Functional abdominal pain disorders in children: therapeutic strategies focusing on hypnotherapy
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GENERAL INTRODUCTION & OUTLINE OF THE THESIS

PARTS OF THIS INTRODUCTION HAVE BEEN PUBLISHED AS:
Chapter 23.3: Chronic abdominal pain, including functional abdominal pain, irritable bowel syndrome and abdominal migraine
Juliette M.T.M. Rutten, Arine M. Vlieger, Marc A. Benninga
Hamilton, IL. [in press]

Chronische buikpijn bij kinderen
Juliette M.T.M. Rutten, Arine M. Vlieger, Marc A. Benninga
Praktische Pediatrie, nascholingstijdschrift over kindergeneeskunde 2013;7:20-5
INTRODUCTION

Chronic abdominal pain is one of the most commonly encountered symptoms in childhood and adolescence and accounts for 2 to 4% of pediatric office visits. It is characterized by chronic, recurrent or continuous abdominal pain which is 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 symptoms of depression and/or anxiety and distress leading to significant school absence. Studies of these children revealed self-reported quality of life (QoL) scores comparable to children with inflammatory bowel diseases, highlighting the clinical significance of this problem. Many pathologic conditions can cause chronic or recurrent abdominal pain, but in the vast majority of children, no objective evidence for an underlying organic disease can be found. These children are diagnosed as having one of the abdominal-pain related functional gastrointestinal disorders (AP-FGIDs) according to the Rome III criteria. Five AP-FGIDs can be distinguished: functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine (AM), functional abdominal pain (FAP) and functional abdominal pain syndrome (FAPS). The pediatric Rome III criteria for these functional abdominal pain disorders are shown in Table 1. According to adult Rome III criteria, IBS can be classified into subtypes based on the predominant bowel habit, which are constipation predominant (IBS-C), diarrhea predominant (IBS-D), and mixed type with alternating episodes of both constipation and diarrhea (IBS-M). If abnormality of stool consistency is not sufficient to meet criteria for IBS-C, -D, or -M, IBS is classified as unsubtyped (IBS-U). These criteria for IBS subtyping are not available for children and therefore adult criteria are commonly used.

EPIDEMIOLOGY

AP-FGIDs are common worldwide, with prevalence rates of 0.3 to 19% (median 8.4%) in western countries. This very wide range in prevalence rates is likely to be caused by differences in methodologies used to assess the diagnosis. AP-FGIDs are also prevalent in developing countries, with prevalence rates up to 22.6% in recent studies conducted in Sri Lanka, China and Turkey. IBS is most frequently diagnosed in up to 45% of pediatric AP-FGIDs. There is evidence to suggest a bimodal age peak in which the symptoms of abdominal pain are more prevalent in children below 5 years of age and between 8 and 10 years of age. Females seem to have a higher prevalence of AP-FGIDs compared to males (ratio 1.4:1), but this difference manifests not earlier than around puberty. Other factors associated with a higher prevalence of AP-FGIDs are familial factors, such as a single parent household (odds ratio 2.9) and having a parent with gastrointestinal complaints (odds ratio 5.3). A lower socioeconomic environment has also been associated with AP-FGIDs and children of immigrants reported recurrent abdominal pain in a significantly higher proportion compared to the indigenous population.

PATHOPHYSIOLOGY

The exact etiology and pathogenesis of AP-FGIDs are unknown, but there is a growing body
of evidence that the pain is resulting from a dysfunction of the brain-gut axis, involving both efferent and afferent pathways by which the enteric and central nervous systems communicate.\textsuperscript{16}

Table 1. Rome III criteria for functional abdominal pain disorders\textsuperscript{5}

