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Management of functional abdominal pain and irritable bowel syndrome in children and adolescents

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Abstract

Functional abdominal pain (FAP) and irritable bowel syndrome (IBS) are among the most commonly diagnosed medical problems in pediatrics. Symptom-based Rome III criteria for FAP and IBS have been validated and help the clinician in making a positive diagnosis. The majority of patients with mild complaints improve with reassurance and time. For a distinct subset of patients with more severe and disabling illness, finding effective treatment for these disorders remains a challenge. Over the years, a wide range of therapies have been proposed and studied. The lack of a single, proven intervention highlights the complex interplay of biopsychosocial factors probably involved in the development of childhood FAP and IBS, and the need for a multidisciplinary, integrated approach. This article reviews the current literature on the efficacy of pharmacologic, dietary and psychosocial interventions for FAP and IBS in children and adolescents.

Keywords

children; cognitive–behavioral therapy; dietary therapy; functional abdominal pain; irritable bowel syndrome; pharmacotherapy; psychosocial intervention; recurrent abdominal pain

Functional abdominal pain (FAP) and irritable bowel syndrome (IBS), both of which typically present with chronic abdominal pain, are common complaints in the pediatric population. Estimates on the prevalence of abdominal pain are varied, but community- and school-based studies have reported that as many as 13–38% of children and adolescents experience abdominal pain weekly, with up to 24% of children reporting symptoms persisting longer than 8 weeks [1,2]. For the vast majority of patients, an underlying inflammatory, anatomic, metabolic or neoplastic cause for recurrent abdominal discomfort is not found on evaluation [3]. A significant proportion of these patients are subsequently diagnosed with FAP or IBS. Both entities are included under the larger heading of functional gastrointestinal disorders (FGIDs), which are characterized by chronic or recurrent gastrointestinal symptoms that are not explained by structural or biochemical abnormalities [4]. The diagnosis of FAP or IBS is symptom-based and new criteria have been defined by the Rome III group (BOX 1) [4]. In addition to recurrent abdominal pain, children with IBS also experience disturbances in defecation, ranging from lumpy or hard stools to loose, watery stools or both. Adult patients

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have been classified into subtypes based on the predominant stool pattern, for example IBS with constipation, IBS with diarrhea or mixed IBS [5]. It seems that these subtypes are also present in children, but there is no prospective information that has reliably determined their prevalence.

Box 1

Diagnostic Rome III criteria for functional abdominal pain and irritable bowel syndrome

Diagnostic criteria for childhood functional abdominal pain

Must include all of the following criteria, fulfilled at least once per week for at least 2 months prior to diagnosis:

- Episodic or continuous abdominal pain
- Insufficient criteria for other functional gastrointestinal disorders
- No evidence of an inflammatory, anatomic, metabolic or neoplastic process that explains the subject's symptoms

Diagnostic criteria for childhood irritable bowel syndrome

Must include both of the following criteria, fulfilled at least once per week for at least 2 months prior to diagnosis:

- Abdominal discomfort or pain associated with two or more of the following at least 25% of the time:
  - Improvement with defecation
  - Onset associated with a change in frequency of stool
  - Onset associated with a change in the form (appearance) of stool
- No evidence of an inflammatory, anatomic, metabolic or neoplastic process that explains the subject's symptoms

Data from [4].

Functional abdominal pain and IBS have been associated with significant impairment in children and adolescents. Children with FAP have self-reported quality of life scores lower than healthy children and comparable to children with inflammatory bowel disease [6]. Increased rates of school absenteeism, health-care utilization and family disruption are also common. The financial burden of FAP and IBS in children is not exactly known but is probably significant, considering the frequent need for multiple medical visits and extrapolating data, which estimate that billions of dollars are spent each year for the management of adults with IBS [7,8].

Although most children and adolescents with mild symptoms of FAP or IBS will improve with physician reassurance and time, long-term follow-up studies have shown that a significant number continue to experience symptoms into adulthood [9]. Furthermore, those with more severe, disabling or persistent illness often present a diagnostic, as well as management, challenge for both the primary physician and pediatric gastroenterologist.

Over the years, research in FGIDs has evolved to emphasize a comprehensive, biopsychosocial model of illness, replacing the approach of identifying a single underlying biological etiology [10]. The biopsychosocial model for FGIDs is based on the complex interplay of genetic, physiological (e.g., motility, inflammation) and psychological (e.g., social support, stress)

factors to conceptualize the etiology of FGIDs. Despite ongoing efforts to identify causes and contributing factors of FAP and IBS, successful management is ultimately limited by the incomplete understanding of the pathophysiology underlying these disorders. Recent efforts to categorize FGIDs in children into subtypes based on age and symptoms, such as FAP and IBS, may lead to better understanding of the causes of these disorders and promote investigation of therapeutic options [4].

This article will focus on the experimental and clinical data regarding the management of FAP and IBS in children and adolescents using pharmacological, dietary, psychosocial and complementary/alternative approaches. Management of other subtypes of FGIDs that also present with recurrent abdominal pain, such as abdominal migraine or functional dyspepsia, is beyond the scope of this article. We acknowledge that much of the previous pediatric literature refers to the term recurrent abdominal pain (RAP), first introduced by Apley and Naish in the late 1950s [11]. However, RAP represents more of a description encompassing several different etiologies rather than a unique diagnosis. The considerable overlap between patients originally identified with RAP and those now formally diagnosed with FAP or IBS warrants the examination of articles that used RAP as an entry criterion. In addition, selected adult studies of IBS have been included for the discussion of treatment modalities for which there are currently no pediatric data.

