Definitions of Pediatric Functional Abdominal Pain Disorders and Outcome Measures: A Systematic Review

Judith Zeevenhooven, BSc, Merel L. Timp, MD, Maartje M. J. Singendonk, MD, PhD, Marc A. Benninga, MD, PhD, and Merit M. Tabbers, MD, PhD

Objective To systematically review definitions of functional abdominal pain orders (FAPDs) and outcome measures used in therapeutic randomized controlled trials in pediatric FAPDs adhering to the Outcome Measures in Rheumatology recommendations.

Study design Cochrane, MEDLINE, Embase, and Cinahl databases were systematically searched from inception to April 2018. English-written therapeutic randomized controlled trials concerning FAPDs in children aged 4-18 years were included. Definitions of FAPDs, interventions, outcome measures, measurement instruments, and outcome assessors of each study were tabulated descriptively. Quality was assessed using the Delphi List.

Results A total of 4771 articles were found, of which 64 articles were included (n = 25, 39% of high methodologic quality). The Rome III (50%), Rome II (17%), Apley (16%), and author-defined (17%) criteria were used to define FAPDs. Fourteen studies (22%) assessed a pharmacologic, 25 (39%) a dietary, and 25 (39%) a psychosocial intervention. Forty-four studies (69%) predefined their primary outcomes. In total, 211 reported predefined outcome measures were grouped into 23 different outcome domains; the majority being patient-reported (n = 27, 61%). Of the 14 studies that evaluated a pharmacologic intervention, 12 (86%) reported on adverse events.

Conclusions Studies on pediatric FAPDs are of limited methodologic quality and show large heterogeneity and inconsistency in defining FAPDs and outcome measures used. Development of a core outcome set is needed to make comparison between intervention studies possible. *(J Pediatr 2019;212:52-9)*.

Functional abdominal pain disorders (FAPDs) are the most common cause of chronic abdominal pain in children, with a worldwide pooled prevalence of 13.5%.[1] According to the Rome IV pediatric criteria, they include functional dyspepsia, irritable bowel syndrome (IBS), abdominal migraine, and functional abdominal pain—not otherwise specified (FAP-NOS; **Table I** [available at www.jpeds.com]).[2] Pathophysiologic mechanisms underlying FAPDs remain largely unclear. Conceptualization is based on the biopsychosocial model, which explains FAPDs through a complex interplay between genetic, psychosocial, and physiologic subsystems, such as early life events, stress, personality traits, altered mucosal immune function, and disturbed gut microbial environment.[3] Standard medical treatment consists of education, reassurance, dietary advice, and nonspecific pain-reducing agents.[4,5] If symptoms persist, either a pharmacologic, psychological, or dietary intervention should be considered.[4,5]

Despite the wide variety of treatments available, management remains challenging, as efficacy results of therapeutic trials are inconclusive and hard to compare.[6-8] This might lead to overtreatment and disruption of the therapeutic alliance between physician and patients and their families, which is a cornerstone in the management of FAPDs.[4,5] Designing studies to compare results of trials that assess different treatment strategies in children with FAPDs encounters several difficulties. Although it is recommended by the US Food and Drug Administration to use clinically meaningful endpoints that measure the way patients survive, feel, and function, there is a lack of standardized selection, measurement, and reporting of patient-reported outcome measures in pediatric FAPDs.[9,10]

The development of a standardized consensus-derived core outcome set (COS) for children with FAPDS is therefore of great importance.[11,12] Patient perspectives on health and functioning become increasingly important in clinical practice and can improve patient-centered care.[13] Ideally, such a COS should be composed of both clinically observed and measurable aspects

CBT	Cognitive behavioral therapy
COS	Core outcome set
FAP	Functional abdominal pain
FAPD	Functional abdominal pain disorder
FAP-NOS	Functional abdominal pain—not otherwise specified
IBS	Irritable bowel syndrome
OMERACT	Outcome Measures in Rheumatology
RCT	Randomized controlled trial

From the Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Pediatric Gastroenterology, Amsterdam, the Netherlands

The authors declare no conflicts of interest.

Portions of this study were presented as a poster at the European Society for Pediatric Gastroenterology, Hepatology And Nutrition (ESPGHAN) Congress, May 9-12, 2018, Geneva, Switzerland.

https://doi.org/10.1016/j.jpeds.2019.04.048

as well as patient-reported outcomes, which is in accordance with the recommendations of outcome initiative the OMERACT (Outcome Measures in Rheumatology), which is a widely used method to establish such COS in several areas of health.[11,14] The OMERACT initiative first requires the evaluation of definitions and outcomes reported in current literature by systematic review. Furthermore, the recently provided framework OMERACT Filter 2.0 allows for development and validation of domains and measures for many health conditions. Therefore, the aim of the present study was to systematically review definitions of FAPDs and outcome measures used in therapeutic randomized controlled trials (RCTs) in pediatric FAPDs adhering to the OMERACT recommendations.

Methods

Search Strategy

The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and CINAHL databases were systematically searched from inception up to April 2018, in collaboration with a clinical librarian (**Table II**; available at www.jpeds.com). Bibliographies of included systematic reviews were searched by hand to identify additional studies.

Study Eligibility and Selection

Studies were therefore eligible for inclusion if the study was a (systematic review of) therapeutic RCT(s), the study population consisted of children aged 4-18 years, with a diagnosis of chronic or recurrent abdominal pain, abdominal migraine, IBS, functional dyspepsia, FAP, FAPS, or FAP-NOS as clearly defined by the authors, and the study was written in English. Studies were excluded if the study included patients with an organic cause for abdominal pain (including but not limited to inflammatory bowel disease, peptic ulcer).

Two reviewers independently determined the eligibility of studies based on the titles and abstracts. Thereafter, full-text evaluation of the identified studies was performed to assess eligibility according to inclusion criteria. If no full-text was available, authors were approached by e-mail. Disagreements between reviewers were resolved by consensus and discussion with a third reviewer.

Data Extraction

Data extraction was performed using structured collection forms. Definitions used to describe FAPDs, primary and secondary outcome measures regarding FAPDs, and measurement instruments used to assess these outcome measures were extracted from the included trials. Furthermore, the following characteristics were extracted: year of publication, country of origin, study setting, sample size, age range of study participants, type of intervention, diagnoses of study participants, and assessor of the primary outcomes. As most self-report forms are approved suitable for children ≥8 years old, results on outcome assessors were separated for studies that recruited children with an age <8 years and children aged ≥8 years.[10] Primary and secondary outcome measures were qualified as predefined outcome measures if they were reported as such in the Methods section. A single outcome measure could consist of an individual parameter or a set of parameters. Predefined primary and secondary outcome measures were grouped and tabulated. Non-predefined outcome measures were extracted from the original studies in the best possible way and presented descriptively.

Methodologic quality was assessed using the Delphi list.[15] This list has been developed as a standardized list to assess the quality of RCTs, with a scale ranging from 0 (minimum) to 10 (maximum). A score of ≥6 points is defined as high quality, a score 4-6 as average quality, and a score of ≤3 as low quality.

OMERACT Core Areas

To ensure content validity of a COS, the OMERACT Filter 2.0 recommends to specify all key aspects of a health condition in each of the 4 core areas: 3 areas describe the impact of health conditions, namely "death," "life impact," and "resource use." The fourth area delineates "pathophysiological manifestations."[11] Within a core area, disease-specific domains were created. Outcome measures were accommodated to each of the 4 core areas. **Table III** explains the definitions of several key terms. The mapping of outcome measures to outcome domains was done independently and in duplicate by 2 reviewers, and a third clinician reviewer resolved disagreements when necessary.

Data Analyses

To assess heterogeneity in definitions of FAPDs and outcome measures among studies, data were tabulated and descriptively recorded. Descriptive statistics were only used to describe study and patient characteristics. No parametric tests were used. For the reporting of outcome measures, a distinction was made between predefined primary outcome measures, predefined secondary outcome measures, and non-predefined outcome measures.

Results

Search

After we removed duplicates, 4771 of 6891 unique records were screened, of which 4155 were irrelevant to our search question. After full-text assessment, another 546 articles were excluded, because of the following reasons: adult population (n = 262), inappropriate study design (n = 90), wrong patient population (n = 48), conference abstract of study published in full-text (n = 39), mixed pediatric and adult population (n = 26), no full-text available (n = 25), duplicates (n = 14), language other than English (n = 7). Twenty-eight of the identified studies concerned systematic reviews of RCTs. Checking the bibliographies of these reviews resulted in one additional RCT eligible for inclusion. Six studies[17-22] were follow-up studies of already included

Table III. Glossary of key terms

Term	Definition
Core area	An essential aspect of health or a health condition that needs to be measured to properly and comprehensively describe the effects of intervention on health conditions.[11]
(Sub)Domain	Component of core area: a concept to be measured, a further specification of an aspect of health, categorized within a core area.[11]
Measurement instrument	A tool to measure a quality or quantity of a variable, in this context a (sub)domain. The tool can be a single question, a questionnaire, a score obtained through physical examination, a laboratory measurement, a score obtained through observation of an image, and so on. [11]
Outcome measure	Any identified result in a (sub)domain arising from exposure to a causal factor or a health intervention. Has often been used interchangeably with "Outcome" and "Endpoint." [11]
Parameter	A measurable characteristic of a population that is often estimated by a statistic, eg, mean, standard deviation, regression coefficients.[16]

original RCTs. Results of these studies were added to the relevant original study as secondary outcomes. In sum, 64 studies were included in the qualitative synthesis (Figure 1).

Study and Patient Characteristics

In total, 4509 patients were included in 64 studies. Median sample size was 58 (range 12-316 children). Mean age at recruitment was reported in 59 studies and ranged from 6.3 years to 16.3 years. Five studies reported a median age at recruitment, ranging from 8.0 to 15.3 years. The predominant sex was female (n = 2771; 65%), with 4 trials (105 patients) not reporting on sex. Most of the trials were conducted in North America (41%) or Europe (36%). Thirty-eight studies (61%) were performed in tertiary care, 18 (28%) in a combination of care settings, 4 (6%) in primary care, 3 (5%) in secondary care, and unknown setting in 1 study (2%). Study characteristics are described in Table IV (available at www.jpeds.com). A statement on sample size calculation was reported in 37 studies (58%). Fifty-five (86%) of the trials reported drop-out rates.

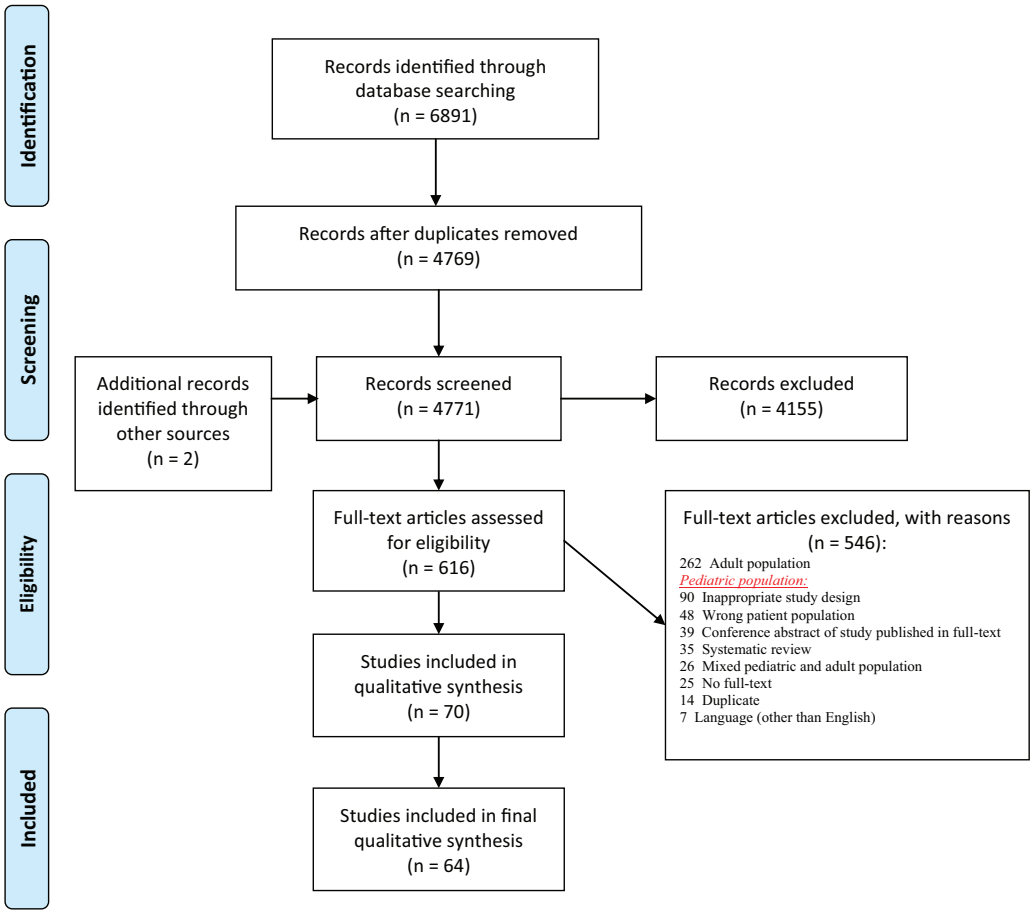

Figure 1. PRISMA 2009 flow diagram.

