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## Non-pharmacological management of pediatric functional abdominal pain disorders: Current evidence and future perspectives

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### Abstract

Functional abdominal pain disorders (FAPDs) are an important and prevalent cause of functional gastrointestinal disorders among children, encompassing the diagnoses of functional dyspepsia, irritable bowel syndrome, abdominal migraine, and the one not previously present in Rome III, functional abdominal pain not otherwise specified. In the absence of sufficiently effective and safe pharmacological treatments for this public problem, non-pharmacological therapies emerge as a viable means of treating these patients, avoiding not only possible side effects, but also unnecessary prescription, since many of the pharmacological treatments prescribed do not have good efficacy when compared to placebo. Thus, the present study provides a review of current and relevant evidence on non-pharmacological management of FAPDs, covering the most commonly indicated treatments, from cognitive behavioral therapy to meditation, acupuncture, yoga, massage, spinal manipulation, moxibustion, and physical activities. In addition, this article also analyzes the quality of publications in the area, assessing whether it is possible to state if non-pharmacological therapies are viable, safe, and sufficiently well-based for an appropriate and effective prescription of these treatments. Finally, it is possible to observe an increase not only in the number of publications on the non-pharmacological treatments for FAPDs in recent years, but also an increase in the quality of these publications. Finally, the sample selection of satisfactory age groups in these studies enables the formulation of specific guidelines for this age group, thus avoiding the need for adaptation of prescriptions initially made for adults, but for children use.

**Key Words:** Functional abdominal pain disorder; Pediatrics; Rome IV; Behavioral intervention; Non-pharmacological treatment; Complementary medicine

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**Core Tip:** Functional abdominal pain disorders are an important and prevalent cause of functional gastrointestinal disorders among children. In the absence of sufficiently effective and safe pharmacological treatments for this public problem, non-pharmacological therapies emerge as a viable means of treating these patients. Thus, the present study provides a review of current and relevant evidence on non-pharmacological management of these disorders, as cognitive behavioral therapy, meditation, acupuncture, and others. This article also analyzes the quality of publications in the area, assessing whether it is possible to state if non-pharmacological therapies are viable, safe, and sufficiently well-based for an appropriate and effective prescription.

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## INTRODUCTION

Functional gastrointestinal disorders (FGIDs) are a group of diseases defined by morphological and physiological changes that affect from the gastrointestinal tract (GIT) to the central nervous system (CNS). Among the main changes listed in this group, there are disorders of intestinal motility, visceral hypersensitivity, and changes in the mucosa and in the host's immune responses, in addition to possible changes in the normal microbiome of the intestinal environment[1].

FGIDs are stratified in alphabetical letters from A to H, with the present article focused on non-pharmacological treatment specifically for group H (FGIDs in children or adolescents), subtype H2, defined as functional abdominal pain disorders (FAPDs) by the Rome IV criteria. This group consists of functional dyspepsia (H2a), irritable bowel syndrome (IBS) (H2b), abdominal migraine (H2c), and functional abdominal pain not otherwise specified (H2d), with the latter not previously present in Rome III[2].

With regard to the diagnosis of FGIDs, the 2016 Rome IV criteria removed the obligation to rule out organic causes using complementary tests, making the clinical evaluation criteria sufficient for diagnosis, thus avoiding the exposure of these patients to unnecessary testing[1]. In this sense, complementary/laboratory examinations are not required for diagnosis after careful clinical examination and in the absence of alarm criteria that suggest organic causes or complications of FAPDs. The following is considered alarm criteria: Family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease; persistent right upper or right lower quadrant pain; dysphagia; odynophagia; persistent vomiting; gastrointestinal blood loss; nocturnal diarrhea; arthritis; perirectal disease; involuntary weight loss; deceleration of linear growth; delayed puberty and unexplained fever[1]. The stratified diagnostic criteria for FAPDs are shown in Table 1.

Regarding the prevalence of FAPDs, it is estimated that about 13.5% (95% confidence interval [CI]: 11.8-15.3) of the children worldwide present one of the diseases in this group, with emphasis on IBS, representing 8.8% (95%CI: 6.2-11.9) of that number. In addition, risk factors for the development of FAPDs were identified as being female (15.9% prevalence *vs* 11.5% male) and the presence of anxiety, depression, stress symptoms, or traumatic life events[3].

In view of the important prevalence of FAPDs, it is necessary to establish effective and adequate treatments, ensuring not only the control of symptoms but also the safety of patients. In addition, because studies of pharmacological safety in an age group are insufficient, the use of efficient non-pharmacological therapies in the treatment of the pediatric public is ideal. Thus, the aim of this article is to understand, through a review of the literature available in the main databases, the use of different non-pharmacological therapies in the treatment of FAPDs in children, analyzing from how they have been indicated to the levels of evidence that sustains their prescription.

