg/kg/d, SMX 30 mg/kg/d in 2 doses a d Treatment period: 7 d	Pain Intensity Instrument: VAS (0 to 10) Adverse events reported	Very Low
Antihistaminic				
Sadeghian et al[36] (2008), Iran	Children 4–12 y (N = 36) FAP (Rome II criteria)	Cyproheptadine versus placebo Dosage: 0.25-0.5 mg/kg (maximum 12 mg/24h [2-6 y], max 16 mg/24 h [7-14 y]) Treatment period: 2 wk	Treatment success Definition: response to treatment defined as no pain or become better Instrument: self-report on a 4-point scale, from 1 (no pain) to 4 (become worse) Pain frequency and intensity: Instrument: self-reported dairy (scale 1 to 6) Adverse events Instrument: recorded by research nurse	Low

Author; Location	Participants	Intervention	Outcome Measures and Instruments	Quality
Symon and Russell[39] (1995), United Kingdom	Children 5–13 y (N = 16) AM (Apley Criteria)	Pizotifen syrup versus placebo Dosage: 0.5 mg (0.25 mg/5mL) in 2 divided doses/d (first mo). 0.75 mg/d mo 2–4 if no improvement Treatment period: 4 months	Pain frequency Instrument: daily dairy card Pain intensity Instrument: daily dairy card (index of severity; mild = 1, moderate = 2, severe = 3) Adverse events Instrument: daily dairy card	Very Low
Antiemetic				
Karunanayake et al[45] (2018), Sri Lanka	Children 5–12 y (N = 100) AP-FGIDs (Rome III criteria)	Domperidone versus placebo Dosage: 10 mg 3 times daily Treatment period: 8wk	Treatment success Definition: cure defined when a patient fulfilled all of the following 3 criteria: • Abdominal pain <4 episodes per month. • Average severity of abdominal pain <25 mm in the VAS. • None of the pain episodes being severe enough to disrupt the daily activities of the child (eg, sleep, play, schooling) Pain frequency Instrument: symptom diary Pain intensity Instrument: VAS (0 to 100) Adequate relief Instrument: 2 questions: "Overall how do you feel your problem is? (better, same or worse)" and "How did the medication relieve your pain? (excellent, good, fair, poor)" Improvement: ''Better'' and "Excellent" were regarded as positive results Adverse events Instrument: reported during weekly telephone inquiries	Low

Author; Location	Participants	Intervention	Outcome Measures and Instruments	Quality
Tegaserod				
Khoshoo et al[46] (2006), United States	Children 13–18 y (N = 48) IBS constipation-predominant (Rome II criteria)	Polyethylene glycol 3350 + tegaserod versus polyethylene glycol 3350 Dosage: Polyethylene glycol 3350: 17 g dissolved in 8 fluid ounces (30 mL), once daily; tegaserod: 6 mg twice daily Treatment period: 4 wk	Treatment success Improvement: as a reduction in pain by 3 points or more Instrument: VAS (0 to 10) Pain intensity Instrument: VAS (0 to 10) Frequency of defecation Instrument: symptom diary	Very Low
H_2-receptor antagonist				
See et al[38] (2001), United States	Children 5–18 y (N = 25) FD (Apley criteria)	Famotidine versus placebo Dosage: 0.5 mg/kg/d twice daily Treatment period: 3 + 3 wk (cross-over)	Treatment success Definition: response to treatment defined as become better Instrument: self-reporting Global improvement in symptoms ("Have you felt better, not better or worse?") Pain intensity/frequency Definition: abdominal pain score (pain frequency+ pain intensity + peptic index) Instrument: self-reported pain dairies	Low
Buspirone				
Badihian et al[41] (2020), Iran	Children 6–18 y (N = 117) FAP (Rome III criteria)	Buspirone versus placebo Dosage: patients <10 y: 2.5 mg/d in the first wk, increasing to 5 mg/d for remaining 3 wk; patients 10–15 y: 5 mg/d in the first wk, increasing to 5 mg twice daily for remaining 3 wk; patients 15–18 y: 5 mg/d in the first wk, increasing to 5 mg twice daily for the second wk, increasing to 5 mg 3 times daily for remaining 2 wk Treatment period: 4 wk	Treatment success Improvement: 2 point reduction Instrument: WBFPRS Rating scale (WBFPRS, score 0–5) Pain intensity Instrument: WBFPRS Rating scale (WBFPRS, score 0–5) Depression Instrument: CDI Anxiety Instrument: RCMAS Adverse events reported Instrument: checklist including common side effects of buspirone	Low

