Complementary therapies in paediatric gastroenterology: prevalence, safety and efficacy studies

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Chronic Abdominal Pain
Including functional abdominal pain, irritable bowel syndrome and abdominal migraine

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Introduction

Chronic abdominal pain is one of the most commonly encountered symptoms in childhood and adolescence with reported prevalence’s of 1 to 19% and accounting for 2 to 4% of paediatric office visits.\(^1,2\) It is characterized by chronic, recurrent or continuous abdominal pain not well localized. The pain may wax and wane, with asymptomatic episodes interposed with painful periods and can profoundly affect daily activities. Children often have feelings of anxiety and distress leading to significant school absence and their parents tend to be very worried. Studies of these children revealed self-reported quality of life scores comparable to children with inflammatory bowel diseases, highlighting the clinical significance of this problem.\(^3\)

Many pathologic conditions such as infectious, inflammatory, metabolic or anatomic disorders can cause recurrent abdominal pain, however in the vast majority of these children the pain is functional, that is without objective evidence of an underlying disorder. In the last years chronic or recurrent abdominal pain is classified according to the revised Rome criteria into 5 different abdominal pain related functional gastrointestinal disorders (FGIDs).\(^4\) The aetiology and pathogenesis of these disorders are still largely unknown, but a growing body of evidence suggests that the pain is a result of disordered brain-gut communication. Visceral hypersensitivity, altered conscious awareness of gastrointestinal sensory input and gastrointestinal dysmotility play a role. This chapter places particular emphasis on new insights in the pathophysiology of chronic, functional abdominal pain and abnormalities found at the level of the gut and the brain are discussed.

Children with chronic abdominal pain may present a sometimes frustrating challenge to their treating physicians since they have to determine which children might have an organic disorder and need further diagnostic tests. This chapter tries to provide guidance for the clinician in the diagnostic evaluation of the child with chronic abdominal pain. The importance of the recognition of so-called alarm symptoms and “red flag” signs is discussed. Finally, evidence based treatment options for children with functional abdominal pain are discussed including medications, dietary interventions, and psychological and complementary therapies. For the treatment of organic causes of chronic abdominal pain, readers are referred to the specific chapters on those diseases.

Definitions

In 1958 Apley and Naish defined recurrent abdominal pain (RAP) as 3 or more episodes of abdominal pain, severe enough to affect daily activities, occurring over a period of at least three months.\(^5\) For decades these criteria have been widely used, although often the original term recurrent abdominal pain was replaced by chronic or functional abdominal pain. Nowadays, the terms recurrent and chronic abdominal pain are abandoned and
replaced by “pain-related functional gastrointestinal disorders”. Functional gastrointestinal disorders (FGIDs) are defined as a variable combination of chronic or recurrent gastrointestinal symptoms not explained by structural or biochemical abnormalities. In
1999 in Rome, a group of experts in the field of paediatric gastroenterology made an attempt to set criteria for functional gastrointestinal disorders in childhood, the so-called Rome II criteria. These criteria have provided clinicians for the first time with a method for standardizing their definition of clinical disorders and have allowed researchers from various fields to study the pathophysiology and treatment of the same disorders from different points of view. At that time, however, no evidence was available to support a classification for recurrent abdominal pain in children in 4 pain-related FGIDs; i.e. functional dyspepsia (FD), irritable bowel syndrome (IBS), functional abdominal pain (FAP) and abdominal migraine. Furthermore, the inter-observer reliability in diagnosis while using the paediatric Rome II criteria among paediatric gastroenterologists and fellows was low. In recent years however, a preliminary validation of a questionnaire on paediatric gastrointestinal symptoms and features related to FGIDs, as defined by the Rome II criteria was reported. Since then three publications using the same questionnaire documented the prevalence of FGIDs in tertiary care clinics and in African American children in primary care in the United States. In Europe a study reported the prevalence of FGIDs in Italian children consulting primary care paediatricians. These publications have offered valid criticism of some disorders and provided preliminary validation of others.

Based on these latter studies, clinical experience and consensus between the members of the Rome III committee, the revised and updated Rome III paediatric criteria appeared in 2006. Because of the great variability in the severity and phenotypic presentation of children with abdominal pain–related FGIDs, the previously inclusive category of functional abdominal pain was divided into 2 separate disorders, childhood functional abdominal pain and childhood functional abdominal pain syndrome (FAPS). Furthermore, the required duration of symptoms was changed from to 3 to 2 months. More importantly, and in contrast to the Rome II criteria, the Rome III criteria for functional abdominal pain in childhood now differs from the criteria in adults. The new classifications for functional abdominal pain in children are listed in Table 1. These new Rome III paediatric criteria need to be validated in prospective studies on children with functional abdominal pain. Furthermore their relevance in terms of therapeutic interventions or predicting prognosis must be evaluated in long-term follow up studies.

**Epidemiology**

Chronic or recurrent abdominal pain is one of the most common paediatric complaints with reported prevalences in western countries of 0.3 to 19% and a median of 8.4%. This very wide range is caused by different methodologies used to assess the diagnosis such as personal interviews versus questionnaires and different criteria used to make the diagnosis of RAP. There is evidence to suggest a bimodal age peak in which the
symptoms of RAP are more prevalent. Apley and Naish observed already in their original study a steady rise in children below 5 years of age and then another rise between 8 and 10 years of age. This observation has been supported by many others studies evaluating the prevalence of RAP. Females seem to have a higher prevalence of RAP compared to males, but this difference manifests not earlier than around puberty. Other factors associated with a higher RAP prevalence are familial and socioeconomic factors. Bode et al demonstrated that a single parent household (odds ratio 2.9) and having a parent with gastrointestinal complaints (OR 5.3) were significantly associated with having a child with RAP. Furthermore, a lower socioeconomic environment has been associated with RAP and in addition, children of immigrants reported RAP in a significantly higher proportion compared to the indigenous population. No population-based study has prospectively evaluated the incidence of RAP in children over time. Several studies have investigated the relative frequency of the different pain-related functional gastrointestinal disorders, defined by the paediatric Rome II criteria as described in the section above. Irritable bowel syndrome was diagnosed in 0.2% of children seen by primary care paediatricians, in 13 to 20% of Chinese and Russian adolescents and in 22%-45% of children aged 4-18 years presenting to tertiary care clinics for a FGID. The prevalence of functional dyspepsia was 0.3% in primary care, 22% in Russian adolescents and between 12.5% and 15.9% in tertiary care settings. Abdominal migraine and functional abdominal pain are less prevalent; in paediatric gastroenterology clinics, abdominal migraine was diagnosed in 2.2 to 5% of the children and FAP in 0 to 7.5%. The figures from tertiary care clinics in North America with a predominance of IBS and FD are in contrast to the findings of Rowland et al: in a group of 125 Irish children with recurrent abdominal pain only 3% fulfilled the Rome II criteria for IBS and 5% for functional dyspepsia. Whether this remarkable difference is caused by geographical factors or a different interpretation of the Rome criteria is unknown. Eleven to 24% of the patients with recurrent abdominal pain did not meet the Rome II criteria for any FGID. Most common reasons were 1) having too few symptoms to meet the criteria for IBS or abdominal migraine but too many for FAP and 2) the pain episodes were less frequent than the 12 weeks required by the Rome II criteria for FAP. Since in the Rome III criteria the required duration of symptoms has changed from 3 to 2 months, the number of patients not meeting the criteria will probably decrease. It may be clear that large studies, using the recently revised Rome III criteria, need to be performed, not only among referred patients but also in unselected populations to validate the new criteria and to assess epidemiology of the different subtypes of pain related FGIDs.
Pathophysiology of functional abdominal pain

There is general agreement that functional pain is genuine and not simply social modelling, imitation of parental pain or a means to avoid an unwanted experience. The exact aetiology and pathogenesis of the pain are unknown. Yet there is a growing body of evidence that the pain is the result of disordered brain-gut communication involving both the efferent and afferent pathways by which the enteric and central nervous system communicate. It is not clear whether the different subcategories of functional pain result from a heterogeneous group of disorders with different pathophysiological mechanisms or represent variable expressions of the same disorder. The frequent occurrence of upper and lower symptoms in the same patient, for example dyspepsia and IBS suggests that the latter scenario may indeed be the case. Most of the studies evaluating the pathophysiological mechanisms in functional pain syndromes have been performed in adults with IBS. Since it has been shown that RAP in children can progress to IBS in adults\textsuperscript{19,20}, it seems logical to assume that the aetiology of functional pain syndromes in children does not differ much from functional pain syndromes in adults and nowadays RAP is seen as a possible precursor of IBS. The higher rate of spontaneous remission in children (30 to 70%), however, suggests that self-limiting developmental factors may also be involved in the pathophysiology of abdominal pain in children. 