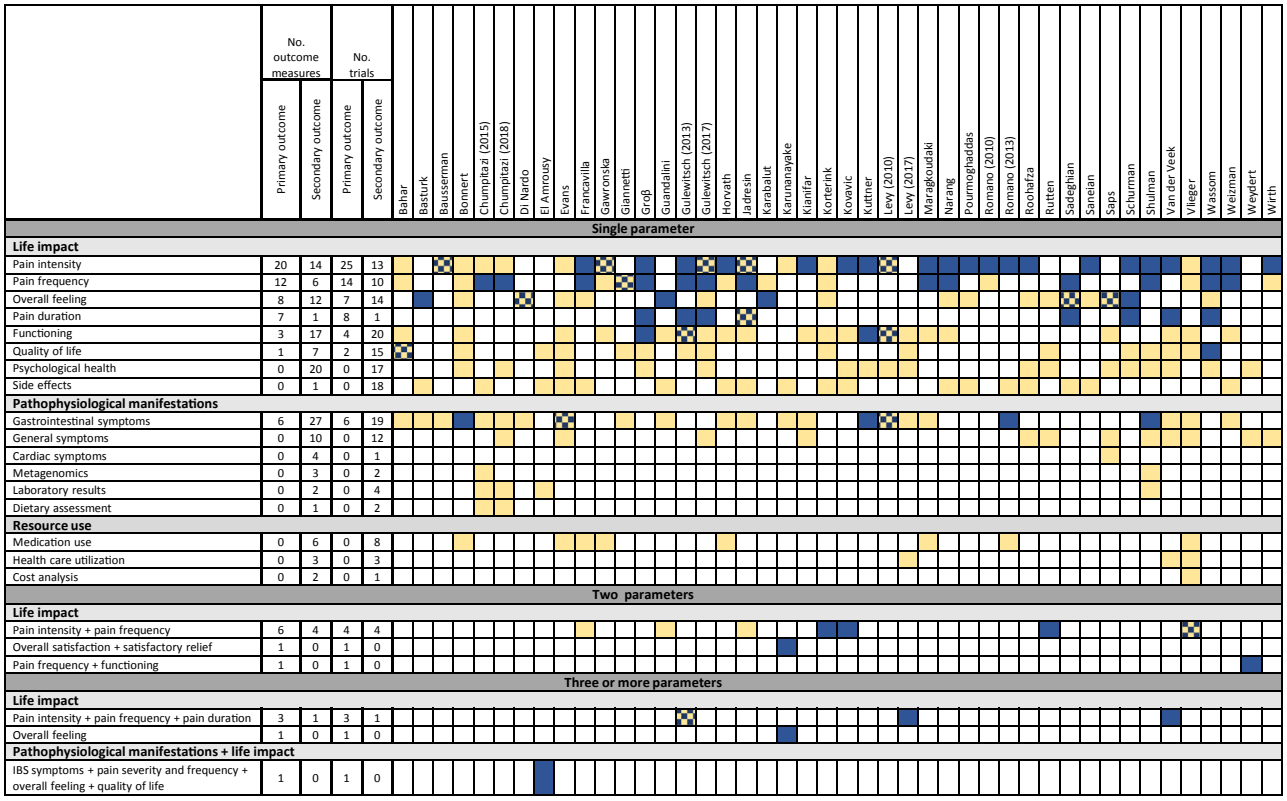

Figure 3. Predefined primary and secondary outcome measures used for FAPDs presented by OMERACT core area. *Blue (dark) boxes* indicate outcome domain used as predefined primary outcome measure; *yellow (light) boxes* indicate outcome domain used as predefined secondary outcome measure; and *dotted boxes* indicate outcome domain used as predefined primary and secondary outcome measure. *IBS*, irritable bowel syndrome; *No*., number of.

Definitions

The majority of studies (n = 32; 50%) used the Rome III criteria, followed by the Rome II criteria (n = 11; 17%) and the Apley criteria (10 studies, 16%) (**Tables I** and **IV**). Eleven studies (17%) used their own definition for FAPDs. Eighteen trials (28%) included children with a diagnosis of recurrent abdominal pain, mostly defined according to the Apley criteria (56%). Fourteen trials (22%) included only patients with IBS, mostly defined according to the Rome III criteria (57%). Seven studies (11%) included only patients with FAP, and 2 trials (3%) included only patients with functional dyspepsia. Three studies (5%) included children with FAP according to a definition created by the authors themselves as one of the inclusion criteria. Twenty-one trials (33%) recruited children with various different FAPDs (eg, children with IBS or FAP or functional dyspepsia).

Interventions

Figure 2 (available at www.jpeds.com) depicts all therapeutic interventions (n = 27). Twenty-five studies (39%) assessed a psychosocial intervention, with cognitive behavioral therapy (CBT) being the most studied treatment (n = 10). A dietary intervention was used in 25 studies (39%), of which 13 were probiotic-based. Finally, 14 studies (22%) evaluated a pharmacologic intervention, of which 4 assessed an antispasmodic agent.

Identification of Outcomes

Predefined Primary and Secondary Outcome Measures. Forty-four studies (69%) predefined their primary and secondary outcome(s), using a total of 211 different outcome measures that could be grouped into 23 different outcome domains (**Figure 3**). According to the OMERACT filter 2.0, 13 outcome domains were assigned to the core area "life impact," 6 to "pathophysiological mechanisms," 3 to "resource use," and 1 to both "pathophysiological mechanisms" and "life impact." One study reported a predefined primary outcome measure that was grouped into 5 domains that could be grouped under 2 core areas, namely "pathophysiological manifestations" and "life impact." Seventeen (74%) outcome domains included outcome measures of 1 single parameter rather than a set of parameters (eg, measuring pain intensity *or* pain frequency vs pain intensity *and* frequency).

Domains. The most reported primary outcome domains were pain intensity and frequency in, respectively, 38 and 24 studies (**Figure 3**). In total, 52 different outcome measures were used in these studies, including "mean intensity per day" (n = 3 studies), "reduction in pain

intensity" (n = 3 studies), "number of daily abdominal pain episodes (n = 2 studies)," and "number of days with abdominal pain" (n = 2 studies). The second most reported domains were functioning and psychological health, which were most often included as secondary outcomes (n = 24 and n = 17 studies, respectively).

Measurement Instruments. Figure 4 (available at www.jpeds.com) delineates the instruments used to measure the predefined primary and secondary outcomes. Of the 165 different investigational methods, 121 (73%) were validated. A pain diary was used in 28 studies, where 23 used it to assess pain frequency, 13 to measure school absenteeism and daily activities, and 5 to assess pain duration. Seven different facial scales were used in 21 studies to assess pain intensity, of which the Wong Baker Faces Pain scale was used most often in 7 studies. Thirteen studies (30%) included children ≥8 years. In 12 (92%) studies, the primary outcome was assessed by the child and in the other one, by a physician (Table IV). In the 31 studies that included children <8 years, the child was the primary outcome assessor in 48% (n = 15). Eight studies (26%) did not differentiate between the child or the parent as outcome assessor, 4 (13%) used a proxy-reported primary outcome, 2 (6%) used a physician-reported primary outcome, and 2 (6%) did not elucidate who reported the outcome.

Non-predefined Outcomes. Twenty studies (31%) did not predefine their outcome measures. These outcomes are grouped in Table V (available at www.jpeds.com). The most reported domains were pain frequency and intensity (n = 9 studies each), which were respectively defined in 9 and 7 different ways. These domains were followed by the domains overall feeling and functioning (n = 6 studies each).

Adverse Events

Adverse events were reported in 35 studies (55%). Twelve of the 14 studies examining a pharmacologic agent (86%) reported on adverse events, 19 of the 25 studies assessing a dietary intervention (76%) did this too, and 4 of the 25 studies assessing a psychological treatment (16%) reported on adverse events. Of the 35 studies, 20 (57%) included adverse events as a predefined outcome measure (6 of the pharmacologic studies [43%], 11 of the dietary studies [44%], and 3 of the psychological [12%] studies).

Methodologic Quality

Twenty-five studies (39%) had a score of >6, indicating a high methodologic quality (Figure 5; available at www.jpeds.com). Twenty-eight studies (44%) were of average and 11 (17%) of low methodologic quality. The most common reasons for reduced methodologic quality were high or unclear drop-out rates, lack of or unclear treatment allocation, and lack of or unclear intention-to-treat analysis.

Discussion

Our data show inconsistency and heterogeneity in reported definitions, predefined outcome measures, and measurement instruments assessing these FAPD outcome measures. Of the 64 included studies, only 66% used the Rome II or III criteria to define FAPDs. The Rome IV criteria for pediatric FAPDs are developed for children aged 4-18 years and differ from the adult criteria.[2,23] With the publication of the pediatric Rome II criteria in 1999,[24] followed by the Rome III in 2006,[25] almost 40% of the studies did not use these internationally accepted criteria despite the fact that 93% of all included studies were published after 1999. This might be the result of suboptimal clinical and scientific implementation of the Rome criteria for the diagnosis of pediatric FAPDs. Indeed, in a cohort of 362 pediatric gastroenterologists, it was demonstrated that despite 99% being aware of the Rome criteria, only 71% used them in clinical practice and 45% found them useful in a majority of their patients.[26]

To improve the specificity of identifying, Rome IV tried to address this by replacing the general termed FAPD "functional abdominal pain" (ie, FAP) into "functional abdominal pain—not otherwise specified" (ie, FAP-NOS).[2] Heterogeneity in diagnostic criteria directly results in inclusion of heterogeneous study cohorts, thereby hampering comparability of results. The need for stricter use of definitions is supported by the 2016 published Rome Foundation Pediatric Subcommittee guideline for the design of pharmacologic trials, which recommends inclusion of children based on the Rome criteria with at least average pain (≥30 mm on a 100-mm visual analog scale).[10] Furthermore, this guideline advices to perform separate trials for different forms of FAPDs, in particular for different subtypes of IBS (IBS-constipation, IBS-diarrhea), as signs and symptoms of these subtypes differ and therefore might need different kind of treatments. This is in contrast with the finding in our study that merely 22% of the trials included children with solely IBS, and only one of those trials studied one specific subtype of IBS.[27] It is important that future trials critically reflect on their study design with regard to definitions and type of disorder they will include, which will preferably be limited to only one of the FAPDs. In case of IBS, it would preferably be one of the subtypes of IBS.

Treatment interventions varied widely between included studies, which predominantly concerned non-pharmacologic interventions. The biopsychosocial model as a concept for the pathophysiology of FAPDs justifies the use of non-pharmacologic interventions in these disorders.[3] Results of recent Cochrane reviews, using pain as primary outcome measure, demonstrated moderate- to low-quality evidence for the use of hypnotherapy or CBT.[7] However, quality was assessed by the Grading of Recommendations Assessment, Development and Evaluation approach, which takes the blinding of participants into account when scoring the risk of bias. This should be reckoned when interpreting these results, as psychological treatments such

as hypnotherapy and CBT cannot be blinded for patients or parents. Moderate- to low-quality evidence was demonstrated for the effectiveness of probiotics in the management of children with FAPDs.[7,8] Furthermore, the -review that assessed pharmacologic interventions did not find convincing evidence to support the use of drugs in the treatment of FAPDs.[6] However, conclusions of all reviews unambiguously state that higher-quality trials are needed to fully investigate the effectiveness of the different interventions.

One-third of our included trials did not predefine their primary and secondary outcome measures. This is in line with studies on outcome measures of pediatric functional constipation and gastroesophageal reflux disease.[28] Inadequate reporting of endpoints in advance of a trial can induce bias and manipulation of study results.[29] Furthermore, the absence of a predefined primary endpoint precludes a proper sample size calculation, resulting in a lower chance to measure a clinically relevant treatment effect. To increase adequate outcome reporting, registration in either a clinical trial registry or publication of the trial protocol would be highly recommended. Overall, regardless of whether an outcome measure was predefined, most outcome measures could be assigned to the core area life impact with the outcome domains pain frequency and intensity being predominant as primary outcome domains. The domains functioning and psychological health, which are suggested as typical "life impact" domains according to the OMERACT Filter 2.0,[11] were predominant as secondary outcome domains. Integration of the health aspect "life impact" in modern healthcare increasingly is being recognized and perspectives on healthcare from patients and parents are becoming more and more important in clinical practice and research instruments.[11,13,30] When treating children, factors such as health-related quality of life and daily functioning of both the child and the family are essential to take into consideration. No outcomes measures were assigned to the core area death as expected, as symptoms of FAPDs are not life-threatening.

Most of the studies used a diary to assess "pain frequency" and "duration." The use of study diaries is supported by several studies as this instrument minimizes recall bias, however no validation studies in children have been performed.[9,10,31,32] As long as there is no validated diary including a standardized set of outcome measures and measurement instruments, researchers are able to assemble a diary with their preferred outcome measures. This leads to great variability in definitions and measurements of these outcome measures as was demonstrated in our study. Furthermore, it underlines the importance of the creation of a COS and validated measurement instruments to measure the agreed outcomes of the COS. This does not only apply to the pain outcome domains but also to other domains such as functioning, overall feeling, and psychological health. According to the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN)-Core Outcome Measures in Effectiveness Trials (COMET) initiative, the process of selection of outcome measurement instruments for a defined COS starts with a detailed systematic review of measurement instruments.[33] In addition, our observation that at least one-half of the predefined primary outcome measures were patient-reported is important, as a discrepancy between patient- and proxy-reporting has been demonstrated.[32,34] Parents tend to report other degrees of child somatic symptoms compared with their children.[32,34] Therefore, it is recommended that patient-reported outcome measures should be preferred over proxy-reported outcome measures.[10] Our results are partly in agreement with this advice, but awareness to integrate patient-reported outcome measures in clinical practice and research should be increased even more.

