Department of Internal Medicine and Clinical Nutrition

Institute of Medicine

Sahlgrenska Academy

University of Gothenburg

Gothenburg, Sweden

Implementation of Gut-Directed Hypnotherapy for Irritable Bowel Syndrome In Clinical Practice

Perjohan Lindfors

2012

UNIVERSITY OF GOTHENBURG

Front page illustration: "The IBS monster", provided by the artist to illustrate how bothersome this condition can be.

By Bosse Forslund, the first patient, treated with gut-directed hypnotherapy in Gävle.

Published by Sahlgrenska Academy

ISBN: 978-91-628-8555-7

Abstract

Background: Irritable Bowel Syndrome (IBS) is characterized by recurrent abdominal pain or discomfort, related to abnormal bowel habits. This benign and common condition is in severe cases associated with bothersome GI symptoms, decreased quality of life and psychological comorbidity. Many cases can be treated with lifestyle advice and symptom modifying drugs. However, the severe cases are very difficult to treat and no effective medicines targeting the whole symptom complex are currently available. Gut-directed hypnotherapy has been found effective in many refractory cases, but the majority of the studies concerning the effects of this intervention originate from specialized, hypnotherapy research units.

Aims of the thesis: To evaluate the effects of gut-directed hypnotherapy as treatment in refractory Irritable Bowel Syndrome (IBS), when the intervention is delivered outside specialized, hypnotherapy research units and to investigate if there are permanent effects on GI motility after treatment with gut-directed hypnotherapy in IBS.

Material and methods: The patients studied in Paper I - Trial 1, Paper III and Paper IV were from a large randomized controlled trial (RCT), performed in Gothenburg (n=90). In Paper I - Trial 2 the patients came from a smaller RCT, performed in Gävle (n=48). The patients studied in Paper II, came from these RCTs, but a large clinical sample from Stockholm (n=134) was also included. All patients were treated with gut-directed hypnotherapy once a week for 12 weeks by specially trained psychologists. In Paper I we evaluated the short and medium term effects of gut-directed hypnotherapy, whereas the long-term effects of the intervention were assessed in Paper II. In Paper III, factors associated with patient satisfaction after gut-directed hypnotherapy was investigated and in Paper IV, we measured permanent effects of hypnotherapy on GI motility.

Results: In the RCTs (Paper I), the intervention was found to be effective in decreasing IBS symptoms, reducing the level of anxiety and increasing some domains of quality of life. The results were significant in within-group analysis in both Trial 1 and 2, but in the latter there was no significant difference compared to the control group (probably due to a type II error). In Paper II, 49% of the patients were considered as responders directly after treatment and 73% of these patients had continued to improve at follow-up (mean 4 years after treatment). The responders also reported a significantly reduced healthcare utilization at follow-up. Of all treated patients (n=208), 87% reported that they had found hypnotherapy to be worthwhile (100% of responders, 74% of non-responders), confirming the clinical impression that many patients are satisfied with the intervention even in the group with little effect on GI symptoms. This was further investigated in Paper III where patients reported their satisfaction on a 5 degree scale, ranging from 1 (not at all satisfied) to 5 (very satisfied). Sixty-nine percent of the patients scored 4 or 5 on this scale, and when dividing patients into responders and non-responders, 52% of the responders, but also 30% of the non-responders reported that they were very satisfied (score 5) with the intervention. Patient satisfaction was found to be associated with improvement of quality of life and GI symptoms, but only one domain of quality of life was independently associated with patient satisfaction (sexual relations). In Paper IV, we evaluated the results of small bowel manometry and GI transit investigations before and after the intervention, but no permanent effects of gut-directed hypnotherapy on GI motility were detected.

Conclusions: Gut-directed hypnotherapy is an effective treatment in refractory IBS, even when delivered outside specialized hypnotherapy research centres. Besides effects on GI symptoms, there are positive effects on quality of life parameters and anxiety. The effect on GI symptoms is long- lasting and the intervention is generally associated with a high grade of patient satisfaction, even in subjects with no or minor effect on GI-symptoms. Patient satisfaction is associated with improvements in GI symptoms and quality of life but other factors are probably also of importance and need to be further investigated. The result also implicates a potential to reduce healthcare costs when treating IBS patients with hypnotherapy. We found no evidence that the mechanism of action behind the effects of gut-directed hypnotherapy is due to effects on GI motility. The results in this thesis support the introduction of gut-directed hypnotherapy as a part of clinical care in treating patients with refractory IBS

Key-words: Irritable bowel syndrome, gut-directed hypnotherapy, patient satisfaction, GI motility

ISBN: 978-91-628-8555-7

To Airene, Elvira, Embla and Malva

"If your stomach disputes you, lie down and pacify it with cool thoughts"

Satchel Paige 1953

List of publications

I. Lindfors P, Unge P, Arvidsson P, Nyhlin H, BjörnssonE, Abrahamsson H, Simrén M. Effects of gut-directed hypnotherapy on IBS in different clinical settings - results from two randomized controlled studies. Am J Gastroenterol. 2012;107(2):276-85

II. Lindfors P, Unge P, Nyhlin H, Ljótsson B, Björnsson E, Abrahamsson H, Simrén M. Long-term effects of hypnotherapy in patients with refractory irritable bowel syndrome. Scand J Gastroenterol. 2012;47(4):414-20

III. Lindfors P, Ljótsson B, Björnsson E, Abrahamsson H, Simrén M. Patient satisfaction after gut-directed hypnotherapy in irritable bowel syndrome. Neurogastroenterol Motil. 2012. Oct 5. [Epub ahead of print]

IV. Lindfors P, Törnblom H, Sadik R, Björnsson E, Abrahamsson H, Simrén M. Effects on gastrointestinal transit and antroduodenojejunal manometry after gut-directed hypnotherapy in irritable bowel syndrome (IBS). Scand J Gastroenterol. 2012. Oct 10. [Epub ahead of print]