The prevailing viewpoint is that the pathogenesis of functional pain syndromes involves the interrelationship between altered gastrointestinal motility and changes in visceral sensation, the so-called visceral hyperalgesia or hypersensitivity. The symptoms of altered motility can be diarrhoea, constipation, bloating and distension, whereas the symptoms of hypersensitivity are pain and discomfort. Hypersensitivity and dysmotility are probably strongly related. Altered sensitivity may exacerbate motility disturbances by up-regulating sensory-motor reflex loops in the gut and disordered motility may exacerbate hypersensitivity by creating excess stimuli through distension due to poor transit or high pressures due to spasms. Several hypotheses have been put forward to explain the altered motility and hypersensitivity and they will be discussed in the following sections.

Visceral hypersensitivity

In the last decade, visceral hyperalgesia has been recognized as playing an important role in symptom generation in functional abdominal pain syndromes not only in adults but also in children. In one study rectal sensitivity was measured by electric barostat in children with IBS and healthy controls. Children with IBS had a lower threshold for rectal sensations than controls.\textsuperscript{21} This finding was confirmed in another study where gastric and rectal sensitivity was measured in children with functional gastrointestinal disorders. The group of children with functional abdominal pain was hypersensitive in
both upper and lower gastrointestinal tract compared to healthy controls; those with IBS displayed only visceral hypersensitivity in the rectum. In most of the patients, their typical abdominal pain was reproduced by the barostat procedure.\textsuperscript{22} Finally, meal-related visceral sensation was evaluated in adolescents with functional dyspepsia and they experienced an increased postprandial nausea and bloating compared to healthy controls.\textsuperscript{23} In conclusion, visceral hypersensitivity appears to be a reproducible observation in children with functional abdominal pain disorders. Interesting is the finding of differences in the predominant site of hyperalgesia in children with distinct FGIDs. It is hypothesized that the specific site of the hyperalgesia is important for the phenotypic presentation of these children, with the more severe rectal hyperalgesia being associated with IBS symptoms and more generalized (but not as severe in the rectum) hyperalgesia with FAP. The mechanism of hypersensitivity, whether generalized or rectal, is not fully understood yet and can be through changes peripheral in the gut and the enteric nervous system (ENS) or central in the spinal cord or brain. Several factors (i.e. changes in serotonin signalling, genetic, inflammatory, stress, and psychiatric factors) have been proposed as contributing to alterations in enteric and spinal neural function and in CNS modulation of pain perception.

Altered central modulation of sensation

Central processing of pain is complex and occurs through different pathways. Pain is thought to have two dimensions: a sensory-discriminative component and an affective-motivational component.\textsuperscript{24} The discriminative component of gastro-intestinal pain encodes location, intensity and nature of pain and follows a route from the gut, via the dorsal horn of the spinal cord, the ventral posterior portions of the thalamus to the insula, an infolding of the temporal lobe. The affective-motivational component is thought to encode pain affect and suffering and runs through the spinal cord, the reticular formation of the brainstem, via the medial portions of the thalamus to the limbic system, particularly the part called the anterior cingulated cortex (ACC) (Figure 1). The ACC is a critical centre involved in the “unpleasantness” of the pain. Patients with ACC surgical lesions have an impaired pain interpretation and they report they can still feel the pain, but it isn’t bothersome to them.

Advances in functional brain imaging with either positron emission tomography or functional MRI have recently allowed study of these processes in healthy controls and IBS patients. Several studies demonstrated an increased activation of the anterior cingulated cortex in IBS patients compared to healthy controls. This activation occurred both during actual painful stimuli applied to the colon and anticipation of such painful stimuli.\textsuperscript{25,26} The clinical relevance of these altered patterns of activation is supported by several different findings. First, successful pharmacological interventions in IBS patients with either alosetron, a 5-HT3 antagonist or amitriptyline, a tricyclic antidepressant
are associated with reduced activation of the anterior cingulated cortex. Second, gut-directed hypnotherapy has been proven to be a successful therapy for IBS patients (see section on therapy). Several investigators have shown that hypnotic modulation of painful stimuli leads to significant changes within the ACC, suggesting that gut-directed hypnotherapy might have its effect through modulation of the affective-motivational component of pain. The exact mechanism leading to an increased activation of the limbic system is unclear. It is hypothesized that emotional processes like anxiety and cortical factors like previous experience of pain, coping mechanisms and psychosocial stressors could interact with limbic circuits to amplify the pain experience.

Genetics
Familial clustering of functional gastrointestinal disorders has been described and suggests a genetic transmittance of these disorders. Studies completed in adults for example, have demonstrated that IBS is more common in first-degree relatives of individuals with IBS. Furthermore, children with recurrent abdominal pain are more likely to have a parent with functional gastrointestinal complaints. A twin study,
performed by Levy et al, showed a 17% concordance for IBS in monozygotic patients with only 8% concordance in dizygotic twins, supporting a genetic contribution to IBS.34 This study however, also showed that a parental history of IBS was a stronger predictor of IBS than having a twin with IBS, suggesting that social learning is much more important than genetic factors. Recently this was confirmed by Mohammed et al, who found almost similar prevalence’s of IBS in monozygotic (17%) and dizygotic (16%) twins, showing that genetic factors are probably of little or no influence on IBS.35 It is therefore more likely that familial clustering is a reflection of a shared exposure to environmental factors including learned responses to abdominal complaints than of a genetic predisposition. Finally, studies, that examined possible associations between polymorphisms in the human serotonin transporter gene and IBS, have offered little evidence to suggest a genetic transmittance of functional gastrointestinal disorders.36

Role of serotonin

Serotonin (5-HT) is a neurotransmitter found both in the enteric and the central nervous system (CNS). It has emerged as a key mediator in modulating visceral sensitivity and motility.37 5-HT is synthesized and stored in the gut in a subset of epithelial cells, the so-called enterochromafin cells (EC-cells) from where it is released in response to luminal stimuli. This leads to activation of local secretory and motor reflexes as well as stimulation of afferent sensory nerves to the CNS. Serotonin uses different receptor types such as 5-HT1a-e, 5-HT2a,b,c, 5-HT3, 5-HT4, 5-HT5, 5-HT6, and 5-HT7. Some of these receptors have been identified only in the gut, while others are being located in the nervous system.38 Activation can lead to different effects, for example some receptors will inhibit and others will stimulate the peristaltic reflex. The signal of 5-HT is terminated mainly through a serotonin-selective reuptake transporter (SERT), that is expressed on gut epithelial cells, nerve endings and platelets. The different effects of 5-HT can be augmented by selective serotonin reuptake inhibitors (SSRI’s) as well as 5-HT receptor agonists or partial antagonists (see section on therapy).