**Table 1 Diagnostic criteria for functional abdominal pain disorders in children and adolescents**

<b>H FGIDs in children or adolescents</b>	
H2	Functional abdominal pain disorders
H2a	Diagnostic criteria for functional dyspepsia <p>One or more of the following symptoms at least 4 d per month: (1) Postprandial fullness; (2) Early satiation; (3) Epigastric pain or burning not associated with defecation; and (4) After appropriate evaluation, the symptoms cannot be fully explained by another medical condition</p> <p>Within FD, the following subtypes are now adopted: (1) Postprandial distress syndrome; and (2) Epigastric pain syndrome</p>
H2b	Diagnostic criteria for irritable bowel syndrome <p>All of the following: (1) Abdominal pain at least 4 d per month (associated with one or more of the following: (a) Related to defecation; (b) Change in frequency of stool; and (c) Change in appearance of stool); (2) In children with constipation, the pain does not resolve with resolution of the constipation; and (3) After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.</p>
H2c	Diagnostic criteria for abdominal migraine <p>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; (2) Episodes are separated by weeks to months; (3) The pain is incapacitating and interferes with normal activities; Stereotypical pattern and symptoms in the individual patient; (4) The pain is associated with 2 or more of the following: (a) Anorexia; (b) Nausea; (c) Vomiting; (d) Headache; (e) Photophobia; and (f) Pallor; and (5) After appropriate evaluation, the symptoms cannot be fully explained by another medical condition</p>
H2d	Diagnostic criteria for functional abdominal pain not otherwise specified <p>All of the following at least 4 times per month: Episodic or continuous abdominal pain that does not occur solely during physiologic events; Insufficient criteria for irritable bowel syndrome, functional dyspepsia, or abdominal migraine; After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition</p>

All criteria must be fulfilled for at least 2 mo before diagnosis[1,2]. FGIDs: Functional gastrointestinal disorders; FD: Functional dyspepsia.

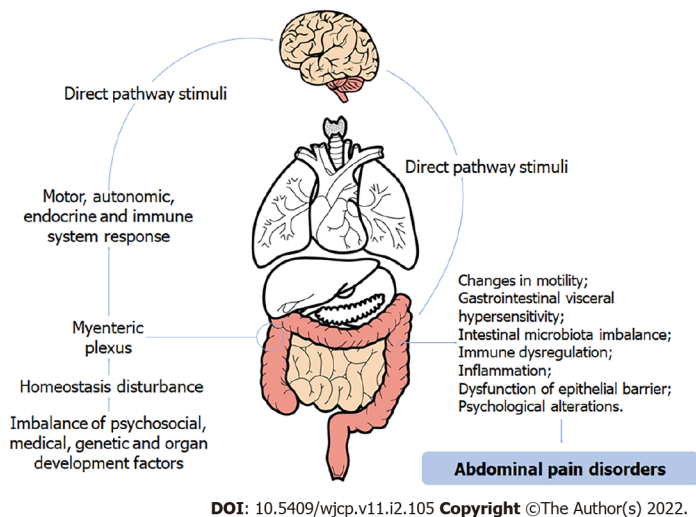
## PATHOGENESIS

The pathogenesis of FAPDs in children is not well understood; however, it has currently been observed that the microbiota-intestine-brain axis plays an important role in these diseases, as pathophysiological development seems to be linked to changes in its integrity and/or functionality[4]. This neuroanatomical axis has an integrated and complex circuit that processes information about the emotional, sensory, and cognitive situation. In this sense, there are direct connections from the CNS and the GIT with myenteric plexus act on the individual's motor, autonomic, endocrine and immune system[5]. The influence of this neuronal circuit has a direct reflex on the CNS and can trigger responses that result in changes in motility, gastrointestinal visceral hypersensitivity, intestinal microbiota, immune dysregulation, inflammation, and dysfunction of barriers[6]. This is the most accepted hypothesis in the biopsychosocial model of FAPDs in children, and is linked to psychosocial, medical, genetic, and developmental factors of the organs and circuits involved in this axis. Disturbances on these systems and their homeostasis may result in some disorders. This axis is represented graphically in Figure 1.

A study with patients with IBS demonstrated that gastrointestinal motility problems are linked to delayed gastric emptying and increased intestinal transit[7]. In another study conducted in Texas, USA, impaired myoelectric activity in the gastric environment was observed in patients with functional dyspepsia. The result of measuring myoelectric activity suggested a decrease in normal slow waves and an excessive amount of arrhythmic waves, resulting in impaired coordination of gastric slow waves[8]. Riezzo *et al*[9] evaluated 52 children with non-ulcer dyspepsia and 114 healthy children, and changes in the electrical activity of the gastric environment and delayed gastric emptying were also observed. In addition, serotonin receptors and transporters may play an important role in this integrated response relationship of the gut-brain axis[10]. Further studies on this topic are needed, since there are still few publications on the contribution of altered gastric motility in children with these functional disorders, and most of these are with adult patients.