Contents

Abstract 2

List of publications 4

Contents 5

List of Abbreviations 8

Introduction 9

Background 10

Epidemiology of IBS 10

Diagnosis and consultation patterns 10

Prevalence 11

Natural course and associated symptoms 11

Quality of life 12

Socioeconomic impact of IBS 12

Psychological comorbidity 12

Pathophysiology of IBS 13

GI motility 13

Disturbed gas handling 13

GI hypersensitivity 14

Brain- gut interaction 14

Stress – “the vicious circle” 15

Treatment of IBS 16

The consultation 16

Lifestyle advice and interventions 17

Pharmacological treatment 17

Psychological treatment 18

Psychodynamic therapy 18

Cognitive behavioural therapy (CBT) 19

Gut-directed hypnotherapy 20
Aims of the thesis 25
Paper I 25
Paper II 25
Paper III 25
Paper IV 25
The studies 26
The hypnotherapy project 26
Methodological overview 26
Subjects 26
Intervention 28
Treatment protocol for gut-directed hypnotherapy 28
Control groups 31
Outcome measures 31
IBS symptoms 31
Quality of life 32
Psychological comorbidity 32
Cognitive function 32
Sense of coherence 33
Patient satisfaction 33
Subjective assessment questionnaire (SAQ) 33
GI transit measurements 34
Small bowel manometry 34
Statistical methods 37
Results 38
Effects of hypnotherapy on IBS symptoms 38
Effects of hypnotherapy on quality of life 42
Effects of hypnotherapy on psychological comorbidity 44

Effects of hypnotherapy on cognitive functioning 44
Effects of hypnotherapy on sense of coherence 45
Long-term effects of hypnotherapy 45
Healthcare utilization at follow-up 45
Use of IBS symptom modifying drugs at follow-up 46
Use of alternative treatments at follow-up 46
Continued hypnotherapy practice at follow-up 47
Patient satisfaction with hypnotherapy 47
Effects of hypnotherapy on GI physiology 49
Methodological considerations 50
General discussion 52
Effects on IBS symptoms 53
Effects on quality of life and psychological parameters 54
Patient satisfaction 54
Other long-term results of gut-directed hypnotherapy 55
Effects of gut-directed hypnotherapy on GI motility 56
General comments 56
Conclusions 57
Acknowledgements 58
Populärvetenskaplig sammanfattning 60
Bakgrund 60
Övergripande syfte med avhandlingsarbetet 61
Resultat 61
Slutsatser 62
References 63

List of Abbreviations

IBS	Irritable bowel syndrome
IBS-D	IBS with diarrhoea
IBS-M	Mixed IBS
IBS-C	IBS with constipation
IBS-U	Unsubtyped IBS
RCT	Randomized controlled trial
QoL	Quality of life
GI	Gastointestinal
CBT	Cognitive behavioural therapy
ICBT	Internet delivered cognitive behavioural therapy
TCA	Tricyclic antidepressants
SSRI	Selective Serotonin reuptake inhibitors
PEG	Polyethylene glycol
NNT	Numbers needed to treat
CSBD	Cognitive scale for functional bowel disorders
GSRS-IBS	Gastrointestinal symptom rating scale-IBS version
IBSQOL	Irritable bowel syndrome quality of life questionnaire
SF-36	Short form-36
HAD	Hospital anxiety and depression scale
ACC	Anterior cingulate cortex

Introduction

When, in the late 1990s, I started my training in gastroenterology at Gävle Hospital, it became obvious to me how few treatment options we had to offer patients with severe Irritable Bowel Syndrome (IBS), who did not respond favourably to lifestyle adjustments and symptom-modifying medication. Driven by this, I began to search for other therapeutic options and came across an original paper published in The Lancet in 1984, in which Dr Whorwell and colleagues from Manchester reported astonishing results when treating refractory IBS with gut-directed hypnotherapy. After further literature studies, and contact with Dr Henry Nyhlin and Psychologist Marta Sjöberg at Ersta Hospital in Stockholm, who had clinical experience in the field, I discussed this with my clinical supervisor, Dr Peter Unge, and we decided to start a local project. Patrik Arvidsson, a licensed psychologist, was recruited to administer the treatment and was formally trained in gut-directed hypnotherapy by Martha Sjöberg. Subsequently we designed a randomized controlled trial (RCT) comparing gut-directed hypnotherapy with waiting list controls. The trial started in 2001. At the same time Dr Magnus Simrén and colleagues at Sahlgrenska University Hospital, Gothenburg had become interested in gut-directed hypnotherapy, and were performing a very similar RCT, but with a higher number of participants, an active control group and also investigations before and after the treatment period, evaluating effects on gastrointestinal (GI) physiology. Eventually Dr Simrén and I decided to link up the projects and I began working on this thesis with Dr Simrén as my main supervisor in 2006. Besides the RCTs, we also conducted a long-term follow-up study, addressing the long-lasting effects of gut-directed hypnotherapy, and in this study we also included a large clinical sample from Ersta Hospital.

In spite of the impressive results in earlier trials, the intervention is not widely available, which may be due to the fact that most of the earlier reports concerning effects of this treatment modality derive from large centres specializing in gut-directed hypnotherapy, and little was known about the effect when the treatment was given outside such centres.

This thesis describes our work to investigate and evaluate short- and long-term effects of gut-directed hypnotherapy, when the treatment is delivered outside specialized hypnotherapy centres, and to increase our general knowledge about this intervention.

My intention is that we, by doing this, can contribute to an increasing awareness among gastroenterologists for this type of treatment and also to motivate a wider clinical use. I am convinced that this may be of great clinical importance for this group of patients, who often have severe IBS symptoms, which impact negatively on their quality of life

Background

Epidemiology of IBS

Diagnosis and consultation patterns

Recurrent abdominal pain or discomfort associated with disturbed bowel habit are the core symptoms of IBS, but also bloating and a sense of incomplete evacuation of stools are common symptoms (1). This type of symptoms could potentially be caused by a variety of other diseases, such as celiac disease, inflammatory bowel disease or colorectal cancer(2). However, to rule out all potential differential diagnosis in all cases and consider IBS to be a diagnosis of exclusion has not been found to be a useful strategy in clinical practice, since it is very rare to find other underlying diseases than IBS in cases presenting with typical symptoms, and this is also a very expensive way of making the diagnosis(2, 3). IBS has, based on this and the fact that there are no specific clinically useful pathophysiological findings to base the diagnosis upon, become a criterion-based diagnosis (4).