Adverse events were only reported in little over one-half of the included studies. This low number is driven by the predominance of psychosocial interventions assessed in this study, of which the majority refrained from reporting adverse events. Postulated potential negative adverse events of psychologic interventions include resurface of unpleasant memories, feeling more stress, and experiencing more anxiety.[35] Four of the included studies assessing a psychological intervention reported on adverse events. In 2 studies, adverse events were reported (a bruised knee during yoga class[36] and ear discomfort due to percutaneous nerve field stimulation[37]), whereas in the other 2 studies no adverse events were reported to occur.[38,39] Nevertheless, it remains of importance that future trials assessing these interventions also report on the occurrence of adverse events by including them as a core outcome measure.

A limitation of our study is that we only included articles written in English. This may have introduced bias by missing outcome measures and definitions of pediatric FAPDs from RCTs published in other languages. Furthermore, as the Rome IV criteria for FAPDs differ considerably for adults and children, we excluded 26 studies that did not separate data for the pediatric and adult population. One of the strengths of our study is that we identified a wide range of definitions, outcome measures, and measurement instruments for FAPDs in children and structurally grouped them according to the OMERACT Filter 2.0 to guide the next stage of COS development. The Delphi list was considered the most appropriate tool to assess methodologic quality of included studies as the goal of the present study was not to perform a meta-analysis to assess the efficacy of different treatments but to give an overall judgment of the quality of the included trials.[15] In conclusion, we found considerable heterogeneity and inconsistency in the reporting of definitions of FAPDs, outcome measures, and measurement instruments in therapeutic trials in pediatric FAPDs. The lack of consensus on the choice of definitions of FAPDs and outcome measures has important implications for both researchers and clinicians, as comparison of results of different treatments is hampered. This might lead to a lower quality of patient care.[11,12] To allow comparison of results in future studies, the development of a minimum COS for clinical research in pediatric FAPDs is recommended as the next

step. Stakeholders such as healthcare professionals and caregivers will be involved in this step. ■

Submitted for publication Nov 15, 2018; last revision received Mar 19, 2019; accepted Apr 24, 2019.

Reprint requests: Judith Zeevenhooven, BSc, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Pediatric Gastroenterology, Room C2-312, PO Box 22700, 1100 DD Amsterdam, the Netherlands. E-mail: j.zeevenhooven@amsterdamumc.nl

References

1. Korterink JJ, Diederen K, Benninga MA, Tabbers MM. Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis. PLoS One 2015;10:e0126982.
2. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Childhood Functional Gastrointestinal Disorders: Child/Adolescent. Gastroenterology 2016;150:1456-68.e2.
3. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. Gastroenterology 2016;150:1262-1279.e.
4. Chiou E, Nurko S. Management of functional abdominal pain and irritable bowel syndrome in children and adolescents. Expert Rev Gastroenterol Hepatol 2010;4:293-304.
5. Korterink J, Devanarayana NM, Rajindrajith S, Vlieger A, Benninga MA. Childhood functional abdominal pain: mechanisms and management. Nat Rev Gastroenterol Hepatol 2015;12:159-71.
6. Martin AE, Newlove-Delgado TV, Abbott RA, Bethel A, Thompson-Coon J, Whear R, et al. Pharmacological interventions for recurrent abdominal pain in childhood. Cochrane Database Syst Rev 2017;3:CD010973.
7. Abbott RA, Martin AE, Newlove-Delgado TV, Bethel A, Thompson-Coon J, Whear R, et al. Psychosocial interventions for recurrent abdominal pain in childhood. Cochrane Database Syst Rev 2017;1:CD010971.
8. Newlove-Delgado TV, Martin AE, Abbott RA, Bethel A, Thompson-Coon J, Whear R, et al. Dietary interventions for recurrent abdominal pain in childhood. Cochrane Database Syst Rev 2017;3:CD010972.
9. Fax D. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims Clinical/Medical Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims [Internet]. 2009 [cited 2018 Jun 22]. p. 301-443. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. Accessed June 22, 2018.
10. Saps M, van Tilburg MAL, Lavigne JV, Miranda A, Benninga MA, Taminiau JA, et al. Recommendations for pharmacological clinical trials in children with irritable bowel syndrome: the Rome foundation pediatric subcommittee on clinical trials. Neurogastroenterol Motil 2016;28:1619-31.
11. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino M-A, et al. Developing Core Outcome Measurement Sets for Clinical Trials: OMERACT Filter 2.0. J Clin Epidemiol 2014;67:745-53.
12. Sinha I, Jones L, Smyth RL, Williamson PR. A systematic review of studies that aim to determine which outcomes to measure in clinical trials in children. PLoS Med 2008;5:e96.
13. Alonso J, Bartlett SJ, Rose M, Aaronson NK, Chaplin JE, Efficace F, et al. The case for an international patient-reported outcomes measurement information system (PROMIS®) initiative. Health Qual Life Outcomes 2013;11:210.
14. Kapadia MZ, Joachim KC, Balasingham C, Cohen E, Mahant S, Nelson K, et al. A core outcome set for children with feeding tubes and neurologic impairment: a systematic review. Pediatrics 2016;138:e20153967.
15. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol 1998;51:1235-41.
16. Last JM. A Dictionary of epidemiology. 4th ed. Oxford: Oxford University Press; 2001.
17. Chogle A, Saps M. Electrocardiograms changes in children with functional gastrointestinal disorders on low dose amitriptyline. World J Gastroenterol 2014;20:11321-5.
18. Groß M, Warschburger P. Chronic Abdominal Pain: Psychosocial Strain and Treatment-Associated Changes in Coping. Verhaltenstherapie 2013;23:80-9.
19. Levy RL, Langer SL, Walker LS, Romano JM, Christie DL, Youssef N, et al. Twelve-month follow-up of cognitive behavioral therapy for children with functional abdominal pain. JAMA Pediatr 2013;167:178-84.
20. van Barreveld M, Rutten J, Vlieger A, Frankenhuis C, George E, Groeneweg M, et al. Cost-effectiveness and cost-utility of home-based hypnotherapy using compact disc versus individual hypnotherapy by a therapist for pediatric irritable bowel syndrome and functional abdominal pain (syndrome). Value Health 2015;18:A628.
21. Vlieger AM, van den Berg MM, Menko-Frankenhuis C, Bongers MEJ, Tromp E, Benninga MA. No change in rectal sensitivity after gut-directed hypnotherapy in children with functional abdominal pain or irritable bowel syndrome. Am J Gastroenterol 2010;105:213-8.
22. Vlieger AM, Rutten JMTM, Govers AMAP, Frankenhuis C, Benninga MA. Long-term follow-up of gut-directed hypnotherapy vs. standard care in children with functional abdominal pain or irritable bowel syndrome. Am J Gastroenterol 2012;107:627-31.
23. Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel disorders. Gastroenterology 2016;150:1393-407.e5.
24. Rasquin-Weber A, Hyman PE, Cucchiara S, Fleisher DR, Hyams JS, Milla PJ, et al. Childhood functional gastrointestinal disorders. Gut 1999;45(suppl 2):II60-8.
25. Hyman PE, Milla PJ, Benninga MA, Davidson GP, Fleisher DF, Taminiau J. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology 2006;130:1519-26.
26. Sood MR, Di Lorenzo C, Hyams J, Miranda A, Simpson P, Mousa H, et al. Beliefs and attitudes of general pediatricians and pediatric gastroenterologists regarding functional gastrointestinal disorders: a survey study. Clin Pediatr (Phila) 2011;50:891-6.
27. Khoshoo V, Armstead C, Landry L. Effect of a laxative with and without tegaserod in adolescents with constipation predominant irritable bowel syndrome. Aliment Pharmacol Ther 2006;23:191-6.
28. Kuizenga-Wessel S, Heckert SL, Tros W, van Etten-Jamaludin FS, Benninga MA, Tabbers MM. Reporting on outcome measures of functional constipation in children—a systematic review. J Pediatr Gastroenterol Nutr 2016;62:840-6.
29. Evans S. When and how can endpoints be changed after initiation of a randomized clinical trial? PLoS Clin Trials 2007;2:e18.
30. World Health Organization. International Classification of Functioning, Disability and Health (ICF) [Internet]. Geneva; 2001. http://www.who.int/classifications/icf/en/. Acccessed June 26, 2018.
31. Chogle A, Sztainberg M, Bass L, Youssef NN, Miranda A, Nurko S, et al. Accuracy of pain recall in children. J Pediatr Gastroenterol Nutr 2012;55:288-91.
32. Self MM, Williams AE, Czyzewski DI, Weidler EM, Shulman RJ. Agreement between prospective diary data and retrospective questionnaire report of abdominal pain and stooling symptoms in children with irritable bowel syndrome. Neurogastroenterol Motil 2015;27:1110-9.
33. Prinsen CAC, Vohra S, Rose MR, Boers M, Tugwell P, Clarke M, et al. How to select outcome measurement instruments for outcomes included in a "Core Outcome Set"—a practical guideline. Trials 2016;17:449.
34. Garber J, Van Slyke DA, Walker LS. Concordance between mothers' and children's reports of somatic and emotional symptoms in patients with recurrent abdominal pain or emotional disorders. J Abnorm Child Psychol 1998;26:381-91.
35. Rozental A, Kottorp A, Boettcher J, Andersson G, Carlbring P. Negative effects of psychological treatments: an exploratory factor analysis of the negative effects questionnaire for monitoring and reporting adverse and unwanted events. PLoS One 2016;11:e0157503.

36. Evans S, Lung KC, Seidman LC, Sternlieb B, Zeltzer LK, Tsao JCI. Iyengar yoga for adolescents and young adults with irritable bowel syndrome. J Pediatr Gastroenterol Nutr 2014;59:244-53.
37. Kovacic K, Hainsworth K, Sood M, Chelimsky G, Unteutsch R, Nugent M, et al. Neurostimulation for abdominal pain-related functional gastrointestinal disorders in adolescents: a randomised, double-blind, sham-controlled trial. Lancet Gastroenterol Hepatol 2017;2:727-37.
38. Weydert JA, Shapiro DE, Acra SA, Monheim CJ, Chambers AS, Ball TM. Evaluation of guided imagery as treatment for recurrent abdominal pain in children: a randomized controlled trial. BMC Pediatr 2006;6:29.
39. Korterink JJ, Ockeloen LE, Hilbink M, Benninga MA, Deckers-Kocken JM. Yoga therapy for abdominal pain-related functional gastrointestinal disorders in children: a randomized controlled trial. J Pediatr Gastroenterol Nutr 2016;63:481-7.

50 Years Ago in *The Journal of Pediatrics*

Recurrence Rate of Streptococcal Pharyngitis Related to Oral Penicillin

Green JL, Ray SP, Charney E. J Pediatr 1969;75:292-4

The study by Green et al aimed to demonstrate that recurrent Group A streptococcal (GAS) pharyngitis was more common in children who were nonadherent to their 10-day oral penicillin therapy compared with those who were adherent. The 128 children who were culture-positive submitted a urine sample, which was tested for penicillin, on the ninth day of therapy to assess adherence. Subjects then returned for a follow-up culture at 3 weeks: 12% of adherent subjects were positive vs 32% who were not.

Although these results make biological common sense, the study design presented multiple concerns. The results of the ninth-day urine sample reflected recent penicillin dosing but likely only approximated adherence throughout the 10-day course. Moreover, in the absence of an intervening negative throat culture, the authors could not distinguish between recurrence and persistence. Third, there was no clinical description of the subjects at the 3-week follow up, and hence it is uncertain how many had pharyngitis, recurrent or persistent, at all. Thus, it is probable that the authors actually were measuring differences in microbiological cure rates rather than the comparative rates of recurrent pharyngitis, as implied in their title.

Even this more modest outcome, however, presents issues. Admittedly many studies have tested the relative effectiveness of regimens for GAS pharyngitis using eradication of the organism as a study endpoint, but the goal of therapy for GAS pharyngitis is the avoidance of suppurative complications and acute rheumatic fever. Both are very uncommon events in contemporary children receiving any therapy for GAS pharyngitis, despite residual streptococci in the throat in 10% or more after a full antibiotic course. Many children with persistently positive cultures likely represent those with viral pharyngitis and coincident chronic GAS carriage, the latter a state that has essentially no pathologic or epidemiologic consequence; hence, why expert groups dissuade routine follow-up throat cultures in children treated for GAS pharyngitis. These current remarks should not discourage pediatricians from emphasizing adherence to the recommended full course of therapy for GAS pharyngitis but rather highlight the difficulties, encountered by Green et al, in establishing an ideal regimen for a common condition that has rare consequences that are not clearly associated with persistence of the organism in the infected space.