<table>
<thead>
<tr>
<th>Functional Dyspepsia (FD)</th>
<th>Persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus)</th>
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<tr>
<td></td>
<td>Not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e. not IBS)</td>
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<td></td>
<td>Criteria fulfilled at least once per week for at least 2 months before diagnosis</td>
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<tr>
<th>Irritable Bowel Syndrome (IBS)</th>
<th>Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time:</th>
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<tbody>
<tr>
<td></td>
<td>1) Improved with defecation</td>
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<td></td>
<td>2) Onset associated with a change in frequency of stool</td>
</tr>
<tr>
<td></td>
<td>3) Onset associated with a change in form (appearance) of stool</td>
</tr>
<tr>
<td></td>
<td>Criteria fulfilled at least once per week for at least 2 months before diagnosis</td>
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</table>

Symptoms that cumulatively support the diagnosis of IBS are:

- a) abnormal stool frequency (4 or more stools per day and 2 or less stools per week)
- b) abnormal stool form (lumpy/hard or loose/watery stool)
- c) abnormal stool passage (straining, urgency, or feeling of incomplete evacuation)
- d) passage of mucus
- e) bloating or feeling of abdominal distension

<table>
<thead>
<tr>
<th>Abdominal Migraine (AM)</th>
<th>Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 hour or more</th>
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<tr>
<td></td>
<td>Intervening periods of usual health lasting weeks to months</td>
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<td></td>
<td>The pain interferes with normal activities</td>
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<td></td>
<td>The pain is associated with 2 or more of the following:</td>
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<tr>
<td></td>
<td>a) Anorexia</td>
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<tr>
<td></td>
<td>b) Nausea</td>
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<td></td>
<td>c) Vomiting</td>
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<td></td>
<td>d) Headache</td>
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<td></td>
<td>e) Photophobia</td>
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<tr>
<td></td>
<td>f) Pallor</td>
</tr>
<tr>
<td></td>
<td>All above criteria must be included and fulfilled ( \geq 2 ) times in the preceding 12 months</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Functional Abdominal Pain (FAP)</th>
<th>Episodic or continuous abdominal pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Insufficient criteria for other AP-FGIDs</td>
</tr>
<tr>
<td></td>
<td>Criteria fulfilled at least once per week for at least 2 months before diagnosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Childhood Functional Abdominal Pain Syndrome (FAPS)</th>
<th>Must include functional abdominal pain at least 25% of the time and 1 or more of the following:</th>
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<tbody>
<tr>
<td></td>
<td>1) Some loss of daily functioning</td>
</tr>
<tr>
<td></td>
<td>2) Additional somatic symptoms such as headache, limb pain, or difficulty sleeping</td>
</tr>
<tr>
<td></td>
<td>Criteria fulfilled at least once per week for at least 2 months before diagnosis</td>
</tr>
</tbody>
</table>

In all subgroups, no evidence is found of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms.
**Biopsychosocial model**

The cornerstone for understanding of the etiology of AP-FGIDs is the biopsychosocial model (Figure 1). This model is based on a complex interplay of genetic, environmental, physiological and psychosocial factors and their influence on symptoms and illness. 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.

![Biopsychosocial Model](image)

**Genetics**

Familial clustering of AP-FGIDs has been described and suggests a genetic transmittance of these disorders. Adult studies have demonstrated that IBS is more common in first-degree relatives of individuals with IBS. Furthermore, children with chronic abdominal pain are more likely to have a parent, especially a mother, with functional gastrointestinal complaints. A twin study showed a 17% concordance for IBS in monozygotic patients with only 8% concordance in dizygotic twins, supporting a genetic contribution to IBS. Drawing any conclusions on genetic factors associated with AP-FGIDs however is not yet possible, since it has also been shown that parental history of IBS was a stronger predictor of IBS than having a twin with IBS. This finding suggests that the contribution of social learning, that is a tendency to report more symptoms, to consult doctors more often and to have more school or work absenteeism, is more important than genetic factors and that familial clustering of AP-FGIDs is a reflection of a shared exposure to environmental factors.
Visceral hypersensitivity

