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REVIEW ARTICLE

The Management of Paediatric Functional Abdominal Pain Disorders: Latest Evidence

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Abstract Recurrent abdominal pain (RAP) is one of the most common health complaints in both children and adults. Although RAP is considered a functional disorder rather than an organic disease, affected children and their families can still experience anxiety and concerns that can interfere with school, sports, and regular daily activities and lead to frequent attendances at pediatric emergency departments or pediatric gastroenterology clinics. Our review shows experts do not agree on a universally proven management that will work on every child presenting with functional abdominal pain (FAP). Treatment strategies include both non-pharmacological and pharmacological options. Non-pharmacological treatments are usually very well accepted by both children and their parents and are free from medication side effects. Nevertheless, they may be as effective as the pharmacological interventions; therefore, according to many experts and based on the majority of current evidence, a non-pharmacological approach should be the first intervention attempt in children with RAP. In particular, the importance of the bio-psychosocial approach is highlighted, as a majority of children will improve with counselling and reassurance that no serious organic pathologies are suspected, especially when the physician establishes a trustful relationship with both the child and their family. Placebo and pharmacological interventions could be attempted when the bio-psychosocial approach is not applicable or not efficacious. In some difficult cases, finding an effective treatment for FAP can be a challenge, and a number of strategies may need to be tried before symptoms are controlled. In these cases, a multidisciplinary team, comprising a pediatric gastroenterologist, dietician, psychologist, and psychotherapist, is likely to be successful.

Key Points

Recurrent abdominal pain (RAP) is one of the most common health complaints in both children and adults.

There is no agreement among experts on a universally proven management that will work on every child presenting with RAP.

An effective treatment for functional abdominal pain can be a challenge, and a number of strategies may need to be tried before symptoms are controlled; in some cases, only a multidisciplinary approach is likely to be successful.

1 Introduction

Recurrent abdominal pain (RAP) is one of the most common health complaints in both children and adults. In the majority of cases, RAP represents a non-severe chronic medical condition that is not associated with a properly defined pathology of the gastrointestinal tract and that is characterized by intermittent abdominal pain associated with variety of symptoms that include distension, bloating,

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an irregular number of daily bowel movements (i.e., varying from constipation to the opposite and diarrhea), nausea or vomiting, lack of appetite or precocious stomach fullness, tiredness, and a general feeling of unhappiness [1]. When RAP is not associated with a detectable organic issue or pathology, this medical condition can be renamed functional abdominal pain syndrome (FAPS) or, better, according to the recent European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Rome IV criteria, functional abdominal pain disorders (FAPDs) [2]. Although RAP is considered a functional disorder rather than an organic disease, affected children and their families can still experience anxiety and concerns that can interfere with school, sports, and regular daily activities and lead to frequent attendances at pediatric emergency departments or pediatric gastroenterology clinics.

Historically, RAP syndrome was described for the first time in 1958 by Apley and colleagues in a group of scholar students [2, 3]; despite nearly 50 years of scientific efforts aiming to clarify etiopathogenic ambiguities and possible treatments, the management of this syndrome remains a time-consuming and frustrating clinical challenge for most physicians and gastroenterologists. We reviewed the recognized and recent medical literature on RAP in pediatric patients with the aim of disclosing and summarizing the current best management options for this common medical condition. We analysed a selection of recent and relevant scientific contributions on the management of FAP in pediatric patients. The following keywords were used to search among the world medical library collections (MEDLINE, Embase, Cochrane, and Cinahl): abdominal pain-related functional gastrointestinal disorders, functional abdominal pain disorders, functional gastro-intestinal disorders, recurrent abdominal pain, functional dyspepsia, irritable bowel syndrome, and FAPD. Preference for the inclusion of studies was given to recent scientific contributions, official medical society guidelines, and reviews over randomized controlled trials (RCTs) and evidence-based medicine. We focused our search on the "non-pharmacological," "pharmacological," and "placebo" treatment of the functional abdominal pain of children aged 2–18 years, and we covered the period 1 January 2005 to 30 October 2017.

2 Definitions

The proper definition of RAP is the presence of three or more episodes of abdominal pain over a period of at least 3 months that are sufficiently severe to affect daily activities. Moreover, RAP is a term that, from a strict definition should include both organic and non-organic (i.e., functional) causes of chronic abdominal pain, whereas other terms such as FAPS or FAPDs must be representative of a chronic RAP that is not due to an organic, structural, or metabolic disease, as far as can be detected by common examinations [3]. However, as only very few cases of RAP are related to a defined organic pathology, RAP is a term that is often used as a synonym of FAPS or FAPDs. In addition, in clinical practice, most physicians will consider a diagnosis of RAP for any intermittent and relapsing abdominal pain that exceeds 1 or 2 months in duration.