Management of children with FAP & IBS

Once a diagnosis of FAP or IBS has been made, the management approach should be based on the biopsychosocial model for FGIDs, which highlights the importance of the child's physical and social setting, as well as psychological comorbidities. Success in treating patients with FAP or IBS begins with the establishment of an effective patient–physician relationship. The physician should adopt an 'active listening approach' and an enthusiastic, positive and encouraging attitude towards treatment [12]. The physician should elicit any patient concerns or fears, as well as provide reassurance that a positive diagnosis of FAP or IBS is not a failure to identify an underlying illness. Setting up an expectation for normal results to laboratory testing or investigations, when appropriate, may assist in establishing acceptance of a functional disorder diagnosis. Explaining the pathophysiology of visceral pain and associated complaints in the context of a brain–gut axis can be helpful, but symptoms should be validated as being real. It is also important to make clear that treatment response is often gradual and to set realistic goals, such as improved coping with symptoms and maintenance of normal daily living activities, rather than expectation of a prompt cure. Overall, management should be multidisciplinary and tailored to the patient's specific symptoms and identifiable triggers.

Regardless of the specific therapeutic interventions that are employed, physicians need to be cognizant of the potential power of the placebo effect. In several studies of FAP and IBS, the failure of an intervention to demonstrate significant benefit was not because of an absolute lack of improvement, but may have been due to the observation of a strong placebo effect. For example, in a study by Saps *et al*., 58% of patients who received placebo reported feeling better at the end of the study, compared with 63% of patients who received amitriptyline [13]. Clearly, engaging in a positive patient–physician relationship is very important, and should be the foundation for promoting a therapeutic response to all treatments for FAP and IBS. The four major therapeutic approaches that will be reviewed here include: dietary, psychosocial, pharmacologic and complementary/alternative medicine interventions.

Dietary therapy

Restrictive diets

Lactose intolerance has long been implicated as a possible factor in IBS, especially for patients with predominant symptoms of diarrhea. Brush border lactase activity peaks at around 3 years of age then gradually decreases with age. A diagnosis of lactase deficiency is unlikely in younger children, but can be considered for older children and adolescents, although data to support empiric recommendation of a lactose-free diet are weak. Dearlove *et al*. studied 21 children with RAP in a double-blind, crossover trial [14]. Patients were given a lactose-free diet for 2 weeks, then for the next 2 weeks they were given either lactose or placebo. At the end of the study, there were no differences in pain symptoms or the number of children reporting relief between the lactose or placebo group. Lebenthal *et al*. performed lactose tolerance testing (2 g/kg) on 69 children (aged 6–14 years) with RAP [15]. Of this group, 21 children were found to have abnormal results, documented by a blunted rise in blood glucose. These patients then underwent three successive 6-week, double-blinded diet trials of cow's milk formula containing lactose, soy-based and lactose-free formula, and normal diet and milk consumption. Pain frequency was increased in ten out of 21 patients after being given the cow's milk formula compared with their regular diet. However, pain was also increased in seven out of 21 patients after being given the lactose-free soy formula. In addition, a 12-month trial of a lactose-free diet did not result in any difference in abdominal pain for patients determined to be lactose tolerant versus intolerant.

Malabsorption of other carbohydrates, such as fructose, has also been implicated in the pathogenesis of chronic abdominal pain. Persistence of fructose in the GI tract, especially in the form of high-fructose corn syrup, is postulated to cause an osmotic diarrhea, as well as serve as a substrate for fermentation by colonic bacteria, resulting in the production of gas. Gomara *et al.* administered fructose breath tests with random amounts of fructose (1, 15 or 45 g) to children presenting with persistent unexplained abdominal pain [16]. Higher doses of fructose administered in the tolerance test were associated with increased GI symptoms, such as nausea, bloating and abdominal pain. Out of 32 children studied, 11 were found to have abnormal test results in the form of elevated breath hydrogen levels above baseline. When these 11 children underwent dietary restriction of fructose, nine children reported a rapid improvement of their gastrointestinal complaints. After 2 months, all nine children continued to report improvement, especially for symptoms of abdominal pain and bloating ($p < 0.05$).

Dietary fiber

Many physicians routinely recommend the use of bulking agents or dietary fiber to produce more regular bowel movements and to decrease abdominal pain associated with FAP or IBS. These agents are thought to help by softening stool and enhancing colonic transit. In adults, evidence to support the use of fiber is limited by conflicting results and poor-quality studies. In a meta-analysis, the benefit of dietary fiber for adults with IBS was limited to psyllium hydrophilic mucilloid (ispaghula husk); wheat bran and corn bran were no better than placebo [17].

In children, the data on dietary fiber are even sparser. The role of fiber in RAP is somewhat supported by a case-controlled study comparing children with RAP with normal controls, which found that 78% of subjects in the RAP group had low intake of fiber below the recommended level, compared with 51% of the control group ($p = 0.021$) [18]. For treatment of RAP, Feldman *et al*. randomized 52 children with a history of having at least one attack of unexplained abdominal pain per week over at least 2 months and having pain severe enough to affect activity, to receive either a 5 g corn fiber cookie or placebo cookie twice daily for 6 weeks [19]. In total, 13 out of 26 (50%) patients in the fiber group reported at least a 50%

decrease in the frequency of pain episodes compared with 27% in the placebo group ($p < 0.05$). However, a recent *Cochrane* review questioned whether the appropriate statistical analysis was performed in the original study and reanalysis of the same data found no difference between the two treatment groups [20].