Gastrointestinal visceral hypersensitivity is the most widespread and accepted mechanism of abdominal pain in the literature[11]. The perceptual response of hyperalgesia is characterized by changes in the signal processing of the primary neurons afferent from the enteric nervous system to the CNS, which interprets this stimulus as abdominal pain and triggers a series of reflexes that are recognized as pain[11,12]. Therefore, visceral sensitivity is also regulated at various levels of the microbiota-intestine-brain axis, such as the enteric mucosa and submucosa, medulla, thalamus, and cerebral cortex[12], which demonstrates an integrated sensory response throughout this axis. In a study of 51 children, a decrease in sensory threshold was observed in patients with FGIDs when compared to children with organic diseases[13], which indicates that this decreased sensory threshold associated with changes in neuronal stimuli is possibly the explanation of visceral hypersensitivity in FGIDs.





**Figure 1** Graphical representation of the gut-brain axis in the pathogenesis of functional abdominal pain in pediatric populations.

Evidence shows that the microbiota of patients with FGIDs differs from healthy people[14]. In a recent systematic review with patients with IBS, with three studies included with children, a significant increase in the bacterial population of the family *Enterobacteriaceae* and *Lactobacillaceae* and genus *Bacteroides* in patients with IBS when compared with the control group was observed. In addition, there was a decrease in bacterial colonization of *Bifidobacterium spp.*, *Faecalibacterium spp.*, and *Faecalibacterium prausnitzii*[15], which plays an important role in the balance of the immune system in the intestine[16]. However, the role of the microbiota in relation to functional diseases in children is not well established. Most studies evaluated fecal samples from adult patients with IBS and have limitations in relation to sample collection, and diet and medication used by the patient. In this sense, more studies would be important in order to understand the influence that the way of delivery, metabolome and other microorganisms have on the intestinal microbiota of these children.

Homeostasis of the microbiota-intestine-brain axis is essential to maintain the integrity of the immune system, and disturbances in this balance can generate uncontrolled inflammation in the gastrointestinal mucosa. Interestingly, infiltration of mast cells, eosinophils, and lymphocytes has been observed in intestinal environment of patients with functional disorders. In particular, mast cell recruitment is involved in epithelial and neuromuscular dysfunction[17]. These inflammatory cells are close to neurosensory fibers of the GIT mucosa and have a relevant role in altering neurogenic inflammatory pathways and in perception of pain in response to harmful stimuli[18]. In addition, the degree of inflammation in the GIT mucosa can cause injuries and, consequently, a rupture of barriers that restrict bacterial colonization under normal conditions. As a result, bacterial overgrowth can be observed, which can culminate in FGIDs[12,19].

High self-perceived prevalence of food intolerances has been reported in children with IBS[20]. These symptoms are associated with nutritional behavioral changes and children's diet[21]; however, the knowledge about how nutritional factors influence functional gastrointestinal diseases is still unclear. Therefore, greater knowledge about a possible adequate nutritional pattern for maintaining the balance of the microbiota-intestine-brain axis may be ideal for a better understanding of the relationship between food and the intestinal microbiota in that axis.

The psychological factors and their relationship to intestinal motility are well understood. Some studies have already demonstrated the physiological effects on the GIT, triggered by anger, fear, and anxiety[12]. In a recent review, the authors concluded that although it is still unclear whether FGIDs may have psychological factors as their etiology, there is strong evidence that these factors exacerbate and contribute to maintenance of pain[22]. An interesting correlational study found a decrease in the symptoms of functional disorders in children in summer, when compared to spring ( $P = 0.017$ ). The authors correlated this improvement to the vacation period when they are exposed to fewer stressors, but were unable to distinguish what is the cause and what is the effect of decreasing symptoms[23]. Also, the hypothalamus-pituitary-adrenal axis may have an interaction with the microbiota-intestine-brain axis, releasing cortisol and corticotropin, which stimulate metabolic stress and cause a release of mast cells and pro-inflammatory cytokines[4]. Stress factors can also deregulate the balance of the intestinal microbiota, increasing the permeability of epithelial tissue, and facilitating the entry of pathogens that can create an inflammatory environment. In addition, the release of cytokines such as IFN $\gamma$ , IL-1, and IL-6 can stimulate an immune response in the CNS and reflect an exacerbation of psychological symptoms[24]. With this, it becomes increasingly important that children with symptoms related to FGIDs receive the integration of the psychological examination in their global care[25].

In view of all these factors discussed, it is clear that the pathogenesis of these functional disorders does not affect only one organic system. Although not well understood, the etiologies of these disorders are found in all areas of the individual's biopsychosocial being, and are present in organic, nutritional, and psychological neuronal axes. More robust studies with better levels of evidence on the pathogenesis of these functional disorders in children are needed.