Functional gastrointestinal disorders (FGIDs) is a term that is commonly used interchangeably with FAPS or FAPDs but, according to the recent Rome IV criteria, should be used to group all the chronic gastrointestinal issues of uncertain origin, including dyspepsia, cyclic vomiting, and others, as presented in Table 1. FAPDs represent a subgroup of FGIDs that includes four defined diagnoses: functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine (AM), and functional abdominal pain—not otherwise specified (FAP-NOS) [4]. Although not included in the FGIDs group, chronic abdominal wall pain (CAWP) is another kind of long-term, intermittent, abdominal pain in which the pain arises from the abdominal wall rather than from visceral organs, with minimal or no relationship to food intake or defecation [5].

3 Diagnosis

The diagnosis and proper sub-classification of FGIDs is mostly clinical and based on the Rome IV criteria (Table 2). According to the most recent criteria, FAP can generally be clinically diagnosed (i.e., without the requirement of additional diagnostic aids) [6] when the

Table 1 Functional gastrointestinal disorders: children and adolescents

H1. Functional nausea and vomiting disorders
H1a. Cyclic vomiting syndrome
H1b. Functional nausea and functional vomiting
H1c. Rumination syndrome
H1d. Aerophagia
H2. Functional abdominal pain disorders
H2a. Functional dyspepsia
H2b. Irritable bowel syndrome
H2c. Abdominal migraine
H2d. Functional abdominal pain—not otherwise specified
H3. Functional defecation disorders
H3a. Functional constipation
H3b. Non-retentive fecal incontinence

Table 2 Diagnostic criteria for different groups of abdominal pain-related functional gastrointestinal disorders

Functional dyspepsia
Functional dyspepsia has been defined by the Rome IV criteria and must include one or more of the following bothersome symptoms at least 4 days per month for at least 2 months before the diagnosis is made:
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
IBS
IBS has been defined by the Rome IV criteria, and all these must be fulfilled for at least 2 months before a diagnosis of IBS can be made:
1. Abdominal pain at least 4 days per month associated with one 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
Abdominal migraine
The Rome IV criteria have specified certain characteristics for the diagnosis of abdominal migraine, and all these criteria should be fulfilled at least twice in the preceding 6 months:
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 two or more of the following:
a. Anorexia
b. Nausea
c. Vomiting
d. Headache
e. Photophobia
f. Pallor
6. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition
Functional abdominal pain—not otherwise specified epidemiology
This has been described in the Rome IV criteria for FGIDs and is characterized by a set of criteria, all of which should be fulfilled at least four times per month for at least 2 months before a diagnosis is made:
1. Episodic or continuous abdominal pain that does not occur solely during physiologic events (e.g., 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

*FGID*s functional gastrointestinal disorders, *IBS* irritable bowel syndrome, *RAP* recurrent abdominal pain

physical examination of the child is overall normal and there are no alarming signs or symptoms. Compared with the Rome III criteria, a relatively new concept is that physicians no longer need to virtually exclude all the other organic causes of abdominal pain before making the diagnosis of FGIDs. Thus, in the new diagnostic criteria for each different group of FGIDs, the previous sentence "no evidence for organic disease" is replaced with the new "after appropriate medical evaluation the symptoms cannot be attributed to another medical condition" (see Table 2).

In diagnosing FAP, then, according to the new ESPGHAN guidelines, physicians are not obliged to perform numerous medical exams to virtually exclude any organic cause of abdominal pain but can choose to narrow the exams down to a few select tests and finally make the diagnosis. The cornerstone of the diagnosis is an accurate anamnesis: a detailed history about the abdominal pain and any other associated symptoms, including onset, duration, frequency, site, characteristics, and triggering or relieving factors [4]. Laboratory tests and radiological investigations

are generally not mandatory for the diagnosis of FAP; they should be considered whenever concerns of an organic pathology must be ruled out or when, during the physical examination of the child, the physician recognizes some of the "red flag" signs. It is important to underline that sometimes FGIDs can coexist with other organic or other pathological medical conditions [7, 8]; therefore, in ambiguous cases or when concerns about IBS or other underlying gastrointestinal diseases arise, children should be referred to a pediatric gastroenterologist for further investigation.

4 Management

The review of the current literature on RAP does not highlight a unique effective strategy to treat the symptoms of this peculiar condition. The most important step is to make an absolutely correct diagnosis. If specific causes for the pain are discovered, then the management is specific and directed to treat them. When no organic causes and no alarming signs are found, the abdominal pain is then named functional pain (i.e., FAPS), but this does not mean the child does not need medical treatment to relieve symptoms. Children with FAPS frequently report significant limitations to life activities and may also manifest distinct psychopathologies, including depression, anxiety, and somatoform disorders. Moreover, parents of affected children are often very worried and obsessively seek health advice or painkiller prescriptions.