The pathogenesis of AP-FGIDs may involve the interrelationship between altered gastrointestinal motility and changes in visceral sensation, called visceral hyperalgesia or hypersensitivity. Symptoms of altered motility can include diarrhea, constipation, bloating and distension, whereas symptoms of hypersensitivity are pain and discomfort. Studies on hypersensitivity however, are inconclusive and it has been shown that a large proportion of IBS patients have perception thresholds within the normal range, despite similarities in symptomatology.\(^\text{21}\) Three pediatric studies showed lower pain thresholds for rectal sensation in IBS children compared to healthy controls.\(^\text{22-24}\) Studies in children with FAP on the other hand show conflicting results. Two studies showed that FAP children were hypersensitive in both the upper and lower gastrointestinal tract compared to healthy controls,\(^\text{23,24}\) while another study did not find hypersensitivity.\(^\text{22}\) Another study reported visceral hypersensitivity to be present in only 23\% of children with IBS or FAP and showed that rectal sensitivity scores were not correlated with symptom severity. Furthermore, response to treatment was not associated with improvement in rectal sensitivity.\(^\text{25}\) Increased colonic sensitivity in adult IBS patients was shown to be strongly influenced by psychological tendency to report pain and urge rather than increased neurosensory sensitivity.\(^\text{26}\) A pediatric IBS study reported that emotional instability seems to modulate the perception response to visceral stimulations.\(^\text{27}\) These findings question the central role of visceral hypersensitivity in the etiology of AP-FGIDs.

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. The discriminative component of gastrointestinal pain encodes location, intensity and nature of pain and follows a route from the gut, through the dorsal horn of the spinal cord, the ventral posterior portions of the thalamus to the insula. 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 anterior cingulated cortex (ACC), which is a critical center involved in the 'unpleasantness' of pain. Information from both the insula and ACC reach the frontal cortex, where cognitive processing occurs.\(^\text{28}\)

Several studies demonstrated an increased activation of the ACC 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.\(^\text{29,30}\) It is hypothesized that emotional processes like anxiety and depression and cortical factors like previous experience of pain, coping mechanisms and psychosocial stressors can interact with limbic circuits to amplify the pain experience.\(^\text{31,32}\) Serotonin (5-HT) is a neurotransmitter found both in the enteric and central nervous system. It has emerged as a key mediator in modulating the brain-gut axis and it has been shown that various elements of serotonin signaling differ in patients with IBS. Studies on the role of serotonin, however are inconsistent and it is not yet understood whether changes in serotonin
signaling contribute to altered motility and sensitivity or are in fact a response to altered gut functioning.\textsuperscript{33}

**Inflammation**

Low-grade mucosal inflammatory processes may also play a role in AP-FGIDs, since experiencing of a bacterial gastroenteritis has been shown to be associated with the development of IBS in children.\textsuperscript{34,35} Post-infectious IBS seems to occur particularly after Campylobacter and Shigella enteritis and it has been suggested that the severity of tissue damage and ulceration in these infections is a key factor in developing post-infectious IBS. Increased numbers of inflammatory cells have also been detected in the gastrointestinal tract of IBS patients and mediators released by activated inflammatory cells can affect the brain-gut axis, thereby causing gastrointestinal symptoms, such as abdominal pain.\textsuperscript{36}

**Gastrointestinal microbiota**

Recent insights indicate that the composition of intestinal microbiota may be of importance in the pathogenesis of AP-FGIDs, especially IBS. The human body is inhabited by a complex community of approximately 10\textsuperscript{14} microbes of which the vast majority is found in the gastrointestinal tract. Firmicutes, Bacteriodetes and Actinobacteria predominate in the colon. The occurrence of post-infectious IBS in a subset of patients supports the hypothesis that gut microbiota play a role in the pathogenesis.\textsuperscript{37} Qualitative and quantitative differences in bacterial components of the gut microbiome of IBS children compared to healthy controls were shown, with greater proportions of Proteobacteria in IBS, while Bacterioides were enriched in healthy children. Moreover, IBS-C and IBS-D could be distinguished by global microbiome analyses.\textsuperscript{38} It is hypothesized that changes in the microbiome may contribute to IBS symptoms through alterations in the brain-gut axis.\textsuperscript{37}