Christensen *et al*. performed a randomized double-blinded placebo-controlled study of 40 children with a diagnosis of RAP, which was defined as having at least two pain episodes in the preceding 6 weeks that were severe enough to affect activity [21]. Patients received either ispaghula husks (66% fiber) or placebo (2% fiber) in the form of cereal twice daily for 7 weeks. During the last 6 weeks of the study, there was no significant difference in the mean number of pain episodes in the fiber group compared with the placebo group (13.5 vs 13 episodes, respectively). The benefit of dietary fiber in the treatment of RAP and IBS in children is unclear and should be weighed against the low but potential risk of increased pain and bloating, which has been reported in some adult studies of IBS patients given bran fiber [22]. On the other hand, an empiric trial of psyllium husk fiber may be reasonable, especially if there are associated symptoms of constipation.

Probiotics

Commensal bacteria of the GI tract are believed to play an important role in homeostasis, while alterations to these populations have been implicated in dysmotility, visceral hypersensitivity, abnormal colonic fermentation and immunologic activation [23,24]. This hypothesis has been further supported by reports of IBS triggered by gastrointestinal infections and antibiotic use, both of which can disrupt normal enteric bacteria, as well as the finding of significantly decreased populations of normal *Lactobacillus* and bifidobacteria in patients with diarrhea-predominant IBS [25]. Probiotics commonly contain *Lactobacillus*, bifidobacteria or other living microorganisms thought to be healthy for the host organism when ingested in sufficiently large amounts. Probiotics may improve IBS symptoms by restoring the microbial balance in the gut through metabolic competition with pathogens, by enhancing the intestine's mucosal barrier or by altering the intestinal inflammatory response [26]. Different methods, formulations, dosages and outcome measures have made it difficult to make conclusions about the efficacy of probiotics. A recent meta-analysis concluded that probiotics as a class appeared to be efficacious for adults with IBS, although the magnitude of benefit and most effective species, strain and dosing are not clear [27].

Data in pediatric studies have been equally conflicting. In a double-blind placebo-controlled trial, Bausserman *et al*. randomized 64 children with IBS according to Rome II criteria to receive either *Lactobacillus* GG (1×10^{10} colony forming units) or placebo twice daily for 6 weeks [28]. Patients had similar rates of abdominal pain relief regardless of treatment: 44% in the *Lactobacillus* GG group compared with 40% in the placebo group. There was no significant difference in other gastrointestinal symptoms, except for decreased perception of abdominal distension for patients receiving *Lactobacillus*.

Gawronska *et al*. studied children with either FAP, IBS or functional dyspepsia, all diagnosed according to Rome II criteria [29]. Patients were stratified by diagnosis and then randomized to *Lactobacillus* GG (3×10^9 colony forming units) capsules versus placebo twice daily for 4 weeks. In the subset of 37 patients with IBS, 33% of those treated with *Lactobacillus* reported no pain at the end of treatment compared with 5% in the placebo group ($p = 0.04$). IBS patients also reported a significantly decreased frequency of pain episodes with *Lactobacillus* ($p = 0.02$). However, for patients with FAP or functional dyspepsia, *Lactobacillus* did not provide any significant benefit over placebo.

Finally, in a study conducted by Bu and colleagues, 45 children under the age of 10 years with chronic constipation and abdominal pain were randomized to receive either *Lactobacillus casei*

rhamnosus, magnesium oxide or placebo twice daily for 4 weeks [30]. Patients receiving either *Lactobacillus* or magnesium oxide had increased bowel movement frequency ($p = 0.03$) and improved stool consistency ($p = 0.01$) compared with placebo. Frequency of abdominal pain was significantly decreased in the probiotic group compared with both magnesium oxide and placebo ($p = 0.03$).

Overall, there is no conclusive evidence that dietary carbohydrate restriction, fiber supplementation or probiotic supplementation are effective in the management of FAP and IBS. Further studies are needed to evaluate the role of dietary interventions; until then, these options may be considered on a case-by-case basis after careful discussion with the patient and family.

Cognitive–behavioral therapy & other psychosocial interventions

Acceptance of the biopsychosocial model of FGIDs has provided the basis for the use of psychosocial interventions, including parental education, family therapy, cognitive–behavioral techniques, relaxation, distraction, hypnotherapy, guided imagery and biofeedback. Many of these strategies aim not only to have direct effects on somatic symptoms, but also promote the child's ability to self-manage symptoms. Meta-analyses have found that, as a class, psychological treatments are effective in treating somatic symptoms in both adults and children with functional gastrointestinal disorders [31,32].

The goal of psychoeducation is to communicate information to patients and families about abdominal pain and its connection with psychological triggers, as well as factors that may exacerbate pain, such as social reinforcement and school avoidance [33]. Family therapy targets family interactions and relationships rather than the individual patient in order to change maladaptive behaviors, increase tolerance of symptoms and encourage independent coping skills [34]. Parental attention to children's symptom complaints has been shown to significantly increase those complaints when compared with alternatives, such as distraction [35].

Cognitive–behavioral therapy (CBT), the most common type of psychotherapy employed for FGIDs, is based on the complex interactions between thoughts, feelings and behaviors. The aims of CBT include learning better coping and problem-solving skills, identification of triggers and reduction of maladaptive reactions to them. Specific techniques can include keeping a diary of symptoms, feelings, thoughts and behaviors; adopting relaxation and distraction strategies; using positive and negative reinforcement for behavior modification; confronting assumptions or beliefs that may be unhelpful; and gradually facing activities that may have been avoided. The American Academy of Pediatrics subcommittee on chronic abdominal pain recently concluded that CBT may be useful in "improving pain and disability outcome in the short term" [36].