It is becoming increasingly clear that changes in serotonin signalling occur in patients with IBS. Various elements of 5-HT signalling that have been reported to be different in IBS patients are the number of EC-cells, 5-HT content in EC-cells, expression of SERT and free serum 5-HT levels (studies reviewed by Mawe).39 The results of the studies performed so far are, however, not entirely in harmony, so the exact role of serotonin in the pathophysiology of IBS remains unclear. It is also not fully understood yet whether the changes in 5-HT signalling contribute to the alterations in motility and sensitivity or are just a response to altered gut function. In other words, what is cause and what is effect? Further studies are required to answer this question and also to gain a more complete picture of the changes that are occurring, not only in 5-HT signalling in patients with IBS, but also in patients with other pain-related FGIDs.
Inflammation

Evidence exists that a low-grade mucosal inflammatory process may play a role in IBS pathogenesis. First, it is well known that a proportion of patients with IBS describe that their symptoms have begun after an acute enteric infection. This observation was confirmed by Gwee et al. who reported that 20-25% of adult patients admitted to the hospital for bacterial gastroenteritis developed symptoms consistent with IBS in the first three months. Post-infectious IBS (PI-IBS) seems to occur particularly after Campylobacter and Shigella enteritis and it has been suggested that the severity of tissue damage and ulceration, which is a marked feature of these two infections, is a key factor in developing PI-IBS. Both in animal studies and patients with PI-IBS elevations of the number of EC-cells and 5-HT levels are found. These observations suggest that transient inflammation may result in persistent changes in the neuromuscular apparatus of the gut.

Second, an increased number of inflammatory cells (e.g. mast cells, T-lymphocytes, macrophages) has been detected in the colonic and ileal mucosa as well as in the muscularis externa of the jejunum of patients with IBS (summarized by Barbara et al.). These activated inflammatory cells can release many different mediators, including interleukins, nitric oxide, histamine and proteases. These mediators are capable of affecting the ENS leading to altered bowel function and an increased visceral sensory input generating feelings of abdominal discomfort and pain. So far, one has not been successful yet to influence the inflammatory process in IBS. An attempt to reduce intestinal inflammation with steroids in post-infectious IBS failed to demonstrate any symptomatic improvement, but further studies are now awaited.

Stressful events

Early stressful childhood events, both physical and psychological, have been theorized to be a contributory factor towards sensitization of visceral afferents, with possible life-long consequences. In an animal study it has been demonstrated that rats subjected to maternal separation were more likely to develop visceral hyperalgesia and increased colonic motility later in life. Furthermore, neonatal rats subjected to colonic mechanical or chemical irritation developed visceral hypersensitivity as adults. Clinical observations have also supported the theory that stress factors during early childhood may be influential towards the development of visceral hyperalgesia. Loss and separation during childhood, conflicting maternal relationships and an environment of physical, sexual or emotional abuse are all associated with the development of irritable bowel syndrome. Much attention has been given to the role of abuse. Population and clinic-based studies have consistently suggested that a considerable number of individuals with IBS report histories of physical, emotional and sexual abuse. Prevalence’s of physical abuse range from 6.2 to 26%, significantly higher than the prevalence rates observed in the general population. Sexual abuse is the most common type of abuse reported by people with
IBS and the rates range from 13 to 54%, depending on the methods of assessment and definitions of abuse used (reviewed by Koloski). Also in children with RAP a clear association with stressful events has been found. Two studies in the eighties demonstrated that children with RAP had experienced significantly more traumatic events such as illness, hospitalization and death, and had more stress associated with these events than did healthy children. These results were confirmed by two other studies reporting stressful life-events to be important predictors of recurrent abdominal pain in children. Every paediatrician is also aware of the association of RAP with frequently occurring social and behavioural factors like marital turmoil, pestering by peers and tendency to perfectionism. There are no data yet on the incidence of physical or sexual abuse in children with RAP. However, the high incidence of abuse among adult patients with IBS and the fact that RAP is seen as a precursor of IBS suggest that abuse can be an important factor in the aetiology of RAP in childhood and that paediatricians should be well aware of this possibility.

Stressful events later in life also play a role in IBS. Adult patients often describe a correlation between stress and the onset or exacerbation of their symptoms. Moreover, patients who develop an intercurrent bacterial enteritis are more likely to develop a post-infectious IBS if the infection occurs at the time when there are more stressful life events in the individual’s life.

One of proposed mechanisms in which stress, both early and later in life could modulate symptoms in functional pain syndromes is through the corticotrophin releasing factor (CRF), one of the important hormones involved in the stress response. Studies have shown that stress early in life results in both acute and chronic changes in the activity and regulation of the hypothalamo-pituitary-adrenal (HPA) -axis, particularly in the form of hypersecretion of CRF. CRF can induce an increase in colonic motility and in IBS this motility effect is markedly increased compared to normal individuals. CRF also increases the sensitivity of the colon to balloon distension, analogous to visceral hypersensitivity in IBS. It is thus possible that IBS patients have a perturbation in their stress-CRF response leading to increased motility and sensitivity. Another possible mechanism is through the activation of mast-cells in the gut. It is known from animal studies that mast cell degranulation can be evoked by stimulation of the central nervous system. Since it has been shown that symptomatology in IBS patients was correlated with the presence of activated mast cells in the colonic mucosa, this brain-to-mast cell connection could also be a good candidate to link psycho-emotional status like stress to gastrointestinal symptomatology. More research is needed in this area, preferably also in paediatric patients, since early modulation of the stress response could be an interesting therapeutic target.
Psychiatric factors
Several investigators have addressed the issue of psychiatric symptoms in children with recurrent abdominal pain. An anxiety disorder is found in approximately 80% of the children and almost 40% meets the criteria for a depressive disorder.57-59 These percentages may seem high, but are not surprising since decades of similar cross-sectional surveys already have shown that chronic pain, depression and anxiety often coexist. Potential explanations for the observed associations are [1] pain causes mood and anxiety disorders; [2] affective disorders cause or increase pain; [3] a common biological predisposition underlies both pain and affective disorders; or [4] pain or affective disorders do not directly cause the other but frequently associate with a true causal variable such as somatization, social stress or ineffective coping style.60 In primary care settings it has been shown that a persistent pain disorder at baseline predicted the onset of mood or anxiety disorders to the same degree that a baseline psychiatric disorder predicted the subsequent onset of chronic pain.61 So, evidence exists for bidirectional causal links between pain and mood.
It is also possible that pain and mood are both the result of a biological factor, for example an aberrant functioning HPA-axis due to stress as stated above. Apart from increasing colonic motility and hypersensitivity of the gut,52,53 changes in the HPA-axis also induce alteration in the serotonergic system, which in turn may contribute to the onset of depression and anxiety.51 Finally there is also evidence for the fourth proposed mechanism, i.e. both pain and symptoms of depression and anxiety are the result of ineffective mechanisms of coping with stress. A study performed by Thomsen et al. showed that successful coping mechanisms like problem solving, acceptance and positive thinking were associated with less pain, anxiety and depression in children with RAP.62 Less successful coping mechanisms like involuntary engagement (rumination and catastrophizing) or disengagement (escape and inaction) were associated with more somatic symptoms and higher levels of anxiety and depression. Recently it was also demonstrated that victims of bullying, who are likely to have less effective coping mechanisms, have higher chances of developing new psychiatric symptoms like anxiety and depression and somatic complaints like abdominal pain.63 It is clear that complex relationships exist between abdominal pain, stress and psychiatric symptoms and these relationships need to be examined more carefully in longitudinal, prospective studies.