## PHARMACOLOGICAL TREATMENTS

The published literature on treatments for FAPDs is still scarce, and the effectiveness of pharmacological therapy lacks studies that provide quality scientific evidence[26]. Although there are a large number of studies indicating pharmacological efficacy in relation to placebo, most studies that analyze pharmacological intervention have a small sample size, are uncontrolled or non-randomized, and even present controversial or incomplete results. In addition, most studies have methodological flaws that prevent authors from drawing significant conclusions about effectiveness[27-31]. Therefore, the current guidelines and studies recommend that the initial approach to pediatric patients with these disorders be non-pharmacological and then choose the pharmacological one, observing for possible side effects[32]. Potential pharmacological treatments for FAPDs have been identified based on the gut-brain axis, mainly including antispasmodics, antidepressants, secretagogues, antihistamines, anti-reflux agents, calcium channel blockers, serotonin antagonists, laxatives, antibiotics, and hormone therapy[33].

### Antispasmodics

This category includes drugs that reduce intestinal contraction through different mechanisms of action. Kline *et al*[34] in his double-blind study of 50 children with IBS, found reduced pain severity in 76% of patients at 2 wk after using peppermint, against 19% by placebo. The use of peppermint is based on its menthol component that reduces colon spasms by blocking  $\text{Ca}^{2+}$  channels and no side effects have been reported. Pourmoghaddas *et al*[35] and Karabulut *et al*[36] evaluated, respectively, the use of mebeverine and trimebutine, medications that have specific action on smooth muscle cells. In the first study, the authors found no statistically significant differences in relation to the use of placebo[35]. In the second, the results indicated a relief in abdominal pain, but they were obtained based on questions asked to parents, and not to children, just as the study was not blinded or controlled[36]. The only other study that reported the use of trimebutine in children was that of Giannetti *et al*[37], but the number of patients treated was very low, and the study was not intended to assess the effectiveness of this particular medication, but rather a variety of other approaches. Narang *et al*[38] tested drotaverine compared to placebo in 132 children for 4 wk, and although the authors reported a decrease in episodes of abdominal pain, they did not describe the intensity of the pain.

### Antidepressants

Amitriptyline has been studied in FAPDs, mainly in adults, due to a probable change in pain perception. Bahar *et al*[28] found improved quality of life (measured through a questionnaire) and diarrhea, and inconsistent pain improvement in some, but not in all, areas of the abdomen and only at certain times *vs* placebo. The study conducted by Saps *et al*[29] also using amitriptyline *vs* placebo for 4 wk treatment did not indicate a significant difference between groups. The group using amitriptyline stood out only in improving anxiety. Another antidepressant, citalopram, was tested by Roohafza *et al*[39] in their study with 115 children with abdominal functional disorders. There was also no significant difference in symptom improvement between the treated group and the placebo group. Cooper *et al*[40] reported, in a review, very low quality evidence to support the use of amitriptyline, citalopram, and gabapentin, in addition to which none of the studies analyzed achieved the desired primary result of abdominal pain relief of 30% or more.

### Antihistamines

The change in the concentration of serotonin in the intestine may be responsible for causing visceral dysmotility and hypersensitivity. Therefore, this class may have potential in the treatment of abdominal pain in children. Cyproheptadine was evaluated by Sadeghian *et al*[27] in a double-blind, placebo-controlled study with 29 children over 2 wk. At the end of the study, cyproheptadine demonstrated a better decrease in the intensity and frequency of pain, as well as an improvement in the assessment of general condition. However, this study showed limited follow-up, low methodological quality, and use of non-validated questionnaires. Madani *et al*[41], in a follow-up of pediatric patients for 7 years, indicated that cyproheptadine was effective in 73% of patients and safe in 68%. In a recent review, the same authors confirmed the effectiveness of this medication[42].

### Antibiotics

Used in an attempt to alter the harmful intestinal microbiota in two different trials with a small sample of pediatric patients, rifaximin (approved in 2015 by the FDA for the treatment of adults with IBS-D) and cotrimoxazole did not indicate statistical differences compared to the placebo group[30,43]. In the



first study, the authors assessed abdominal pain, episodes of diarrhea and constipation, feeling of incomplete or effective evacuation, urgency to evacuate, effort to evacuate, and the presence of some fecal secretion. Erythromycin, another antibiotic that appears to have agonist properties of the motilin receptor in the stomach, has been reported to be useful in relieving symptoms of abdominal pain and dyspepsia in adults, but there is still insufficient pediatric data for clinical indication[44].

### **Serotonin antagonists**

One of the only medications in this class reported in studies was pizotifen. Symon *et al*[45] comparing it to placebo, reported that the children in the study showed a reduction in the “Severity Index” related to abdominal pain. However, this study presented a small sample of 16 patients with abdominal migraine, was interrupted before more patients were included in the study, and used a scale with no validation [45].