The first diagnostic criteria for IBS was presented by Manning et al in 1978 (1) and these have since then gradually been developed and changed by the Rome committees(5)with the Rome I criteria (6) being from 1992, Rome II criteria(7) from 1999, and the diagnosis is currently defined by the Rome III criteria(8) from 2006 (Box 1). The criteria have been developed for use in both clinical practice and research, even though they have mainly been used in research studies. The Rome III criteria focus on abdominal pain and discomfort associated with disturbed bowel habit, such as constipation and/or diarrhoea, where the symptoms should be chronic (symptom onset at least 6 months prior to diagnosis) and recurrent. Other common IBS symptoms, such as bloating and a feeling of incomplete evacuation are not mandatory, but support the diagnosis. There are also Rome III criteria for sub-grouping IBS into subtypes: IBS-D (IBS with diarrhoea), IBS-M (Mixed IBS with both diarrhoea and constipation), IBS-C (IBS with constipation) and IBS-U (unsubtyped IBS) (8)

In clinical practice the diagnosis is made mainly from a typical history and fulfilment of the Rome III criteria, but a certain number of further investigations are often made to rule out organic diseases, especially when alarm symptoms such as weight loss, severe diarrhoea, onset of IBS symptoms after the age of 45 years and a history of blood in the stools are present. In the typical case with classical symptoms and without alarm symptoms, few investigations are needed. The only laboratory test that has proven to be valuable in this group of patients is transglutaminase antibodies to screen for celiac disease (4). However, a limited panel of blood tests, such as CRP and blood counts are usually included in the diagnostic work-up, even in cases with typical symptoms and no alarm symptoms, to rule out inflammation and anaemia.

Most IBS sufferers are non-consulters or visit doctors infrequently, but in spite of this, IBS is the most common GI diagnosis seen by general practitioners(9) and they account for approximately half the workload in a gastroenterology outpatient clinics(10, 11)

Box 1.Irritable Bowel Syndrome ROME III Diagnostic criterion(8)

Recurrent abdominal pain or discomfort* at least 3 days/month in the last
3 months associated with *two or more* of the following:
1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

Criterion fulfilled for the last 3months with symptom onset at least 6months prior to diagnosis
* "Discomfort" means an uncomfortable sensation not described as pain.

Prevalence

IBS is the most common functional GI disorder and is prevalent all over the world (12). However, the prevalence varies considerably between different epidemiological studies, mainly depending on the criteria which have been used. When using the more inclusive Manning criteria, the prevalence of IBS has been estimated to be as high as 32% (13), and when using the more restrictive Rome I and II criteria as low as 1-2% (14). When comparing the Rome II and III criteria in the same population, the prevalence figures were 5% and 13%, respectively(13). In recent reviews, it is reported that by using the Rome III criteria the number of IBS sufferers in society is found to be 10-12% in the adult population (12, 15, 16), which may be closer to the true prevalence. The condition is about twice as common among women as among men, and this difference is even larger in patients with more severe IBS symptoms, presence of extraintestinal symptoms and psychological comorbidity (17).

Natural course and associated symptoms

Although IBS is considered to be a chronic disorder, the severity of symptoms vary considerably over time and there is also an overlap between different functional GI disorders, especially between IBS and functional dyspepsia (18). In an epidemiological study by Agreus et al (19), 55% of IBS patients retained their IBS diagnosis 7 years after the initial diagnosis, but only 13% reported that they were free of symptoms at follow-up, whereas 11% were diagnosed with functional dyspepsia or gastro-oesophageal reflux disease. In two studies investigating the natural history of IBS 10 years after the initial diagnosis, 67% (20)and 43-61% (13), respectively, retained the IBS diagnosis. A study from Halder et al (21) showed that 30% of the IBS patients were symptom-free 12 years after the initial diagnosis and that 25% were diagnosed with another functional GI disorder at follow-up. Patients with post-infectious IBS seem to have a better prognosis than patients with IBS without a history of onset after an infection (22, 23). In general it could be concluded that at the group level, the IBS symptom burden decreases over the years and that some patients eventually will become free of GI symptoms. A variety of extraintestinal symptoms associated with IBS have also been described (24), the most common ones being lethargy, headache, dysuria, fibromyalgia, psychological distress (see below) and dyspareunia.

Quality of life

Functional gastrointestinal disorders have a substantial impact on quality of life (25-27) and this relationship is positively correlated with the IBS symptom severity(28). Investigating the impact of IBS on health-related quality of life has mainly been performed by using self-administered questionnaires(29-32). Health-related quality of life measurements seek to encompass the emotional and social dimensions of the patient's illness, in addition to that of physical function, and all these aspects are impaired in IBS patients compared to healthy controls and the impact increases with IBS symptom severity(33). Health-related quality of life in IBS is impaired to a comparable degree to e.g. depression, gastro-oesophageal reflux disease and other from a medical point of view more severe diseases(34).

Socioeconomic impact of IBS

The socioeconomic impact of IBS is considerable. IBS patients in general consume more healthcare resources, have more time off work and are less productive at work compared to healthy controls. IBS patients have shown to be three times more likely to be absent from work or school compared to healthy controls(35) and the corresponding numbers when comparing the percentage of "non – productive work time" between the groups is 20% and 6% respectively(36). Longstreth et al estimated the increase in healthcare costs associated with IBS to be 51% and that IBS symptom severity was positively correlated with an increase in healthcare costs (37). IBS patients utilizes healthcare resources at almost double the cost compared to persons without IBS (38). In Finland, IBS care is estimated to account for up to 5% of the national direct outpatient and pharmacological expenditures (39). The mean annual direct healthcare cost in the US has been estimated to be $ 5,049 per treatment-seeking IBS patient (40). With an IBS prevalence of at least 10% the costs for society are therefore substantial.