As a specific cure is not possible, children with FAP should be evaluated and treated in a manner that includes a bio-psychosocial approach, thus engaging in a therapeutic patient–physician partnership. Proper communication between the physician and both the child and their parents become mandatory to reassure that no serious underlying diseases exist but that the abdominal pain is fully recognized and accepted as a real disorder by the physician rather than being considered something that is "just in the head". Sometimes, the mere acceptance of this psychosocial point of view of the illness could help greatly in the resolution of the functional abdominal pain.

The treatment options can be classified as non-pharmacological, placebo, or pharmacological. Any therapeutic interventions should aim to reduce suffering and improve overall quality of life (QOL). The primary goal is to achieve complete remission of the symptoms; if this is not possible, then the abdominal pain and its exacerbated episodes should be minimized.

Different aspects of behavioral habits of affected children, such as specific diet, gut microbiota, defecation pattern, stress, and psychosocial aspects of the illness, may represent targets of treatment on a case-by-case basis.

4.1 Non-Pharmacological Treatment Strategies

Non-pharmacological therapies include (1) dietary modification, (2) probiotic supplementation, and (3) bio-psychosocial intervention.

4.1.1 Dietary Interventions

Modification of the diet is one of the most commonly used strategies to approach a child with FGIDs and is usually happily accepted by both children and parents. Dietary intervention may involve excluding or reducing a specific ingredient or a group of foods from the diet, such as lactose; fructose; dairy products; fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs); and gluten, or even increasing the daily intake of other foods, such as fiber-rich food and water.

Despite the very high number of possible dietary arrangement interventions, only a few large and concrete studies have investigated the role of diet in children with FGIDs. In summary, the current literature does not highlight concrete long-term effectiveness for reducing abdominal pain frequency and intensity, but in clinical practice, dietary interventions are often tried, and some children may truly benefit from excluding certain ingredients, especially when food allergies or intolerances are suspected or ascertained.

Despite that various dietary intervention strategies have been successfully tested, data are not consistent enough to definitively recommend a specific diet regimen for children with FAPS.

4.1.1.1 Lactose and Fructose Lactose and fructose are considered substrates for bacterial fermentation and gas production [9]. Malabsorption and intolerance to these carbohydrates may therefore cause bloating and osmotic diarrhea, thus resulting in abdominal pain.

Several authors have reported an association between FGIDs and abnormal lactase activity [10, 11]. However, a series of studies investigating a lactose-containing diet compared with a lactose-free diet in children with FGID proved that, in most of the cases, a diet without lactose was not helpful, even in children with a positive hydrogen breath test (HBT) [4].

Two prospective studies identified fructose malabsorption as a frequent cause of FAPD in children with unexplained chronic abdominal pain and positive HBT. In 2012, Wintermeyer et al. [12] observed that abdominal pain in 75 children aged 3–14 years resolved or greatly improved after following a fructose-restricted diet for 4 weeks. Escobar et al. [13] confirmed the positive effect of a fructose-free diet on 222 children in 2014. Specifically, the conclusions of this trial were that fructose intolerance was

present in 54% of the 222 children and that 76.9% of them reported the resolution of symptoms by adhering to a low-fructose diet ($p < 0.0001$). Interestingly, in the same study, 55 of 101 patients (54.4%) with negative HBT reported resolution of symptoms without a low-fructose diet ($p = 0.37$) [13]. Moreover, Wirth et al. [14] published a prospective blinded randomized intervention trial in 103 children in 2014, demonstrating that a fructose-restricted diet was efficacious in diminishing abdominal pain intensity and frequency, regardless of the result of the HBT.

4.1.1.2 FODMAPs In addition to lactose and fructose, many other short-chain carbohydrates, grouped under the acronym FODMAPs, are believed to be poorly absorbed in the intestine and therefore considered a possible target for dietary intervention in children with FGIDs. The typical low-FODMAP diet is a two-phased intervention that consists of a 2- to 6-week complete elimination of all slowly absorbed or indigestible short-chain carbohydrates, followed by—if symptoms have decreased substantially—a structured reintroduction of specific FODMAPs, according to tolerance [1]. However, the efficacy of a low-FODMAP diet is well-established, but the success of maintaining this regimen for the long term, as for other similar dietary intervention, remains controversial and is currently under investigation [15].

Wheat is also considered to possibly induce bloating, changes in bowel habits, and abdominal pain. In non-celiac children, mechanisms involved in wheat-associated clinical effects could be the malabsorption of wheat carbohydrates and wheat proteins, such as FODMAPs and gluten, respectively. Non-celiac children and adults with unexplained abdominal pain who benefit from a gluten-free diet are often referred to as having a relatively new and still-controversial diagnosis of "gluten sensitivity". We found no relevant studies that specifically tested the efficacy of a gluten-free diet compared with a low-FODMAP diet in non-celiac children with FGIDs.