### **H2 receptor antagonists**

In the study of See *et al*[46], 25 children with dyspepsia and functional abdominal pain were treated with famotidine or placebo. At the end of the study, there was no significant difference in treatment regarding the frequency of abdominal pain, pain intensity, and dyspeptic symptoms. In addition, the group that received famotidine had an improvement in the overall assessment of 66.7%, while the group that received placebo had a 15.4% improvement in this same parameter. However, the authors provided insufficient data to establish a confidence interval between these percentages[46].

### **Prokinetics**

Domperidone was used in a placebo controlled trial to assess the response in children with functional dyspepsia[47]. According to the results, patients did not show a different cure rate between domperidone and placebo after 8 wk, and no data was reported to indicate improvement in nausea - an important symptom in this pathology. However, after being followed for 6 mo, the children who received the medication showed an increase in the cure rate and in the overall assessment. Prokinetics have been used mainly in situations where functional abdominal pain is accompanied by constipation or delayed gastric emptying, as in IBS. Nevertheless, in several regions of the world, they have their commercialization restricted due to its side effects, including cardiovascular events[48].

### **Proton pump inhibitors**

Proton pump inhibitors are usually indicated for the treatment of dyspeptic symptoms, since they end up acting in the acidic environment of the digestive tract. Karjoo and Kane[49], in their study with 153 patients aged 6 to 18 years with abdominal pain and dyspepsia, reported a significant improvement in symptoms, especially those who were resistant to the use of H2 antagonists. The patients in this study were treated with high-dose ranitidine hydrochloride and omeprazole as the main proton-pump inhibitor[49].

### **Hormonal treatments**

Melatonin, a hormone produced by the pineal gland, has also been studied in the treatment of these pathologies, and its use is justified by a possible improvement in sleep. Zybach *et al*[50] analyzed the efficacy of melatonin in children with functional dyspepsia for 2 wk in a double-blind, randomized, placebo-controlled crossover study with a small sample of 12 patients. They found a positive clinical response in 42% of individuals with melatonin *vs* 50% of individuals who received placebo. In this sense, no efficacy was observed in the use of melatonin for the relief of abdominal pain in functional conditions[50].

### **Secretagogues**

Some secretagogues have been evaluated in functional conditions that generate abdominal pain, such as IBS with a predominance of constipation. In an uncontrolled trial in children and adolescents, the use of lubiprostone was shown to be beneficial in increasing the frequency of spontaneous evacuation and pain[31]. In another double-blind, randomized, controlled study[51], the frequency of bowel movements, pain, effort, and consistency of stools did not show a statistically significant difference when comparing lubiprostone and placebo. Thus, further controlled studies are needed to confirm the effectiveness of this medication for the treatment of abdominal pain specifically, as they are already confirmed to be beneficial in the treatment for constipation. On the other hand, linaclotide is currently approved by the FDA and the European Medicines Agency for the therapy of chronic constipation in adults. At the moment, there are no published studies reporting efficacy and safety of the use of linaclotide in children, but there is a double-blind multicenter study under development, with children and adolescents, to assess this (NCT02559817)[52].

In view of the high prevalence of FAPDs in children, their high impact on quality of life, and lack of significant studies, there is still a gap in the search for safe and effective pharmacological therapies, with well-developed, randomized, controlled and multicenter studies. It is also important to highlight that this process is important to prevent maleficent effects of these drugs in a system that is still ongoing

neuroplasticity changes and growth development. In addition, it is necessary to pay attention to the cost-benefit ratio that the medication will offer, especially in relation to placebo and non-pharmacological therapies[51,52].

## NON-PHARMACOLOGICAL TREATMENTS

The incorporation of integrative and complementary non-pharmacological interventions in management of the pediatric chronic pain has demonstrated to be viable and effective for this population[53, 54]. Such methods can lead to long-term results due to changes in the neural circuits that regulate habits, affection, and cognitive responses to pain[55]. Thereby, treatments such as cognitive behavioral therapy (CBT), acupuncture, spinal manipulation, exercise, among others come to assist the health professionals in pediatric chronic pain therapy. As an aim of this study, we based the classification of integrative and complementary practices on the structure proposed by the database Biblioteca Virtual de Saúde – Medicinas Tradicionales Complementares e Integrativas das Américas (BVS-MTCI), developed by the Traditional Complementary and Integrative Medicine Web of America[56].

### *Mind-body therapies*

**Cognitive behavioral therapy:** CBT is based on the premise that thoughts, emotions, and behaviors are linked, as well as how someone perceives a situation can significantly influence emotional, behavioral and physiological responses[54]. CBT involves the teaching of coping and distraction strategies and relaxation techniques; identification and change of pain-related thoughts; and modification of family responses to pain. This method can involve the family itself or may focus only on the child, as well as be performed face-to-face or remotely[57,58]. Family approach seeks to alter environmental factors that might reinforce the child's pain behavior within the family and to identify and treat factors that may precipitate in it[58].