Parental factors
Chronic abdominal pain is more common in families with higher rates of reported physical illness and psychological symptoms like anxiety.14,19,64,65 The relation between abdominal pain in childhood and these parental factors suggests that parental anxiety...
and preoccupation with physical health may reinforce the child’s own concerns about physiological and minor medical bodily sensations. The children may adopt the pain behaviour of their parents and one could hypothesize that this pain behaviour might attribute to visceral hyperalgesia. Several studies have also demonstrated the importance of the acceptance by parents of the role of psychological factors like stress for the resolution of recurrent abdominal pain in children. This suggests that these children may have learned to complain of pain or adopt the sick role model rather than to deal with stress or other emotional problems.

Another parental factor that has considerable impact on symptom severity in children with functional abdominal pain is the parents’ direct response to their child’s symptoms. When children express pain, parents are faced with a variety of choices like ignoring the pain behaviour, distracting the child, or expressing sympathy. Parents often believe that attention to somatic complaints is a good thing and distraction is potentially harmful. The opposite however, seems true. In a randomized controlled trial Walker et al. compared the effect of parent’s attention versus distraction or no instruction following induction of visceral discomfort in their child. Compared to the “no instruction” group, symptom complaints nearly doubled in the attention group and were reduced by half in the distraction group. The children in the distraction group rated parents as making them feel better compared to the attention group. Although more research is needed, this study demonstrates the importance of parents’ response to their child’s pain, which potentially has therapeutic consequences.

Dysmotility

In addition to a greater intestinal sensitivity, patients with functional bowel disorders may display abnormal gut motility. Exaggerated intestinal motor responses have been shown in adults with IBS after meal ingestion, stress or mechanical stimulation. Furthermore there is evidence that gas may be propelled abnormally through the gut: in normal subjects, gas experimentally infused in the small bowel was propelled rapidly through the bowel and consequently expelled. Conversely, a high proportion of IBS patients retained a significant amount of gas resulting in complaints of abdominal discomfort and bloating. Motility studies have been performed also in paediatric patients with FGIDs. Heterogeneous abnormalities in antroduodenal motility have been described in small groups of children with recurrent abdominal pain (reviewed by Dilorenzo). Furthermore, children with IBS have been shown to have altered contractile responses in the rectum to a meal. The relevance of these findings remains elusive for several reasons. First, in most studies an association between motor abnormalities and patient’s symptoms perception could not be found. Second, these motility changes are not found in all patient with IBS or FAP.
and third, drugs that have targeted gut motility such as antispasmodics or prokinetics have traditionally provided disappointing results. It is therefore now believed that motility disorders are more likely to be the result of other disturbances, rather than being a primary causal factor.

Role of intestinal gas and aerophagia

So-called gas-related symptoms such as flatulence, bloating and distension are common among patients with functional abdominal pain and especially IBS. The origin of these symptoms seems to be a combination of impaired gas clearance, hypersensitivity to normal amounts of gas and an excessive gas production. The gut in healthy subjects is able to transport and evacuate large gas loads, virtually up to any demand, without discomfort. IBS subjects, however, have an impaired capability to propel intestinal gas infused in the jejunum, leading to symptoms. Furthermore, this impaired propulsion is coupled to a visceral hypersensitivity to normal amounts of gas and gas retention in response to physiological concentrations of intestinal lipids. Moreover, it has been suggested that gas production could be increased due to small intestinal bacterial overgrowth. The changes in the intestinal microbiota may only be subtle with local increases in gas production, sufficient enough to be sensed as bloating or distension in patients with hypersensitivity, but too low to lead to a detectable elevation in breath hydrogen excretion. The fact that some patients benefit from manipulation of the intestinal flora by either antibiotics or probiotics adds prove to this hypothesis. The role of gas in children with abdominal pain is less well studied and most attention has been on infantile colic’s and aerophagia. Pathologic childhood aerophagia (PCA), i.e. the swallowing of excessive volumes of air, can cause burping, abdominal cramps, bloating, flatulence and even chronic diarrhoea. Therefore, it is not surprising that PCA frequently is diagnosed as functional dyspepsia, recurrent abdominal pain or irritable bowel syndrome. PCA, however, is seen as a distinct clinical entity and should be distinguished from other functional gastrointestinal syndromes. Essential diagnostic criteria are an abdominal distension that increases progressively during the day, increased flatus on sleep, visible or audible air swallowing and an oesophageal air sign in a chest radiograph.

Concluding remarks on pathophysiology

The very different findings described above support the concept that a simple universal aetiology for IBS does not exist. It is likely that there is a complex interaction of bio-psycho-social factors that generate the symptoms we know as IBS (Figure 2). Genetic influences and early social learning may result in a predisposition that is influenced by later psychological experiences and physiological factors. The relative contribution of each of these factors may vary among patients. Whether this pathophysiological concept is also
applicable to all Rome III subtypes of functional abdominal pain in childhood is far from clear and more research has to be done to elucidate this.

**Diagnosis of functional abdominal pain**

Because the exact aetiology and pathogenesis of abdominal pain related FGIDs are unknown and no specific diagnostic markers exist for any of them, functional abdominal pain (syndrome), irritable bowel syndrome, functional dyspepsia and abdominal migraine are often perceived as diagnosis of exclusion. Physicians are tempted to perform multiple tests to rule out an organic disease at all costs, before they are willing to make the diagnosis of functional abdominal pain. This is often traumatic for the child and expensive for the health service system. Negative test results generally do not reassure the patient, but rather reinforce a medical model of disease, making it more difficult to introduce the diagnosis of a functional disorder. It is therefore important to keep diagnostic investigations to a minimum. It is the clinical presentation, together with a well-structured medical history and physical examination, that usually indicates that a functional gastrointestinal disorder is the likely diagnosis in an individual child presenting with chronic abdominal pain.

**History and physical examination**

Many pathologic conditions such as infectious, inflammatory, metabolic or anatomic disorders can cause chronic or recurrent abdominal pain, however in the majority
of paediatric patients the pain is functional, that is without objective evidence of an underlying organic disorder. In his original study, Apley reported an organic disorder in only 8% of the studied patients. Others found an identifiable cause up to 27%; these higher percentages may be due to selection bias in tertiary centres or reflect improved diagnostic abilities. A long list of differential diagnosis is presented in Table 2. Only few items from medical history and physical examination provide clues for the possibility of an organic disease. Several studies, evaluating histories of children with chronic abdominal pain, have provided some evidence that frequency, severity, location, and timing (postprandial, waking during the night) of abdominal pain do not help distinguishing between organic and functional abdominal pain. The same can be said for so-called associated symptoms: children with chronic abdominal pain are very likely to have associated symptoms like anorexia, nausea, episodic vomiting, altered bowel movements, headache, back pain, arthralgia, or eye problems. Yet, none of these symptoms have been reported to help to distinguish between organic and functional abdominal pain.

Recurrent abdominal pain can result in interference with normal school attendance and performance, peer relationships, participation in organizations and sports, and other personal and family activities. Liebman found that only 1 of 10 children with functional abdominal pain attended school regularly and that absenteeism was greater than 1 day in 10 in 28% of patients. Again, inability to attend school is not associated with organic disease; only with the decision to consult a physician. As described in the section on pathophysiology, stressful life events, emotional symptoms like anxiety and depression and family factors play a role in functional abdominal pain. Several studies have evaluated whether the psychosocial history of the patient is relevant in the differential diagnosis of chronic abdominal pain and can be of value in predicting the existence of a functional disorder. Two small trials found no difference in significant recent life events between children with recurrent abdominal pain and minor organic disease. However, a diary study found that children with recurrent abdominal pain report significantly more daily stressors than healthy children, moreover, the relation between daily stressors and somatic complaints was significantly stronger for patients with abdominal pain than for healthy school children. Thus, although there is no evidence that life stress helps to distinguish between functional abdominal pain and organic disease, attention must be paid to this part of the history especially with respect to treatment options. It is also known that children with chronic abdominal pain are more often anxious or depressed than healthy children, but again this aspect cannot be used to differentiate from children with organic disease, since no studies have found a significant difference between patients with abdominal pain that is functional or organic in aetiology with respect to their emotional and behavioural symptoms. Finally, also family characteristics have not proven useful in distinguishing between functional and organic abdominal pain.
### Table 2 Differential diagnosis of chronic or recurrent abdominal pain

