Treatment of the child with functional abdominal pain: what does the evidence say?

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Introduction

More than one third of elementary and middle school children complain of weekly abdominal pain with persistence of symptoms for more than 8 weeks in 24% of children (1). Irritable bowel syndrome (IBS) type symptoms have been noted in 17% of high school students and 8% of middle school otherwise healthy students (2). Children with abdominal pain miss more school than their peers and their parents frequently miss work in order to take care of children not able to attend age appropriate daily activities. Pediatric studies have shown an association of chronic or recurrent abdominal pain with higher depression and anxiety scores both at the primary and the subspecialty level (3). Children with functional abdominal pain report lower quality of life compared with their healthy peers and have quality of life scores similar to children with inflammatory bowel disease (4). The parents' perception of the quality of life of these children is even lower than their children's self-reported scores. Cost associated with the evaluation of children presenting with functional abdominal pain is very high (5) and becomes even higher once the child is referred to a pediatric gastroenterologist (6). Yet, despite the high prevalence, morbidity and impact on health care cost of this condition very little was known until few years ago on what treatment can be used to effectively treat children with functional abdominal pain. In 2005, a technical review of the published evidence of clinical trials for chronic abdominal pain in children and a clinical report endorsed by the American Academy of Pediatrics found only limited evidence to justify the use of any drug or herbal preparation in the treatment of these conditions (7). At that time the only placebo-controlled published studies included a trial of famotidine in a small group of children with mostly functional dyspepsia (8) and a trial evaluating the efficacy of enteric-coated peppermint oil capsules in a small group of children with IBS (9).

Fortunately, in the past ten year great progress has been made in the understanding of the pathophysiology of pain predominant childhood functional gastrointestinal disorders (functional abdominal pain, IBS and functional dyspepsia). The recent publication of two iterations of symptoms based diagnostic criteria (Rome II and Rome III) for childhood functional gastrointestinal disorders (10) has also facilitated research in this otherwise challenging group of children by allowing more uniform study entry criteria. As a consequence, better designed intervention studies have been carried out and there are now several evidence based interventions likely to be helpful to the child presenting with functional abdominal pain.

It is now understood that genetics and environmental factors such as childhood acute gastrointestinal illnesses (infectious, allergic, or inflammatory), emotional, physical and sexual abuse, and gut motor disturbances are some of the factors that may have a long lasting impact in terms of the individual’s susceptibility to different life events. Early life events may be particularly important in sensitizing the gastrointestinal tract to develop an abnormal sensory and motor in response to other triggers experienced later on in life.

Once visceral hyperalgesia and gut motor hyper-responsiveness occur, the child is more likely to experience recurrent episodes of abdominal discomfort. How the environment reacts to the child complaint of pain, has then the potential to either improve or worsen the severity and chronicity of the symptom (11). Anxious parents, school teachers or peers may be overprotective in a harmful way, by keeping the child from attending school and other age appropriate activities, and by expressing anxiety and worries that can be frightening to a child who is already experiencing pain. Apprehensive parents and insecure medical providers may exacerbate the problem by subjecting the child to often fruitless and invariably painful or scary medical tests. On the other hand, when a family's coping style allows the child to maintain his or her activities despite the pain, and encourages independent and active coping style, the child preserves a normal level of functioning.

The understanding of the physical and behavioral components of functional GI disorders and the appreciation of the interplay between the central and peripheral factors leading to symptom generation has led to the use of treatments that address the different components of this disorder. Figure 1 depicts the treatments targeting the different pathophysiologic mechanisms of childhood functional abdominal pain. What follows is a summary of the evidence supporting each treatment strategy (summarized in Table 1)

Evidence based therapies

Reassurance:

Effective reassurance is very successful in every functional disorder. Satisfactory relief of symptoms has been reported in up to 65% of children with functional abdominal pain treated with placebo. The medical provider should point out that functional disorders are common, chronic conditions with an overall favorable prognosis. Comparing them to headaches, another common disorder that most people can relate to, may help putting things in perspective. The physician should encourage the families to ask questions and these should be answered with empathy, validating the symptoms and avoiding appearing judgmental. It is helpful to ask the children and their caretakers what *they* think is causing the child's symptoms, in order to alleviate anxiety about disorders that are exceedingly rare in children, such as cancer or diverticulosis, but that parents may be concerned about. The role of anxiety, stress and the importance of the brain-gut axis in the pathophysiology of symptoms should be explained. It should be made clear that the child should be an active participant in his or her recovery. If the patient is currently missing school, returning to school should be encouraged (12). Children in school are more distracted and less focused on their ailments. Parents can be very effective in maximizing wellness behaviors in their children by modeling appropriate responses to physical symptoms and rewarding healthy adaptive behaviors. A brilliant clinical study by Walker et al well illustrated this concept (and indeed it should be mandatory reading for all parents of children with FGID!) (13). In that study, parents were trained to interact with their children who were experiencing abdominal discomfort in one of three ways: attention, distraction, or no instruction. Compared to the no-instruction subgroup, symptom complaints by either children with chronic abdominal pain or well children

nearly doubled in the attention subgroup and were reduced by half in the distraction subgroup.

Diet:
A Cochrane review (14) identified two trials comparing fiber supplements with placebo, and two studies which compared lactose-containing with lactose-free diets in children with recurrent episodes of abdominal pain. It was concluded that was a lack of high quality evidence on the effectiveness of dietary interventions in this patient population and there was no evidence that fiber supplements or lactose free diets were effective in the management of children with intermittent or chronic abdominal pain.

Antispasmodics:
Functional GI disorders have been for many years equated to "motility disorders". The concept that pain is due to a "spasm" in the gastrointestinal tract is one that is often used to explain the pathogenesis of pain to the affected children and their parents. "Spastic colon" was for many year considered a term synonymous with IBS. Thus, it is not surprising that medications aimed at "relaxing the gut" have been and are still utilized in the treatment of pain predominant functional GI disorders. Unfortunately, although widely used for their antispasmodic effects, anticholinergic drugs such dicyclomine and hyoscyamine have not been not been proven effective in reducing abdominal pain in patients with IBS (15). There are no published studies evaluating anticholinergic drugs in children with functional abdominal pain. In a randomized, double-blind controlled study of pH-dependent peppermint oil capsules children with IBS, there was a reduction of abdominal pain severity in 75% of those children receiving peppermint oil for 2 weeks (9). The exact mechanism of peppermint oil is unknown but is probably related to its spasmolytic effect.

Antidepressants:
Relief of chronic pain in response to the use of antidepressant medications has been documented in adults both in depressed patients and in individuals without clinical depression. Tricyclic antidepressants have also been used in several chronic pain conditions in children (16) and in general they are used at smaller doses (0.2 to 0.4 mg/kg/day, 5-25 mg/day) than needed for the treatment of clinical depression. Two recent studies have evaluated the efficacy of tryciclic antidepressants in the treatment of pain predominant functional GI disorders in children. A randomized clinical trial conducted in a suburban pediatric gastroenterology practice found a beneficial effect of amitriptyline in adolescents with IBS (17). Children were randomized to 10, 20 or 30 mg of active drug depending on their weight or placebo for 8 weeks. The authors reported a beneficial effect of the active drug on quality of life and pain. The improvement of pain was present only in certain areas of the abdomen and at certain times of follow-up and there was an unusual negative placebo effect for pain, a factor which may have been responsible at least partially for the statistical difference found between the two groups. A larger multicenter, randomized, double-blind trial evaluated the efficacy of amitriptyline on 90 children with functional abdominal pain or IBS (18). It showed improvement in 59% of the children receiving amitriptyline in intention to treat analysis with a similar improvement noted also in the children receiving placebo. Both groups of children had also comparable improvement in pain, disability, depression and somatization scores

during the 4 weeks of the trial. No serious side effects were reported in the children receiving amitriptyline.
The efficacy of another antidepressant, the selective serotonin reuptake inhibitor citalopram, in improving abdominal pain of non organic etiology in children was evaluated in a pilot 12-week open label flexible-dose trial (19). Children received an initial daily dose of 10 mg that was progressively increased to 40 mg by week 4 if no symptom improvement was reported. At week 12, approximately half of the study children rated their symptoms as "very much improved". The study also showed an improvement in co-morbid anxiety and depression. However, the absence of blinding of both subjects and clinicians, the absence of a comparative group and lack of randomization does not allow to conclude the observed improvements were due to the effect of citalopram.