Philip Toltzis, MD
Rainbow Babies and Children's Hospital
Cleveland, Ohio

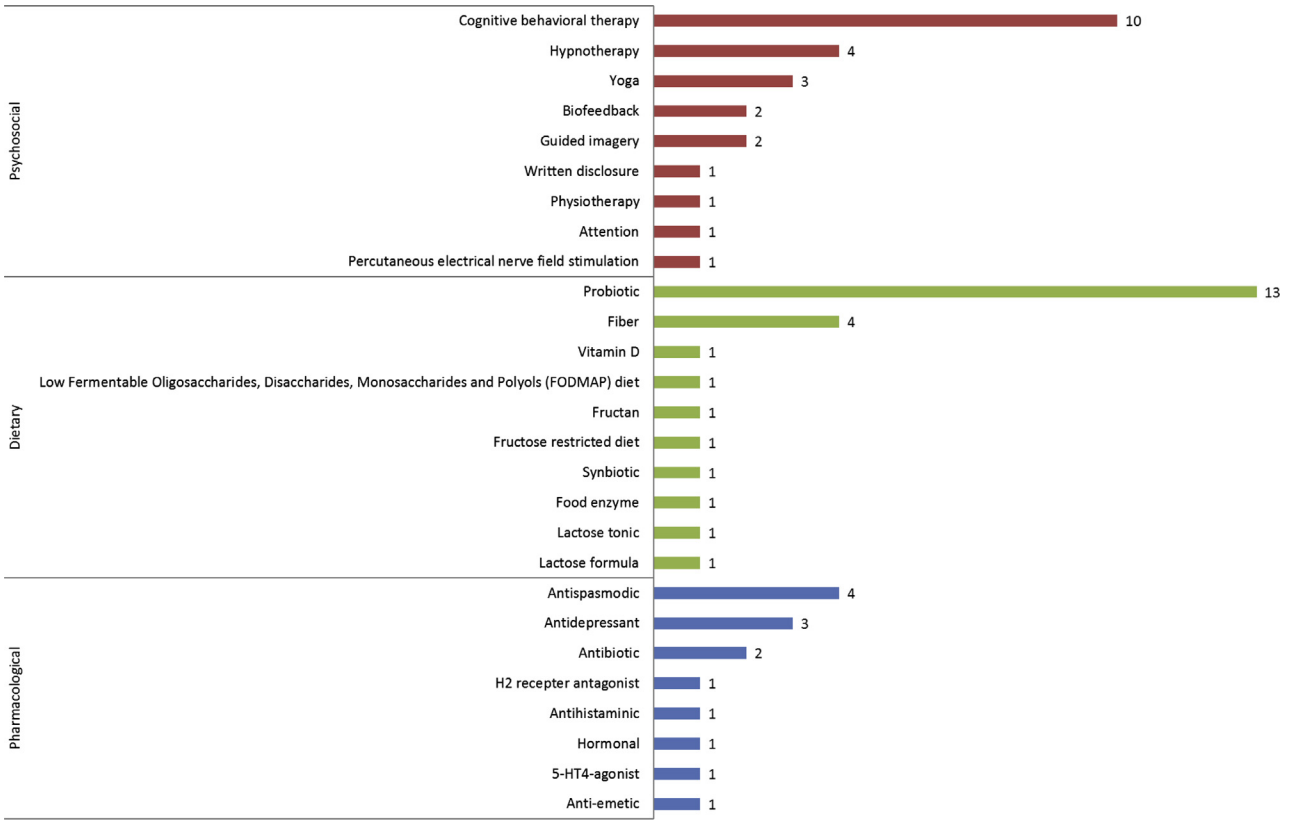

Figure 2. Interventions used for FAPDs.

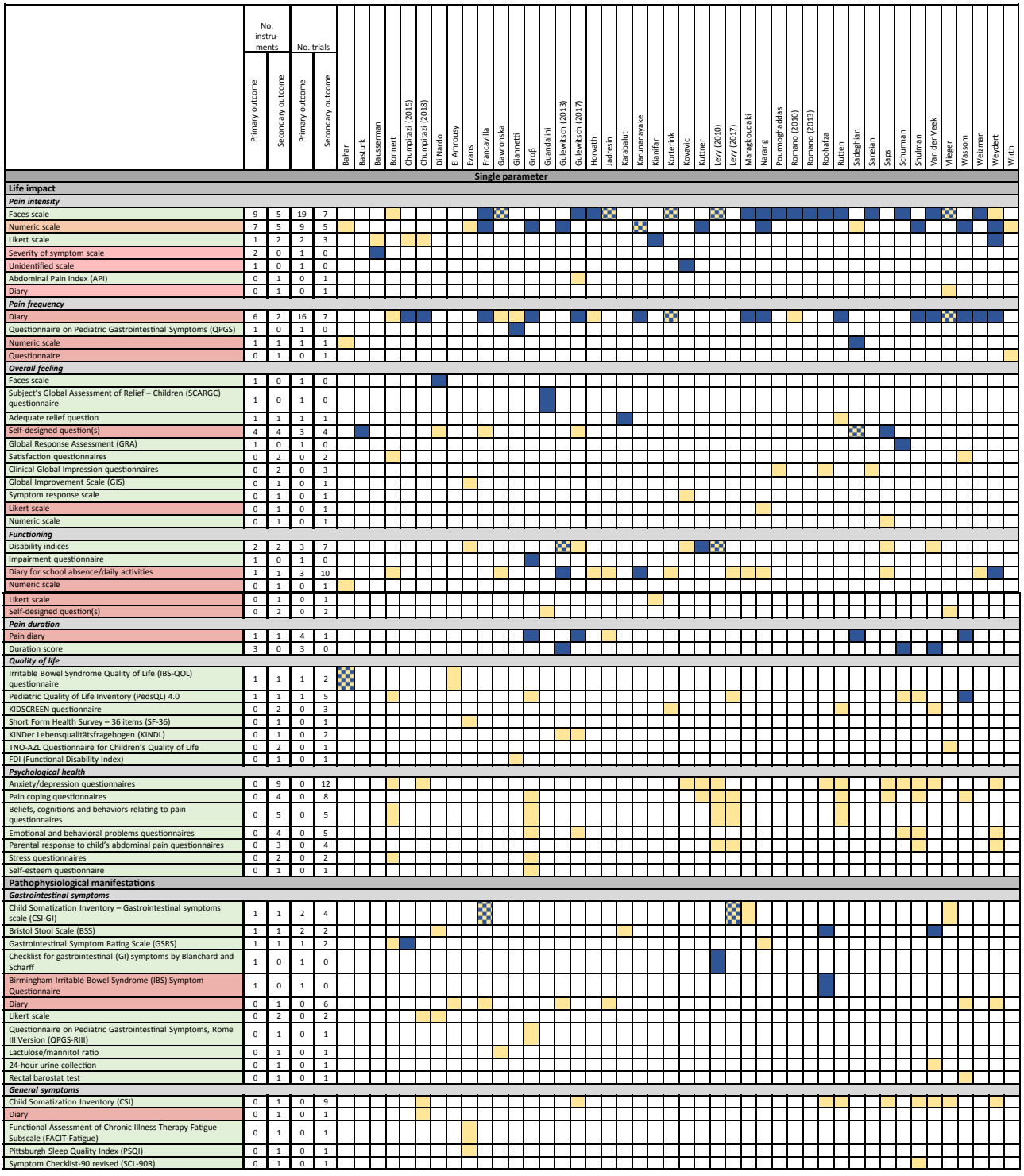

Figure 4. Measurement instruments for predefined outcomes used for FAPDs. *Green shading* indicates validated investigational method; *orange shading* indicates some investigational methods validated, some investigational methods not validated; and *red shading* indicates no validated investigational method. *Red boxes* indicate investigational method for primary outcome measure; *blue boxes* indicate investigational method for secondary outcome measure; and *purple boxes* indicate investigational method for primary and secondary outcome measures. *EKG*, electrocardiogram; *HUI-3*, Health Utilities Index Mark 3. *Scales included: Wong Baker; Faces Pain Scale (WBFPS) (6 faces; 0=no hurt, 5=hurts worst); Affective facial scale (9 faces; A=no pain at all, I= most severe pain); Faces Pain Scale (FPS) (7 faces); Faces Pain Scale – Revised (FPS-R) (6 faces; 0=no pain, 5=very much pain); FPS-R (6 faces; 0=no pain, 10=severe pain); FPS (6 faces; 0=relaxed face, 5=intense pain); FPS-R (4 faces); FPS-R (6 faces; 1-6, 6=worst pain possible); Horizontal pain thermometer scale (10 radio buttons, left: no pain – right: severe pain + additional faces) *(Continues)*

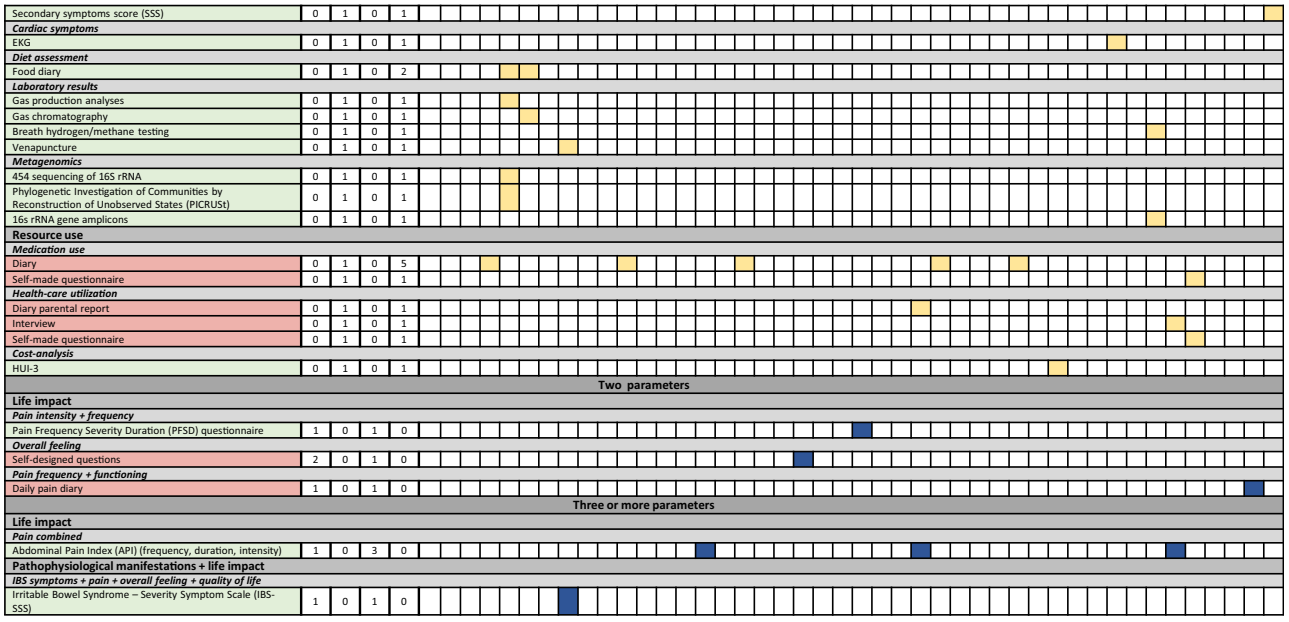

Figure 4. *Continued*

Criteria	Studies																														
	Alfven	Asgarshirazi	Bahar	Basturk	Bausserman	Bonnert	Chumpitazi (2015)	Chumpitazi (2018)	Collins	Dearlove	Di Nardo	Duarte	Eftekhari	El Amrousy	Evans	Feldman	Francavilla	Gawronska	Giannetti	Groß	Guandalini	Gulewitsch (2013)	Gulewitsch (2017)	Heyland	Horvath	Humphreys	Jadresin	Karabalut	Karunanayake	Khoshoo	Kianifar	Kline
1. Was a method of randomization performed?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2. Was the treatment allocation concealed?	/	/	/	/	+	+	/	+	+	/	/	/	/	+	+	/	+	/	/	/	+	/	/	/	+	/	+	/	+	-	/	/
3. Were the groups similar at baseline regarding the most prognostic indicators?	/	+	+	+	+	+	/	/	+	+	+	+	+	+	+	+	+	+	/	+	/	+	+	+	+	+	+	/	+	+	+	+
4. Were the eligibility criteria specified?	-	+	+	-	+	+	-	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+
5. Was the outcome assessor blinded?	-	+	/	+	+	-	/	+	/	/	/	-	/	+	/	+	+	+	+	-	+	-	/	/	+	-	+	/	+	-	+	/
6. Was the care provider blinded?	-	-	/	+	+	-	/	/	/	/	/	-	+	+	-	+	/	/	+	-	+	-	/	/	/	-	+	/	+	-	/	/
7. Was the patient blinded?	-	-	/	+	+	-	/	/	/	+	/	-	+	+	-	+	+	+	+	-	+	-	+	+	+	-	+	/	+	-	+	+
8. Were point estimates and measures of variability presented for the primary outcome measures?	+	+	-	-	+	+	+	+	-	-	+	-	/	+	+	-	+	+	-	+	-	+	+	-	+	+	+	-	+	+	+	-
9. Did the analysis include an intention-to-treat analysis?	-	-	/	-	-	+	-	-	+	-	/	/	/	+	-	-	+	+	+	+	-	+	+	-	-	-	+	/	-	+	-	-
10. Is the withdrawal/drop-out rate <20% and equally distributed?	-	-	/	/	-	+	+	-	+	/	/	/	/	+	-	/	+	+	/	+	+	+	-	/	+	/	+	/	-	+	/	/
Total Score:	2	5	3	5	8	7	3	5	6	3	4	2	6	9	5	6	9	8	6	6	7	6	6	4	8	3	10	1	8	6	6	4