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<td>Celiac disease</td>
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<td>Parasitic infection (Giardia, Blastocystis hominis)</td>
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<td>Inflammatory bowel disease</td>
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<td>Meckel diverticulum</td>
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<td>Malrotation with intermittent volvulus</td>
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<td>Chronic appendicitis</td>
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<td>Galbladder, Liver and Pancreas</td>
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<td>Liver abscess</td>
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<td>Recurrent pancreatitis</td>
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<td>Genitourinary Tract</td>
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<td>Hydronephrosis</td>
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<td>Dysmenorrhea</td>
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<td>Pelvic inflammatory disease</td>
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<td>Miscellaneous causes</td>
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<td>Gilbert syndrome</td>
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<td>Familial Mediterranean fever</td>
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<td>Malignancies</td>
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<td>Sickle cell crisis</td>
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<td>Lead poisoning</td>
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<td>Vasculitis (HSP)</td>
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<td>Angioneurotic edema</td>
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<td>Acute intermittent porphyria</td>
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Physical examination of children with functional abdominal pain has been described rarely. The presence of tenderness on abdominal palpitation has been reported to be characteristic of children with functional abdominal pain when compared to control children. Furthermore, since almost 50% of the children with functional constipation present with chronic abdominal pain, one should carefully look for signs of constipation in this phase of establishing a working diagnosis. In children with functional constipation, a faecal mass is commonly found upon abdominal examination. External examination of the perineum and rectal area may show visible faecal incontinence. Although controversy exits, it is recommended that digital rectal examination be performed at least once.

According to experts, only the presence of so-called alarm symptoms or “red flags” suggests a higher prevalence of organic disease and definitely indicate the performance of diagnostic tests, but so far, no studies have evaluated the value of these red flags in discriminating organic from functional abdominal pain. Alarm signals in the history include: involuntary weight loss, growth retardation, delayed puberty, significant vomiting, significant diarrhoea, gastrointestinal blood loss, unexplained fever, rash, arthritis or a family history of inflammatory bowel disease. Red flags in the physical examination are localized tenderness in the right upper or lower quadrant, localized fullness or mass effect, hepatomegaly, splenomegaly, spine or costovertebral angle tenderness, oral ulcers and perianal fissure or fistula.

In conclusion, the key variables that point toward a functional diagnosis are the absence of alarm symptoms for an organic disorder and a normal physical examination, other than abdominal pressure tenderness.

Laboratory tests

There are no studies that have evaluated the usefulness of common laboratory tests (complete blood count, comprehensive metabolic panel that screens for liver, kidney and pancreatic dysfunction, erythrocyte sedimentation rate, urinalysis, and stool analysis of ova and parasites (eg: G. Lambliae or D. Fragilis) to distinguish between organic and functional abdominal pain. Since these tests are neither very invasive nor expensive, most clinicians will order for these tests, even in the absence of alarm signals. One should however realize that performing multiple tests may provide results that are unrelated to the presenting symptom or have no clinical relevance (such as a mildly elevated sedimentation rate). Repeating these tests to confirm the serendipitous findings may further increase anxiety in patients and parents and undermine the clinical diagnosis of a functional disorder. The value of testing for food allergies by IgE and IgG antibodies is debatable, although many clinicians will still include this in their initial workup.

Apart from the above mentioned tests, the diagnostic workup can include several other investigations, i.e. a celiac panel, screening for H. pylori and a lactose breathing test. Several studies have evaluated the usefulness of screening for celiac disease in children.
with recurrent abdominal pain and the results are conflicting.\textsuperscript{90,91} Because of the high frequency of celiac disease in the general population and the possible long-term consequences, most clinicians do include a celiac panel in their diagnostic work-up. \textit{H. pylori} infection can be found in a small percentage of children with RAP.\textsuperscript{90} This does, however, not necessarily indicate a causal relationship between the two, since children with \textit{H. pylori} infection are not more likely to have abdominal pain than children without \textit{H. pylori}.\textsuperscript{14} Lactose malabsorption can also be found in a subset of children. However, treatment of lactose malabsorption often does not result in resolution of abdominal pain, again questioning the causal relationship and the usefulness of performing this test in children with chronic abdominal pain.\textsuperscript{92,93}

Other diagnostic tests

The usefulness of abdominal ultrasonography has been examined in children with recurrent episodes of abdominal pain without alarm symptoms; abnormalities were found in fewer than 1%. When atypical symptoms were present, such as jaundice, urinary symptoms, back or flank pain, vomiting or abnormal findings on physical examination, the percentage increased to 11%. It was concluded in this study that ultrasonography should be used in children with RAP and atypical clinical features.\textsuperscript{94} In children without alarm symptoms, ultrasonographic examination might be done as a reassurance to parents and patient.

Studies of endoscopy, biopsy and/or oesophageal pH monitoring performed in children with RAP have demonstrated abnormalities in 25 to 56%, but reports have been limited by small sample size, sample bias, variability of findings and questionable specificity and generalizability.\textsuperscript{80} Since there is little evidence so far to suggest that the use of these diagnostic tests in the absence of alarm symptoms has a significant yield of organic disease, the inconvenience associated with these tests and their costs preclude its use in the initial evaluation of children with chronic abdominal pain. However, the reassuring effect of a normal endoscopy can have value in certain cases. Decisions regarding extensive diagnostic testing to rule out organic disease should be individualized, based on the child’s predominant symptoms, degree of impairment and parental anxiety.

Gastric and rectal barostat are increasingly used in scientific studies to detect visceral hyperalgesia (see section on pathophysiology). Since not every patient has an abnormal barostat, these tests cannot be used to distinguish functional from organic abdominal pain. Furthermore, gastric barostat is very invasive and to our opinion should thus only be used in the context of research. Rectal barostat is less invasive and can sometimes have an educational value for the patient by demonstrating rectal hypersensitivity.
Establishing a working diagnosis according to Rome III

When history, physical exam and limited screening tests reveal no abnormalities, the diagnosis of an abdominal pain related functional gastrointestinal disorder can be made. The next step is to classify according to the Rome III criteria as described earlier. Some remarks about this classification need to be made. First, it is not rare that children fulfil criteria of more than one FGID (especially the combination of functional dyspepsia and irritable bowel syndrome can be found) or change from one FGID to another over time. Second, a small percentage of children, who initially have received a diagnosis of FGID can have a change in diagnosis to an organic disease and therefore clinical follow-up to monitor for change in symptoms is mandatory. Finally, the value of sub-classifying chronic functional abdominal pain in different conditions is questioned by some clinicians. So far it is unknown whether recurrent abdominal pain indeed represents a group of heterogeneous conditions, and furthermore, if sub classifying RAP in separate FGIDs benefits the children in terms of treatment or predicting prognosis. Future research is needed to answer these questions.