Psychological comorbidity

It is a well-known fact among clinicians that psychological distress is common in patients with functional gastrointestinal disorders such as IBS, and this has also been thoroughly studied over the years. When investigating the lifetime risk for anxiety and mood disorder, the prevalence among female IBS sufferers was as high as 50% (41). Several specific psychiatric disorders such as depression (42-44), generalized anxiety disorder (42, 45), panic disorder(46), somatization disorders (42, 44) and obsessive compulsive disorders (44) are more prevalent among IBS patients compared to healthy controls. The prevalence among IBS patients for e.g. depression was 30% (42) and for generalized anxiety disorder 16% (45). Patients with a primarily psychiatric disorder have also been found to have a higher prevalence of IBS compared to the general population. As an example of this, Gros et al reported that patients diagnosed with generalized anxiety disorder had a prevalence of IBS of 26% , with the corresponding numbers for patients with panic disorder was 22% and for depression 25%(47).

Pathophysiology of IBS

The pathophysiology of IBS is incompletely understood, but peripheral factors such as alterations in GI motility and visceral hypersensitivity, as well as dysregulation of the brain- gut axis, are important factors. Probably peripheral alterations are key factors in some IBS patients and disturbed central processing of signals from the periphery of greater importance in others.

GI motility

Disturbed bowel habit is a mandatory symptom in IBS and therefore the condition has traditionally been considered as a GI motor dysfunction. Uniform motility pattern of the small bowel, consistently correlated with a specific IBS symptom, has been difficult to demonstrate when using manometry and results from different studies are not consistent (48-52). Small bowel transit studies have, however, shown rather uniform results, correlating small bowel transit time to specific bowel patterns, i.e. an accelerated transit time in IBS-D (53, 54) and delayed transit time in IBS-C (53, 55), although in a more recent study from the Mayo clinic, no clear correlation between transit time and predominant IBS type were found (56). Differences in colorectal motility between IBS patients and healthy subjects have also been investigated thoroughly. An interesting finding is the increased frequency of high amplitude propagating contractions (HAPC) in the colon in non-constipated IBS patients (57, 58) and also the correlation between HAPCs and pain episodes (57, 59),which could be linked to the presence of visceral hypersensitivity. Another interesting finding is an exaggerated colonic motor response to physiological stimuli such as food (57, 60, 61) and stress (62, 63), which could explain the clinical observation that IBS patients often have worse symptoms after food and in stressful situations . To summarize, no IBS-specific disturbances in motor function has been found, though there are differences on a group level between IBS patients and healthy subjects in both motor function of the small and large intestine (64-66). Food intake and different kind of stressors seem to enhance these group differences (60, 63).

Disturbed gas handling

A common symptom in IBS is bloating and abdominal distension (67) and there are probably several pathophysiological factors behind these bothersome symptoms and bloating (sensation of abdominal swelling) and distension (actual increase in girt) may have somewhat different underlying mechanisms. Patients with functional GI symptoms do not seem have larger volumes of gas compared to a non-symptomatic control group (68, 69) and, based on this, it has been proposed that symptoms such as bloating, pain and gas are secondary to disordered intestinal motility combined with an abnormal GI sensitivity. Recent studies have demonstrated that IBS patients complaining of bloating have an impaired transit of exogenous gas load, mainly in the small bowel, leading to gas retention and symptoms of bloating (70) and that this process can be modulated by nutrients (71) and physical activity (72) which is of potential interest when giving these patients lifestyle advice. Abdomino-phrenic dyscoordination has also been found to be of importance in the generation of bloating and abdominal distension in patients with IBS (73, 74).

GI hypersensitivity

Pain or discomfort are mandatory symptoms in IBS and therefore the diagnosis is not likely to be explained solely by disturbed GI motility. Instead, visceral hypersensitivity has been proposed to be an important pathophysiological mechanism behind some of the key symptoms of IBS, such as pain, discomfort and bloating. In line with this reasoning, IBS patients have been found to have an increased sensitivity for balloon distension in the rectum compared to healthy subjects and this method has even been suggested as a diagnostic test for IBS (75) although other research groups disagree on this depending on low specificity of the test in other trials (76). Importantly, visceral hypersensitivity is not present in all IBS patients and there is no clear association between colorectal sensitivity and the predominant bowel habit of the patient (77), but gender seems to affect rectal sensitivity (77, 78).The colorectal hypersensitivity in IBS patients is just like GI motility also enhanced after intake of nutrients, and during stress, which is not the case in healthy subjects (79, 80). Some of the key IBS symptoms seem to be related to visceral hypersensitivity(80), but whether visceral hypersensitivity is due to abnormalities within the enteric nervous system, due to spinal hyper-excitability or a pathologic interpretation of signals in the central nervous system is not known(81).

Brain- gut interaction

An altered brain response to visceral stimuli in IBS has been proposed to be of relevance for GI symptoms(82-85). The majority of studies investigating brain-gut interactions in IBS have used actual and anticipated rectal balloon distensions and evaluated the brain response with different techniques such as functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET). The studies performed so far are heterogeneous, but a quantitative meta-analysis have demonstrated that patients with IBS, compared to healthy controls, have greater engagement of regions associated with emotional arousal and endogenous pain modulation, but similar activation of regions involved in processing of visceral afferent information (86). Moreover, there also seems to be differences in the brain response within the IBS population between males and females (87) and between patients with and without visceral hypersensitivity (88) .

Stress – "the vicious circle"

Although GI motility disturbances, visceral hyperalgesia and abnormal central processing of visceral stimuli are considered as the key underlying mechanisms of IBS, stress is probably an important factor in facilitating the severity of the IBS symptomatology. A number of studies have investigated the impact of daily stressors on IBS symptoms (89, 90), and some studies conclude a causative effect of stressors on IBS symptoms, but others conclude that it is in fact the IBS symptoms that cause the stress (91). The UCLA-group has suggested that conditioned fear of IBS symptom-related stimuli could be an important mechanism behind stress-related IBS symptoms (92). Earlier experience of intense IBS symptoms such as severe abdominal pain or acute need to defecate have often been preceded by other neutral stimuli such as mild sensations from the GI tract (for example feeling of fullness), where the situation took place (for example in the subway) or what activity the patient was involved in (for example when eating). The next time the patient experiences the neutral stimuli, the fear of getting the symptoms actually triggers them and a vicious circle has been established. IBS patients have, compared to healthy controls, demonstrated an increased attention to words associated with pain and the level of attention is positively correlated with the degree of somatic complaints (93). IBS patients also report that they are more vigilant towards bodily symptoms compared to healthy controls (94) and catastrophic thinking of pain is linked to more severe IBS symptoms (95, 96). The association between fear of IBS symptoms and actually getting the symptoms is supported by the findings by Naliboff et al (83), where anticipated and actual painful rectal distension activated areas of the brain involved in processing of negatively charged emotional information and fear of pain. This is also supported in a trial where IBS patients were treated with cognitive behavioural therapy (CBT), resulting in decreased global pain linked to decreased activity in these regions of the brain (97). To conclude; increased visceral anxiety can be a result of IBS symptoms but could at the same time be the driver behind the symptoms.