Relaxation is usually used in conjunction with other psychosocial therapies with the goal of reducing psychological stress by achieving a physiological state that is the opposite of how the body reacts under stress [33]. A variety of methods can be employed with effects such as decreasing heart rate, respiratory rate, blood pressure, muscle tension, oxygen consumption or brain-wave activity [37]. Abdominal or deep breathing stimulates the parasympathetic nervous system to increase feelings of calmness and relaxation. In progressive muscle relaxation, children are guided to systematically tense and relax each muscle group of the body. Patients are then encouraged to maintain attention on the relaxed feeling that results after tensing muscles. Guided imagery is a specific form of relaxed and focused concentration where patients are taught to imagine themselves in a peaceful scene to create an experience void of stress and anxiety. This can be combined with other relaxation techniques to produce a state of increased receptiveness to gut-specific suggestions and ideas, also known as 'gut-directed' hypnotherapy.

Biofeedback uses electronic equipment in combination with controlled breathing, hypnotic or relaxation techniques to generate a visual or auditory indicator of muscle tension, skin temperature or anal control, allowing the child to have external validation of physiological changes.

CBT

In retrospective studies of children with RAP, FAP and IBS, psychosomatic approaches to management resulted in decreased abdominal pain in 70–89% of children [38,39]. Over the years, several small, randomized controlled trials have looked to confirm the efficacy of psychosocial interventions in children. Sanders *et al*. randomized 16 children diagnosed with RAP according to Apley's criteria to either 8 weeks of CBT or waitlist [40]. Children in the CBT group received weekly sessions of instruction in self-monitoring of pain, distraction techniques and relaxation, while parents also received training in ignoring nonverbal pain behaviors, redirection of children to activity after pain complaints and use of positive and negative reinforcement. Parents in the waitlist group were instructed to continue their usual management of pain complaints. Although patients in both groups had improved pain ratings, 87.5% of children in the CBT group were pain-free at 3 months post-treatment, compared with 37.5% of children in the waitlist group. In 1994, Sanders *et al*. conducted a larger follow-up study of 44 children with RAP randomized to 8 weeks of cognitive–behavioral family therapy (CBFT) versus standard care [41]. CBFT included verbal and written instructions for both parents and the child on techniques for dealing with pain. Patients in the standard care group received reassurance. Again, there were reductions in pain for both groups post-treatment, but the CBFT group had significantly higher percentages of pain-free subjects based on parental observation (70.6 vs 38.1%). However, there were no significant differences between groups on continuous measures of pain, pain-related behavior or other measures of coping or adjustment.

Humphreys and Gevirtz randomized 64 children (aged 4–18 years) with RAP to 8 weeks of one of four treatment protocols: dietary fiber, biofeedback, CBT and parental support; dietary fiber, biofeedback and CBT; dietary fiber and biofeedback; or dietary fiber alone [42]. All participants consumed at least 10 g of dietary fiber daily in the form of supplied cookies and bars. Biofeedback involved the use of small thermal devices intended to assist progressive muscle relaxation and self control of pain. CBT consisted of eight sessions of discrimination training, reinforcement schedules, rewards and distraction techniques. Analyses of variance reportedly showed no significant differences among the three active treatment groups in terms of outcome effects or interactions. Therefore, despite substantial differences in interventions, the authors combined these three groups into one larger active treatment group for comparison with the fiber-only group. In total, 33 out of 46 (72%) children in the combined, active-treatment group reported being pain-free at the end of 8 weeks, compared with one out of 14 (7%) in the fiber-only group. It is difficult, however, to determine which psychosocial interventions were responsible for this positive effect. Patients in the active-treatment group also reported greater reductions in pain, sick behaviors, school absences and medication use compared with the fiber-only group.

Robins *et al*. also compared CBT with standard medical care in a randomized controlled trial of 69 children with RAP defined by Apley's criteria (aged 6–16 years) [43]. In the treatment group, 40 children received five sessions of CBT, which included psycho-education, increasing awareness of the relationship between thoughts, feelings and pain, and parental encouragement of positive coping skills. Only 29 children in the control group completed the study owing to higher rates of study refusal. Subjects in the control group received a high-fiber diet, psychoeducation, individualized recommendations and office visits as needed. Both groups reported lower scores on a 50-point abdominal pain index based on pain frequency and intensity

at the end of the study. After adjustment for baseline pain scores, age, gender and parent education, the CBT group had significantly lower scores on the abdominal pain index than controls post-treatment and at 6- and 12-month follow-up. However, the standard deviations of these results were not provided and the clinical significance of these differences in scores is unclear.

Duarte *et al*. studied 32 children with RAP defined by Apley's criteria (aged 5–14 years) in a nonblinded, randomized trial of CBT versus standard medical care [44]. Patients in the CBT group received a total of four monthly sessions of psychoeducation, relaxation and parent training, while patients randomized to receive standard medical care had four sessions with counseling on nutrition, intestinal parasite prophylaxis and accident prevention. By 3 months after beginning the study, patients in the CBT group had a median of two episodes of abdominal pain per month compared with eight episodes per month in the control group, representing a decrease of 86.6 and 33.3%, respectively ($p = 0.001$). No significant differences in intensity of pain or pressure pain thresholds were found between the two groups.

Hicks and colleagues studied a more diverse group of patients, including children complaining of at least three episodes of recurrent headaches, abdominal pain or both within a 3-month period, and randomizing them to either 7 weeks of online psychological treatment or standard medical care waiting list. Patients in the treatment group received online education, homework exercises and communication with researchers via email or telephone. As a whole, significantly more patients in the treatment group (72%) than the control group (14%) achieved a 50% or greater reduction in total pain score between baseline and 3-month follow-up ($p = 0.001$). However, data for patients complaining of only abdominal pain were not reported.