There is growing support for CBT for children with FAPDs[59]. Multiple components are typically used in CBT, such as education about the pain, increasing self-confidence[60], cognitive restructuring of maladaptive thoughts, exposure exercises, relaxation, and parent management techniques[61]. In exposure-based CBT for FAPDs, the patients gradually expose themselves to symptom-provoking stimuli (such as eating pizza) and approach situations in which symptoms are perceived as intolerable (such as being in school). This approach is hypothesized to decrease fear and avoidance related to symptoms and thereby enables symptom reduction[61].

A randomized clinical trial with 104 children aged 7-18 years investigated the effectiveness of a 6 weekly session CBT protocol compared with 6 visits to a pediatric gastroenterologist and the impact of these interventions on pain. This CBT session resulted in a significant reduction of abdominal pain in 60% of children with FAP up to 1 year after treatment, and the CBT is more effective than intensive medical care directly after treatment[62]. Another study showed that children who received CBT improved significantly more than the control group on abdominal pain-related symptoms and coping strategies, as well as parental solicitousness in response to pain behaviors. Moreover, many of these differences were maintained 6 mo after intervention[63].

Furthermore, Internet-delivered CBT (Internet-CBT) may help to bridge this treatment gap. Internet-CBT holds several advantages over traditional face-to-face therapy: It can be delivered to people in remote areas, patients can access the treatment without taking time off from school or work, and it requires fewer therapist hours per patient[64].

One study reported outcomes in adolescents aged 13–17 years with IBS who received a 10-wk session of Internet-delivered exposure CBT, compared with wait-list controls. There was a large change before and after treatment in gastrointestinal symptoms, with a medium effect size, and improved anxiety, school absenteeism, and adolescent-rated and parent-rated quality of life. After 6 mo, the results were stable or significantly improved[65].

Furthermore, a randomized clinical trial with 90 children diagnosed with FAPDs, based on the Rome IV criteria, found that Internet-CBT has the potential to increase the availability of treatment for a number of patients and reduce health care costs[66]. Moreover, more than half of the children in the Internet-CBT group reported a 30% or greater improvement of their gastrointestinal symptom severity at the 10-wk follow-up evaluation *vs* 32% of the children in the treatment-as-usual group[66].

**Meditation:** Meditation can be defined as a form of mental training that aims to improve an individual's core psychological capacities, such as attentional and emotional self-regulation[67]. Meditative techniques include transcendental meditation, mindfulness-based stress reduction, and mindfulness-based cognitive therapy[68]. Of these practices, mindfulness meditation has received most attention in neuroscience[69]. In current clinical and research contexts, mindfulness meditation is typically described as non-judgmental attention to experiences in the present moment and requires both the regulation of attention and the ability to approach one's experiences with openness and acceptance[69,70]. This nonjudgmental focus on present-moment experience appears to be a potentially avenue in helping adolescents attend to pain adaptively[71].

An increasing body of literature has demonstrated that mindfulness interventions are feasible and efficacious in adult pain populations[72,73]. On the other hand, pediatric populations that experienced chronic pain conditions, as neuropathic and abdominal pain, have demonstrated initial feasibility and acceptability of mindfulness-based interventions (MBIs)[74,75]. While preliminary research among pediatric pain populations demonstrates feasibility and acceptability of MBIs, additional studies are necessary to investigate mindfulness in children and adolescents with chronic pain. Thus, this intervention may be low cost or free adjunctive treatments that have fewer side effects as compared to pharmacological interventions[54].

### **Traditional health system**

**Acupuncture:** Acupuncture is an ancient medical procedure that has been practiced in China and other East Asian countries. The technique involves the placement of small needles at various locations in the body and related therapies include electroacupuncture, acupressure, moxibustion (*i.e.*, burning of an herb near an acupoint to create local warming), laser stimulation of acupoints, and non-invasive stimulation of acupoints utilizing a transcutaneous electrical nerve stimulator[54].

The mechanisms of the relationship between acupuncture and improvement of the pain remain uncertain. Studies have shown that the acupuncture may involve normalization of activity in areas of the limbic system often referred to as the “pain matrix” (*i.e.*, the insula, anterior cingulate gyrus, and prefrontal cortex)[76], or can stimulate endorphin release[77]. This method is also postulated to have effects on acid secretion, gastrointestinal motility, and sensation of visceral pain, possibly mediated through the release of opioid peptides in the central and enteric nervous system[38].

However, while substantial research has shown acupuncture to be an effective therapy for pain among the adult population, there is limited research on acupuncture with regard to the treatment of pain among pediatric patients[78]. Despite this scarce literature, a systematic review published identified common minor adverse effects and rare serious harms in pediatric acupuncture[79]. Puncture redness is the most commonly reported side effect, followed by needle pain and light-headedness[80].

A systematic review of randomized controlled trials on the use of acupuncture in infantile colic shows that acupuncture appears to be effective in alleviating the symptoms of colic, including crying and feeding and stooling problems. However, due to the small sample sizes of the included studies, more randomized clinical trials are necessary[81]. Another case series study found that minimal acupuncture in infantile colic is an effective and easy treatment procedure[82].