Therapy

Only few studies exist on the pharmacological and behavioural therapy of functional recurrent abdominal pain in children. Moreover no placebo-controlled trials have been performed with adequate sample size and adequate duration of medications or psychological interventions in the treatment of any of the specific Rome-defined subtypes of pain-related functional gastrointestinal disorders, i.e. paediatric IBS, functional dyspepsia, abdominal migraine or functional abdominal pain (syndrome). Consequently, this section on therapy will focus on functional abdominal pain broadly, defined to mean a FGID where abdominal pain is the predominant symptom. When appropriate, the treatment of the different subtypes will be discussed separately. Relevant studies on adults will be mentioned where paediatric data are missing. Furthermore, one should keep in mind that the evaluation of any therapeutic intervention for the pain-related FGIDs is complicated by an important observation. A very high placebo response rate exists in virtually all clinical trials involving functional gastrointestinal disorders in adults, and no reason to believe that this is different in children. The placebo rate ranges from 20 to 50%, so evaluation of any intervention needs to be compared to this high baseline therapeutic effect of placebo. The high placebo response embraces not only the non-specific response to placebo, but also the natural history of the disease. Although the natural history of pain-related FGIDs in children is not well characterized, it is well appreciated that there is a significant variability in severity over time.
The current practice of many paediatricians in treating children with FAP and IBS is that of support and empathy for the family with the assurance that no serious disease is present and that children will likely outgrow it. With this approach approximately 40 to 70% of the children have resolution of their complaints (see section on prognosis). However, the remainder continues to exhibit symptoms and goes on to be adults with abdominal pain. In this group specific treatment including education, identification and modification of physical and psychological stress factors, dietary interventions, drug therapy and psychological therapies may be needed. Hospitalization is rarely indicated for children with functional abdominal pain.

Education and goals of therapy.

Education of the family and the patient is an important part of the treatment of the child with chronic functional abdominal pain. One need to emphasize that although the pain is real, there is no underlying serious or chronic disease and that this so-called functional pain is the most common aetiology of chronic abdominal pain in children. Reassurance that functional abdominal pain will not affect future health can have positive effects. It may also be helpful to explain what is known so far on the pathogenesis (i.e. visceral hyperalgesia and an altered brain-gut communication) in simple and age-appropriate language. Furthermore, parents and child should be encouraged to ask questions and share their concerns, which must be addressed in depth to avoid fears and misconceptions.

The primary goal of the therapy is not complete eradication of pain, but resumption of a normal lifestyle with regular school attendance, school performance to the child’s ability, participation in desired extracurricular activities and a normal sleep pattern. An important factor in resumption of a normal lifestyle is the parents’ response to the complaints of the child. Parental over involvement in pain behaviour and parent reinforcement of sick role behaviour are thought to be associated with ineffective coping with chronic pain and a perseverance of the complaints. Therefore, the family should be discouraged from reinforcing the symptoms by allowing the child to miss school and leisure activities and from paying too much positive attention to the symptoms. On the other hand, negative attention to pain in children with low self-esteem has also been associated with increased pain behaviour, possibly by creating affective distress that may further contribute to somatic symptoms. Thus, the parents’ attitude towards the pain should be balanced, showing enough support and understanding, but being aware that excessive attention and irregular attendance at school may provide the child with secondary gain.
Identification and modification of stress factors

An important goal in the therapeutic phase is to identify, clarify and possibly reverse physical and psychological stress factors that may have an important role in the onset, exacerbation, or maintenance of pain. In some cases, painful sensations may be provoked by physiologic phenomena, including postprandial gastric or intestinal distension, intestinal contractions, intestinal gas or gastro oesophageal reflux. In these cases pharmacological interventions like antispasmodics or anti reflux therapy might be useful. Psychological stressful life events that may exacerbate abdominal pain include death or separation of a significant family member, school problems, altered peer relationships and family marital or financial problems. Many parents find it difficult to accept that these kinds of psychological factors can influence or even cause the abdominal pain of their child and may be unwilling to discuss this. Nevertheless, it is important to pay attention to these factors since it has been shown that acceptance by parents of a psychological factor in the aetiology of their child’s complaint is important in the resolution of symptoms (see also section on prognosis).66,67

Identification of a child’s physical and psychological stressors can be done by means of a simple pain diary. In this diary frequency, duration and intensity of pain must be noted as well as accompanying symptoms like headaches, defecation, bloating and nausea. Furthermore patients are encouraged to look for a relation between pain and stress factors like those mentioned above or a relation with eating and food substances.

Dietary interventions

Parents frequently believe that food intolerances are to blame for many of the abdominal symptoms of their child as they have noticed that pain episodes often worsen in the postprandial period. Not uncommonly however, this is caused by a non-specific increase in gut and colonic motility that occurs with food ingestion. Given that increased colonic motor activity has been shown to be associated strongly with abdominal pain in patients with IBS.98 it is important for parents and patients to realize that the process of eating, irrespective of what is eaten, may exacerbate the symptoms. Nevertheless, dietary manipulation may result in substantial improvement in symptomatology in patients, provided it is individualized. Below, several options for dietary interventions are discussed.

Fibres

The most common form of dietary advice offered to patients with recurrent abdominal pain has been to increase their intake of fibres. As fibres decrease the whole-gut transit time, fibre-enriched diets may be more useful in the subgroup of patients with constipation.99 In children with RAP two randomized controlled studies have evaluated the effect of adding fibres to the diet.100,101 In the first study the addition of 10 g of
insoluble dietary corn fibre in a cookie was tested during 6 weeks and in the second study the children received fibres in the form of cereals (165g) for a period of 7 weeks. The primary outcomes in both studies were the number of pain episodes. Analyzing the results of both studies it was concluded that the evidence supporting the use of fibre is, at best, weak and, at worse, inconclusive. However, the addition of fibre each day is a simple and inexpensive intervention that might benefit some children with pain-related FGIDs.

**Lactose avoidance**
The role of lactose intolerance in chronic abdominal pain has been addressed by several investigators. Two studies have examined the effect of a trial of lactose avoidance in children with chronic abdominal pain. In both studies all children were tested for lactose malabsorption. During the diet trials, there were no differences in the number of children who claimed relief, whether they were lactose intolerant or tolerant or whether they received lactose or lactose-free milk. Thus, there seems to be no association between recurrent abdominal pain in children and lactose intolerance and a lactose-free diet is unlikely to improve the symptoms of RAP.

**Food allergies**
Many parents are convinced that food allergies play a role in the symptoms of their child, leading to the initiation of a strict dietary regime without first consulting health care professionals. The role of food allergies and especially cow’s milk allergy in recurrent abdominal pain and the best ways of diagnosing these allergies are still under debate, but adverse reactions to food probably are a causative factor in less than 5% of the children with recurrent abdominal pain. Until new and more reliable tests to diagnose food allergy have been developed and implemented in clinical settings, an elimination diet followed by a double-blind placebo-controlled food challenge should be performed when a food allergy is considered. This food challenge should take at least a week considering the suspected immunological delayed-type reactions. When the challenge is considered positive, patients are advised to follow an elimination diet, supervised by a dietician to prevent nutritional deficiencies. In some patients, however, compliance with the dietetic regimen is poor and in others it may be difficult to remove all traces of the offending food from the diet. To overcome these problems one might prescribe sodium cromoglycate. In adult patients with IBS and suspected food allergies, symptoms improved in 60% of patients treated with an elimination diet compared to 67% of those treated with oral cromolyn sodium. Also in an Italian study among 153 children with abdominal pain and diarrhoea treatment with oral sodium cromoglycate (mean 63 mg/kg/day) appeared to be superior to an elimination diet in reducing intestinal symptoms.
Probiotics

A probiotic can be defined as a beneficial species of bacteria that colonizes and replicates in the human intestinal tract and provides a positive benefit to the host. Probiotics play a role in preventing overgrowth of potentially pathogenic bacteria and maintaining the integrity of the gut mucosal barrier. The effects of probiotics have been studied in adults with IBS, but so far the evidence of benefit is not compelling. Improvement of bloating, flatulence and abdominal pain in some studies has been reported, but the studies are difficult to compare because of differences in study design, probiotic dose and strain. Recently O’Mahony et al examined the effect of two probiotics (Lactobacillus salivarius and Bifidobacterium infantis) compared to placebo in 60 adults with IBS. Only B. infantis alleviated significantly symptoms like pain, abdominal distension and bowel movement difficulty. Since, however, an effect on quality of life was not seen, it is questionable if this symptom reduction was relevant. Interestingly, the symptomatic response was associated with normalization of the ratio of an anti-inflammatory cytokine (IL-10) to a proinflammatory cytokine (IL-12), suggesting an immuno-modulating role for this organism.