Author; Location	Participants	Intervention	Outcome Measures and Instruments	Quality
Melatonin				
Zybach et al[31] (2016), United States	Children 8-17 y (N = 14) FD (Rome III criteria)	Melatonin versus placebo Dosage: 5 mg (20mL) once daily Treatment period: 14 d	Treatment success Improvement: a response grade of ≥ 3 Instrument: A Global Clinical Score (grade 1: worse [clinical deterioration with increasing pain intensity and/or frequency] to grade 5: excellent [complete relief of pain])	Low

AP-FGIDs, abdominal pain predominant functional gastrointestinal disorders; CAP, Chronic Abdominal Pain; CDI, Children's Depression Inventory; FAP, functional abdominal pain; FD, functional dyspepsia; FGID, functional gastrointestinal disorder; IBS, irritable bowel syndrome; QoL, quality of life; RAP, recurrent abdominal pain; RCMASTM, Revised Children's Manifest Anxiety ScaleTM; TMP/SMX, Trimethoprim-sulfamethoxazole; VAS, visual analog scale; WBFPRS, Wong-Baker FACES Pain Rating Scale; -, not applicable.

Methodologic Quality

Overall, 8 of the 17 studies (47%) were at high risk of bias in at least 1 domain. High risk-of-bias ratings were given for lack of blinding of participants and outcome assessors, incomplete outcome data, and selective reporting. Other bias was present in 1 study because the dose was changed if there was no response after 4 weeks of treatment, and after 2 months the intervention was changed.[39] Furthermore, risk of bias was evaluated to be unclear as a result of inadequate reporting of methods in 11 of 17 studies (65%). Only 4 studies had low risk of bias across all domains (**Figs 2** and **3**). Detailed information about the risk of bias for the included studies is presented in **Supplemental Tables 19–27**.

The overall certainty of evidence based on the GRADE system was very low to low, with reasons for downgrading of certainty presented in **Supplemental Tables 6–15**.