Gas-related symptoms, such as flatulence, bloating and distension are common among patients with AP-FGIDs. It has been suggested that increased gas production could be due to colonization of the proximal small bowel by fermenting bacteria, as occurs in small intestinal bacterial overgrowth (SIBO).\textsuperscript{37} There is however, conflicting evidence regarding the role of SIBO in AP-FGIDs. A recent Dutch study reported abnormal glucose breath tests, suggesting SIBO, in 14.3\% of children with AP-FGIDs\textsuperscript{39} and an Italian study reported a significantly higher proportion of abnormal lactulose breath tests, suggesting SIBO, among children with IBS compared to healthy controls.\textsuperscript{40} A double-blind, placebo-controlled study showed an abnormal lactulose breath test in 65\% of children with chronic abdominal pain, suggesting SIBO, but there were no significant differences in symptom improvement after antibiotic treatment.\textsuperscript{41} Furthermore, breath tests used to establish the role of SIBO in IBS have not been validated for utility in this group of patients and therefore the role of SIBO in IBS remains unclear.\textsuperscript{37}

**Stressful events**

Early stressful events may cause increased responsiveness of central stress and arousal circuits
and subsequently cause visceral hypersensitivity, which may have life-long consequences.\textsuperscript{42} Prevalence rates of physical and sexual abuse are significantly higher among adults with IBS compared to the general population.\textsuperscript{43} Prevalence rates of 2.1\% and 8.0\% were found in two low quality studies on sexual abuse in children with chronic abdominal pain, but real prevalence rates may be higher.\textsuperscript{44} Indeed, it was recently shown that two-thirds of children with a history of sexual abuse suffered from unexplained abdominal pain, but screening for AP-FGIDs was not performed.\textsuperscript{45} A recent Sri Lankan study showed that AP-FGIDs were significantly more prevalent in children exposed to sexual (34.0\%), emotional (25.0\%) and physical (20.2\%) abuse, compared to children who were not abused. Additionally, symptom scores were significantly higher in abused AP-FGID children compared to children with AP-FGIDs not exposed to abuse.\textsuperscript{46} Stressful life-events are important predictors of AP-FGIDs in children and children who are regularly being bullied have a higher risk of developing a variety of health-related symptoms, including abdominal pain.\textsuperscript{47,48}

Stressful events later in life also play a role in AP-FGIDs. Both adult and pediatric patients often describe a correlation between stress and the onset or exacerbation of their symptoms.\textsuperscript{49} Studies have shown that stress results in both acute and chronic changes in the activity and regulation of the hypothalamo-pituitary-adrenal (HPA) axis, but literature is conflicting. Most studies report increased basal cortisol levels and enhanced responses to physical and psychological stressors in adult IBS patients, but others show a blunted HPA axis response or no difference between IBS patients and controls.\textsuperscript{50} Pediatric studies are lacking.

Another possible mechanism in which stress plays a pathophysiological role is through the activation of mast-cells in the gut. It has been shown that IBS patients show higher numbers and increased activation of mast cells and it has also been shown that presence of activated mast cells in proximity to colonic mucosal innervations, is correlated to both frequency and severity of abdominal pain.\textsuperscript{51,52}

\textbf{Psychiatric factors}

An anxiety disorder is found in approximately 80\% of children with AP-FGIDs and almost 40\% meet criteria for a depressive disorder.\textsuperscript{2,53,54} Evidence exists for a bidirectional causal links between (abdominal) pain and mood,\textsuperscript{55,56} and it is also possible that pain and mood are both the result of a biological factor, such as altered functioning of the HPA axis.\textsuperscript{50} Ineffective mechanisms of coping with stress may contribute, since successful coping mechanisms like problem solving, acceptance and positive thinking are associated with less pain, anxiety and depression in children with AP-FGIDs. Less successful coping mechanisms like involuntary engagement (rumination and catastrophizing) or disengagement (escape and inaction) on the other hand are associated with more somatic symptoms and higher levels of anxiety and depression.\textsuperscript{57}