Probiotics:
Despite evidence that changes in enteric flora may play a role in IBS, convincing evidence for a pathogenic role of bacterial overgrowth or for a beneficial effect of probiotics or antibiotic therapy in pediatrics is still scant (20). Three well designed pediatric studies using different study protocols have evaluated the role of different probiotics in the treatment of children with pain predominant functional GI disorders. One hundred four children were enrolled in a double-blind, randomized controlled trial in which they received Lactobacillus rhamnosus GG (LGG) or placebo for 4 weeks (21). Frequency but not severity of pain was reduced in the LGG group after 4 weeks of therapy compared to placebo and only in the subgroup of children with IBS. These beneficial effects were not seen in the functional dyspepsia group or in those children with functional abdominal pain. In another placebo-controlled study by Bausserman and Michail, Lactobacillus GG showed no benefit in the treatment of abdominal pain but helped to relieve abdominal bloating (22).
In an international, multicenter, randomized, double-blind, placebo-controlled, crossover study, children 4 to 18 years of age with IBS were randomized to receive either VSL#3 (a probiotic preparation containing 8 strains of bacteria) or a placebo for 6 weeks (23). After a "wash-out" period of 2 weeks, each patient was switched to the other group and followed for a further 6 weeks. VSL#3 was found to be significantly superior to placebo in the subjective assessment of global relief of symptoms and in 3 of 4 secondary endpoints: abdominal pain/discomfort, abdominal bloating/gassiness, and family assessment of life disruption.

Other medications:
Cyproheptadine is a piperidine antihistamine. Unlike other antihistamines, cyproheptadine also antagonizes serotonin receptors in smooth muscle in the bowel and other locations and has only weak anticholinergic actions. Blockade of central muscarinic receptors appears to account for its antiemetic effects, although the exact mechanism of its action is unknown. Cyproheptadine is a medication widely used in pediatrics in children with dyspeptic symptoms, poor appetite and as prophylaxis of cyclic vomiting episodes. A double-blind, placebo-controlled trial evaluated the efficacy of cyproheptadine in the treatment of 29 children 4 to 12 years of age with functional abdominal pain who were randomized to cyproheptadine or placebo for 2 weeks (24). At

the end of the study, 86% of children in the cyproheptadine group and 36% of those in the placebo group had improvement or resolution in self reported frequency and duration of abdominal pain.

Montelukast is a leukotriene receptor antagonist commonly used in the maintenance treatment of asthma and to relieve symptoms of seasonal allergies. Based on the finding of duodenal eosinophilia in children with functional dyspepsia, two studies from the same group have evaluated the benefit of montelukast (10 mg/day) in children older than 6 year of age presenting with postprandial symptoms consistent with functional dyspepsia. In the initial double-blind, randomized, placebo-controlled, cross-over study, a significantly better clinical response was found in children receiving montelukast compared with those on placebo (25). Pain assessment scores deteriorated in 45% of montelukast responders after cross-over to placebo and improved in 62% of placebo non-responders on cross-over to montelukast. An open labeled study confirmed such results, despite a lack of change in eosinophil density or activation in duodenal biopsies after treatment (26).

Tegaserod is a $5HT_4$ agonist that was initially approved by the FDA for the treatment of constipation predominant IBS in adults and was subsequently withdrawn form the market due to concerns about its association with an increased risks of heart attack or stroke. A randomized study in post-pubertal adolescents with IBS compared the use of tegaserod and polyethylene glycol 3350 vs polyethylene glycol 3350 alone (27). It was found that polyethylene glycol alone resulted in significant increase in frequency of bowel movements but there was no significant improvement in pain. Treatment with the combination of the laxative and tegaserod led to both significant increase in the frequency of bowel movements and significant reduction in abdominal pain.

Cognitive behavioral interventions:

A metanalysis of pediatric studies concluded that cognitive behavioral therapy may be a useful intervention for children with chronic or recurrent abdominal pain (28).