4.1.1.3 Elimination of Foods and Drugs Another example of a possibly useful dietary intervention is the elimination of foods and drugs that specifically are known to be avoided when gastro-oesophageal reflux and gastritis are suspected. Chocolate, caffeine, spicy and fatty foods; nitrite- and amine-containing foods; and non-steroidal anti-inflammatory drugs may trigger abdominal symptoms in children with FAPS. Several observational studies have proven the beneficial effects of avoiding these foods and drugs [16, 17].

4.1.1.4 Fiber The importance of the amount of fiber in the diet of children with FAPS is also controversial. A randomized, double-blind pilot study in 60 children (aged 8–16 years) with FAP demonstrated that a particular type of fiber, called partially hydrolyzed guar gum (PHGG), may have beneficial effects on symptom control. The mechanisms involved seem to be modulation of the intestinal microbiota, similar to prebiotics, and normalization of stool frequency [18]. Other small studies have demonstrated that a daily fiber intake below the minimum recommended value is possibly linked with RAP [19]. In contrast, a systematic review of the published RCTs on the effect of dietary fibers in children with FAP showed a lack of evidence that a fiber-enriched diet could greatly help relieve FGID-related pain [20]. Finally, the 2017 updated Cochrane review on dietary intervention for RAP in childhood reported that children treated with fiber-based interventions did not experience a great improvement in pain at 3 months post-intervention compared with children receiving placebo (odds ratio [OR] 1.83; 95% confidence interval [CI] 0.92–3.65; two studies; 136 children) [21].

4.1.2 Probiotics Supplementation

The human microbiota is estimated to be composed of more than 1×10^{14} bacterial cells, ten times the number of human cells. The majority of the human microbiota lives inside the gastrointestinal tract, and several lines of evidence indicate that our intestinal microbes carry out the following very important functions: (1) enhancing gut barrier function; (2) inhibiting pathogen binding by binding themselves to small- and large-bowel epithelium and producing substances that inhibit the growth of other pathogenic organisms; (3) modulating the gut inflammatory response by modulating the gastrointestinal lumen towards an anti-inflammatory state [22]; (4) reducing visceral hypersensitivity associated with both inflammation and psychological stress [23]; and (5) altering colonic fermentation by converting undigested carbohydrates into short-chain fatty acids and improving gut function.

Numerous studies have suggested a strong association between modification of the intestinal microbiota and IBS, constipation, diarrhea, and FAP [9, 24, 25]. Over time, several different strains of probiotics have been tested as potential treatments for children with FGID, with the most commonly used being Lactobacilli and Bifidobacteria. In 2010, a daily dose of a probiotic prepared with strains of *Escherichia coli* administered to 203 children aged 4–18 years with chronic IBS resulted in a significant improvement of symptoms [26]. Saneian et al. [27] successfully tested the effectiveness of a symbiotic preparation versus placebo in 88 children. Specifically, 45 children treated with a combination of *Bacillus coagulans* and prebiotics reported a higher response rate than the 43 children receiving placebo (60 vs. 39.5%; $p = 0.044$), but the authors noticed that the positive effects were not long

lasting; after 12 weeks, the response rate was similar between the two groups (64.4 vs. 53.4%; $p = 0.204$) [27]. In 2011, Horvath et al. [28] published a meta-analysis regarding the effects of *Lactobacillus rhamnosus* GG (LGG) as a treatment for children with abdominal pain-related functional gastrointestinal disorders based on the Rome II or Rome III criteria. They reported that, compared with placebo, LGG supplementation was associated with a higher response rate in children with an IBS diagnosis but that no change in pain intensity/severity was found among children with FAP. In 2017, Giannetti et al. [29] conducted an Italian randomized, double-blind, crossover trial in 48 children with IBS and 25 with functional pain and reported similar conclusions. When compared with placebo, the mixture of three Bifidobacteria, (*Bifidobacterium infantis* M-63, *B. breve* M-16V, and *B. longum* BB536) proved useful in diminishing abdominal pain in children with IBS ($p = 0.006$) but not in children with FAP [29]. Another Italian randomized, double-blind, placebo-controlled trial in 60 children (aged 6–16 years) with FAP reported significant lowering of the intensity of abdominal pain in children treated for 4 weeks with *Lactobacillus reuteri* DSM 17938 [30]. Other RCTs with *L. reuteri* DSM 17938 confirmed possible positive effects of this particular strain of probiotics [31, 32]. Guandalini et al. [33] conducted an RCT and reported that another type of probiotic strain mixture (*Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus bulgaricus*, *B. breve, B. longum, B. infantis*, and *Streptococcus thermophilus*) proved useful in children and adolescents with IBS.