Treatment of IBS

Though there is no definite cure for IBS, the present goal in IBS care is to help patients to decrease the symptom burden and to improve quality of life. Treatment of IBS should be individualized and based on a good consultation and lifestyle advice. Pharmacological and psychological treatment options are also important tools.

The consultation

There is very limited research in the field of role of "the good consultation" in IBS and the way to use this is mostly based on clinical experience, but some studies with qualitative standpoints reveal that IBS patients often are dissatisfied with how the healthcare providers manage the consultation (98-100). An effective and empathetic doctor-patient relationship is essential and has been found to be associated with increased patient satisfaction and reduced number of consultations (101).In the consultation, it is important that the patient is given time and opportunity to tell his/her story, present his/her agenda during the consultation and also describe fears and own ideas concerning the symptoms. After the patient has been given time for this, some additional questions can be asked and then often the typical history of IBS appears. As early as this, it is important to give the patient information on the suspected diagnosis and, if some additional investigation is planned to rule out other causes of the symptom, it is important to reveal the agenda of such investigations: "I think that it is IBS that is causing your symptoms, but to be sure we will do xx investigation to rule out yy and zz". After doing necessary, additional investigations, the patient comes back for a new consultation and if the investigations are negative (as they will be for IBS), the patient will find it easier to accept and understand the diagnosis. On the other hand, if another underlying cause is found, the patient will just experience the feeling that "the doctor was very thorough" based on the information in the first consultation. Unfortunately, it is often the case that the healthcare provider first starts talking about IBS only after doing multiple, stepwise investigations, signalling that "nothing was found so you must be suffering from a functional diagnosis", making it harder for the patient to then accept and understand the IBS diagnosis. After confirming the diagnosis, it is important that further actions are taken based on the patient's agenda. Sometimes the patient just wants an explanation of the symptoms and sometimes it is worries about a serious illness behind the symptoms that need to be ruled out. It could also be the bothersome symptoms level or the impact of quality of life that drives the patient to consult and in this case it is important to acknowledge this and give lifestyle advice, medical treatment or, when indicated, psychological treatment. It is also important to have follow-up contacts, evaluating the effect of eventual intervention. This technique for carrying out the consultation has helped me in managing patients with functional GI disorders, but is based on general consultation research (102, 103) and clinical experience, and it would be interesting to further explore this is in more depth from a scientific perspective concerning the IBS consultation.

Lifestyle advice and interventions

When giving this type of advice it is important not to dictate lifestyle regimes that are too complicated because they are hard to follow. Patients often complain of meal-related symptoms, which are very common in this group of patients (104, 105) and they have frequently tried to exclude different types of nutrients with inconsistent results. There is a common belief among patients that food-related IBS symptoms are in fact due to a food allergy, but the scientific support for this is weak (106). The best advice is probably to just avoid such nutrients that in the individual patients always or almost always give rise to symptoms and focus more on "how" rather than "what" they are eating. Traditionally IBS patients have been recommended a high-fibre diet (107), but many of the patients in fact react negatively to a high-fibre diet (108). Carbohydrates are also often reported to aggravate symptoms in IBS patients. However, a study investigating the connection between carbohydrate malabsorption and hypersensitivity or dysmotility in IBS patients was negative (109). Abnormal colonic fermentation has been suggested as an alternative explanation (110). Patients often benefit from eating slowly and more often, with regular, small meals. This is probably due to the fact that the visceral postprandial reflexes, which have been proven to be exaggerated in IBS patients (60, 61, 111), become less prominent, thus decreasing the symptoms. This type of diet advice can easily be given by the physician during the consultation, but sometimes when there are more complex questions concerning this, it is wise to let the patient consult with a dietician. Exercise has been described as decreasing the burden of IBS symptoms (112) and should be recommended as a part of the lifestyle intervention. The type of exercise seems less important than to exercise regularly with a type of activity that is appealing to the individual patient. Information about the negative effect of stress on IBS is also important to highlight, although as stress is impossible to avoid, achieving an understanding of the relationship is probably most important, to better cope and understand the symptoms. Also structured patient education has been found to be helpful (113, 114). In a randomized controlled trial by Ringström et al, the intervention reduced IBS symptoms and GI specific anxiety and had a positive effect on some quality of life parameters (115).

Pharmacological treatment

The current pharmacological treatment is based on treating the predominant, individual IBS symptoms such as abdominal pain, constipation and diarrhoea by using spasmolytic agents, bulking agents, polyethylene glycol (PEG), loperamide and cholestyramine, but the scientific evidence of the effectiveness of these drugs in IBS is weak (116). Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRI) in small doses can reduce the severity of IBS symptoms, and in meta-analyses a NNT (numbers needed to treat) between 3 and 4 has been demonstrated (117), and the scientific evidence on the effect on IBS symptoms is considered to be moderate to good(116). No pharmacological treatment, developed for treating IBS, targeting the whole complex of symptoms is currently available. In the late 1990s and early 2000s, new compounds targeting serotonin receptors in the gut were introduced. First Alosetron, a 5-HT_3 receptor antagonist intended for women with

IBS-D, was introduced in the US, but was later withdrawn due to the risk of serious side effects (ischemic colitis) and is now only available in the US under restricted use (118). Tegaserod, a 5-HT_4 receptor agonist with the indication IBS-C was then introduced in the US and Europe, but due to post-marketing reports of cardiovascular side effects this compound is now only available under licensed use (119). After those disappointments it has taken until recent years before new interesting compounds have been developed, mainly for the indication IBS-C and chronic constipation. A more selective 5 HT-4 receptor agonist (Prucalopride) with the indication chronic constipation has just been introduced in Sweden (120, 121). A guanylate cyclase –C receptor agonist (Linaclotide) (122, 123) is currently under evaluation in Europe for the indications chronic constipation and IBS-C. There are also several other interesting compounds in "the pipeline" that probably will come into clinical use in the near future(124).