Criteria	Studies																														
	Korterink	Kovavic	Kuttner	Lebenthal	Levy (2010)	Levy (2017)	Maragkoudaki	Narang	Pourmoghaddas	Robins	Romano (2010)	Romano (2013)	Roohafza	Rutten	Sadeghian	Sanders (1989)	Sanders (1994)	Saneian	Saps	Schurman	See	Shulman	Van der Veek	Van Tilburg	Vlieger	Walker	Wallander	Wassom	Weizman	Weydert	Wirth	Zybach
1. Was a method of randomization performed?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	/	+	+	+	+	+	+	+	/
2. Was the treatment allocation concealed?	/	+	/	/	/	/	/	+	+	+	+	/	+	+	+	/	/	+	/	+	/	/	/	/	+	/	/	/	+	-	/	/
3. Were the groups similar at baseline regarding the most prognostic indicators?	+	+	+	/	+	+	+	+	+	-	+	+	-	+	+	/	+	+	+	/	+	+	+	+	+	+	+	+	+	+	-	/
4. Were the eligibility criteria specified?	+	+	-	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+
5. Was the outcome assessor blinded?	-	+	-	/	+	+	+	+	+	-	/	/	+	-	+	-	-	+	+	-	+	+	-	-	+	-	-	-	+	+	-	/
6. Was the care provider blinded?	-	+	-	+	-	+	/	+	+	+	+	/	+	-	+	-	-	+	/	-	+	/	-	-	-	-	-	-	+	-	-	/
7. Was the patient blinded?	-	+	-	+	-	-	+	+	+	-	+	+	+	-	+	-	-	+	+	-	+	+	-	-	-	+	-	-	+	-	-	/
8. Were point estimates and measures of variability presented for the primary outcome measures?	-	+	+	-	+	+	+	+	+	-	+	+	+	+	-	+	+	+	-	+	-	+	+	-	-	+	+	+	+	+	+	-
9. Did the analysis include an intention-to-treat analysis?	+	+	-	-	+	+	-	-	+	-	-	+	+	+	-	/	/	-	+	+	+	-	+	+	+	/	-	-	-	-	/	-
10. Is the withdrawal/drop-out rate <20% and equally distributed?	-	-	-	-	+	-	+	-	-	-	+	+	-	+	/	/	/	-	+	+	+	+	+	+	+	/	+	-	+	+	+	+
Total Score:	4	9	3	4	7	7	7	8	9	3	8	6	8	7	7	3	4	8	7	6	8	7	5	4	7	5	4	4	9	6	4	2

Figure 5. Quality assessment by Delphi list. *Red boxes* indicate a low quality score (score ≤3); *orange boxes* indicate an average methodologic quality (score 4-6); and *green boxes* indicate a high methodologic quality (score >6). +, yes; −, no; /, unsure.

Table I. Definitions for FAPDs

Rome IV[1]	Rome III[2]	Rome II[3]	Apley[4]
Functional dyspepsia			
Must include 1 or more of the following bothersome symptoms at least 4 days per month: 1. Postprandial fullness 2. Early satiation 3. Epigastric pain or burning not associated with defecation 4. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition. *Criteria fulfilled for at least 2 mo before diagnosis.* *Within functional dyspepsia, the following subtypes are now adopted:* 1. Postprandial distress syndrome includes bothersome postprandial fullness or early satiation that prevents finishing a regular meal. Supportive features include upper abdominal bloating, postprandial nausea, or excessive belching 2. Epigastric pain syndrome, which includes all of the following: bothersome (severe enough to interfere with normal activities) pain or burning localized to the epigastrium. The pain is not generalized or localized to other abdominal or chest regions and is not relieved by defecation or passage of flatus. Supportive criteria can include (1) burning quality of the pain but without a retrosternal component and (2) the pain commonly induced or relieved by ingestion of a meal but may occur while fasting.	Must include all of the following: 1. Persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus) 2. Not relieved by defecation or associated with the onset of a change in stool frequency or stool form (ie, not IBS) 3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms *Criteria fulfilled at least once per week for at least 2 mo before diagnosis*	In children mature enough to provide an accurate pain history, at least 12 wk, which need not be consecutive, within the preceding 12 months of: 1. Persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus); and 2. No evidence (including at upper endoscopy) that organic disease is likely to explain the symptoms; and 3. No evidence that dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form.	NA
IBS			
Must include all of the following: 1. Abdominal pain at least 4 d per month associated with 1 or more of the following: a. Related to defecation b. A change in frequency of stool c. A change in form (appearance) of stool 2. In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not irritable bowel syndrome) 3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition *Criteria fulfilled for at least 2 mo before diagnosis*	Must include all of the following: 1. Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time: a. Improved with defecation b. Onset associated with a change in frequency of stool c. Onset associated with a change in form (appearance) of stool 2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms *Criteria fulfilled at least once per week for at least 2 mo before diagnosis*	In children old enough to provide an accurate pain history, at least 12 wk, which need not be consecutive, in the preceding 12 mo of; 1. Abdominal discomfort or pain that has 2 of 3 features: a. Relieved with defecation; and/or b. Onset associated with a change in frequency of stool; and/or c. Onset associated with a change in form (appearance) of stool; and 2. There are no structural or metabolic abnormalities to explain the symptoms.	NA
Abdominal migraine			
Must include all of the following occurring at least twice: 1. Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting 1 h or more (should be the most severe and distressing symptom) 2. Episodes are separated by weeks to months. 3. The pain is incapacitating and interferes with normal activities 4. Stereotypical pattern and symptoms in the individual patient 5. The pain is associated with 2 or more of the following: a. Anorexia b. Nausea c. Vomiting d. Headache e. Photophobia f. Pallor	Must include all of the following: 1. Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 h or more 2. Intervening periods of usual health lasting weeks to months 3. The pain interferes with normal activities 4. The pain is associated with 2 or more of the following: a. Anorexia b. Nausea c. Vomiting d. Headache e. Photophobia f. Pallor	1. In the preceding 12 mo, 3 or more paroxysmal episodes of intense, acute midline abdominal pain lasting 2 h to several days, with intervening symptom-free intervals lasting weeks to months; and 2. Evidence of metabolic, gastrointestinal, and central nervous system structural or biochemical diseases is absent; and 3. Two of the following features: a. Headache during episodes; b. Photophobia during episodes; c. Family history of migraine; d. Headache confined to one side only; e. An aura or warning period consisting of either visual disturbances (eg,	NA

(*continued*)

Table I. Continued

Rome IV[1]	Rome III[2]	Rome II[3]	Apley[4]
6. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition. *Criteria fulfilled for at least 6 mo before diagnosis.*	5. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process considered that explains the subject's symptoms *Criteria fulfilled 2 or more times in the preceding 12 mo*	blurred or restricted vision), sensory symptoms (eg, numbness or tingling), or motor abnormalities (eg, slurred speech, inability to speak, paralysis).	
FAP-NOS	**FAP**	**FAP**	**FAP**
Must be fulfilled at least 4 times per month and include all of the following: 1. Episodic or continuous abdominal pain that does not occur solely during physiologic events (eg, eating, menses) 2. Insufficient criteria for irritable bowel syndrome, functional dyspepsia, or abdominal migraine 3. After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition *Criteria fulfilled for at least 2 mo before diagnosis.*	Must include all of the following: 1. Episodic or continuous abdominal pain 2. Insufficient criteria for other FGIDs 3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms *Criteria fulfilled at least once per week for at least 2 mo before diagnosis*	At least 12 wk of: 1. Continuous or nearly continuous abdominal pain in a school-aged child or adolescent; and 2. No or only occasional relation of pain with physiological events (eg, eating, menses, or defecation); and 3. Some loss of daily functioning; and 4. The pain is not feigned (eg, malingering); and 5. The patient has insufficient criteria for other functional gastrointestinal disorders that would explain the abdominal pain	NA
	FAPS		
NA	Must include childhood functional abdominal pain at least 25% of the time and 1 or more of the following: 1. Some loss of daily functioning 2. Additional somatic symptoms such as headache, limb pain, or difficulty sleeping *Criteria fulfilled at least once per week for at least 2 mo before diagnosis*	NA	NA
	RAP		
NA	NA	NA	At least 3 bouts of abdominal pain, severe enough to affect activities, over a period of at least 3 mo

FAPS, functional abdominal pain syndrome; *FGID*, functional gastrointestinal disorder; *NA*, not applicable; *RAP*, recurrent abdominal pain.

References

1. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Functional disorders: children and adolescents. Gastroenterology 2019. in press.
2. Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology 2006;130:1527-37.
3. Rasquin-Weber A, Hyman PE, Cucchiara S, Fleisher DR, Hyams JS, Milla PJ, et al. Childhood functional gastrointestinal disorders. Gut 1999;45(suppl 2):II60-8.
4. Apley J, Naish N. Recurrent abdominal pains: a field survey of 1,000 school children. Arch Dis Child 1958;33:165-70.

Table IV. Study characteristics

Authors, country	Year	Study population	Diagnosis	Definition	Clinical setting	Outcome assessor	Intervention Treatment duration
Alfvén and Lindstrom,[1] Sweden	2006	83 subjects 6-18 y Mean 9.87 y	RAP	Apley	Primary/secondary/tertiary	Child	Physiotherapy vs physiotherapy + psychological vs psychological NR
Asgarshirazi et al,[2] Iran	2015	88 subjects 3-13 y Mean 7.3 y	Functional dyspepsia, IBS, FAP, FAPS	Rome III	Tertiary	Child/parent	Colpermin vs lactol vs placebo 4 wk
Bahar et al,[3] US	2008	33 subjects 12-18 y Mean 14.75 y	IBS	Rome II	Tertiary	Child	Amitriptyline vs placebo 8 wk
Basturk et al,[4] Turkey	2016	71 subjects 4-16 y Mean 10.88 years	IBS	Rome III	Tertiary	NR	Symbiotic (*B lactis* B94 + inulin) vs probiotic (B. lactis B94) vs prebiotic (inulin) 4 wk
Bausserman et al,[5] US	2005	50 subjects 6-20 y Mean 12.0 y	IBS	Rome II	Tertiary	Child/parent	*Lactobacillus* GG vs placebo 6 wk
Bonnert et al,[6] Sweden	2017	101 subjects 13-18 y Mean 15.54 years	IBS	Rome III	Primary/secondary/tertiary	Child	Internet-cognitive behavioral therapy (CBT) vs wait-list control 10 wk
Chumpitazi et al,[7] US	2015	33 subjects 7-17 y Mean 11.5 y	IBS	Rome III	Tertiary	NR	Low-FODMAP diet vs typical American childhood diet 2 d
Chumpitazi et al,[8] US	2018	23 subjects 7-18 y Mean 12.4 y	IBS	Rome III	Primary/tertiary	Child	Fructan (inulin-fructooligosaccharides) vs placebo 3 d
Collins and Lin,[9] US	2011	75 subjects 8-18 y Mean 12.7 y	Functional dyspepsia, IBS, abdominal migraine, FAP	Rome II	Secondary/tertiary	Child	Rifaximin vs placebo 10 d
Dearlove et al,[10] United Kingdom	1983	21 subjects NR Mean 10.4 y	Recurrent periumbilical pain	Other	Secondary	Parent	Lactose-tonic vs placebo 2 wk
Di Nardo et al,[11] Italy	2013	52 subjects 4-17 y Median 8.0 y	Gas-related disturbance	Other	Tertiary	Child/parent	α-galactosidase vs placebo 2 wk
Duarte et al,[12] Brazil	2006	32 subjects 5-14 y Mean 9.15 y	RAP	Apley	Tertiary	Child	Cognitive-behavioral family intervention vs standard pediatric care 16 wk
Eftekhari et al,[13] Iran	2015	80 subjects 4-16 y Mean 6.26 y	FAP	Rome III	Secondary/tertiary	Physician	*Lactobacillus reuteri* vs placebo 4 wk
El Amrousy et al,[14] Egypt	2018	112 14-18 y Mean 16.3 y	IBS	Rome III	Tertiary		Vitamin D3 (2000 IU/d) vs placebo 24 wk
Evans et al,[15] US	2014	30 subjects 14-17 y NR	IBS, RAP	Rome III	Primary/secondary/tertiary	Child	Iyengar yoga vs usual care waitlist control group 6 wk
Feldman et al,[16] US	1985	52 subjects 5-15 y Mean 9.37 y	RAP	Other	Primary	Child/parent	Corn fiber cookies vs placebo 6 wk

(*continued*)