In summary, although evidence supporting the use of probiotics as a first-line treatment in children with FAPDs is not yet strong, interest regarding their use in clinical practice is increasing. Probiotics have been demonstrated to be safe and should be considered a possible therapy for FAPD, especially in children with suspected IBS or when symptoms have been triggered following an episode of gastroenteritis or after an antibiotic course [27].

4.1.3 Bio-Psychosocial Modifying Therapies

Hypnotherapy acts by normalizing altered visceral sensation, reducing colonic contractions, and reversing patients' negative thoughts about their condition. In gut-directed hypnotherapy, trained therapists induce a hypnotic state, and the child is guided to respond to suggestions towards control and normalization of gut functioning, stress reduction, and ego strengthening. Various studies have demonstrated the beneficial effect of hypnotherapy in children with FAPD, which persists for up to 5 years after the completion of therapy [34, 35].

A recent systematic review including three RCTs evaluating hypnotherapy to control symptoms found that one trial reported statistically significant improvement in QOL and two trials reported improvement in school attendance; the benefit was persistent even 1 year after the completion of therapy. The authors of the review found hypnotherapy to be superior to standard medical care and recommended it as first-line therapy in the management of children with FAPD [36]. The latest and largest study was an RCT in 250 children aged 8–18 years. In this study, patients were randomly allocated to hypnotherapy performed by a therapist (iHT group) or home-based hypnotherapy with exercises on audio CD (CD group). The author confirmed the usefulness of hypnotherapy in children with IBS and FAPD and observed a significant improvement in QOL and pain beliefs [37].

Several RCTs have demonstrated the effectiveness of psychological therapies, particularly cognitive behavioral therapy (CBT), for pediatric FAPD. CBT demonstrates its psychotherapeutic effect by addressing dysfunctional emotions, maladaptive behaviors, and cognitive processes and contents through a number of goal-oriented, explicit systematic procedures [38–40]. Behavioral procedures include the identification of verbal and non-verbal pain behavior and how family members, teachers, and caregivers react to it and are addressed by interventions such as physical exercise to promote relaxation, breathing exercises, and muscle relaxation techniques taught by trained therapists. Cognitive procedures may include stopping thoughts related to pain and replacing negative thoughts with positive ones; distracting oneself when pain arises (i.e., watching television or playing games, doing mental arithmetic); and using imagination to encourage the child to think about pleasant things when confronted with pain. The most recent RCT, based on a prospective, longitudinal trial in children and their parents, investigated the use of social learning and CBT, whether in person or by phone, and phone-based education and support. There were no results in regard to pain symptoms or QOL, but the social learning CBT showed that this method was capable of improving outcomes by changing the parental responses to children's pain [41]. These results are in line with another study specifically addressing the mothers of children with FAP: A group of these children was treated with CBT, and the waiting list was used as the control group. The intervention group improved significantly in the management of children's symptoms [42]. Yoga could be considered a particular type of CBT; in some studies, yoga resulted in a significant reduction in pain intensity in children with FAP and IBS [43]. Although the evidence is not yet strong enough to recommend yoga as a treatment, it can nonetheless be utilized together with standard medical care when requested, as it is not at all harmful.

In summary, CBT could be a potential tool in children with FAPD, but the evidence remains weak, and the need for multiple sessions and the scarce availability of therapists mean this therapy is more difficult to fulfil.

Acupuncture is another possible strategy that has been evaluated. In particular, a Korean study of 40 children observed that pain intensity and the requirement for medication were significantly reduced in children who received acupuncture therapy ($n = 20$) for RAP compared with the control group ($n = 20$) [44].

Children with CAWP may benefit from physiotherapy, as described in an observational study from the UK in which 42 of 49 children (85%) aged 6–16 years showed improvement following physiotherapy. The beneficial effect is likely due to correction of the eccentric use of abdominal muscles and their retraining (work concentrically provides better support with less effort). Another study [45] in 35 children with RAP found treatment with a combination of somatic and psychological methods was effective in reducing pain and tender points scores compared with physiotherapy alone or a combination of physiotherapy and psychological treatment.

In conclusion, bio-psychosocial-modifying therapies seem to be an effective treatment strategy in children and adolescents with RAP.

4.2 Pharmacological Treatment

Several studies have been performed over time to test the efficacy of different pharmacological drugs in the treatment of FAPD. The results have been contradictory and doubtful: Some studies confirmed the efficacy of specific molecules, whereas others denied their efficacy. Moreover, many studies were of very low quality because they had either small populations or methodological flaws. On the other hand, pharmacodynamic elements to better clarify the rational use of the different molecules in FADP treatment are lacking.

The most recent review on this argument extrapolated no convincing data on the use of drugs to treat RAP in children [46]. The review selected 16 studies with a total of 1024 children and assessing the efficacy and safety of several treatments. Here, we discuss and update the latest results regarding the main treatments evaluated.