\textbf{DIAGNOSIS}

Since the exact pathophysiological mechanisms underlying AP-FGIDs are unknown and no diagnostic markers are available, a thorough history and physical examination are key in the
diagnosis of AP-FGIDs. Frequency, severity, location, and timing (postprandial, waking during the night) of abdominal pain do not help distinguishing between organic and functional abdominal pain.\textsuperscript{58} In addition, children with AP-FGIDs are very likely to have associated symptoms, such as anorexia, nausea, episodic vomiting, headache, back pain or arthralgia, but none of these associated symptoms have been reported to help in distinguishing between organic abdominal pain and AP-FGIDs.\textsuperscript{59} There is also no evidence that psychosocial history helps to distinguish between AP-FGIDs and organic disease, but psychosocial history taking is especially important with respect to treatment options.

Only the presence of so-called alarm symptoms or red flags suggests a higher prevalence of organic disease and indicate the performance of diagnostic tests (Table 2).\textsuperscript{58} Joint pain and waking from sleep occur similarly between AP-FGID patients and patients with Crohn’s disease and should therefore not be considered red flags.\textsuperscript{60}

<table>
<thead>
<tr>
<th>Table 2. Alarm symptoms / red flags for organic disease\textsuperscript{58}</th>
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<tbody>
<tr>
<td>- involuntary weight loss</td>
</tr>
<tr>
<td>- growth retardation</td>
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<tr>
<td>- significant vomiting</td>
</tr>
<tr>
<td>- chronic, significant diarrhea</td>
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<tr>
<td>- gastrointestinal blood loss</td>
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<tr>
<td>- persistent, localized tenderness in the right upper or lower quadrant</td>
</tr>
<tr>
<td>- unexplained fever</td>
</tr>
<tr>
<td>- family history of inflammatory bowel disease</td>
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\textbf{Additional diagnostic testing}

Since common laboratory blood, urine and feces (parasitical) tests are neither very invasive nor expensive, clinicians are likely to perform these tests, even in the absence of alarm signals. However, there are no studies that have evaluated the usefulness of these tests to distinguish between organic disease and AP-FGIDs.\textsuperscript{58} The common diagnostic workup of children with chronic abdominal pain was found to include numerous tests, but none of these tests resulted in any meaningful abnormality. Instead, exposure to radiation, inconvenience for patients and costs were significant and these results were likely to cause confusion and lead to more (unnecessary) invasive testing and procedures.\textsuperscript{61} Additional diagnostic testing in the absence of alarm symptoms, also does not influence the prognosis of AP-FGIDs.\textsuperscript{62} A recent study in a cohort of 220 children with RAP, however, showed that 88\% of these children had at least one abnormal test that could be the cause of the abdominal pain. These results, however, should be interpreted carefully and clinical relevance of these findings remains to be established, because an abnormal test result does not necessarily indicates a causal relationship.\textsuperscript{63} In the last years, fecal calprotectin levels of school-aged children with AP-FGIDs were shown to be within normal limits and therefore calprotectin may be a useful and non-invasive test to distinguishing AP-FGIDs and inflammatory bowel diseases in these children.\textsuperscript{11}

In children without alarm symptoms, ultrasonography and endoscopy might be done as a reassurance to parents and patient. Abdominal ultrasonography and endoscopy, however, were not shown to have significant diagnostic yield in the absence of alarm symptoms.\textsuperscript{64–66}
Furthermore, negative outcome of endoscopy did not improve clinical outcome[^67] and quality of life and did not result in reassurance of parents[^66].

**MANAGEMENT**

Education is an important part of the treatment of children with AP-FGIDs. It needs to be emphasized that although the pain is real, there is no underlying serious or chronic disease and that a positive diagnosis of an AP-FGID is not a failure to identify underlying organic illness. The primary goal of therapy is 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[^68].