Psychological treatment

A number of psychological treatment options of IBS have been evaluated. The most studied interventions are gut-directed hypnotherapy, cognitive behavioural therapy and brief psychodynamic therapy.

Psychodynamic therapy

Svedlund et al developed a protocol concerning brief psychodynamic therapy as treatment for IBS in the early 1980s, consisting of 10 sessions where the treatment was mainly supportive, focusing on coping with stress and emotional problems and not unconscious processes as traditionally is a part of the psychodynamic theory. The results were presented in the first RCT concerning psychological treatment for IBS in 1983 (125). In this study, 101 IBS patients were randomized to psychotherapy or to a control group. Post-treatment, there was a significant improvement in IBS symptoms in the treatment group vs. the control group and the difference was even more pronounced at the one-year follow-up. Another study from Guthrie et al (126) from 1991 confirmed these results and concluded that psychodynamic therapy was feasible and effective in up to two thirds of IBS patients that had not responded to standard medical therapy. In a more recent study from Creed et al (127) from 2003, a large group of IBS patients were randomized to psychodynamic therapy, SSRI therapy or "treatment as usual". In this study, no significant differences in abdominal pain could be detected, but a positive effect on health-related quality of life was seen in both the SSRI group and the psychotherapy group. In the following year, psychotherapy but not SSRI treatment was associated with a significant reduction in healthcare costs compared with "treatment as usual."

Cognitive behavioural therapy (CBT)

The first study including an element of CBT as treatment for IBS was presented by Blanchard et al in 1987 (128), where 14 patients underwent a multi-component treatment program including relaxation training, biofeedback and training in stress-coping strategies. In this small study, 65% of the patients were clinically improved. The results were subsequently confirmed in a randomized controlled trial by the same group (129), but later also contradicted by the same authors in two additional RCTs where this intervention failed to show any significant superiority to a control group. The first study of a "pure" CBT treatment for IBS was published in 1994 (130) by the same group. Twenty IBS patients were randomized to either 10 sessions of individual CBT or to a waiting list control. At the three-month follow-up, 80% of the CBT group vs. 10% of the control group reported a significant clinical improvement. The treatment protocol was subsequently evaluated in two additional studies, first with a control group controlled for attention (131) and then in a group format (132). In both studies, CBT was superior to the control group in reducing IBS symptoms. To follow up these promising results, the same group performed a large RCT, where 210 IBS patients were randomized to group CBT, attention control group or waiting list control(133). However, no significant differences in effect on IBS symptoms between the CBT group and the attention control group could be detected. The first study where a CBT protocol, specifically developed for treating IBS, was used was presented by Toner et al in 1998 (134), but this study also failed to show superiority over an attention control condition in reducing IBS symptoms. The same treatment protocol was further evaluated in a large RCT by Drossman et al 2003 (135) leading to the same conclusion. In order to develop CBT as treatment for IBS, a new protocol including exposure exercises was evaluated by Boyce et al, first in a small pilot study (136) with promising results, but in the subsequent, larger RCT (137), comparing CBT, relaxation training and "standard care", no significant differences between the groups were detected. In spite of the varying results in the studies described above, a recent meta-analyses from Ford et al calculated the number needed to treat (NNT) with CBT to 3, but the beneficial effect was dependent on which studies had been included(138). Recently, minimal contact CBT treatments have been evaluated in a randomized controlled fashion. Several studies have found comparable and marked effects of minimal contact interventions and classic face-to-face CBT treatment compared to a control group (139-141), stating that this could be a way of making CBT more widely available for this large group of patients. To take this further, Hunt et al presented in 2009 the first study describing internet delivered CBT (ICBT) for IBS (142). This protocol included relaxation training, cognitive restructuring, exposure exercises and behavioural experiments. The treatment was delivered over the internet, using e-mail contact with the therapist, leading to large improvements in IBS symptoms compared to waiting list control. ICBT in the treatment of IBS has also been explored by Ljotssón et al in a series of trials evaluating this type of treatment with a 10-week treatment protocol based on three themes: education about a psychological model of IBS, mindfulness and acceptance, and exposure exercises. The protocol was first tested in a pilot study in a group format with significant effects on IBS symptoms, IBS-related fear and quality of life (143). In subsequent randomized controlled studies, the treatment was delivered as ICBT and was equally associated with the same positive effects, both when comparing the effect of ICBT in a self-referred sample vs. waiting list control (144) and a self-referred sample vs. internet-delivered stress management (active control group) (145). The protocol has also showed a

similar result when treating a consecutively recruited clinical sample, randomized to ICBT or waiting list control (146). This ICBT treatment protocol has also been proven to have positive long-term effects and to be cost-effective (147).

Gut-directed hypnotherapy

Effects on IBS symptoms

Gut-directed hypnotherapy as treatment in severe, refractory IBS was first described by the Manchester group in 1984 (148). In a randomized controlled trial, 30 IBS patients, refractory to other therapies, were randomly allocated to treatment with gut-directed hypnotherapy or supportive psychotherapy and placebo. Both interventions were carried out by Dr Whorwell and consisted of seven half-hour sessions of decreasing intensity over a three-month period. Patients were also given a tape for daily autohypnosis after the third session. Hypnotherapy was solely directed at general relaxation and control of intestinal motility, and no attempt was made at hypnoanalysis. Hypnosis was induced by an arm-levitation technique followed by a combination of several standard deepening procedures depending on the patient´s progress and visualization abilities. After a general comment about improvement of health and well-being, attention was directed to the control of intestinal smooth muscle (before hypnosis the patient was given a simple account of intestinal-smooth- muscle physiology.) The patient was asked to place his/her hand on the abdomen, feel a sense of warmth and relate this to asserting control over gut function. Reinforcement by visualization (for example, imagining a riverside scene and relating the slow flow of the river to the smooth rhythmic action of their own gastrointestinal tract, gaining control over the gut function) was used if the patient had the ability. All sessions were concluded with standard ego-strengthening suggestions. The results were outstanding. The hypnotherapy group reported significantly less abdominal pain, less distension and more regular bowel habits compared to the control group, which reported a small but significant improvement when comparing pre- vs. post-treatment measurements in all symptoms except bowel habits. The reported general well-being was also greatly improved in the hypnotherapy group and the post-treatment difference compared to the control condition was highly significant. In the hypnotherapy group, symptoms were either mild or absent in all 15 patients. The authors concluded that hypnotherapy is highly effective in the treatment of refractory IBS and a follow-up study to evaluate the long-term effects was presented by the same group in 1987(149). The original 15 hypnotherapy patients had now been followed for an average of 18 months and had booster sessions every third month during this time. During the follow-up period, two single cases of symptom relapses were reported and these could be treated with an extra session of hypnotherapy. At the end of the follow-up, all patients remained in remission with symptoms not significantly different from the end of the previous study. In this study, another 35 IBS patients with refractory IBS had been treated and the combined results of the whole group of patients were presented in an uncontrolled fashion. The new patients were divided into three groups: classical cases (abdominal pain, distension and disturbed bowel habits), atypical cases (lacking one of the symptoms mandatory to be classified as a classical case) and patients with coexisting psychopathology. The original study only included patients in the first group (classical cases). Patients were judged as “improved” only if