4.2.1 Antispasmodics

This category includes several drugs that decrease gut contraction through different mechanisms of action.

Peppermint oil has been tested in adult patients with IBS. Its proven efficacy is due to its menthol component, which blocks Ca^{2+} channels, possibly reducing colonic spasms. Few studies have been performed in children. Kline et al. [47] performed a double-blind RCT in 50 children aged 8–17 years with IBS. These children were treated for 2 weeks with peppermint oil or placebo and then evaluated for pain severity, changes in symptoms, and side effects. At the end of the trial, a significant improvement was reported in children receiving peppermint oil, in both the severity of symptom scale (76% with peppermint oil vs. 19% with placebo) and the change of symptoms scale (71% with peppermint oil vs. 43% with placebo). No side effects were reported. Asgarshirazi et al. [48] compared the effects of peppermint oil, a synbiotic Lactol (*Bacillus coagulans* + fructooligosaccharide), and placebo in a three-arm RCT including 120 children treated for 4 weeks. Pain duration and frequency were more decreased in the peppermint oil and Lactol groups than in the placebo group. Furthermore, pain severity decreased more in the peppermint oil group than in the Lactol group. No other studies have assessed the efficacy and safety of peppermint oil in the treatment of FAPD.

Narang et al. [49] tested drotaverine, a selective phosphodiesterase-4 inhibitor, versus placebo in 132 children with RAP for 4 weeks. Episodes of abdominal pain were significantly reduced in children receiving drotaverine compared with those receiving placebo; the authors reported no results for pain severity.

Mebeverine is a beta-phenylethylamine derivative of reserpine that has relatively specific action on smooth muscle cells and directly blocks voltage-operated sodium channels and inhibits intracellular calcium accumulation [50]. Pourmoghaddas et al. [51] evaluated this musculotropic spasmolytic effect on smooth muscle spasms of the gastrointestinal tract. In this first randomized placebo-controlled trial, 115 children were treated with mebeverine or placebo; the authors reported a relatively higher treatment response rate with mebeverine after 4 and 8 weeks of therapy; however, the differences were not statistically significant.

Karabulut et al. [52] reported a significant benefit from the use of trimebutine in children with IBS, but results were assessed by asking the parents rather than the children. Moreover, the study was neither blinded nor placebo controlled [52]. The only other study to report the use of trimebutine in children was that by Giannetti et al. [53], but the number of patients treated with trimebutine was too low, and the study itself did not aim to assess the efficacy of pharmacological treatment.

4.2.2 Antidepressants

RAP has been recognized as being associated with depressive disorders and more so with anxiety disorders. It can indeed coexist with one or both of these disorders or can predict their emergence in adult life. For this reason,

antidepressant drugs have been tested as a possible treatment. Amitriptyline has proven efficacious in adults with IBS and FD. In low doses, amitriptyline is believed to work primarily by inducing pain tolerance through central or peripheral antinociceptive properties and anticholinergic effects. Its efficacy was evaluated in a total of 123 children in two double-blind randomized placebo-controlled trials. Bahar et al. [54] conducted a study with a duration of treatment of 8 weeks; the primary outcome measure was improvement of overall QOL, evaluated with a questionnaire. At baseline, differences in mean QOL scores between the two groups were borderline significant. Immediately and 3 weeks after treatment, significantly more children in the amitriptyline group reported at least a 15% improvement in QOL scores on almost all IBS-associated symptoms; however, interference with daily life and pain frequency and intensity did not differ between groups. No adverse effects were reported. In the study by Saps et al. [55], the treatment lasted for 4 weeks, and the primary outcome was an overall assessment of satisfactory relief and satisfaction with treatment. At the end of the trial, there was no significative difference between the amitriptyline and placebo groups, both in results and in adverse effects. Thus, the therapeutic effects of amitriptyline demonstrated in adults are not confirmed in children. The results of the study by Bahar et al. [54] are still in fact limited because the baseline scores were already substantially higher in the placebo group, and the absolute mean QOL scores after treatment did not differ significantly. It is conceivable that the dose used in children (10–30 mg) was too low to be effective compared with the 75 mg used in adults with IBS. Moreover, a higher placebo success rate in children with IBS (53%) compared with adults with the same condition (40%) may explain the lack of significant difference in favor of the drug.

Citalopram was tested in a 12-week, flexible-dose open-label trial in 25 children and adolescents with RAP. The study showed good results, in terms of both tolerance (the drug was generally well tolerated) and effectiveness (84% of the patients were classified as responders), so citalopram was considered a promising treatment for pediatric FAPD [56]. These results were not confirmed by Roohafza et al. [57], who compared the drug with placebo in 115 children with FAP. In this study, there was no difference in the response rate at 4 and 12 weeks post-intervention, but there were more side effects in the treatment group than in the placebo group.