Guided imagery

Weydert *et al*. aimed to evaluate the efficacy of guided imagery as a treatment for RAP in children [45]. Over four weekly therapy sessions, 22 children were randomized to learn either breathing exercises alone or guided imagery techniques with progressive muscle relaxation. At baseline, the children in the guided imagery group reported significantly more days of pain during the month preceding the study than children in the control group (23 vs 14 days; $p = 0.04$). The number of days with pain decreased more significantly in patients in the guided imagery group compared with those learning breathing exercises alone after 1 month (67 vs 21%; $p = 0.05$) and 2 months (82 vs 45%; $p < 0.01$). The number of days with missed activities also decreased more significantly. It is not clear, however, whether substantial differences in the baseline measures of these two groups accounted for some of the statistical significance observed in the results.

Hypnotherapy

Vlieger *et al.* implemented a randomized controlled trial that compared a group of 28 children with chronic FAP or IBS (Rome II criteria) who received hypnotherapy with a control group of 25 children with FAP or IBS who received standard medical care [46]. Hypnotherapy consisted of six 50-min sessions conducted over a 3-month period, with a focus on general relaxation and control of abdominal pain and GI tract function. Standard medical treatment included education, dietary advice and supplemental fiber and pain medications as needed. In both groups, pain intensity scores and pain frequency scores decreased significantly at the final end point of 1 year after therapy. Patients in the hypnotherapy group had significantly greater reductions in both pain intensity and frequency compared with the standard medical therapy group ($p < 0.002$ and $p < 0.001$, respectively). Overall, 85% of the treatment group were considered to be in clinical remission at the end of 1 year (defined as >80% reduction in both pain intensity and pain frequency scores), compared with 25% in the standard medical therapy group ($p < 0.001$). These findings support an earlier, uncontrolled study by Anbar and

colleagues that also reported resolution of pain after teaching self-hypnosis techniques to children with FAP [47].

Overall, CBT appears to be an efficacious treatment for children with chronic abdominal pain. However, several of the reviewed studies incorporated multiple interventions in combination with CBT, which makes it more difficult to determine the specific contributions of CBT towards improving symptoms of FAP and IBS. There are also limited but strong data that support the use of hypnotherapy. In general, incorporation of psychological treatments into the management of patients appears to be a reasonable consideration. Variability in the details of treatment protocols should be taken into account. Ultimately, additional studies are needed to elucidate the benefits of psychosocial interventions and understand the role of placebo effects in the pediatric FGID population.

Pharmacotherapy

Potential pharmacological treatments for FAP and IBS have been identified based on our emerging understanding of the interactions between the CNS, enteric nervous system and GI tract, also known as the ‘brain–gut axis’ [48]. A significant degree of abdominal pain in functional disorders is believed to be associated with abnormal perception of visceral sensations or alterations in motility. Targets for modulation have included smooth muscle cells of the GI tract, peripheral neurotransmitter receptors for various stimuli, interneurons of the spinal cord that transmit information bidirectionally and cortical areas responsible for the perception of pain [48]. Medications initially indicated for the treatment of depression, anxiety and seizures have also been adopted for the management of FGIDs because of their effects on both the CNS and peripheral nervous system.

Antidepressants

Antidepressants are among the most studied pharmacologic agents for FGIDs. Mechanisms of action are thought to include reduction of pain perception, improvement of mood and sleep patterns, as well as modulation of the GI tract, often through anticholinergic effects. A recent review of adult studies found that antidepressants, such as tricyclic antidepressants (TCAs) and selective serotonin-reuptake inhibitors (SSRIs), were beneficial for the treatment of FGIDs [49]. However, in the last few years, overall use of antidepressant medications in children and adolescents has been somewhat tempered by concerns for increased suicidal thoughts and/or behavior, especially after the US FDA issued formal ‘black-box’ warnings in 2004. A subsequent meta-analysis did not find evidence that these suicidal thoughts or behaviors led to an increased risk of suicide [50].

Tricyclic antidepressants primarily act through noradrenergic and serotonergic pathways but also have antimuscarinic and antihistaminic properties. Anticholinergic effects on the GI tract in terms of slowing transit can be beneficial for patients with IBS characterized by diarrhea, but may worsen constipation. Additional side effects include the potential for inducing cardiac arrhythmias, so evaluation for prolonged QT syndrome with a baseline ECG is recommended by the American Heart Association [51]. Owing to sedative properties, TCAs should be given at bedtime. The usual starting dose is 0.2 mg/kg and is increased to a therapeutic dose of approximately 0.5 mg/kg.

Two recent pediatric trials studied the efficacy of amitriptyline, a tertiary amine TCA, for the treatment of IBS and FAP. Bahar *et al*. studied 33 adolescents newly diagnosed with IBS according to Rome II criteria and randomized them to 8 weeks of 10, 20 or 30 mg of amitriptyline (based on weight) versus placebo [52]. The primary outcome was improvement in overall IBS quality of life score, which was measured along with IBS symptoms after 4 and 8 weeks of treatment, as well as after a 3-week washout period. Compared with placebo,

patients receiving amitriptyline were more likely to have an improvement in overall quality of life from baseline at all three time points ($p = 0.019$, 0.004 and 0.013, respectively). Baseline scores for patients in the amitriptyline group were significantly lower than the placebo group to begin with: 109.4 versus 127.5, respectively ($p = 0.05$). There was also an unusual negative placebo effect seen in the control group, which may have contributed to the statistically significant differences seen in comparisons between the two groups. Patients receiving amitriptyline were found to have inconsistent improvement of pain in some, but not all, areas of the abdomen and only at certain times of follow-up. There was no significant improvement in any other IBS-related symptoms.