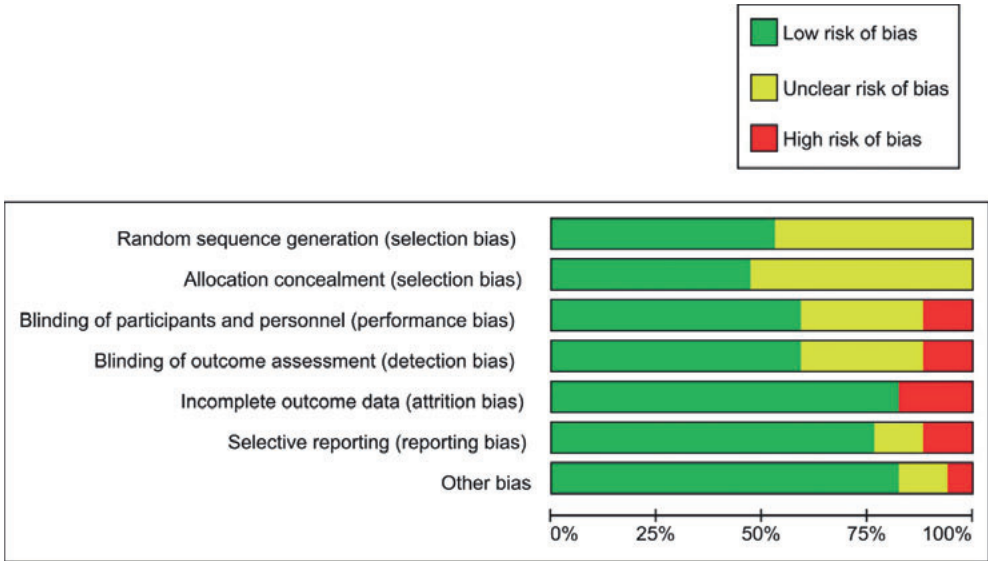

Figure 2. *Risk-of-bias Graph.*

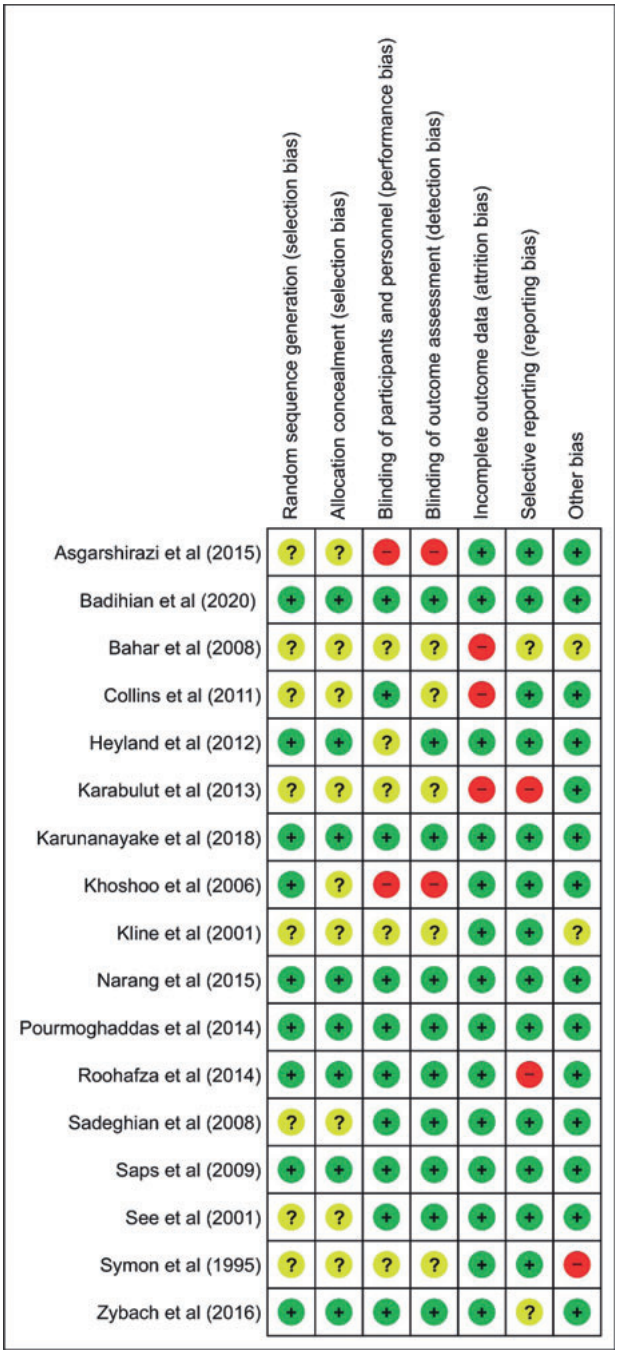

Figure 3. *Risk-of-bias Summary. Green, low risk of bias; Yellow, unclear risk of bias; Red, high risk of bias*

Outcomes

All reported primary outcomes will be described per pharmacologic intervention. Secondary outcomes of all studies are described in **Table 3**. All (serious) adverse events are shown in a separate table (**Table 4**).

Antidepressants

Three double-blind randomized placebo-controlled trials including 223 participants met the prespecified inclusion criteria.[34,37,42] Bahar et al[42] and Saps et al[37] investigated the comparison of amitriptyline versus placebo, and Roohafza et al[34] randomly assigned patients to receive either citalopram or placebo.

Primary Outcomes

Treatment success

All studies reported treatment success as the primary outcome. In their study, Bahar et al[42] used overall improvement in quality of life scores, quality-of-life scores, finding an improvement in 7 of 18 in the amitriptyline group versus 0 of 17 in the placebo group; however, the baseline scores in the amitriptyline group were significantly lower than the placebo group. Saps et al[37] reported overall response to treatment as reported by patients, with 27 of 46 in the amitriptyline group and 23 of 44 in the placebo group reporting they felt better at the end of the study. Finally, Roohafza et al[34] reported an outcome of ≥2 point reduction in pain scores and found 31 of 59 in the citalopram group versus 23 of 56 in the placebo group responded.

Pain frequency and intensity

Bahar et al[42] reported pain frequency scores using a visual analog scale (VAS), in which no significant differences were apparent. Pain intensity scores were reported in the studies of Bahar et al[42] and Saps et al[37], with both studies using a VAS. No statistically significant differences were found between the two groups.

Withdrawal due to adverse events

Bahar et al[42] reported no withdrawals due to adverse events. Saps et al[37] reported 3 withdrawals due to adverse events (fatigue [n = 1], rash and headaches [n = 1] [amitriptyline], and dizziness [n = 1] [placebo]), and none of the adverse events

were considered to be serious. Roohafza et al[34] reported 5 withdrawals due to adverse events (drowsiness [n = 1], dizziness [n = 3], and nausea [n = 1]).