4.2.3 Antihistaminic Agents

Cyproheptadine is thought to act by blocking calcium channels and by having an antiserotonin effect and has been successfully applied for migraine. Sadeghian et al. [58] tested the effects of cyproheptadine in a double-blind placebo-controlled trial in children with FAP. The primary outcome was self-reported change in frequency and intensity of abdominal pain; the global assessment of improvement was also measured. After 2 weeks of treatment, cyproheptadine proved superior to placebo in reducing/resolving pain, both in frequency (86.7% of children receiving cyproheptadine vs. 35.7% receiving placebo) and in intensity (86.7 vs. 28.6%). The global assessment of improvement reported by children was significantly better in the cyproheptadine group than in the placebo group (86.7 vs. 35.7%). Nonetheless, the results should be interpreted cautiously because of the very low methodological quality, the use of non-validated questionnaires, and the limited follow-up of 2 weeks. The retrospective open-label study by Rodriguez et al. [59] in 80 children with dyspeptic symptoms (caused either by organic pathologies or by FD) demonstrated a response to treatment in 55% of patients and the presence of side effects—all mild—in 30%. Madani et al. [60] retrospectively evaluated the effect of cyproheptadine in patients with abdominal pain-related functional gastrointestinal disorders (AP-FGIDs) over 7 years. Cyproheptadine proved efficacious in 110/151 patients (73%) and safe in 102/151 (68%). Adverse effects, the most important of which were sleepiness and weight gain, were more likely to occur in non-responders. Remarkably, the authors reported body mass index (BMI) as the single best predictor of clinical improvement. Krasaelap and Madani [61] recently reviewed the studies conducted to date on the use of cyproheptadine and confirmed its efficacy. They concluded that cyproheptadine could indeed be classified as an etiological treatment given that the latest studies showed that 5-HT alterations in the gut may be responsible for dysmotility and visceral hypersensitivity [61].

4.2.4 Antireflux Agents

A study by See et al. [62] included 25 children aged 5–18 years with RAP (according to the Apley criteria) and dyspeptic symptoms (such as epigastric pain, pain before and after eating, chest pain, nausea, vomiting, and loss of appetite). Children were randomly assigned to a 3-week-long treatment (treatment period 1) with famotidine or placebo administered twice daily. If symptoms persisted at the end of treatment period 1, crossover occurred directly afterward and continued for another 3 weeks (treatment period 2); patients who improved after treatment period 1 underwent crossover only in the case of symptom recurrence and persistence for 3 weeks. The aim was to assess modifications in abdominal pain (frequency, severity, peptic symptoms) and global improvement. No significant difference in abdominal pain score was shown between

both groups, whereas global improvement was significantly higher in the famotidine group (66.7 vs. 15.4% with placebo).

4.2.5 Calcium-Channel Blockers

Flunarizine is a calcium-channel blocker with anti-H1 effects and is currently used in the prophylaxis of migraine in both adults and children. It was evaluated as a prophylaxis in a trial in children with AM. The trial included ten children and demonstrated a reduction in both the frequency and the duration of AM attacks [63]. Boccia et al. [64] confirmed these results: They tested flunarizine in ten children with a diagnosis of AM compared with ten children with the same pathology who did not receive treatment and nine healthy children. The study showed a net improvement in the frequency of both abdominal pain and headache and in the duration of headache [64].

4.2.6 Serotonin Antagonists

No recent evidence or studies confirm the usefulness of this type of drug in the treatment of FAPDs. We found only one study [65] on pizotifen in the literature. This drug is usually used to treat migraine and was tested in children with AM. The results were encouraging, but the study had only a small sample and was stopped early.

4.2.7 Laxatives

Khoshoo et al. [66] compared a 4-week-long treatment with PEG 3350 alone and in combination with tegaserod in children with constipation-predominant IBS according to the Rome II criteria. All patients received the same dosage, and abdominal pain and frequency of bowel movements were monitored. The combination therapy proved more efficacious than PEG 3350 alone in reducing abdominal pain (66.7 vs. 18.5%). Tegaserod acts upon 5-HT_4 gastrointestinal receptors, which play a key role in motility and moderate visceral sensitivity. However, tegaserod has been associated with serious cardiovascular ischemic events and was therefore withdrawn from the market by the US FDA.

4.2.8 Antibiotics

Two different trials have tested rifaximin [67] and co-trimoxazole [68] versus placebo in a total of 112 children. In both studies, no differences were observed between the intervention and control groups for any of the outcomes. Moreover, the quality of these studies was very low because of their small sample sizes and lack of reliable outcome data. Therefore, there is no evidence indicating a role for antibiotics in the treatment of FAPDs.