In a multicenter study by Saps *et al*., 83 children diagnosed with IBS, FAP or functional dyspepsia according to Rome II criteria were randomized to 4 weeks of placebo or amitriptyline (10 or 20 mg daily depending on weight) [13]. The primary outcome was overall response to treatment based on the child's report of pain relief and sense of improvement. A substantial proportion of patients in both groups reported feeling better, but there was no significant difference between patients receiving amitriptyline versus placebo (63 vs 57.5%, respectively). Patients in the amitriptyline group had reduced anxiety scores ($p < 0.0001$), but there was no difference in improvement in pain, disability, depression or somatization scores during the 4-week trial. Children who had more severe pain at baseline in both groups had worse outcomes ($p = 0.0065$). The authors postulated that the lack of significant findings may have been due to issues with insufficient statistical power, clinical heterogeneity of patients, relatively lower dosing of amitriptyline and shorter treatment duration (4 weeks), as well as the high placebo response observed.

Selective serotonin-reuptake inhibitors act by blocking uptake of 5-hydroxytryptamine (5-HT), increasing its concentration at presynaptic nerve endings. In addition to its CNS effects on mood and anxiety, SSRIs may also be beneficial for gastrointestinal complaints, since serotonin is an important neurotransmitter in the GI tract and greater than 80% of the body's stores are located in enterochromaffin cells of the gut [48]. The exact role of serotonin in the GI tract has not been fully elucidated, but it has been implicated in the modulation of colonic motility and visceral pain in the gut.

Well-controlled randomized pediatric trials on the use of SSRIs for either FAP or IBS are lacking. Campo *et al*. conducted a prospective, open-label, flexible-dose study of citalopram for children (aged 7–18 years old) with 'functional recurrent abdominal pain' [53]. In total, 25 patients were started on 10 mg of citalopram daily for the first week and increased to 20 mg daily for the second week. If no clinical response was obtained and the medication was well-tolerated it was increased to 40 mg daily in week 4. Four patients withdrew from the study prematurely, including one subject owing to reported visual side effects. At the end of 12 weeks of treatment, 84% of subjects were classified as responders on a global illness improvement scale. Improvements in abdominal pain, anxiety, depression, other somatic symptoms and function compared with baseline were also reported [53]. Although these findings are promising, they need to be confirmed with additional clinical trials. In a recent randomized placebo-controlled trial of citalopram for adult patients with IBS, there was no significant benefit after 8 weeks of treatment [54].

Monoamine uptake inhibitors, such as duloxetine and venlafaxine, represent a newer group of antidepressant medications with effects on serotonergic and adrenergic pain inhibition systems. These medications have shown evidence of analgesia in patients with fibromyalgia and diabetic neuropathy, but there have been no studies on the treatment of pediatric FGIDs [48].

Antispasmodics

Antispasmodic medications, such as peppermint oil and hyoscyamine, are thought to be helpful for FAP and IBS through their effects on decreasing smooth muscle spasms in the GI tract that may produce symptoms such as pain. In a recent meta-analysis, antispasmodics as a class were superior to placebo in the treatment of adults with IBS [17]. There was a significant amount of variability among included studies in terms of antispasmodic preparation, measured outcomes and overall methodological quality. Several agents included in the meta-analysis, such as otilonium, cimetropium and pinaverium, are not currently available in the USA.

The active ingredient in peppermint oil, menthol, is a cyclic monoterpene with calcium channel blockade properties believed to be active on ileal and colonic smooth muscle. Reported side effects include rectal burning, esophageal pain or heartburn and allergic reactions. To date, there has only been one pediatric study of antispasmodic medication for FGIDs. Kline *et al*. performed a small, randomized placebo-controlled trial of peppermint oil in 42 children with IBS [55]. Subjects in the peppermint oil group received either 187 or 374 mg three-times daily depending on their weight, while control subjects received placebo capsules containing peanut oil. At the end of the 2-week trial, 76% of the children receiving peppermint oil reported improvement on an IBS symptom severity scale compared with 19% in the placebo group ($p < 0.001$). However, there was no difference between groups in terms of heartburn, belching, stool pattern or stool consistency [55].

Hyoscyamine and dicyclomine are both considered antispasmodics owing to their anticholinergic effects on smooth muscle. Hyoscyamine has occasionally been used in children on a short-term basis for gastrointestinal symptoms of pain, but long-term use has been associated with anticholinergic side effects such as dry mouth, urine retention, blurred vision, tachycardia, drowsiness and constipation. There have been no studies of either medication for pediatric FAP or IBS, but hyoscyamine was found to have consistent evidence of efficacy in an adult meta-analysis [17].

Cyproheptadine

Cyproheptadine is a medication with multiple mechanisms, including antihistaminic, anticholinergic and antiserotonergic properties, as well as possible calcium channel blockade effects. It has been used in appetite stimulation and prevention of pain and vomiting in abdominal migraine and cyclic vomiting syndrome. Sadeghian *et al*. studied the use of cyproheptadine in 29 children and adolescents (aged 4.5–12 years) diagnosed with FAP in a 2-week, double-blind placebo-controlled trial. At the end of the study, 86% in the cyproheptadine group had improvement or resolution of abdominal pain compared with 35.7% in the placebo group ($p = 0.003$) [56]. These results need to be confirmed with additional larger trials.