Antispasmodics

Five RCTs (n = 495, age 4–18 years), of which 2 trials used peppermint oil and 3 used drotaverine, mebeverine, or trimebutine, met the prespecified inclusion criteria and were included in this systematic review.[30,32,33,35,40]

Primary Outcomes

Treatment success

In 3 studies, researchers predefined the primary outcome "treatment success." Karabulut et al[32] reported overall clinical recovery, with 37 of 39 in the trimebutine group and 8 of 39 in the group with no treatment ($P < .0001$). Kline et al[33] concluded that 71% (peppermint oil group) versus 43% (placebo group), respectively, reported improvements in the change of symptom scale ($P < .001$). Pourmoghaddas et al[35] showed that treatment response was reported in 32 of 59 (41%) in the mebeverine group compared with 23 of 56 (30%) in the placebo group ($P = .117$). Asgarshirazi et al[40] and Narang et al[30] did not predefine treatment success.

Pain frequency and intensity

Pain severity was reported by Kline et al.[33] The mean severity of pain symptoms in the peppermint oil group was significantly lower than that in the placebo group (Wilcoxon Signed-Ranks: $_T$ [60] = 1.99, $P < .03$). Narang et al[30] reported a significant reduction of pain episodes in the drotaverine group compared with the placebo group (mean [SD]: 10.3 [14] vs 21.6 [32.4], $P = .01$). The study by Asgarshirazi et al[40] revealed that improvement in pain severity in the peppermint oil group (3.11 ± 1.36) was significantly better than in the lactol (3.93 ± 1.06, $P = .373$) and placebo (4.24 ± 1.33, $P = .001$) groups. Pain duration and frequency decreased significantly more in the peppermint oil group (respectively, 26.17 ± 11.61 and 2.00±0.98) than the Lactol (respectively, 37.06±25.51 [$P = .012$] and 2.34 ± 0.87 [$P = .0001$]) and placebo groups (respectively, 51.60 ± 23.74 [$P = .0001$] and 3.40 ± 1.41 [$P = .0001$]).[37]

Withdrawal due to adverse events

In 4 studies (n = 377), researchers reported withdrawals due to adverse events.[30,33,35,40] Narang et al[30] reported 1 discontinuation due to urticaria in the drotaverine group, the study investigating mebeverine reported 3 withdrawals due to adverse events (drowsiness and nervousness [n = 2], nausea [n = 1]),[35] and in the 2 peppermint oil studies,[33,40] no patients discontinued the interventions because of adverse events.

Antibiotics

Two double-blind randomized placebo-controlled trials including 115 participants met the prespecified inclusion criteria.[43,44] Collins et al[43] investigated rifaximin versus placebo and Heyland et al[44] randomly assigned patients to receive either trimethoprim-sulfamethoxazole (TMP-SMX) or placebo.

Primary Outcomes

Treatment success

Treatment success was not defined in both studies.[43,44]

Pain frequency and intensity

Pain intensity scores were reported in both studies by using a VAS.[43,44] Collins et al[43] reported no significant differences apparent (absolute scores were lacking). Heyland et al[44] reported no significant differences between the 2 groups with a decrease from 6.9 to 4.1 in the TMP-SMX group and 7.4 to 3.0 in the placebo group.

Withdrawal due to adverse events

In both studies (n = 115), the authors predefined withdrawals due to adverse events as outcome measure. Collins et al[43] reported 1 withdrawal from the study because of abdominal pain after taking 1 day of rifaximin. Heyland et al[44] found no withdrawals due to adverse events.

Antihistaminic

Two RCTs (n = 52, age 4–13 years), one using cyproheptadine and one using pizotifen, met the prespecified inclusion criteria and were included in this systematic review.[36,39]

Primary Outcomes

Treatment success

Sadeghian et al[36] reported treatment success as a child's assessment on response to treatment defined as "no pain/become better." A total 13 of 15 children in the cyproheptadine group versus 5 of 14 children in the placebo group reported no pain/become better at the study's end (P = .005).

Pain frequency and intensity

After 2 weeks of treatment, children in the cyproheptadine group reported significantly more reduction in pain frequency (86.7 vs 35.7%; P = .002) and pain intensity (86.7 vs 28.6%; P = .001) compared with the placebo group.[36] In the study by Symon and Russell,[39] children in the pizotifen group reported a significant improvement of the drug on the index of severity and index of misery (severity: MD = −16.21 [95% CI −26.51 to −5.90], P = .005; misery: MD = −56.07 [95% CI −94.07 to −18.07], P = .007), and fewer days of abdominal pain compared with the placebo group (MD = 8.21 [95% CI 2.93 – 13.48], P = .005).