An important factor in management of pediatric AP-FGIDs is the parental response to the abdominal pain of the child. Parents often believe that attention to somatic complaints is beneficial and distraction is potentially harmful. The opposite however, seems true, when looking at a randomized controlled trial on the effects of parental attention versus distraction or no instruction following induction of visceral discomfort in the child. Compared to the “no instruction” group, symptom complaints nearly doubled in the attention group and were reduced by half in the distraction group[^69]. Parental over-involvement in pain behavior and reinforcement of sick role behavior are thought to be associated with ineffective coping with chronic pain and a perseverance of symptoms. However, negative attention to pain in children with low self-esteem has also been associated with increased pain behavior, possibly by creating affective distress that may further contribute to somatic symptoms[^70].

Another important therapeutic goal is to identify, clarify and possibly reverse physical and psychological stressors that may play an important role in the onset, exacerbation or maintenance of abdominal pain. Acceptance of a biopsychosocial model of illness by parents has been shown to be important for the resolution of symptoms in children with AP-FGIDs[^71,72].

**Pharmacologic and nonpharmacologic treatment**

Management of children with AP-FGIDs can be very challenging, due to the incomplete pathophysiological understanding and treatment therefore remains mainly symptomatic. A wide variety of treatments are available in treating pediatric AP-FGIDs. Dietary interventions are frequently used in AP-FGIDs, since many patients and some physicians consider symptoms being meal related[^73]. Pharmacologic therapy for AP-FGIDs has generally been directed at symptom alleviation, rather than at precise pathophysiological abnormalities. However, due to increased understanding of the pathophysiological role of the brain-gut axis, potential targets for pharmacologic treatment were identified including smooth muscle cells throughout the gastrointestinal tract, peripheral receptors, central interneurons and cortical regions involved in conscious perception of pain[^74]. Due to the strong association with stress, psychological factors and psychiatric comorbidity, psychological interventions aiming to teach alternative responses to stress, such as cognitive behavioral therapy and hypnotherapy, are frequently used in pediatric AP-FGIDs[^75].
Efficacy and safety of all available pharmacologic and nonpharmacologic treatments for pediatric AP-FGIDs are described in detail in chapter 4 and 5.

**Placebo effect**

In interpreting therapeutic AP-FGID-trials, the placebo effect must be taken into account. Placebo responses in adult IBS trials vary from 16.0%-71.4%\(^76\) and high placebo rates up to 53% have been reported in RCTs in children and adolescents with IBS.\(^77\)-\(^79\) High placebo responses may also display the natural course of functional gastrointestinal disorders with fluctuating symptoms.\(^16\) Treatment and placebo effects are often additive, so enhancing the placebo component increases response to treatment. Patient-practitioner relationship and active listening approach are known to be important in mediating the placebo response, which may be especially important in nonpharmacologic therapies for AP-FGIDs.\(^80,81\)

**PROGNOSIS**

A significant proportion of 25 to 66% of children with AP-FGIDs were shown to have either continued abdominal pain symptoms throughout adolescence and adulthood or develop other symptoms, such as chronic headache, back pain, fibromyalgia, anxiety and sleep disturbances.\(^62,82-85\)

Adverse prognostic factors that play a role include a family history of IBS, parental refusal to acknowledge the role of psychological factors in the genesis and maintenance of symptoms and increased healthcare consumerism.\(^71,72\) High baseline levels of anxiety or depression, more negative life-events, lower self-worth, obesity and a ‘high pain dysfunctional profile’ with low perceived pain coping efficacy, high levels of negative affect, pain catastrophizing and functional disability, are associated with persistence of symptoms.\(^86-88\)
OUTLINE OF THE THESIS

Pediatric abdominal pain related functional gastrointestinal disorders (AP-FGIDs) comprise five common, heterogenic disorders, in which understanding of underlying pathophysiological mechanisms is incomplete. This incomplete pathophysiological understanding hampers management. Irritable bowel syndrome (IBS) and functional abdominal pain (syndrome) (FAP(S)) are most commonly diagnosed and can have significant impact on the child and their family. Part I of this thesis discusses clinical characteristics of children with IBS or FAP(S) and their parents and in Part II management strategies for pediatric IBS and FAP(S) pass in review. Part III of this thesis focusses on gut-directed hypnotherapy as treatment for children with IBS and FAP(S).