Acid suppressants

Acid suppression agents, such as H2 blockers and proton pump inhibitors, are among the most common medications that are used in children with abdominal pain. Famotidine was studied by See *et al*. in a randomized, double-blind, placebo-controlled crossover trial of 25 children (aged 5–18 years) who met Apley's crieteria for RAP and reported symptoms of dyspepsia [57]. Children who met criteria for IBS were excluded. Patients received famotidine 0.5 mg/kg per dose twice daily for at least 14 days, although the total treatment length was variable depending on symptom response. On a subjective global assessment scale, more patients reported improvement on famotidine (68%) versus placebo (12%). However, there was no significant difference between famotidine and placebo on quantitative measures of symptom frequency and severity. There have been no controlled studies on the use of proton pump inhibitors for FAP or IBS.

Prokinetics

Prokinetic agents that stimulate gastrointestinal motility have been employed for patients with FGIDs, especially for conditions involving constipation or delayed gastric emptying, such as IBS and functional dyspepsia [58]. Tegaserod is a serotonin agonist that induces acceleration of small bowel and colonic transit through activation of 5-HT_4 receptors in the enteric nervous system. When combined with polyethylene glycol (PEG) 3350, tegaserod was found to be more effective in alleviating abdominal pain and increasing the number of bowel movements in adolescents with constipation-predominant IBS compared with PEG 3350 alone [59]. However, owing to an increased rate of cardiovascular events in adults taking the medication, tegaserod was removed from the market in March 2007. Two other serotonin-based agents with actions upon the 5-HT_3 receptor, alosetron and cilansetron, were also shown to be effective for adults with diarrhea-predominant IBS, but complications of severe constipation, ischemic colitis and perforations prompted withdrawal of these medications from the market in 2000 [60]. Dopamine (D2) receptor antagonists, such as metoclopramide and domperidone, improve gastric motility, but their use in pediatric FAP and IBS is limited by concerns for side effects including extrapyramidal reactions, drowsiness, agitation, irritability and fatigue [61]. Erythromycin, an antibiotic with motilin receptor agonist properties in the stomach at doses of 1–2 mg/kg per dose may also be helpful for symptoms of pain or dyspepsia, but there are no pediatric data to support its routine use in FAP or IBS [62].

Other agents

Several agents have been studied for the treatment of conditions such as dyspepsia, constipation, diarrhea, abdominal migraine or small bowel bacterial overgrowth in conjunction with FAP or IBS. Lubiprostone is a member of a new class of bicyclic fatty acid derivatives known as prostones. Lubiprostone acts on type-2 chloride channels located on the apical side of gastrointestinal epithelial cells to promote electrolyte and fluid secretion into the small intestine and may also stimulate colonic motility. In two clinical trials of adults with constipation-predominant IBS, 17.9% of patients treated with lubiprostone reported improvement in IBS symptoms compared with 10.1% of those treated with placebo ($p = 0.001$) [63]. A pediatric trial of lubiprostone for functional constipation has been completed, and preliminary data suggest that it was efficacious in the treatment of children with constipation.

Loperamide is an opioid-receptor agonist that slows colonic transit by acting on myenteric plexus receptors of the large intestine. Although loperamide is commonly used for treating diarrhea and urgency in patients with diarrhea-predominant IBS, adult studies have shown efficacy only against symptoms of diarrhea and not abdominal pain [64]. For patients with FAP or IBS associated with constipation, stool softeners and laxatives have been likewise employed. In the previously mentioned study of adolescents with constipation-predominant IBS conducted by Khoshoo *et al.*, patients treated with PEG 3350 oral solution as sole therapy did have a significant increase in number of bowel movements, but no improvement in abdominal pain [59].

Finally, bacterial fermentation of undigested carbohydrates in small bowel bacterial overgrowth has been suggested as a potential cause of IBS symptoms such as abnormal gas production and bloating. Treatment of bacterial overgrowth with antibiotics such as neomycin and rifaxamin has been found to be beneficial in adults with IBS [65,66]. Similar studies in children and adolescents are currently lacking.

Despite the wide range of potential pharmacologic options, the lack of good quality, well-controlled, pediatric trials prompted a recent *Cochrane* review to conclude that the “true efficacy of drugs for FGIDs in children remains to be elucidated” [67]. A technical review endorsed by the American Academy of Pediatrics and the North American Society for Pediatric

Gastroenterology, Hepatology and Nutrition similarly found limited evidence to justify the use of drugs or herbal preparations for chronic abdominal pain in children [68]. The use of low-dose antidepressants may be beneficial for a select group of patients, especially those with anxiety or other psychological comorbidities.

Complementary & alternative therapies

Approximately 36–41% of children with gastrointestinal complaints use complementary and alternative medicine (CAM) each year [69–71]. By definition, complementary medicine is used alongside conventional medicine, while alternative medicine is used in place of conventional medicine. CAM includes techniques such as acupuncture, chiropractics, homeopathy, herbal medicine and spiritual healing. It is important for clinicians to be aware of some of the more common forms of CAM, especially since some therapies can have adverse effects and may interfere with conventional, allopathic medications. Not surprisingly, evidence to support the use of CAM modalities in children is lacking, and there is a serious need for further research in this area.

Several herbal preparations, including Chinese herbal medications, ginger, bitter candytuft monoextract and peppermint oil (which was discussed previously in this article) have been employed for the treatment of FGIDs. Bensoussan *et al*. found that adults with IBS who received Chinese herbal medications in a randomized double-blind trial of 116 patients had significant improvements in bowel symptom scores as rated by patients ($p = 0.03$) and by gastroenterologists ($p = 0.001$) when compared with placebo [72]. Patients receiving Chinese herbal medications also reported significantly higher overall scores on a global improvement scale. On the other hand, in a later study by Leung *et al*., traditional Chinese herbal medications were not found to be superior to placebo in terms of symptoms and quality of life in adult patients with diarrhea-predominant IBS [73].