Withdrawal due to adverse events

In both studies, researchers reported no withdrawals due to adverse events.[36,39]

Antiemetic

One double-blind randomized placebo-controlled trial including 100 participants met the prespecified inclusion criteria. Karunanayake et al[45] investigated the comparison of domperidone versus placebo.

Primary Outcomes

Treatment success

Although the number of children who reported success was higher in the domperidone group (22 of 50) than in the placebo group (14 of 50), differences were not statistically significant.

Pain frequency and intensity

The difference in percentage of reduction of pain intensity scores was statistically significant between the 2 groups in favor of the intervention (54% vs 30%; $P = .008$).

Withdrawal due to adverse events

No withdrawals due to adverse events were reported.[42]

5-HT4 Agonist

One RCT including 48 participants met the prespecified inclusion criteria. Khoshoo et al[46] investigated the comparison of group A (polyethylene glycol 3350 oral solution) versus group B (treatment with polyethylene glycol 3350 and tegaserod [5-HT4 agonist]).

Primary Outcomes

Treatment success

Khoshoo et al[46] reported a successful outcome as ≥3 point reduction in pain scores and found this success in 14 of 21 in the tegaserod and laxative group (group B) versus 5 of 27 in the polyethylene glycol 3350 group (group A) ($P < .05$).

Pain frequency and intensity

Khoshoo et al[46] reported pain intensity scores using a VAS. The difference in reduction of pain intensity scores was statistically significant between the 2 groups in favor of the tegaserod group ($P < .05$).

Withdrawal due to adverse events

Withdrawals due to adverse events were not adequately reported.[46]

H_2-Receptor-Antagonist

In a randomized crossover trial, See et al[38] compared famotidine versus placebo. In total, 25 children (aged 5–18 years) with a diagnosis of FD were included.

Primary Outcomes

Treatment success

Treatment success was defined as "become better", by using a self-reporting global improvement in symptoms scale. In total, 66.7% children receiving famotidine significantly improved compared with 15.4% receiving a placebo (odds ratio 11.0 [95% CI 1.6 to 75.5]; $P = .015$).

Pain frequency and intensity

Abdominal pain was assessed by using a combined pain score (pain frequency, pain intensity, and peptic index). No significant difference in abdominal pain scores was found between both groups.[38]

Withdrawal due to adverse events

No withdrawals due to adverse events were reported.[38]

Buspirone

One double-blind randomized placebo-controlled trial including 117 participants met the prespecified inclusion criteria. Badihian et al[41] buspirone (azapirone: a group of neuromodulators targeting 5-HT serotonin receptors) versus placebo.

Primary Outcomes

Treatment success

Analysis revealed no significant differences in treatment success rates between the buspirone and placebo groups (47.5% vs 48.3%; $P = .929$).

Pain frequency and intensity

Improved pain scores were reported in both groups after 4 weeks of treatment.[38] No significant differences in improvement in pain scores were found between the 2 groups at 4 weeks (buspirone 1.50 (±1.24) vs placebo 1.60 (±1.25); $P = .708$).

Withdrawal due to adverse events

Two participants in the placebo group and 3 patients in the buspirone group withdrew from the study.[38] No details were given.

Melatonin

One double-blind randomized placebo-controlled crossover trial comparing melatonin with placebo, including 14 participants, met the prespecified inclusion criteria.[31] Only data before the crossover occurred were extracted.

Primary Outcomes

Treatment success

Because information regarding 1 subject on initial treatment was lacking, only data of 11 participants before the crossover occurred could be extracted. A positive clinical response (a response grade of ≥3) was achieved in 1 of 6 (17%) subjects on initial treatment with melatonin versus 2 of 5 (40%) subjects initially treated with placebo (P = not significant).