Table IV. Continued

Authors, country	Year	Study population	Diagnosis	Definition	Clinical setting	Outcome assessor	Intervention Treatment duration
Francavilla et al,[17] Italy	2010	136 subjects 5-14 y Mean 6.4 y	IBS, FAP	Rome II	Primary	Child	*Lactobacillus* GG vs placebo 8 wk
Gawronska et al,[18] Poland	2007	104 subjects 6-16 y Mean 11.55 y	Functional dyspepsia, IBS, FAP	Rome II	Tertiary	Child	*Lactobacillus* GG vs placebo 4 wk
Giannetti et al,[19] Italy	2017	73 subjects 8-17 y Median 11.4 y	Functional dyspepsia, IBS	Rome III	Tertiary	Physician	Mixture of 3 *Bifidobacteria* vs placebo 6 wk
Groß and Warschburger,[20] Germany	2013	29 subjects 7-12 y Mean 9,6 y	CAP	Rome III	Primary	Child	Pain management training for children and their parents vs wait-list control 8 wk
Guandalini et al,[21] US	2010	59 subjects 4-18 y Mean 12.5 y	IBS	Rome II	Tertiary	Child/parent	VSL#3 vs placebo 6 wk
Gulewitsch et al,[22] Germany	2013	38 subjects 6-12 ears Mean 9.37 y	IBS, FAP	Rome III	Community/secondary/Tertiary	Child	Hypnotherapeutic behavioral intervention vs wait-list control 4 wk
Gulewitsch and Schlarb,[23] Germany	2017	32 subjects 6-17 y Mean 11.9 y	IBS, FAP	Rome III	Primary/secondary/tertiary	Child	Gut-directed hypnotherapy vs unspecific hypnotherapy 12 wk
Heyland et al,[24] Switzerland	2012	37 subjects 3-16 y Mean 11.0 y	RAP	Apley	Tertiary	Child	TMP/SMX vs placebo 7 d
Horvath et al,[25] Poland	2013	89 subjects 7-17 y Mean 11.45 y	Functional dyspepsia, IBS, FAP	Rome III	Tertiary	Child	Glucomannan vs placebo 4 wk
Humphreys and Gevirtz,[26] US	2000	61 subjects 4-18 y Mean 9.75 y	RAP	Other	Primary	Child	Increased DF vs increased DF + BFB assisted cultivated low arousal vs increased DF + BFB assisted cultivated low arousal + cognitive behavioral interventions vs increased DF + BFB assisted cultivated low arousal + cognitive behavioral interventions + parental support 8 wk
Jadresin et al,[27] Croatia	2016	55 subjects 4-18 y Median 10.0 y	IBS, FAP	Rome III	Tertiary	Child	*Lactobacillus reuteri* DSM 17938 vs placebo 12 wk
Karabulut et al,[28] Turkey	2013	78 subjects 4-18 y Mean 9.79 y	IBS	Rome III	Tertiary	Parent	Trimebutine maleate vs no medication/ usual care 3 weeks
Karunanayake et al,[29] Sri Lanka	2018	100 subjects 5-12 y Mean 7.96 y	Functional dyspepsia, IBS, FAP	Rome III	Tertiary	Physician	Domperidone vs placebo 8 wk
Khoshoo et al,[30] USA	2006	48 subjects 13-18 y Mean 15.23 y	IBS-C	Rome II	Primary	Child	Laxative vs laxative + tegaserod 5 wk

(*continued*)

Table IV. Continued

Authors, country	Year	Study population	Diagnosis	Definition	Clinical setting	Outcome assessor	Intervention Treatment duration
Kianifar et al,[31] Iran	2015	52 subjects 4-18 y Mean 7.1 y	IBS	Rome III	Tertiary	Physician	*Lactobacillus* GG vs placebo 4 wk
Kline et al,[32] US	2001	42 subjects 8-17 y Mean 12 y	IBS	Manning or Rome II	Tertiary	Physician	Colpermin vs placebo 2 wk
Korterink et al,[33] The Netherlands	2016	69 subjects 8-18 y Mean 12.15 y	Functional dyspepsia, IBS, FAP(S)	Rome III	Secondary	Child	Hatha yoga vs standard medical care (SMC) 10 wk
Kovacic et al,[34] US	2017	101 subjects 11-18 y Median 15.3 y	Functional dyspepsia, IBS, abdominal migraine, FAP, FAPS	Rome III	Tertiary	Child	Active PENFSD vs sham device 4 wk
Kuttner et al,[35] Canada	2006	25 subjects 11-18 y Mean 14.15 y	IBS	Rome I	Primary/secondary	Child	Yoga vs waitlist control group 4 wk
Lebenthal et al,[36] US	1981	38 subjects 6-14 y NR	RAP	Other	Tertiary	Parent	Lactose containing infant formula (Enfamil) vs non-lactose-containing formula (soy-based) (Prosobee) vs normal diet 6 wk
Levy et al,[37] US	2010	200 subjects 7-17 y Mean 11.21 y	RAP	Other	Primary/secondary/tertiary	Parent	SLCBT vs ES 3 wk
Levy et al,[38] US	2017	316 subjects 7-12 y Mean 9.4 y	IBS, FAP	Rome III	Tertiary	Parent	SLCBT (in person) vs SCLBT-R (phone) vs education support (by phone) 3 wk
Maragkoudaki et al,[39] Greece	2017	54 subjects 5-16 y Mean 9,1 years	FAP	Rome III	Tertiary	Child/parent	*Lactobacillus reuteri* DSM 17938 vs placebo 4 wk
Narang et al,[40] India	2015	132 subjects 4-12 y Mean 7.25 y	RAP	Apley	Tertiary	Child	Drotaverine hydrochloride vs placebo 4 wk
Pourmoghaddas et al,[41] Iran	2014	87 subjects 6-18 y Mean 8.5 y	FAP	Rome III	Tertiary	Child	Mebeverine vs placebo 4 wk
Robins et al,[42] US	2005	69 subjects 6-16 y Mean 11.25 y	RAP	Apley	Primary/tertiary	Child/parent	CBT + SMC vs SMC 10 wk
Romano et al,[43] Italy	2010	56 subjects 6-16 y Mean 9.9 y	FAP	Rome III	Tertiary	Parent	*Lactobacillus reuteri* DSM 17938 vs placebo 4 wk
Romano et al,[44] Italy	2013	60 subjects 8-16 y Mean 12.8 y	IBS, CAP	Rome III	Tertiary	Child	Partially hydrolyzed guar gum vs placebo 4 wk
Roohafza et al,[45] Iran	2014	86 subjects 6-18 y Mean 9.45	FAP	Rome III	Tertiary	Child	Citalopram vs placebo 4 wk
Rutten et al,[46] The Netherlands	2017	250 subjects 8-18 y Mean 13.35 y	IBS, FAP(S)	Rome III	Secondary/tertiary	Child	Hypnotherapy via CD vs individual hypnotherapy 12 wk

(*continued*)

Table IV. Continued

Authors, country	Year	Study population	Diagnosis	Definition	Clinical setting	Outcome assessor	Intervention Treatment duration
Sadeghian et al,[47] Iran	2008	29 subjects 4.5-12 y Mean 7.45 y	FAP	Rome II	Tertiary	Child/parent	Cyproheptadine vs placebo 2 wk
Sanders et al,[48] Australia	1989	16 subjects 6-12 y Mean 9.0 y	RAP	Apley	Primary/secondary	Child/parent	Cognitive behavioral therapy for parent and child vs waitlist control 8 wk
Sanders et al,[49] Australia	1994	44 subjects 7-14 y Mean 9.2 y	RAP	Apley	NR	Child	Cognitive-behavioral family intervention vs standard pediatric care 8 wk
Saneian et al,[50] Iran	2015	88 subjects 6-18 y Mean 8.5 y	FAP	Rome III	Tertiary	Child	Synbiotic (Bacillus coagulans + FOS) vs placebo 4 wk
Saps et al,[51] US	2009	90 subjects 8-17 y Mean 12.7 y	Functional dyspepsia, IBS, FAP	Rome II	Tertiary	Child	Amitriptyline vs placebo 4 wk
Schurman et al,[52] US	2010	20 subjects 8-17 y Mean 12.2 y	Functional dyspepsia	Other	Tertiary	Child	SMC + biofeedback-assisted relaxation training (BART) vs SMC 6 wk
See et al,[53] US	2001	25 subjects 5-18 y Mean 10.5 y	RAP	Apley	Tertiary	Child	Famotidine vs placebo 3 wk
Shulman et al,[54] US	2017	84 subjects 7-18 y Mean 13.0 y	IBS	Rome III	Primary/tertiary	Child	Psyllium vs placebo 6 wk
Van der Veek et al,[55] The Netherlands	2013	104 subjects 7-18 y Mean 11.9 y	IBS, FAP(S)	Rome III	Secondary/tertiary	Child/parent	CBT sessions children and parents vs intensified medical care control condition 6 wk
Van Tilburg et al,[56] US	2009	34 subjects 6-15 ys Mean 10.2 y	RAP	Other	Tertiary	Child/parent	Guided imagery + SMC vs SMC 8 wk
Vlieger et al,[57] The Netherlands	2007	52 subjects 8-18 y Mean 13.3 y	IBS, FAP	Rome II	Tertiary	Child	Hypnotherapy vs SMC 12 wk
Walker et al,[58] US	2006	110 subjects 8-16 y Mean 11.46 y	RAP	Other	Tertiary	Child	Parental attention vs parental distraction vs no instruction 1 d
Wallander et al,[59] US	2011	56 subjects 11-18 y Mean 13.62 y	RAP	Apley	Tertiary	Child	Writing self-disclosure + SMC vs SMC 3 mo
Wassom et al,[60] US	2013	15 subjects 13-18 y Mean 15.16 y	Functional dyspepsia, IBS	Rome III	Tertiary	Child	Gutstrong (CD-rom + workbook) + SMC vs SMC 4 wk
Weizman et al,[61] Israel	2016	93 subjects 6-15 y Mean 11.95 y	Functional dyspepsia, IBS, abdominal migraine, FAP	Rome III	Primary/tertiary	Child	*Lactobacillus reuteri* DSM 17938 vs placebo 4 wk
Weydert et al,[62] US	2006	22 subjects 5-18 y Mean 11.1 y	RAP	Apley	Secondary/tertiary	Child/parent	Guided imagery with progressive muscle relaxation vs breathing techniques 4 wk

(*continued*)

Table IV. Continued

Authors, country	Year	Study population	Diagnosis	Definition	Clinical setting	Outcome assessor	Intervention Treatment duration
Wirth et al,[63] Germany	2014	103 subjects 3.4-16.4 y Median 8.8 y	RAP	Other	Secondary	Child/parent	Fructose-restricted diet vs control group (no restrictions) 2 wk
Zybach et al,[64] US	2016	12 subjects 8-17 y Mean 13.8 y	Functional dyspepsia	Rome III	Tertiary	NR	Melatonin vs placebo 4 wk

BART, biofeedback-assisted relaxation training; *BFB*, biofeedback; *C*, constipation; *CAP*, chronic abdominal pain; *DF*, dietary fiber; *ES*, education support; *FODMAP*, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; *NR*, not reported; *PENFSD*, percutaneous electrical nerve field stimulation auricular device; *SLCBT*, social learning and cognitive-behavioral therapy; *SMC*, standard medical care; *TMP/SMX*, trimethoprim-sulfamethoxazole.