their symptoms became mild or absent and they required no medication for IBS with the exception of bulking agents. The overall success rate was 84% but the classical cases responded best (94%). Atypical patients responded in 43% and patients with coexisting psychopathology in 60% of the cases. Patients reported significant improvements in all parameters (abdominal pain, distension, bowel habits and general well-being) when comparing pre- vs. post-treatment measurements. To further evaluate gut-directed hypnotherapy as a treatment for severe IBS, Harvey at al (150) presented a study in 1989, with 33 patients randomized to group or individual hypnotherapy. The treatment consisted of five 40-minute sessions of either group or individual hypnotherapy with decreasing intensity over a five-month period. The treatment protocol was identical to the one used in earlier studies. A composite scale measuring the degree of abdominal pain, distension and bowel symptom was used. At the end of the study, 13 patients showed no improvement, 9 patients less symptoms and 11 patients were symptom- free. No significant difference in effect was found between the patients that had been treated individually or in group. A total of 60% of the patients was at least somewhat improved but when comparing the result with earlier studies, considering the symptom- free group as responders, 33% were responders compared to 84% in the previous studies from Manchester. In 1996, Talley et al (151) presented a systematic review of 14 articles, reporting the effects of psychological treatment of IBS. In this review, all types of psychological treatments, investigated in a randomized controlled fashion, were assessed according to methodological quality. Only Whorwell's study of gut-directed hypnotherapy from 1984 was considered as methodologically acceptable. In an attempt to replicate the original study by Whorwell et al. in 1998, Galovski and Blanchard (152) included 12 patients in a randomized controlled study, comparing a 12-week course of hypnotherapy (30 min/week) to a symptom monitoring control condition. The patients in the control condition were crossed over to hypnotherapy treatment after six weeks, so that all subjects started receiving treatment. The treatment protocol was identical to the Manchester protocol and the treatment was performed by a therapist certified in hypnosis. Eighty % of the patients in the hypnotherapy group were clinically improved compared to 0% in the control condition. When the controls were crossed over to hypnotherapy, 67% of these patients also reached clinically significant improvement. When comparing the individual IBS symptoms pre- vs. post-treatment, only abdominal pain, constipation and flatulence reached a significant improvement. In a study from Palsson et al (153), the hypnotic intervention was conducted individually in 45-minute sessions every other week for 12 weeks, following written, standardized scripts, mainly based on the Manchester protocol, administered by a clinical psychologist with experience of hypnosis. In total, 42 patients were treated in this RCT, which for methodological reasons was divided in two smaller studies for studying other endpoints (see below). Significant improvement was seen within the hypnotherapy groups concerning abdominal pain, bloating, stool consistency and in one of the studies also in the frequency of bowel movements. No effect was seen within the control group, and the overall change in IBS symptoms between the groups after treatment was highly significant. The patients were also asked to provide a global rating of symptom status 10 months after treatment, and the mean estimated degree of improvement in IBS symptoms compared with pretreatment level was 68%. Gut-directed hypnotherapy has also been evaluated in a primary care setting (154) where patients were randomized to five 30-minute, weekly sessions of gut-directed hypnotherapy or to "standard management". At 3 months, the intervention group had significantly less pain, less diarrhoea and lower overall symptom scores ($P<0.05$) compared to the control group, but the differences was not

maintained over time. The results from these RCTs support the findings from the Manchester group that gut-directed hypnotherapy is effective in treating refractory IBS. However, the effect in these later studies does not reach the same impressive level of efficacy as the original study from Manchester. Webb et al concluded in a Cochrane review from 2007, based on the results on the above described RCTs and came to the conclusion that the therapeutic effect of hypnotherapy was superior to that of a waiting list control or usual medical management, for abdominal pain and composite primary IBS symptoms, in the short term in patients who had failed standard medical therapy(155). Further experience from the Manchester group (156), reporting results from their clinical service in a large cohort (n=250), confirms the effectiveness of the intervention both in reducing IBS symptoms and extraintestinal symptoms. In this study, factors influencing responsiveness were investigated and males with IBS-D responded less favourably to hypnotherapy. Also, in a smaller clinical sample from Amsterdam(157), similar results concerning the effect on IBS symptoms have been reported. In a recent meta-analyses by Ford et al (138), the NNT when treating IBS with gut-directed hypnotherapy was two. Subsequently, the long-term effects on IBS symptoms have been investigated by Gonsalkorale et al (158). A total of 204 IBS patients, previously treated with hypnotherapy, were investigated 1-6 years after treatment. Of the 71% of patients initially responding to treatment, 81% maintained their improvement at follow-up. There was also a significant long-term effect on extraintestinal symptoms and the only negatively correlated baseline parameter associated with non-responder status was male gender. Most of the above described studies derive from one specialized, research-centre for gut-directed hypnotherapy, making it difficult to interpret the results into a setting closer to standard clinical routine care. Only one earlier study investigates the long-term effects of the intervention, which needs to be confirmed, preferably with the treatment performed outside specialized, hypnotherapy centres.