Withdrawal due to adverse events

Withdrawals due to adverse events were not reported.[46]

Table 3. Secondary outcomes

Study	Quality of life	Anxiety/depression	Adequate relief	School attendance/ performance	Frequency of defecation
Antidepressants					
Roohafza et al[34]; *citalopram*	–	Depression: no significant difference; anxiety: no significant difference	–	–	–
Saps et al[37]; *amitriptyline*	–	Depression: no significant difference; anxiety: significant improvement in the amitriptyline ($P < .0001$) versus placebo ($P = .40$)	–	–	–
Bahar et al[42]; *amitriptyline*	Significantly greater improvements in overall IBS-QoL after at 6, 10 and 13wk ($P = .019$, $P = .004$, and $P = .013$)	–	–	–	–
Antispasmodics					
Asgarshirazi et al[40]; *peppermint oil*	–	–	–	–	–
Karabulut et al[32]; *trimebutine*	–	–	–	–	–
Kline et al[33]; *peppermint oil*	–	–	–	–	–
Narang et al[30]; *drotaverine*	–	–	–	School absence: at 4 wk 6% (drotaverine) versus 14% (placebo) ($P = .034$)	–
Pourmoghaddas et al[35]; *mebeverine*	–	–	–	–	–
Antibiotics					
Collins et al[43]; *rifaximin*	–	–	–	–	–

Study	Quality of life	Anxiety/depression	Adequate relief	School attendance/ performance	Frequency of defecation
Heyland et al[44]; *TMP/SMX*	–	–	–	–	–
Antihistaminc					
Sadeghian et al[36]; *cyproheptadine*	–	–	–	–	–
Symon and Russell[39]; *pizotifen*	–	–	–	–	–
Antiemetic					
Karunanayake et al[45]; *domperidone*	–	–	Significant difference in patient-reported general improvement (P = .013)	–	–
Tegaserod					
Khoshoo et al[46]; *tegaserod*	–	–	–	–	Significantly greater improvements in frequency of bowel movements in tegaserod + laxatives versus laxatives (P < .05)
H_2-receptor antagonist					
See et al[38]; *famotidine*	–	–	–	–	–
Buspirone					
Badihian et al[41]; *buspirone*	–	Depression: no significant difference; anxiety: significant improvement in both buspirone (P = .001) and placebo (P = .002)	–	–	–
Melatonin					
Zybach et al[31]; *melatonin*	–	–	–	–	–

H_2, histamine 2; –, not applicable.

Table 4. Details of side effects

Study	Intervention	Control
Antidepressants		
Roohafza et al[34]; citalopram	Dry mouth (n=19),* drowsiness (n=16),** loss of appetite (n=14), fatigue (n=8), headache (n=3), nausea (n=3), insomnia (n=2), allergic reaction (n=1), dizziness (n=1)	Dry mouth (n=10),* loss of appetite (n=8), drowsiness (n=7),** fatigue (n=6), dizziness (n=2), headache (n=1), insomnia (n=1), nausea (n=1)
Saps et al[37]; amitriptyline	Fatigue (n=1), rash and headaches (n=1)	Dizziness (n=1)
Bahar et al[42]; amitriptyline	None	None
Antispasmodics		
Asgarshirazi et al[40]; peppermint oil	None	None
Karabulut et al[32]; trimebutine	NR	NR
Kline et al[33]; peppermint oil	None	None
Narang et al[30]; drotaverine	*Total N = 30 (47%)*[a] Fever (n=10), cough (n=8), vomiting (n= 7), nausea (n=6), cold (n=5), diarrhea (n=4), giddiness (n=4), macular rash (n=4), headache (n=3), urticaria (n=1), eating poorly than usual (n=1)	*Total N = 28 (47%)*[a] Vomiting (n=8), fever (n=6), cough (n=7), headache (n=5), cold (n=4), eating poorly than usual (n=3), giddiness (n=2), nausea (n=2), diarrhea (n=3), black stools (n=1), epistaxis (n=1), macular rash (n=1)
Pourmoghaddas et al[35]; mebeverine	Dry mouth (n=19),*** drowsiness (n=8), loss of appetite (n=8), fatigue (n=4), insomnia (n=4), headache (n=3), nausea (n=3), dizziness (n=2), vomiting (n=1)	Dry mouth (n=10),*** loss of appetite (n=8), drowsiness (n=7), fatigue (n=6), dizziness (n=2), headache (n=1), insomnia (n=1), nausea (n=1)
Antibiotics		
Collins et al[43]; rifaximin	Abdominal pain (n=1)	None
Heyland et al[44]; TMP/SMX	None	None
Antihistaminic		
Sadeghian et al[36]; cyproheptadine	Hypoactive airway (n=1) and increased appetite (n=1)	None
Symon and Russell[39]; pizotifen	Drowsiness (n=1) Mean wt gain: 1.25kg****	Increased appetite (n=1) Mean wt gain: 0.38kg****
Antiemetic		
Karunanayake et al[45]; domperidone	Skin rash (n=1)[b]	None