Acupuncture, also adapted from traditional Chinese medicine, is postulated to have effects on acid secretion, gastrointestinal motility and sensation of visceral pain, possibly mediated through the release of opioid peptides in the CNS and enteric nervous system. Two recent adult trials, however, did not find evidence to support the superiority of acupuncture compared with sham acupuncture in the treatment of IBS [74,75]. There have been no studies using acupuncture to treat children with FAP or IBS. A small, noncontrolled study of 17 children with chronic constipation reported an increased frequency of bowel movements with true acupuncture compared with placebo acupuncture [76]. Massage therapy has been hypothesized to reduce excitation of visceral afferent fibers and possibly dampen central pain perception processing, but there are limited data on the usefulness of massage therapy for FAP or IBS.

Expert commentary

Although most children with functional gastrointestinal disorders, such as FAP and IBS, will improve with time and reassurance, a subset of patients may present to the primary care physician or gastroenterologist with more complex, severe or persistent problems. The development of a biopsychosocial model of functional disease has helped, as it frames the disease in terms of being a positive diagnosis and not a diagnosis of exclusion. Much of the challenge in managing patients with functional disorders is linked to our incomplete understanding of the responsible pathologic mechanisms. The newly revised Rome III diagnostic criteria hold promise in enhancing ongoing research efforts through better categorization of patients by age and symptoms into separate disorders that may differ in etiology and responsiveness to treatment.

As it stands, there are little data to support the routine use of any pharmacological agent as a first-line therapy for FAP or IBS. Until larger studies with adequate power are conducted and

are able to demonstrate efficacy, use of medications should be carefully considered and tailored to each patient's specific symptoms and associated complaints. Differences in intervention and dosing, small sample sizes and inconsistent results of previous dietary intervention trials have likewise failed to provide enough good evidence to recommend empiric use of fiber supplementation, probiotics or lactose restriction for FAP and IBS in children.

The weakness of evidence in these studies may be due in part to methodological limitations, rather than a true failure of the interventions being studied. For example, larger adult studies of ispaghula husk fiber and *Lactobacillus* have both shown apparent benefit for IBS. Until more definitive studies are conducted in children, it may, therefore, be reasonable for the clinician to consider either of these relatively benign interventions. A 2–3-week trial of lactose restriction for older children and adolescents with IBS may also be considered, depending on the clinical history and presentation.

The largest numbers of studies on the treatment of RAP, FAP or IBS in children have focused on CBT and psychosocial interventions. As with pharmacologic and dietary approaches, evidence for the effectiveness of these treatments has been limited by small trials and clinical heterogeneity. Several studies employed a combination of multiple therapeutic approaches, making it difficult to determine which component was responsible for efficacy. Even among studies that only looked at CBT as a treatment, differences in specific therapeutic strategies and a lack of detailed descriptions hinder the ability to apply these therapies in clinical practice or make a strong conclusion about their efficacy. Nevertheless, consistent results supporting the benefit of CBT in general suggest that it may be a useful intervention in children. Indeed, the importance of psychological factors in patients with FAP and IBS is highlighted by large placebo responses seen in the control groups of several studies we reviewed, across all types of intervention.

There is a need for further trials to confirm the efficacy of interventions that have shown promise, in addition to evaluating new therapeutic options that have become available. For now, however, effective management of FAP and IBS in children and adolescents will require a multifaceted approach, customized to address each patient's specific symptoms and underlying triggers. It is crucial that physicians develop a positive therapeutic alliance with patients and their families with the goal of helping them understand the concept of the brain–gut axis as well as establishing reasonable expectations for symptom improvement.

Five-year view

Over the next 5 years, refinements in the Rome III diagnostic criteria for FAP and IBS will be reflected in more studies targeting specific phenotypes of symptoms, rather than recurrent abdominal pain in general. These changes will hopefully continue to shed light on potential etiological pathways, as well as guide research into new therapies. Increased recognition of the biopsychosocial model as the main framework for the evaluation and treatment of children with FAP and IBS will change the focus of their evaluation and management, moving away from FGIDs being perceived as a diagnosis of exclusion, and therefore obviating costly, unnecessary and potentially invasive testing and therapies. Psychosocial interventions will no doubt continue to remain an important tool in the management of FAP and IBS, especially as our understanding of the placebo effect in children with FGIDs improves. Ideally, studies will be able to elucidate the specific factors that influence or enhance the placebo response. Pharmacologic interventions hold the greatest potential for growth and development, with several candidate medications already in the pipeline based on recent advances in our understanding of neurotransmitters in the brain–gut axis. These include drugs that act on the serotonin receptor and transporter system: antidepressants, norepinephrine-reuptake inhibitors, opioids, cholecystokinin antagonists, neurokinin antagonists, chloride channel activators,

guanylate cyclase C agonists, atypical benzodiazepines, probiotics and antibiotics [77]. More sophisticated methods for evaluating gastrointestinal motility and transit may also prove helpful in demonstrating therapeutic efficacy in addition to subjective measures of improvement.

Key issues

- Diagnosis of functional abdominal pain and irritable bowel syndrome in children is based on signs and symptoms, and should take into account the biopsychosocial model of functional gastrointestinal disorders.
- Development of a positive therapeutic alliance between the physician and the patient/family is crucial.
- Management should be multidisciplinary and customized to address each patient's specific symptoms and underlying triggers.
- There are currently little scientific data to support the routine use of pharmacotherapy or dietary interventions. Meta-analyses have found that, as a class, psychosocial treatments are effective in treating somatic symptoms in both adults and children with functional gastrointestinal disorders.
- There is a need for further trials to confirm the efficacy of interventions that have shown promise, in addition to evaluating new pharmacologic options as they become available over the next 5 years.

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