A difficulty in treating the pediatric population is children’s fear of needles. The treatment periods are reduced compared with the treatment of adults and closely monitored. Non-invasive modalities, such as electrical stimulation or laser, on acupoints and acupressure seem to be well accepted by younger children[80].

Although acupuncture is safe when administered by appropriately trained and credentialed practitioners, there are some children who have a fear of needles or for medical reasons such as low platelet count or immunodeficiency that may not be recommended to receive acupuncture. For those patients, other techniques such as acupressure[78], laser acupuncture, topical magnets, and acupressure beads may be used. They may also be used as adjunctive treatments following needle placement[83].

**Moxibustion:** A meta-analysis compared the effectiveness of the use of moxibustion with conventional drugs for inflammatory bowel disease and concluded that this method may be useful in the treatment of the disease. There was a significant improvement of general symptoms related to the disease ( $P = 0.0001$ ); however, regarding specific symptoms, only abdominal distension ( $P = 0.03$ ) and frequency of defecation ( $P = 0.02$ ) were significant. Moreover, the authors highlighted that there is a low number of clinical trials evaluating this treatment[84]. In a recent study, Liu and Zeng[85] evaluated the effectiveness of the umbilical therapy combined with moxibustion for diarrhea in pediatric patients. The results showed that the treatment significantly improved the symptoms of diarrhea ( $P = 0.05$ ) and was associated with a shorter recovery time for the children ( $P = 0.05$ )[85]. Another Chinese study used moxibustion to treat 120 children with abdominal pain. The effectiveness rate of the treatment after 3 mo was 94.78%, compared to 80.77% in the control group[86].

**Yoga:** Yoga has been shown to be an exercise that provides several benefits for children, including improvements in the emotional control, anxiety, and depression[87,88]. Moreover, it seems to be effective in assuaging pain associated with some abdominal disturbances in that population[26]. A study carried out by Brands *et al*[89] evaluated the repercussions of Yoga practice in 20 children (age range: 8-18 years) with inflammatory bowel syndrome or abdominal pain. The children participated in 10 Yoga sessions, lasting 1.5 h each, being observed that the exercises reduced the severity and frequency of abdominal pain immediately after the classes. Moreover, after 3 mo of continued exercises at home, the children continued to report improvements; however, the status of the preexisting conditions was not modified[89]. A recent study enrolling adolescents aged from 14 to 17 years with inflammatory bowel disease demonstrated that the use of Yoga for 6 wk resulted in an improvement of abdominal pain, sleep, and visceral hypersensitivity among responding participants. Nonetheless, the findings for the abdominal symptoms were not statistically significant ( $P = 0.8$ ) and the study sample was small ( $n = 18$ )[90]. As for Evans *et al*[91], the study showed that an intervention with Yoga as a

complementary treatment benefits young adults with IBD with a reduction of symptoms. In contrast, a systematic review has stated that the existing studies on Yoga and inflammatory bowel disease do not present satisfactory scientific quality. Therefore, it concluded that, although Yoga is a safe practice for pediatric patients, there are no official recommendations for its use[92].

### Manual therapy

**Massage:** Therapeutic massage has been associated with a significant improvement among pediatric patients with chronic pain due to several diseases, including abdominal disturbances. A study evaluated various techniques such as compression, triggering points, petrissage, tapotement, and effleurage, and concluded that the use of massages is a reasonable option as an adjuvant treatment since they reduce pain, agony, discomfort, and humor alterations[93]. Nam *et al*[94] observed the effects of flavoring massages of the abdominal meridians in children with cerebral lesions and concluded that the use of the therapy 3 to 5 times a week was associated with an improvement in constipation. Another study including patients aged from 4 to 18 years demonstrated that the combined use of isometric training of abdominal muscles, respiratory exercises, and abdominal massages resulted in the reduction of the frequency of evacuation among patients with chronic functional constipation ( $P = 0.01$ ). The treatment was based on sessions of 40 min each, two times a week, for 12 wk[95]. A systematic review evaluated the occurrence of adverse events related to massotherapy in premature babies and reported that it may lead to mild and severe side effects including hematoma, status epilepticus, and volvulus. However, the study identified publication bias and, therefore, it was not possible to identify the causal relationship between the adverse events and massotherapy, though authors recommend caution to perform this method in premature newborns[96]. Moreover, a study including 40 babies showed that abdominal massage with lavender oil has the potential to reduce colic in children aged from 2 to 6 mo. The results were obtained based on the frequency of weekly cries of the patients, and those who underwent massage with lavender oil used to cry less often than the individuals from the control group ( $P < 0.05$ ) [97]. In a recently published study, Al Qahtani and Ahmed recommended the development of educational programs aiming to teach abdominal massage and feet reflexology techniques for parents, since it is an effective way to improve abdominal colic in babies[98].