4.2.9 Melatonin

Zybach et al. [69], in a recent pilot study aiming to evaluate the efficacy of melatonin in functional dyspepsia, performed a double-blind, randomized, placebo-controlled crossover trial in which patients were treated continuously for 2 weeks. They observed no significant impact on pain in children treated with melatonin compared with those treated with placebo [69].

4.2.10 Placebo

A large proportion of patients with FAPDs respond to placebo in clinical trials. A placebo response is defined as the outcome caused by a placebo manipulation. However, it is important to make clear that this includes the "true placebo effect" and other factors, such as the natural course of the disease, spontaneous symptoms fluctuations, and regression to the mean [70–72]. This high placebo response rate has important implications for both researchers and clinicians. In research, a high placebo response results in reduced assay sensitivity (i.e., the ability of a trial to detect true differences between active treatment and placebo), which may lead to inefficient trials. On the other hand, in clinical practice, the placebo response can be considered a valuable and powerful clinical tool [73]. A recent systematic review and meta-analysis by Hoekman et al. [74] on 21 RCTs of children with FAPDs demonstrated pooled placebo rates of improvement and no pain of 41 and 17%, respectively. There was a significant association between lower dosing frequency and longer duration of treatment and a higher proportion of subjects with no pain on placebo. The association between lower dosing frequency (once daily instead of twice daily) and a higher proportion of subjects with no pain on placebo (29.9 vs. 10.6%, respectively) is in contrast with other studies, which found a higher placebo response rate correlated with a higher dosing frequency. This may be explained by arguing that a lower dosing frequency might indirectly reduce the focus of the child on their complaints and disease, which may lead to a greater decrease in their symptoms. The important study by Walker et al. [75] supported this suggestion: They found that children who were distracted from their complaints by their parents had a greater reduction in pain than children who received more attention for their symptoms. In contrast, other studies support an association between longer treatment duration and significantly greater placebo response and is probably because patients who are treated for longer may feel they are getting more treatment, which may increase their expectation of responding to

treatment. Other studies on this subject have suggested that children and adolescents respond more than adults to placebo [76, 77]. This contrasts with the results of Hoekman et al. [74], who showed a placebo response rate in line with that of previous meta-analyses of RCTs in adult patients with IBS [78–80]. This may be because the study population was predominantly adolescent (indeed, the meta-analysis by Bridge et al. [81] of children with major depression found that adolescents had a lower placebo response rate than children aged < 12 years), but, in fact, no association was found between age at inclusion and placebo response. Other factors significantly associated with the absence of pain were a higher placebo dropout rate and a study with a statistically significant effect in favor of the active agent over placebo. The magnitude of the placebo response on the Faces Pain Scale (FPS) was instead significantly correlated with the trial location, description of randomization schedule, and percentage of females.

5 Conclusions

The management of children with FAPD can be tricky and pose a challenge to pediatricians. According to the Rome IV criteria, currently, a positive diagnosis of FAPD in children can be made without necessarily excluding every other possible cause of abdominal pain. Nevertheless, physicians may need to take some time and conduct some useful tests to make a proper diagnosis; this process is indeed mandatory, especially to exclude chronic gastrointestinal conditions such as inflammatory bowel disease or celiac disease, which may mimic the clinical picture of FAP, before commencing any sort of treatment.

This review shows there is no agreement among experts on a universally proven management that will work on every child presenting with FAP. Treatment strategies include both non-pharmacological and pharmacological options. Non-pharmacological treatments are usually very well accepted by both children and their parents and are free from negative pharmacological side effects. Nevertheless, they may be as effective as the pharmacological interventions; therefore, according to many experts and based on the majority of current evidence, a non-pharmacological approach should be the first intervention attempt in children with FAPDs. In this review, the importance of the bio-psychosocial approach is highlighted, as most children will improve with counselling and reassurance that no serious organic pathologies are suspected, particularly when the physician establishes a trustful relationship with both children and their families. In our experience, constipation or abnormal defecation patterns are frequently involved and should be the target of interventions. Dietary modifications and probiotic supplementation could greatly improve abdominal symptoms, but it is recommended that dietary modifications (i.e., the exclusion of FODMAPs or other specific foods as well as fiber or guar gum supplementation) should be initiated and monitored by a specialist pediatric dietician to ensure adequate nutritional intake, particularly in small children. Placebo and pharmacological interventions both showed efficacy and could be attempted, especially in cases when the bio-psychosocial approach is not applicable or not efficacious. Our personal thought is that since the efficacies of placebo and pharmacological interventions showed comparable results in many RCTs [82–84], one may speculate that any kind of medication actually produces an organic effect in diminishing pain.

However, in some difficult cases, finding an effective treatment for FAPDs could be a challenge, and several strategies may need to be tried before symptoms can be controlled. In these cases, a multidisciplinary team, comprising a pediatric gastroenterologist, dietician, psychologist, and psychotherapist, is likely to be more successful.

Compliance with Ethical Standards

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