PART I – CHARACTERISTICS OF CHILDREN AND THEIR PARENTS

It has been suggested that different subcategories of childhood AP-FGIDs are not separate clinical entities, but instead represent variable expressions of the same functional gastrointestinal disorder. In chapter 1, clinical and psychological characteristics of children with IBS and FAP(S) are compared to shed some more light on the issue whether IBS and FAP(S) must be considered different entities. Parental factors are suggested to play a role in causing, maintaining or exacerbating symptoms in children with AP-FGIDs, since familial clustering of these disorders is common. Chapter 2 therefore describes physical health status, psychological distress, personality and child-rearing style of mothers and fathers of children with IBS or FAP(S), since this may improve insight in the etiology of these disorders and may lead to more systemic treatment approaches.

PART II – MANAGEMENT

Chronic abdominal pain is one of the most important reasons for parents to consult a doctor and accounts for 25 to 50% of referrals to a (tertiary) pediatric gastroenterology clinic. Additionally, children with IBS or FAP(S) report increased usage of health care services. These disorders are therefore thought to have significant impact on health care costs and in chapter 3 annual costs of care for children are assessed, since data on costs of care for children with IBS or FAP(S) are not available to this date. Management of children with IBS or FAP(S) can be challenging and a wide variety of both pharmacologic and nonpharmacologic treatments are available. Different kinds of treatments are mostly prescribed by health care professionals based on their own clinical experiences and results of adults studies, since pediatric data are often scarce. Chapter 4 systematically reviews available evidence on safety and efficacy of pharmacologic treatments for children with AP-FGIDs, whereas chapter 5 describes a systematic review on the quantity and quality of evidence for the efficacy and safety of different kinds of nonpharmacologic treatments available for pediatric AP-FGIDs.
PART III – GUT-DIRECTED HYPNOTHERAPY

Spontaneous remission of symptoms occurs in a lot of children with IBS or FAP(S), but a significant proportion of children continues to experience symptoms of abdominal pain, even into adulthood.\textsuperscript{16,62,85} In the last 30 years, multiple trials have demonstrated that gut-directed hypnotherapy (HT) is an effective therapy in adult patients with IBS.\textsuperscript{91} The systematic review described in chapter 6 summarizes available evidence for efficacy and safety of gut-directed HT in children with IBS and FAP(S). Gut-directed HT was shown to have long-lasting beneficial effects in adult IBS patients.\textsuperscript{92,93} Between 2002 and 2005, a randomized controlled trial (RCT) was conducted in the Netherlands to compare the effects of standard medical care plus supportive therapy and gut-directed HT in 52 pediatric patients with long-lasting IBS or FAP.\textsuperscript{94} To assess whether effects of HT are also long-lasting in children with IBS or FAP, we performed a follow-up study of this RCT and results of this study are described in chapter 7.

Gut-directed HT performed by a therapist has been shown to be effective in children with IBS or FAP(S), but it is still unavailable to many children due to costs, a lack of qualified child-hypnotherapists and because it requires a significant investment of time by child and parent(s).\textsuperscript{94,95} Home-based HT by means of exercises on CD has been shown effective as well, and has potential benefits, such as lower costs and less time investment.\textsuperscript{96} We therefore performed a non-inferiority RCT to compare the (cost-)effectiveness of individual HT performed by a qualified therapist with HT by means of CD recorded self-exercises at home in children with IBS or FAP(S). Chapter 8 describes the protocol of this non-inferiority RCT. Chapter 9 focusses on the results of this trial with respect to efficacy, while chapter 10 discusses the results of the cost-effectiveness and -utility analyses.
REFERENCES