References

1. Alfvén G, Lindstrom A. A new method for the treatment of recurrent abdominal pain of prolonged negative stress origin. Acta Paediatr 2007;96:76-81.
2. Asgarshirazi M, Shariat M, Dalili H. Comparison of the effects of pH-dependent peppermint oil and synbiotic lactol (*Bacillus coagulans* + Fructooligosaccharides) on childhood functional abdominal pain: a randomized placebo-controlled study. Iran Red Crescent Med J 2015;17:e23844.
3. Bahar RJ, Collins BS, Steinmetz B, Ament ME. Double-blind placebo-controlled trial of amitriptyline for the treatment of irritable bowel syndrome in adolescents. J Pediatr 2008;152:685-9.
4. Baştürk A, Artan R, Yılmaz A. Efficacy of synbiotic, probiotic, and prebiotic treatments for irritable bowel syndrome in children: a randomized controlled trial. Turk J Gastroenterol 2016;27:439-43.
5. Bauserman M, Bausserman M, Michail S. The use of *Lactobacillus* GG in irritable bowel syndrome in children: a double-blind randomized control trial. J Pediatr 2005;147:197-201.
6. Bonnert M, Olén O, Lalouni M, Benninga MA, Bottai M, Engelbrektsson J, et al. Internet-delivered cognitive behavior therapy for adolescents with irritable bowel syndrome: a randomized controlled trial. Am J Gastroenterol 2017;112:152-62.
7. Chumpitazi BP, Cope JL, Hollister EB, Tsai CM, McMeans AR, Luna RA, et al. Randomised clinical trial: gut microbiome biomarkers are associated with clinical response to a low FODMAP diet in children with the irritable bowel syndrome. Aliment Pharmacol Ther 2015;42:418-27.
8. Chumpitazi BP, McMeans AR, Vaughan A, Ali A, Orlando S, Elsaadi A, et al. Fructans exacerbate symptoms in a subset of children with irritable bowel syndrome. Clin Gastroenterol Hepatol 2018;16:219-25.e1.
9. Collins BS, Lin HC. Double-blind, placebo-controlled antibiotic treatment study of small intestinal bacterial overgrowth in children with chronic abdominal pain. J Pediatr Gastroenterol Nutr 2011;52:382-6.
10. Dearlove J, Dearlove B, Pearl K, Primavesi R. Dietary lactose and the child with abdominal pain. Br Med J (Clin Res Ed) 1983;286:1936.
11. Di Nardo G, Oliva S, Ferrari F, Mallardo S, Barbara G, Cremon C, et al. Efficacy and tolerability of α-galactosidase in treating gas-related symptoms in children: a randomized, double-blind, placebo controlled trial. BMC Gastroenterol 2013;13:142.
12. Duarte MA, Penna FJ, Andrade EMG, Cancela CSP, Neto JCA, Barbosa TF. Treatment of nonorganic recurrent abdominal pain: cognitive-behavioral family intervention. J Pediatr Gastroenterol Nutr 2006;43:59-64.
13. Eftekhari K, Vahedi Z, Kamali Aghdam M, Noemi Diaz D. A randomized double-blind placebo-controlled trial of lactobacillus reuteri for chronic functional abdominal pain in children. Iran J Pediatr 2015;25:e2616.
14. El Amrousy D, Hassan S, El Ashry H, Yousef M, Hodeib H. Vitamin D supplementation in adolescents with irritable bowel syndrome: is it useful? A randomized controlled trial. Saudi J Gastroenterol 2018;24:109-14.
15. Evans S, Lung KC, Seidman LC, Sternlieb B, Zeltzer LK, Tsao JCI. Iyengar yoga for adolescents and young adults with irritable bowel syndrome. J Pediatr Gastroenterol Nutr 2014;59:244-53.
16. Feldman W, McGrath P, Hodgson C, Ritter H, Shipman RT. The use of dietary fiber in the management of simple, childhood, idiopathic, recurrent, abdominal pain. Results in a prospective, double-blind, randomized, controlled trial. Am J Dis Child 1985;139:1216-8.
17. Francavilla R, Miniello V, Magistà AM, De Canio A, Bucci N, Gagliardi F, et al. A randomized controlled trial of *Lactobacillus* GG in children with functional abdominal pain. Pediatrics 2010;126:e1445-52.
18. Gawrońska A, Dziechciarz P, Horvath A, Szajewska H. A randomized double-blind placebo-controlled trial of *Lactobacillus* GG for abdominal pain disorders in children. Aliment Pharmacol Ther 2007;25:177-84.
19. Giannetti E, Maglione M, Alessandrella A, Strisciuglio C, De Giovanni D, Campanozzi A, et al. A Mixture of 3 Bifidobacteria decreases abdominal pain and improves the quality of life in children with irritable bowel syndrome. J Clin Gastroenterol 2017;51:e5-10.

20. Groß M, Warschburger P. Evaluation of a cognitive-behavioral pain management program for children with chronic abdominal pain: a randomized controlled study. Int J Behav Med 2013;20:434-43.
21. Guandalini S, Magazzù G, Chiaro A, La Balestra V, Di Nardo G, Gopalan S, et al. VSL#3 improves symptoms in children with irritable bowel syndrome: a multicenter, randomized, placebo-controlled, double-blind, crossover study. J Pediatr Gastroenterol Nutr 2010;51:24-30.
22. Gulewitsch MD, Müller J, Hautzinger M, Schlarb AA. Brief hypnotherapeutic-behavioral intervention for functional abdominal pain and irritable bowel syndrome in childhood: a randomized controlled trial. Eur J Pediatr 2013;172:1043-51.
23. Gulewitsch MD, Schlarb AA. Comparison of gut-directed hypnotherapy and unspecific hypnotherapy as self-help format in children and adolescents with functional abdominal pain or irritable bowel syndrome. Eur J Gastroenterol Hepatol 2017;29:1351-60.
24. Heyland K, Friedt M, Buehr P, Braegger CP. No advantage for antibiotic treatment over placebo in Blastocystis hominis-positive children with recurrent abdominal pain. J Pediatr Gastroenterol Nutr 2012;54:677-9.
25. Horvath A, Dziechciarz P, Szajewska H. Glucomannan for abdominal pain-related functional gastrointestinal disorders in children: a randomized trial. World J Gastroenterol 2013;19:3062-8.
26. Humphreys PA, Gevirtz RN. Treatment of recurrent abdominal pain: components analysis of four treatment protocols. J Pediatr Gastroenterol Nutr 2000;31:47-51.
27. Jadrešin O, Hojsak I, Mišak Z, Kekez AJ, Trbojević T, Ivković L, et al. *Lactobacillus reuteri* DSM 17938 in the Treatment of Functional Abdominal Pain in Children: RCT Study. J Pediatr Gastroenterol Nutr 2017;64:925-9.
28. Karabulut GS, Beşer OF, Erginöz E, Kutlu T, Cokuğraş FÇ, Erkan T. The incidence of irritable bowel syndrome in children using the Rome III Criteria and the effect of trimebutine treatment. J Neurogastroenterol Motil 2013;19:90-3.
29. Karunanayake A, Devanarayana NM, de Silva A, Gunawardena S, Rajindrajith S. Randomized controlled clinical trial on value of domperidone in functional abdominal pain in children. J Pediatr Gastroenterol Nutr 2018;66:725-31.
30. Khoshoo V, Armstead C, Landry L. Effect of a laxative with and without tegaserod in adolescents with constipation predominant irritable bowel syndrome. Aliment Pharmacol Ther 2006;23:191-6.
31. Kianifar H, Jafari SA, Kiani M, Ahanchian H, Ghasemi SV, Grover Z, et al. Probiotic for irritable bowel syndrome in pediatric patients: a randomized controlled clinical trial. Electron Physician 2015;7:1255-60.
32. Kline RM, Kline JJ, Di Palma J, Barbero GJ. Enteric-coated, pH-dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children. J Pediatr 2001;138:125-8.
33. Korterink JJ, Ockeloen LE, Hilbink M, Benninga MA, Deckers-Kocken JM. Yoga therapy for abdominal pain-related functional gastrointestinal disorders in children: a randomized controlled trial. J Pediatr Gastroenterol Nutr 2016;63:481-7.
34. Kovacic K, Hainsworth K, Sood M, Chelimsky G, Unteutsch R, Nugent M, et al. Neurostimulation for abdominal pain-related functional gastrointestinal disorders in adolescents: a randomised, double-blind, sham-controlled trial. Lancet Gastroenterol Hepatol 2017;2:727-37.
35. Kuttner L, Chambers CT, Hardial J, Israel DM, Jacobson K, Evans K. A randomized trial of yoga for adolescents with irritable bowel syndrome. Pain Res Manag 2006;11:217-23.
36. Lebenthal E, Rossi TM, Nord KS, Branski D. Recurrent abdominal pain and lactose absorption in children. Pediatrics 1981;67:828-32.
37. Levy RL, Langer SL, Walker LS, Romano JM, Christie DL, Youssef N, et al. Cognitive-behavioral therapy for children with functional abdominal pain and their parents decreases pain and other symptoms. Am J Gastroenterol 2010;105:946-56.
38. Levy RL, Langer SL, van Tilburg MAL, Romano JM, Murphy TB, Walker LS, et al. Brief telephone-delivered cognitive behavioral therapy targeted to parents of children with functional abdominal pain: a randomized controlled trial. Pain 2017;158:618-28.
39. Maragkoudaki M, Chouliaras G, Orel R, Horvath A, Szajewska H, Papadopoulou A. *Lactobacillus reuteri* DSM 17938 and a placebo both significantly reduced symptoms in children with functional abdominal pain. Acta Paediatr 2017;106:1857-62.
40. Narang M, Shah D, Akhtar H. Efficacy and safety of drotaverine hydrochloride in children with recurrent abdominal pain: a randomized placebo controlled trial. Indian Pediatr 2015;52:847-51.
41. Pourmoghaddas Z, Saneian H, Roohafza H, Gholamrezaei A. Mebeverine for pediatric functional abdominal pain: a randomized, placebo-controlled trial. Biomed Res Int 2014;2014:191026.
42. Robins PM, Smith SM, Glutting JJ, Bishop CT. A randomized controlled trial of a cognitive-behavioral family intervention for pediatric recurrent abdominal pain. J Pediatr Psychol 2005;30:397-408.
43. Romano C, Ferrau V, Cavataio F, Iacono G, Spina M, Lionetti E, et al. *Lactobacillus reuteri* in children with functional abdominal pain (FAP). J Paediatr Child Health 2014;50:E68-71.
44. Romano C, Comito D, Famiani A, Calamarà S, Loddo I. Partially hydrolyzed guar gum in pediatric functional abdominal pain. World J Gastroenterol 2013;19:235-40.
45. Roohafza H, Pourmoghaddas Z, Saneian H, Gholamrezaei A. Citalopram for pediatric functional abdominal pain: a randomized, placebo-controlled trial. Neurogastroenterol Motil 2014;26:1642-50.
46. Rutten JMTM, Vlieger AM, Frankenhuis C, George EK, Groeneweg M, Norbruis OF, et al. Home-based hypnotherapy self-exercises vs individual hypnotherapy with a therapist for treatment of pediatric irritable bowel syndrome, functional abdominal pain, or functional abdominal pain syndrome. JAMA Pediatr 2017;171:470-7.
47. Sadeghian M, Farahmand F, Fallahi GH, Abbasi A. Cyproheptadine for the treatment of functional abdominal pain in childhood: a double-blinded randomized placebo-controlled trial. Minerva Pediatr 2008;60:1367-74.
48. Sanders MR, Rebgetz M, Morrison M, Bor W, Gordon A, Dadds M, et al. Cognitive-behavioral treatment of recurrent nonspecific abdominal pain in children: an analysis of generalization, maintenance, and side effects. J Consult Clin Psychol 1989;57:294-300.
49. Sanders MR, Shepherd RW, Cleghorn G, Woolford H. The treatment of recurrent abdominal pain in children: a controlled comparison of cognitive-behavioral family intervention and standard pediatric care. J Consult Clin Psychol 1994;62:306-14.
50. Saneian H, Pourmoghaddas Z, Roohafza H, Gholamrezaei A. Synbiotic containing Bacillus coagulans and fructo-oligosaccharides for functional abdominal pain in children. Gastroenterol Hepatol Bed Bench 2015;8:56-65.
51. Saps M, Youssef N, Miranda A, Nurko S, Hyman P, Cocjin J, et al. Multicenter, randomized, placebo-controlled trial of amitriptyline in children with functional gastrointestinal disorders. Gastroenterology 2009;137:1261-9.
52. Schurman JV, Wu YP, Grayson P, Friesen CA. A pilot study to assess the efficacy of biofeedback-assisted relaxation training as an adjunct treatment for pediatric functional dyspepsia associated with duodenal eosinophilia. J Pediatr Psychol 2010;35:837-47.
53. See MC, Birnbaum AH, Schechter CB, Goldenberg MM, Benkov KJ. Double-blind, placebo-controlled trial of famotidine in children with abdominal pain and dyspepsia: global and quantitative assessment. Dig Dis Sci 2001;46:985-92.
54. Shulman RJ, Hollister EB, Cain K, Czyzewski DI, Self MM, Weidler EM, et al. Psyllium fiber reduces abdominal pain in children with irritable bowel syndrome in a randomized, double-blind trial. Clin Gastroenterol Hepatol 2017;15:712-9.e4.
55. van der Veek SMC, Derkx BHF, Benninga MA, Boer F, de Haan E. Cognitive behavior therapy for pediatric functional abdominal pain: a randomized controlled trial. Pediatrics 2013;132:e1163-72.
56. van Tilburg MAL, Chitkara DK, Palsson OS, Turner M, Blois-Martin N, Ulshen M, et al. Audio-recorded guided imagery treatment reduces functional abdominal pain in children: a pilot study. Pediatrics 2009;124:e890-7.
57. Vlieger AM, Menko-Frankenhuis C, Wolfkamp SCS, Tromp E, Benninga MA. Hypnotherapy for children with functional abdominal

pain or irritable bowel syndrome: a randomized controlled trial. Gastroenterology 2007;133:1430-6.
58. Walker LS, Williams SE, Smith CA, Garber J, Van Slyke DA, Lipani TA. Parent attention versus distraction: impact on symptom complaints by children with and without chronic functional abdominal pain. Pain 2006;122:43-52.
59. Wallander JL, Madan-Swain A, Klapow J, Saeed S. A randomised controlled trial of written self-disclosure for functional recurrent abdominal pain in youth. Psychol Health 2011;26:433-47.
60. Wassom MC, Schurman JV, Friesen CA, Rapoff MA. A pilot study of "Gutstrong" for adolescents with functional gastrointestinal disorders. Clin Pract Pediatr Psychol 2013;1:201-13.
61. Weizman Z, Abu-Abed J, Binsztok M. Lactobacillus reuteri DSM 17938 for the Management of Functional Abdominal Pain in Childhood: A Randomized, Double-Blind, Placebo-Controlled Trial. J Pediatr 2016;174:160-4.e1.
62. Weydert JA, Shapiro DE, Acra SA, Monheim CJ, Chambers AS, Ball TM. Evaluation of guided imagery as treatment for recurrent abdominal pain in children: a randomized controlled trial. BMC Pediatr 2006;6:29.
63. Wirth S, Klodt C, Wintermeyer P, Berrang J, Hensel K, Langer T, et al. Positive or negative fructose breath test results do not predict response to fructose restricted diet in children with recurrent abdominal pain: results from a prospective randomized trial. Klin Pädiatrie 2014;226:268-73.
64. Zybach K, Friesen CA, Schurman JV. Therapeutic effect of melatonin on pediatric functional dyspepsia: a pilot study. World J Gastrointest Pharmacol Ther 2016;7:156-61.