A clinical trial of hypnotherapy in the treatment of functional abdominal pain in children has provided convincing evidence of the efficacy of this treatment. The study randomized 53 children to six sessions of either hypnotherapy or supportive "traditional" medical care over 3 months (29). Hypnotherapy was superior to the standard therapy and significantly reduced pain intensity and frequency as compared to the controlled group at all times during and even after discontinuation of therapy.

Guided imagery, sometimes known as "visualization", is a technique that uses the patient imagination to achieve behavioral changes and improvement of symptoms. During the process of guided imagery a state of deep relaxation is induced using thoughts and suggestions. Three studies have shown benefit of guided imagery for the treatment of functional abdominal pain in children (30-32). Despite the general agreement that cognitive behavioral interventions benefit children with intermittent or chronic pain syndrome it is often lamented that access to therapists knowledgeable in the use of this technique is inadequate. Thus, there has been an attempt to devise guided imagery techniques that are child friendly and can be used at home. In a study of 34 children, 6 to 15 years of age, with a diagnosis of functional abdominal pain, patients were assigned randomly to receive 2 months of standard medical care with or without home-based guided imagery treatment (33). Children on the home treatment arm of the study listened to guided imagery CDs daily for at least 5 days per week for 8 weeks. In an intention-to-

treat analysis, 63% of children in the guided imagery treatment group were considered treatment responders, compared with 26.7% in the standard medical care-only group. When the children in the standard medical care group also received guided imagery treatment, 61% became treatment responders. Treatment effects were maintained for 6 months.

How the environment (family, school, physicians) reacts to the child experiencing pain is likely to have great influence on whether the child will continue to be hypervigilant and anxious about the symptom or will learn how to cope with it effectively. Thus, involvement of the parents in the treatment is likely to provide additional benefit. In the largest to date treatment study of children with functional GI disorders, 200 children with persistent functional abdominal pain and their parents were randomly assigned to either a 3-session cognitive-behavioral treatment targeting *parents' responses* to their children's complaints of pain and *children's coping* responses or a three-session educational intervention that controlled for time and attention (34). Children in the cognitive-behavioral condition demonstrated greater decreases in pain and gastrointestinal symptom severity than children in the comparison condition. Parents in the cognitive-behavioral condition also reported greater decreases in solicitous responses to their child's symptoms.

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TABLE 1: TREATMENT OF CHILDHOOD FAP/IBS

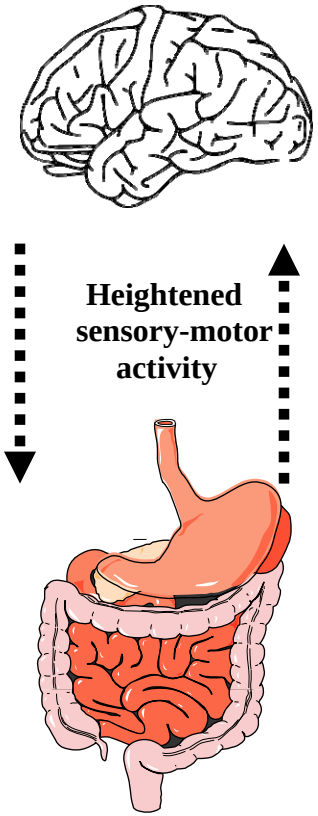
Intervention	*Strength of the evidence (pediatric studies)*
Hypnotherapy	++
Guided imagery	++
Dietary changes	-
Probiotics	+
Antispasmodics (peppermint)	+
Cyproheptadine	+
Tegaserod	+
Citalopram	+
Amitriptyline	+/-
Montelukast	+/-
Antibiotics	?
Lubiprostone	?

Figure 1

Pathophysiology

Cognitive/psychosocial factors:

Coping style
Anxiety/depression
Family stress
Secondary gain



Peripheral factors:

Inflammation
Intestinal dysmicrobism
Altered permabiltiy
Luminal mastcells
Neuronal hyperexcitability
Motor hyperactivity

Treatment

Central nervous system:

Hypnotherapy
Guided imagery
Family therapy
TCA
SSRI
Cyproheptadine

Gastrointestinal tract:

Dietary factors
Antispasmodics
Probiotics
Antibiotics
Serotonin agonists and antagonists
Chloride channel activator
Montelukast