In children with abdominal pain disorders two randomized controlled trials have been performed, both with capsules containing Lactobacillus GG or placebo. In the first trial (n=50) no difference in gastrointestinal symptoms was found except for a lower incidence of perceived abdominal distension. In the second study (n=104) an improvement in pain severity was found in IBS patients, but no effect of probiotics was seen in FAP patients nor in FD patients. Clearly further studies are indicated to determine the role of the different strains of probiotics in patients with IBS or FAPS. In these studies, the focus should not only be on symptomatology and quality of life but also on inflammatory and immunological markers to learn more about pathophysiology.

Pharmacological treatment

Drug therapy for pain-related FGIDs has generally been directed at symptom alleviation, rather than at precise pathophysiological abnormalities. However, with an increased understanding on the etiology of visceral hypersensitivity and dysmotility new therapeutic strategies are being developed aiming at modulation of gastrointestinal motor function, neurohormonal stress responses, cytokines involved in inflammation and central processing of pain information.

While awaiting these new strategies, medications for functional abdominal pain in children are best described judiciously as part of a multifaceted, individualized approach to relieve symptoms and disability. This recommendation is based on the fact that in contrast to adults with IBS there is only a paucity of studies examining pharmacologic interventions in children with recurrent abdominal pain and the evidence for these interventions is often inconclusive. The decision to medicate a child must therefore be
considered in the context of this limited knowledge and must balance the potential risks and benefits of the intervention.

**H2 Blockers**

One double-blind, placebo-controlled trial examined the effect of famotidine, an H2-receptor antagonist, in 25 children with abdominal pain. The global evaluation suggested that there was only a small benefit of famotidine over placebo, but the study population was heterogeneous. A subset of patients with dyspeptic symptoms did however show a significant improvement in symptoms. It seems therefore that H2 receptor antagonists might be prescribed to patients with functional dyspepsia.115

**Serotonergic agents**

In the section on pathophysiology, the role of serotonin as a key mediator in modulating visceral sensitivity and motility has been discussed. Serotonin can be modulated by (partial) antagonists as well as serotonin reuptake inhibitors (SSRI’s). Both type of medications can indeed provide symptom relief in patients with functional abdominal complaints, but most studies have been performed in adults. Only pizotifen, a potent antagonist of the serotonin 2A (5-HT2A) receptor and citalopram, a selective serotonin reuptake inhibitor have been studied in children. Pizotifen (0.25 mg twice daily) was compared to placebo in 14 children with abdominal migraine; it was well tolerated and resulted in a decrease in the number of days with abdominal pain.16 However, this drug is not approved in the United States and its use is thus limited. The efficacy, tolerability and safety of citalopram in the treatment of functional paediatric abdominal pain was studied in 25 children in a 12-week, open-label trial.117 Twenty-one subjects (84%) were classified as responders and ratings of abdominal pain, anxiety, depression and other somatic symptoms improved significantly over time. The medication was generally well tolerated. It was concluded that citalopram is a promising treatment, but randomized, controlled studies are needed.

Novel pharmacological approaches in adults with IBS include serotonergic type 3 (5-HT3) antagonists such as alosetron and cilansetron, and tegaserod, a serotonergic type 4 (5-HT4) partial agonist. They all provide a modest symptom improvement, but due to severe side-effects (drug-related ischemic colitis and an unexpected high number of ischemic cardiovascular events) these drugs have been withdrawn from the market. Several other serotonin neuromodulators are in the pipeline, it is unclear however whether they will be more safe and effective.

**Tricyclic antidepressants (TCAs)**

The recommendation in the past for use of TCAs to treat functional abdominal pain in children had been based primarily on anecdotal experience118 and positive results in adults with irritable bowel syndrome. Potential mechanisms of action of TCAs include reduction of central pain perception, alternations in gastrointestinal physiology and
a psychopharmacologic affect. A meta-analysis of 12 studies among adults with IBS suggested efficacy, with 3-4 patients needed to treat to demonstrate benefit over placebo. However, many of the studies included in this report have been criticized as methodologically flawed. A later conducted, well-controlled trial of desipramine versus placebo in 216 adult patients with IBS did not show a significant difference in pain relief. Recently, a small RCT in 33 adolescents with IBS showed improvement in quality of life and reduction of abdominal pain, although the effects decreased after cessation of the drug. The potential side effects of TCAs, including the reports of sudden death in young children, a very low therapeutic index and a lack of efficacy in comorbid depression prevent recommendation as a first line treatment option in children with functional abdominal pain.

Psychological approaches

Because children with RAP are significantly more likely to have high levels of anxiety and depression symptoms, therapies that are capable of addressing these symptoms seem ideal for treating this group of patients. Cognitive behavioural therapy (CBT) has been proven efficacious in the treatment of anxiety and depression disorders in children. Therefore, a strong rationale exists for using CBT in this group of patients. Two Australian and one American randomized-controlled trial have examined the effect of CBT on children with RAP. Treatment programs in the three studies differed slightly and consisted of increasing the understanding of pain and pain management, reinforcement of well behaviour and teaching cognitive coping skills. The first study showed decreased levels of pain in both the experimental and the control group. However, the CBT group improved more quickly, the effects generalized to the school setting and a larger proportion of subjects were completely pain-free by 3 months’ follow-up. In the second study, the CBT group had a higher rate of complete elimination of pain, lower levels of relapse at 6 and 12 months’ follow-up, and lower levels of interference with their activities as a result of pain. After controlling for pre-treatment levels of pain, children’s active self-coping and mothers’ care giving strategies were significant independent predictors of pain behaviour after treatment. Finally in the third study, children and parents participating in the CBT intervention reported significantly less child and parents reported pain immediately following the intervention and up to 1 year after study entry, as well as significantly fewer school absences. However, this last study suffered from methodological limitations such as significant differences at baseline and inadequate randomization procedures. Nevertheless, it can be concluded that there is evidence that cognitive behavioural therapy can be useful in improving pain and disability in children with functional abdominal pain. More studies are needed to assess the cost-benefit of CBT in comparison to standard medical care, the effect on co morbid internalizing psychopathology and the long term follow-up.
Another psychological approach that might be useful in the treatment of children with FAP and IBS is gut-directed hypnotherapy. In this therapy a hypnotic trance is induced in which patients are given suggestions, directed towards control and normalization of gut function in addition to relevant ego-strengthening interventions. The first RCT with gut-directed hypnotherapy was performed in 1984 and involved 30 adult patients with IBS; the hypnotherapy group showed a dramatic improvement in abdominal pain and general well-being. A follow-up study among more than 200 patients with IBS who were refractory to conventional treatments showed that 71% of the patients initially responded to therapy. Of these, 81% maintained their improvement over time, while the majority of the remaining 19% claimed that deterioration of symptoms had only been slight. Not only symptom scores improved, but also quality of life and anxiety and depression scores. Similar findings have also independently been reported by others (reviewed by Tan). The mechanism of action is not well understood yet. Relief of pain could occur at the level of the gut or through modification of central nervous system processes. It has been shown that hypnosis reduces colonic motility and normalizes disordered rectal sensitivity. At the same time, brain imaging studies have demonstrated that hypnosis can modify cerebral processing of pain signals in the anterior cingulate cortex. In children with RAP three uncontrolled studies have shown the feasibility of the use of (self-)hypnosis and guided imagery: 29 out of 33 children showed significant improvement with a decrease in weekly pain episodes. Recently, a RCT in 52 children with either FAP or IBS demonstrated that gut-directed hypnotherapy was highly superior to standard medical therapy with 85% versus 25% of the children in clinical remission one year after treatment.