**Spinal manipulation:** The relationship between spinal manipulation and improvement of symptoms related to abdominal disorders is controversial. Some studies have indicated that the therapy may be associated with an improvement of abdominal pain among children[26,99]. On the other hand, a systematic review of clinical trials was not able to conclude that the spinal manipulation is an effective therapeutic practice against infant colic, and the author stated that the low quality of the studies contributes to the lack of consistent recommendations on that issue[100]. Another recent systematic review showed that the spinal manipulation has some advantages in the control of some types of pain such as lumbar and cervical pain; however, the knowledge on the benefit of that technique against infant colic is still limited since there are many contradictory and low-quality studies evaluating that therapy[101]. In that context, a review evaluated the safety of the performance of spinal manipulation in children and concluded that most side effects reported were mild and that moderate-to-severe adverse events linked to this technique remain unknown[102]. In contrast, Vohra *et al*[103] suggested that the manipulation of the spine may be related to severe side effects in the pediatric population. However, important limitations were highlighted in both studies.

**Physical activities:** Boradyn *et al*[104] carried out a study including 25 children aged from 5 to 11 years to evaluate the impact of the lifestyle in pediatric patients diagnosed with functional abdominal pain. The results showed that the practice of physical activities might increase the frequency of evacuation among children ( $P = 0.031$ ); however, the data regarding the relationship between exercises and abdominal pain were not statistically significant[104]. A recent study observed an association between the practice of physical activities and the development of constipation among children and identified that infants who often practice exercises had a lower odds of acquiring the disorder than sedentary individuals ( $P = 0.016$ )[105]. Complementally, a study that evaluated the effectiveness of alternative complementary medicine for functional abdominal pain observed that 49% of the patients enrolled used to practice exercises to improve their symptoms. Moreover, individuals who rated their condition as severe tend to practice exercises more often than those who rate their disorders as mild or moderate ( $P = 0.043$ )[106]. Kichline *et al*[107] recently observed that young individuals with chronic abdominal pain did not use to practice physical activities 60 min per day. In addition, another study evaluated socioeconomic factors involved in the probability of occurrence of gastrointestinal disorders related to abdominal pain and concluded that the low practice of exercises is positively associated with the disorder ( $P = 0.028$ )[108,109].

In view of the individual discussion of each of these non-pharmacological therapies, the level of evidence for each of them is stratified in Table 2, in addition to the analysis of the public of each study (adults/children) and the timeline of the publications in each of those areas.

**Table 2 Levels of evidence for different non-pharmacological therapies in the treatment of pediatric functional abdominal pain disorders**

Therapy	Year of study	Type of sample	Level of evidence	Ref.
CBT	2010	C	II	[62]
	2013	C	II	[61]
	2017	C	II	[64]
	2019	C	II	[65] <sup>1</sup>
Meditation	2016	C	I	[74]
	2016	A	I	[72]
	2017	C	II	[73] <sup>1</sup>
	2017	A	III	[71]
Acupuncture	2008	A/C	I	[79]
	2011	C	II	[78]
	2011	C	IV	[81]
	2018	C	II	[80] <sup>1</sup>
Yoga	2011	C	IV	[92]
	2014	A/C	III	[94]
	2016	A/C	II	[95]
	2018	C	IV	[93] <sup>1</sup>
Massage	2008	C	III	[96]
	2012	C	III	[100]
	2013	C	III	[97]
	2013	C	III	[98]
	2020	C	III	[99] <sup>1</sup>
	2020	C	IV	[101]
Spinal manipulation	2007	C	II	[99]
	2009	C	II	[96]
	2012	C	II	[95]
	2019	C	II	[97]
	2020	C	II	[98] <sup>1</sup>
	2020	C	III	[26]
Moxibustion	2016	A	II	[100]
	2016	A/C	V	[102]
	2019	C	IV	[101] <sup>1</sup>
Physical activities	2018	C	II	[104]
	2019	C	II	[106]
	2019	C	III	[107]
	2020	C	II	[103] <sup>1</sup>
	2020	C	II	[105]

Adapted from the American Society of Plastic Surgeons rating scale for risk studies, 2011[108].

<sup>1</sup>The references with best-level of evidence and most recent for each non-pharmacological therapy are highlighted.

A: Adults; C: Children; CBT: Cognitive behavioral therapy.



## CONCLUSION

It is possible to conclude that there is a need for safe and effective treatments for the management of FAPDs in the pediatric public. In this sense, and in view of the low quality and insufficient satisfactory results of pharmacological therapies, non-pharmacological treatments emerge as a viable and important solution to this problem of increasing numbers worldwide. In the meantime, it is possible to see a stimulus and an increasing amount of better evidence to support the prescription of these therapies in clinical practice, achieving better results and greater safety for patients. Finally, with these studies being made with sample selections of satisfactory age groups, the formulation of specific guidelines for this age group is made possible, as there is no need for adaptation of prescriptions initially made for adults for children.

## FOOTNOTES

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