Study	Intervention	Control
Tegaserod		
Khoshoo et al[46]; tegaserod	NAR	NAR
H_2-receptor antagonist		
See et al[38]; famotidine	NR	NR
Buspirone		
Badihian et al[41]; buspirone	Drowsiness (n=7), vertigo (n=6), nervousness (n=5), headache (n=3), myalgia (n=3), nausea (n=3), diarrhea (n=1), vomiting (n=1)	Headache (n=5), nervousness (n=4), vertigo (n=4), drowsiness (n=3), nausea (n=2), insomnia (n=1)
Melatonin		
Zybach et al[31]; melatonin	NR	NR

H_2, histamine 2; NAR, not adequately reported (unclear if side effect occurred during intervention/control); NR, not reported.
°some children had >1 adverse event.
[b]not considered to be an adverse effect of treatment.
*P = .034, **P = .025, ***P = .047, ****P = .039,

DISCUSSION

We systematically reviewed 17 articles to determine the efficacy and safety of pharmacologic interventions in children with FAPDs. This systematic review clearly reveals the scarcity of high-quality, placebo-controlled trials. When treatment success is used as the primary end point, peppermint oil, cyproheptadine, and tegaserod might be potential effective and safe treatments, but well-designed intervention studies are needed before this conclusion can be made. In addition, there was no evidence that any other drug treatment has a significant role in the treatment of FAPDs. Therefore, the current evidence is insufficient to recommend any specific pharmacologic compound to treat FAPDs in children.

The findings of the current study are in line with our previous review.[15] Although the previous systematic review included only 6 studies (compared with 17 studies in this update), evidence to support the use of any pharmacologic compound in daily practice of FAPDs is still lacking. An explanation is that the number of studies in which researchers assess the different compounds is often limited to 1 or 2 intervention trials and that the majority of studies only included a small patient group. Interestingly, efficacy studies in adults with FAPD revealed different results.[28] In a systematic review and network meta-analysis, researchers concluded that antispasmodic agents, peppermint oil, and tricyclic antidepressants (TCAs) were significantly more effective than placebo in adults with IBS.[47] In studies in adults with IBS on TCAs, researchers found a positive treatment effect of this group of drugs, whereas in studies of pediatric IBS, researchers found no evidence to recommend the use of antidepressants.[28,48]

In recent years, a large number of new pharmacologic treatments have been developed and reveal promising results for future treatments of pediatric FAPDs.[49] In the population of adults with FAPDs, new mixed μ-opioid receptor agonist and δ-opioid receptor antagonist such as eluxadoline or plecanatide, a guanylyl cyclase agonist, have revealed their efficacy and safety for IBS with diarrhea and irritable bowel syndrome with constipation (IBS-C), respectively.[50–52] Moreover, lubiprostone has revealed positive results in adults with IBS-C.[53] However, evidence on efficacy and safety of these treatments in the pediatric population is lacking. Recently, oral immunoglobulin revealed promising results in children with IBS-C. However, this agent is beyond the scope of this review and therefore is not included.[54,55] Trials on eluxadoline (NCT03339128), linaclotide (NCT02559817), and fecal microbiota transplant (NCT03074227) are ongoing in children with FAPDs.

A placebo might be a potential effective treatment of children with FAPDs as well.[56] This is supported by a meta-analysis, in which researchers found a pooled placebo response of 41% in this population.[57] The significant role of placebo is remarkable yet not surprising because in adult patients with IBS, similar results were found.[58–61] The placebo response consists of the "true placebo effect," which comprises conditioning and expectations, and other factors such as regression to the mean, methodologic bias, and the natural course of the disease.[62,63] The true placebo effect especially has the potential to enhance the physician-patient relationship resulting in higher rates of treatment response.[64,65] These findings have important implications for clinical practice to improve treatment outcomes.