Table V. Non-predefined outcome domains, outcome measures, and measurement instruments used for FAPDs

Outcome domains	Outcome measures	Measurement instruments	Authors	Year
Life impact				
Pain frequency (N = 9 studies)	• Frequency of pain per week	Patient/parental report	Asgarshirazi et al[1]	2015
	• Frequency of pain	Nonvalidated questionnaire	Collins et al[2]	2011
	• Episodes of abdominal pain	Daily score card	Dearlove et al[3]	1983
	• Monthly frequency of pain crises	VAS (50 cm)	Duarte et al[4]	2006
	• Frequency of pain episodes per week	Assessed by researcher	Eftekhari et al[5]	2015
	• Decrease of >50% in frequency of attacks	Stomachache diary	Feldman et al[6]	1985
	• Occurrence of all episodes of abdominal pain per week	Diary	Lebenthal et al[7]	1981
	• Frequency of pain episodes	Nonstructured interview	Sanders et al[8]	1994
	• Abdominal pain frequency	Diary	Wallander et al[9]	2010
Pain intensity (N = 9 studies)	• Severity of pain	NRS (0-10)	Asgarshirazi et al[1]	2015
		Severity of pain scale (1 = excellent, 5 = excellent)	Kline et al[10]	2001
	• Pain crises intensity	VAS (50 cm)	Duarte et al[4]	2006
	• Pain intensity	WBFPS (6 faces)	Eftekhari et al[5]	2015
		VAS (10 cm)	Sanders et al[8]	1994
	• Change in intensity of pain	Stomachache diary (0 = no pain, 5 = so bad that I can't do anything)	Feldman et al[6]	1985
	• Self-reported pain	CPD; VAS (0-7, 0 = total absence of pain, 7 = extreme pain)	Humphreys et al[11]	2000
	• Level of pain	Pain rating scale (0 = no pain, 10 = worst possible pain) + additional faces	Khoshoo et al[12]	2006
	• Total weekly pain intensity score	VAS (10 cm)	Sanders et al[13]	1989
Overall feeling (N = 6 studies)	• Overall symptom improvement	Nonvalidated questionnaire	Collins et al[2]	2011
	• Improvement	Interview: parents were asked if child's symptoms were better, worse or same	Dearlove et al[3]	1983
	• Change in symptoms	Change in symptoms scale (1 = much better, 5 = much worse)	Kline et al[10]	2001
	• Treatment expectancies	Nonvalidated questionnaire	Sanders et al[8]	1994
	• Parent satisfaction	Nonvalidated questionnaire	Sanders et al[8]	1994
	• Global assessment	Nonvalidated question: "since the trial began, have you felt: better/not better/worse"	See et al[14]	2001
	• Global rating	Global rating with 7-point scale ("markedly worse" to "markedly better")	Van Tilburg et al[15]	2009
Functioning (N = 6 studies)	• Impact on daily life	Nonvalidated questionnaire	Collins et al[2]	2011
	• Parental observation of pain	Parents' POR	Humphreys et al[11]	2000
	• School attendance	RSA-1 + 2	Humphreys et al[11]	2000
		Direct school attendance records	Robins et al[16]	2005
		Self-made questionnaire	Van Tilburg et al[15]	2009
	• Functional disability	FDI	Robins et al,[16] Van Tilburg et al[15]	2005 2009
	• Maternal caregiving	7-point Likert scale of different response strategies	Sanders et al[8]	1994
	• Interference with daily activities	Nonstructured interview	Sanders et al[8]	1994
	• Post-interaction between parents and children	Nonvalidated question	Walker et al[17]	2006
Pain combined (N = 6 studies)	• Difference in pain score	Intensity (VAS) + duration (minutes) + frequency/week	Alfvén and Lindstrom[18]	2006
	• Pain index reduction	VAS (0-10) or faces	Heyland et al[19]	2012
	• Abdominal pain	API (frequency, duration, intensity; 6-, 8-, 11-point Likert scales)	Robins et al[16]	2005
	• Quantitative overall score	APS (frequency, severity [9 faces], peptic index)	See et al[14]	2001
	• Abdominal pain score	API frequency + intensity question	Van Tilburg et al[15]	2009
	• Improvement in abdominal pain	GCS	Zybach et al[20]	2016
Psychological health (N = 2 studies)	• Behavioral problems at home	RBPS	Sanders et al[13]	1989
	• Behavioral problems at school	CTRS	Sanders et al[13]	1989
	• Oppositional child behavior	FOS	Sanders et al[13]	1989
	• Child's pain behavior at home	Parental POR	Sanders et al,[13] Sanders et al[8]	1989 1994
	• Child's pain behavior at school	Event record by teacher	Sanders et al[13]	1989

(*continued*)

Table V. Continued

Outcome domains	Outcome measures	Measurement instruments	Authors	Year
	• Children's coping strategies	Child's rating of coping strategies videos, 7-point Likert scale	Sanders et al[8]	1994
	• Psychological adjustment	CBCL	Sanders et al[8]	1994
Pain duration (N = 2 studies)	• Duration of pain in minutes per day	Patient/parental report	Asgarshirazi et al[1]	2015
	• Duration of pain	Nonvalidated questionnaire	Collins et al[2]	2011
Quality of life (N = 2 studies)	• Quality of life	PedsQL	Van Tilburg et al,[15] Wallander et al[9]	2009 2010
Pain location (N = 1 study)	• Location of pain	Nonvalidated questionnaire	Collins et al[2]	2011
Pathophysiological manifestation				
Outcome domain	Outcome measure	Measurement instrument	Source from included studies	
Gastrointestinal symptoms (N = 5 studies)	• Frequency of GI symptoms	VAS (0-10, 0 = absence)	Collins et al[2]	2011
	• Severity of GI symptoms	VAS (0-10, 0 = absence)	Collins et al[2]	2011
	• Episodes of diarrhea	Daily score card	Dearlove et al[3]	1983
	• Episodes of increased flatus	Daily score card	Dearlove et al[3]	1983
	• Frequency of bowel movements/ week	Diary daily	Khoshoo et al[12]	2006
	• Clinical GI symptoms	GSRS	Kline et al[10]	2001
	• GI symptoms in association with abdominal pain episodes	GI symptom index, 5-point Likert scale	Walker et al[17]	2006
General symptoms (N = 3 studies)	• Somatization	CSI	Robins et al,[16] Wallander et al[9]	2005 2010
	• Sleep	Sleep diary + ActiGraph watch (duration + latency)	Zybach et al[20]	2016
Whole body (N = 2 studies)	• Tender points	Somedic (algometer for tender points)	Alfvèn et al[18]	2006
	• Medians of somatic thresholds of pain for 17 body surface areas	Mechanical pressure algometer for somatic Pressure Pain Threshold	Duarte et al[4]	2006
Laboratory results (N = 2 studies)	• Hydrogen and methane concentrations	LBHT	Collins et al[2]	2011
	• Breath hydrogen analysis	Single breath method	Dearlove et al[3]	1983
Lactose tolerance (N = 1 study)	• Glucose determination in blood samples	LTT	Lebenthal et al[7]	1981
Resource use				
Outcome domain	Outcome measure	Measurement instrument	Source from included studies	
Medical use (N = 3 studies)	• Medication use	MR	Humphreys et al[11]	2000
	• Healthcare use	RHCU-F1 + 2	Humphreys et al[11]	2000
		Self-made questionnaire	Van Tilburg et al[15]	2009
	• GI clinic service use count	Review of electronic records	Wallander et al[9]	2010

API, Abdominal Pain Index; *APS*, abdominal pain score; *CBCL*, Child Behavior Checklist; *CPD*, Child's Pain Diary; *CSI*, Child Somatization Inventory; *CTRS*, Conners' Teacher's Rating Scale; *FDI*, Functional Disability Index; *FOS*, Familial Observational Schedule; *GCRS*, Gastrointestinal Symptom Rating Scale; *GCS*, Global Clinical Score; *GI*, gastrointestinal; *LBHT*, lactulose breath hydrogen test; *LTT*, lactose tolerance test; *MR*, medication record; *NRS*, Numeric Rating Scale; *PedsQL*, Pediatric Quality of Life Inventory; *POR*, pain observation record; *RBPS*, Revised Behavior Problem Checklist; *RHCU-F1 + 2*, Record of Health Care Utilization, Form 1 + 2; *RSA-1 + 2*, Record of School Attendance, Forms 1 + 2; *VAS*, visual analog scale; *WBFPS*, Wong Baker Faces Pain Scale.

References

1. Asgarshirazi M, Shariat M, Dalili H. Comparison of the effects of pH-dependent peppermint oil and synbiotic lactol (*Bacillus coagulans* + fructooligosaccharides) on childhood functional abdominal pain: a randomized placebo-controlled study. Iran Red Crescent Med J 2015;17:e23844.
2. Collins BS, Lin HC. Double-blind, placebo-controlled antibiotic treatment study of small intestinal bacterial overgrowth in children with chronic abdominal pain. J Pediatr Gastroenterol Nutr 2011;52:382-6.
3. Dearlove J, Dearlove B, Pearl K, Primavesi R. Dietary lactose and the child with abdominal pain. Br Med J (Clin Res Ed) 1983;286:1936.
4. Duarte MA, Penna FJ, Andrade EMG, Cancela CSP, Neto JCA, Barbosa TF. Treatment of nonorganic recurrent abdominal pain: cognitive-behavioral family intervention. J Pediatr Gastroenterol Nutr 2006;43:59-64.
5. Eftekhari K, Vahedi Z, Kamali Aghdam M, Noemi Diaz D. A randomized double-blind placebo-controlled trial of lactobacillus reuteri for chronic functional abdominal pain in children. Iran J Pediatr 2015;25:e2616.
6. Feldman W, McGrath P, Hodgson C, Ritter H, Shipman RT. The use of dietary fiber in the management of simple, childhood, idiopathic, recurrent, abdominal pain. Results in a prospective, double-blind, randomized, controlled trial. Am J Dis Child 1985;139:1216-8.
7. Lebenthal E, Rossi TM, Nord KS, Branski D. Recurrent abdominal pain and lactose absorption in children. Pediatrics 1981;67:828-32.
8. Sanders MR, Shepherd RW, Cleghorn G, Woolford H. The treatment of recurrent abdominal pain in children: a controlled comparison of cognitive-behavioral family intervention and standard pediatric care. J Consult Clin Psychol 1994;62:306-14.
9. Wallander JL, Madan-Swain A, Klapow J, Saeed S. A randomised controlled trial of written self-disclosure for functional recurrent abdominal pain in youth. Psychol Health 2011;26:433-47.
10. Kline RM, Kline JJ, Di Palma J, Barbero GJ. Enteric-coated, pH-dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children. J Pediatr 2001;138:125-8.
11. Humphreys PA, Gevirtz RN. Treatment of recurrent abdominal pain: components analysis of four treatment protocols. J Pediatr Gastroenterol Nutr 2000;31:47-51.
12. Khoshoo V, Armstead C, Landry L. Effect of a laxative with and without tegaserod in adolescents with constipation predominant irritable bowel syndrome. Aliment Pharmacol Ther 2006;23:191-6.
13. Sanders MR, Rebgetz M, Morrison M, Bor W, Gordon A, Dadds M, et al. Cognitive-behavioral treatment of recurrent nonspecific abdominal pain in children: an analysis of generalization, maintenance, and side effects. J Consult Clin Psychol 1989;57:294-300.

14. See MC, Birnbaum AH, Schechter CB, Goldenberg MM, Benkov KJ. Double-blind, placebo-controlled trial of famotidine in children with abdominal pain and dyspepsia: global and quantitative assessment. Dig Dis Sci 2001;46:985-92.
15. van Tilburg MAL, Chitkara DK, Palsson OS, Turner M, Blois-Martin N, Ulshen M, et al. Audio-recorded guided imagery treatment reduces functional abdominal pain in children: a pilot study. Pediatrics 2009;124:e890-7.
16. Robins PM, Smith SM, Glutting JJ, Bishop CT. A randomized controlled trial of a cognitive-behavioral family intervention for pediatric recurrent abdominal pain. J Pediatr Psychol 2005;30:397-408.
17. Walker LS, Williams SE, Smith CA, Garber J, Van Slyke DA, Lipani TA. Parent attention versus distraction: impact on symptom complaints by children with and without chronic functional abdominal pain. Pain 2006;122:43-52.
18. Alfvén G, Lindstrom A. A new method for the treatment of recurrent abdominal pain of prolonged negative stress origin. Acta Paediatr 2007;96:76-81.
19. Heyland K, Friedt M, Buehr P, Braegger CP. No advantage for antibiotic treatment over placebo in Blastocystis hominis-positive children with recurrent abdominal pain. J Pediatr Gastroenterol Nutr 2012;54:677-9.
20. Zybach K, Friesen CA, Schurman JV. Therapeutic effect of melatonin on pediatric functional dyspepsia: a pilot study. World J Gastrointest Pharmacol Ther 2016;7:156-61.