Complementary therapies
Despite all above described therapeutic interventions, there is still a considerable amount of patients with persisting complaints for whom effective therapies are lacking. A lot of patients with functional bowel disorders have therefore prompted an interest in complementary and alternative therapies such as herbal remedies, acupuncture or massage. It might be useful for paediatricians and gastroenterologists to become familiar with these therapies; it is likely their patients already are. Furthermore, especially herbal medications are not without adverse effects and patients should not take these products without medical supervision.

Different herbal medicines have been tried in patients with IBS and recurrent abdominal pain with mixed results. Most studies have been performed in adults. An Australian randomized-placebo-controlled trial demonstrated that Chinese herbal medicine, both standard and individualized formulations, may offer improvement in adults. Peppermint is commonly found in over-the-counter preparations for IBS and has
been found effective.\textsuperscript{135} The mechanism of action is thought to be from the menthol component of peppermint that relaxes gastrointestinal smooth muscle by blocking calcium channels.\textsuperscript{136} Also in children with IBS the use of peppermint oil seems to be beneficial. In a small randomized, double-blind controlled “only” 2-week trial 76\% of the patients receiving enteric-coated peppermint oil capsules reported a decrease in symptom severity versus only 19\% in the placebo group.\textsuperscript{137} Curcuma and fumitory, two other over-the-counter remedies, did not show any therapeutic benefit over placebo in adult patients with IBS. Finally, ginger (\textit{Zingiber officinale}) is used by some patients, especially those with nausea, dyspepsia or diarrhoea as one of the main complaints. It has a prokinetic action, probably mediated by spasmolytic constituents of the calcium antagonist type.\textsuperscript{138} Ginger has been proven effective for reducing postoperative nausea and vomiting\textsuperscript{139} and nausea in early pregnancy.\textsuperscript{140} It seems to be relatively safe, although abdominal discomfort has been noted in some patients. No RCT’s in paediatric functional gastrointestinal disorders have been performed so far.

Massage therapy is a commonly used complementary medicine modality in patients with chronic pain. Its use is based amongst others on the assumption that massage may reduce excitation of visceral afferent fibres and possibly affect central pain perception and processing. Recently it was shown that massage can increase vagal tone and gastric motility.\textsuperscript{141} In adults with IBS a small, single-blind trial did not show any benefit of reflexology foot massage on abdominal pain, defecation frequency and abdominal distension.\textsuperscript{142} In children one study examined the effect of massage in infants with colicky symptoms.\textsuperscript{143} The authors concluded that the decrease of total and colicky crying hours reflected more the natural course of early infant crying and colic than a specific effect of the intervention. Studies with massage among children with IBS or FAP have not yet been performed.

Acupuncture is part of the traditional Chinese medicine and has become very popular in western countries in the last decades. Acupuncture and acupressure appear to ameliorate postoperative nausea and vomiting and thus might be useful in functional gastrointestinal complaints.\textsuperscript{144} It is claimed that acupuncture is effective for IBS, but there are no data to support this. A recent prospective, blinded and sham/acupuncture controlled study in 59 adult patients with IBS found a small but non-significant difference in response rate (40.7\% versus 31.2\% relief).\textsuperscript{145} A second similar study among 43 patients found no differences and it was concluded that acupuncture in IBS is primarily a placebo response.\textsuperscript{146} No good studies has been performed examining the benefits of acupuncture in children with FGIDs.
Concluding remarks on therapy

Because the pain-related FGIDs tend to be chronic, waxing and waning, a quick cure in every patient by any therapy is unlikely. Because of the high spontaneous remission of 30 to 70%, a step-wise approach is reasonable with the first step being education, identification & modification of stress factors and dietary interventions if necessary. When symptoms persist or reoccur, the next step could be a trial of one of the psychological treatments like cognitive behavioural therapy, (self-)hypnosis or guided imagery. It seems reasonable to reserve pharmacological interventions for patients who fail the above mentioned therapies or are unwilling to consider it. There is no doubt that additional research is needed; randomized, double-blind placebo controlled trial are required for new drugs that are currently tested in adults with FGIDs.

Follow up and prognosis

Scarce data exist on the natural history of abdominal pain in children with only a limited number of longitudinal studies following children with recurrent abdominal pain into adolescence and adult life. In the seventies and eighties several authors regarded paediatric RAP a short-term phenomenon. However, later studies, studying the long-term follow-up (5-30 years) of recurrent abdominal pain in childhood, showed that a significant proportion of 25 to 66% either continues to experience abdominal pain symptoms or develops other symptoms such as chronic headache, back pain, fibromyalgia, anxiety and sleep disturbances throughout adolescence and adulthood. Some studies have evaluated the natural history of childhood abdominal pain and its suggested association with adult irritable bowel syndrome. In an English study, following a cohort of 5362 subjects from birth until age 43, the presence of recurrent abdominal pain was evaluated at 3 time points in childhood (at age 7, 11 and 15) and at adulthood. The prevalence of childhood abdominal pain was more or less 20% on each occasion. Only 2% experienced RAP on all three time points, suggesting that around 10% of the children with recurrent abdominal pain in the general population continue to exhibit symptoms into adolescence. Persistent abdominal pain in childhood was modestly associated with other common physical symptoms in adulthood and was a strong predictor of adult psychiatric disorders. It did not predict, however, abdominal pain in adulthood. This is in contrast to a birth cohort study from New Zealand, where 1037 children were followed until the age of 26. Irritable bowel syndrome at age 26 was significantly more common among individuals with a history of RAP between age 7 and 9 years compared to those with no history of RAP. It is unclear why adult IBS was specifically linked to RAP reported at 9 years, but not at other time reports.
Walker et al. showed that five years after the initial evaluation, 45% of the 76 children with a history of RAP still had frequent abdominal pain compared to 20% of the control subjects. Furthermore, female patients with a history of RAP appeared to be at an increased risk of IBS during adolescence and young adulthood. A recent study by Pace et al. confirms these observations indicating that paediatric RAP can predict later development of IBS. A cohort of 52 patients with RAP was followed up between 5 to 13 years; IBS was present in 29% of the patients at follow-up. Subjects who had developed IBS-like symptoms were almost three times more likely to present at least one sibling with similar symptoms. This suggests that a positive family history on RAP or IBS is an important determinant of persistent abdominal pain in adulthood, possibly through the learning of specific illness behaviour (see also section on pathophysiology).

Two studies examined adverse prognostic factors in children with recurrent abdominal pain. In the first study 28 children with RAP of sufficient severity to necessitate hospitalization were evaluated; 14 continued to complain of pain. Only 1 of 14 parents of children with ongoing pain believed that there was a psychological cause for their child’s pain whereas 11 of 14 parents of the recovered children believed that the cause was attributable to psychological factors. It was concluded that acceptance by parents of a biopsychosocial model of illness is important for the resolution of recurrent abdominal pain in children. These findings were confirmed by Lindley et al. who carried out a retrospective analysis in a cohort of 23 children aged <16 years with functional abdominal pain. Poor outcome, defined as continued pain and failure to return to normal functioning >12 months after onset, was associated with refusal to engage with psychological services and lack of development of insight into psychosocial influences on symptoms. Moreover, involvement of more than three consultants and lodging of a manipulative complaint with hospital management by the child’s family were adverse prognostic factors.

In conclusion, 25 to 66% of children seeking medical help for recurrent abdominal pain continue to experience similar symptoms in adulthood. They are at increased risk of developing other physical symptoms or psychiatric problems like anxiety. A family history of IBS, parental refusal to acknowledge the role of psychological factors in the genesis and maintenance of abdominal pain and an increased healthcare consumerism are associated with persistence of symptoms.
Reference List