In 13 of the 17 studies, researchers reported on side effects; in 4 of those 13 studies, no side effects occurred during the intervention. In 9 studies, researchers reported side effects during the treatment period. However, there was no significant difference between the intervention and control groups. This is in line with another review in which researchers concluded that the risk of side effects in pediatric pharmacologic FAPD treatment is low.[66] These results are supported by a meta-analysis in the adult FAPD population, in which researchers reported that none of the drugs were more likely than placebo to lead to withdrawal from the study because of side effects.[47] Only when comparing the total number of side effects in TCA treatment compared with placebo, a significantly higher number of adverse events were reported in the intervention group.[47]

The major strength of this review is its strict systematic methodology in line with the high-quality standards of Cochrane (previously known as the Cochrane Collaboration). First, the search strategy was developed in consultation with an information specialist from Cochrane. Second, the screening process included 2 independent reviewers. In addition, authors of included studies were contacted for additional data or explanation about their study design. Furthermore, strength of evidence was assessed by using the Cochrane risk-of-bias tool and GRADE to increase the transparency of the grading process and appropriate certainty of data to support readers in interpreting the results.

The limitations of this study are primarily related to the lack of high-quality evidence that is currently available but have no direct relationship with our review process. First, there were few trials with a low risk of bias, and there was evidence of heterogeneity between RCTs in our analyses. This was across multiple

dimensions, including treatment and comparators, length of therapy, and most importantly, the choice of outcome measures. Furthermore, no subgroup analyses were possible because of the small sample size. Many of the studies are of such a small size that it is surprising that ethical approval was granted, and this mirrors a wider problem in the field.[67] Our previous systematic review examining this topic revealed similar findings in terms of the efficacy of pharmacologic treatment.[15] Despite the addition of 11 trials since the publication of our previous review, the overall estimates of the efficacy and safety of these treatments remain almost identical, and this is because of the design and methodologic choices of researchers in the field. Another limitation is that most RCTs included in this review were published before the recommendations for the design of intervention trials on children with FAPDs.[68] In 2016, the Rome Foundation made recommendations for designing trials in pediatric FAPDs.[68] This committee recommends considering abdominal pain as the primary outcome, assessed with daily diaries, and this would address the issue described above. Furthermore, a large sample size, a study duration of at least 4 weeks, and a 6-month follow-up period is recommended, similarly addressing the weaknesses uncovered in this updated review. To set up well-designed (double-blind, placebo-controlled) RCTs in children is difficult because of a high placebo effect (ie, difficult to measure true difference between intervention and placebo group) and complex trial designs, in which participants often refuse to participate because of the possibility of receiving placebo.[56,57] Furthermore, funding is often scarce.[49] Despite these challenges, if studies cannot be done in this fashion, they add nothing to the overall "certainty" of evidence and are unlikely to impact guidelines and practice. Recently, the pediatric FAPD COS was created.[16] This COS aimed to decrease study heterogeneity and increase the comparability of study results by measuring a standardized minimum set of outcome measures. If all future trials will use these outcome measures, as well as associated measurement instruments, it is likely that this may improve the quality of research and information and, finally, GRADE certainty and clinical decision-making.[69]

In clinical practice, the first step in management may consist of education, reassurance, and simple dietary advice.[14] Lately, there is increasing evidence for the effectiveness of nonpharmacologic treatment, such as hypnotherapy and cognitive behavior therapy.[27,49,70] These treatments are not hampered by severe adverse events and may be especially effective in children with lasting symptoms.

Therefore, based on the majority of current evidence and expert opinion, nonpharmacologic therapy could be the first intervention attempt in pediatric FAPDs. However, because the pathogenesis of these disorders remains unclear in children, the optimal treatment strategy is not known. To date, it is preferable to discuss both pharmacologic therapies and nonpharmacologic options during shared decision consultation. This can be used to make a tailor-made approach for each patient.

CONCLUSION

On the basis of the current evidence, it is not possible to recommend any specific pharmacologic agent for the treatment of FAPDs in children because of the low quality of included studies. However, agents such as antispasmodics or antidepressants can be discussed in daily practice because of their favorable treatment outcomes and considering the lack of important side effects. Because a large proportion of children continues to experience FAPD-related symptoms in adulthood, high-quality studies on pharmacologic treatments in pediatric FAPDs are necessary to provide adequate treatment. In future intervention trials, researchers must include homogenous outcome measures and instruments, as recommend by the pediatric FAPD COS, a large sample size, and long-term follow-up.

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SUPPLEMENTARY FILES

Supplementary material of chapter 6 is available online

Supplemental Table 5. Rome IV Criteria for Pediatric FAPDs

Supplemental Tables 6-15. GRADE Profiles

Supplemental Tables 16-18. Details of Excluded Studies

Supplemental Tables 19-27. Risk of Bias of Included Studies