Effects on quality on psychological comorbidity, quality of life and economic features

Hypnotherapy in general is reported to have a positive effect on psychological symptoms such as anxiety, depression and somatization (159). In 1998, Galovski et al evaluated the effects on psychological comorbidity when treating IBS patients with hypnotherapy and detected a significant improvement in anxiety, but not in depression scores, pre- vs. post-treatment(152). The same result was demonstrated by Palsson et al 2002 (153). In this study, there was also a reduction in the degree of somatization post-treatment. Houghton et al compared a group of 25 IBS patients previously treated with gut-directed hypnotherapy to a similar group of patients on the waiting list for the same intervention concerning symptomatology, quality of life and economic futures and found that the treated patients reported significantly fewer severe IBS symptoms and extraintestinal symptoms. Quality of life, such as mental well-being, mood, locus of control, physical well-being and work morale were also significantly and favourably influenced by hypnotherapy. The patients treated with gut-directed hypnotherapy were also significantly less likely to take time off work and visit their general practitioner compared to the control group(160). In another study from the Manchester group (161), especially designed to investigate cognitive effects of hypnotherapy treatment on IBS-

patients, there was a significant improvement in quality of life, depression and anxiety post- vs. pre-treatment, but also a significant improvement in IBS-related cognitions reflected in a reduced total score in the "cognitive scale for functional bowel diseases" (CSFBD) (162). The level of this scale was also found to be directly correlated with the severity of IBS symptoms, extracolonic score and the score of anxiety and depression both before and after hypnotherapy and inversely correlated with the overall quality of life scores. Improvement of cognitions was correlated to the improvement in IBS symptoms and the authors concluded that the improvement of cognitions could be a mechanism behind the effect of hypnotherapy in treating IBS. Also, in the large audit from the same author (156), significant improvements pre- vs. post-treatment were seen in quality of life, depression and anxiety. In a subsequently presented study from the same group (158), positive long-term effects on these parameters have also been described as well as a significant decrease in healthcare utilization and use of symptom modifying medication among the responders compared with non-responders. Our clinical impression is that the majority of the IBS patients, treated with gut-directed hypnotherapy are very satisfied with the intervention, even in cases where small or none effect on GI-symptoms is obtained. Other factors than effects on IBS-symptoms associated with patient satisfaction with hypnotherapy needs therefore to be further investigated.

Effects on gastrointestinal physiology and the central nervous system (CNS)

Little is known about the effects of hypnotherapy on gastrointestinal physiology (163). Hypnosis in general has the ability to modulate the orocecal transit time, which has been shown to be significantly longer during hypnotic relaxation (164). It also reduces colonic motility, and when anger and excitement are induced under hypnosis, the colonic motility is significantly increased (165). To evaluate the effect on rectal sensitivity of gut-directed hypnotherapy on IBS patients, Prior et al (166) compared rectal sensitivity between two groups of IBS patients, 15 patients in the treatment condition and 15 controls. In comparison with the control group, a significant decrease in rectal sensitivity was found among patients with IBS, both after a course of hypnotherapy and during a session of hypnosis. However, this was later contradicted in a study from Palsson et al (153), where no effect on rectal sensitivity was found after a course of hypnotherapy. In a more recent study from the Manchester group, Lea et al (167) investigated another sample of IBS patients before and after 12 weeks of hypnotherapy, this time using modern barostat technology to assess rectal sensitivity. They found that patients who had visceral hypersensitivity to pain before the treatment were less sensitive after hypnotherapy, whereas those with hyposensitivity before instead tended to be more sensitive after the treatment period. Sensitivity thresholds of patients with normal sensitivity were unaffected by the hypnotherapy. This means that the rectal sensitivity in this sample tended to move into the normal range after hypnotherapy. Another publication from the Manchester group (168) demonstrates that, similar to colonic motility, different emotions induced in a hypnotic state (anger, happiness, or relaxation) can also affect rectal sensitivity, More specifically, relaxation reduced rectal sensitivity and anger increased the sensitivity. To further evaluate the effects of gut-directed hypnotherapy on rectal sensitivity, Simrén et al showed that there was no effect of hypnotherapy on rectal sensitivity in a fasting condition, but a reduction in the sensory and motor component of the gastrocolonic response after administration of duodenal lipids was seen(169). The effect on the central nervous system of hypnosis in IBS has not been studied. However, outside IBS research,

modern brain-imaging techniques have been used to investigate the antinociceptive effect of hypnosis (170-172). The anterior cingulate cortex (ACC) has been shown to be selectively correlated with the unpleasantness of pain perception. These findings were then further explored and it was demonstrated that hypnotic modulation of pain is mediated by the ACC (170) and that an increased cerebral functional connectivity can explain the antinociceptive effects of hypnosis (171). The key role of the ACC in the effect of hypnosis on pain perception is interesting, since this is one of the brain regions where IBS patients have been found to differ from healthy controls (83, 85, 173, 174), especially IBS patients with an increased rectal sensitivity(88). Further research evaluating the mechanism of action of gut-directed hypnotherapy as treatment for IBS is needed, both concerning potential permanent effects on GI motility, GI sensitivity and alterations in the central processing of visceral input.

Aims of the thesis

The overall aim of this thesis was to evaluate the effects of gut- directed hypnotherapy as treatment in refractory IBS, when the intervention was given outside of specialized hypnotherapy centres, aiming to motivate a wider spread of this intervention as part of the IBS care in clinical practice. We also aimed to evaluate the effects of gut-directed hypnotherapy on GI motility

Paper I

The aim of this study was to evaluate the effect of gut-directed hypnotherapy as treatment in refractory IBS in two RCTs. We hypothesized that the intervention would improve IBS symptoms, quality of life and psychological comorbidity. We also hypothesized that these effects would be maintained 12 months after the treatment.

Paper II

The aim of this study was to evaluate the long-term effect of gut-directed hypnotherapy as treatment in refractory IBS. We hypothesized that the intervention would lead to long-term improvement of IBS symptoms, reduced healthcare utilization, reduced use of symptom modifying drugs and alternative therapies. We also hypothesized that the patients would find the treatment worthwhile and that the patients would continue to use the technique actively.

Paper III

The aim of this study was to evaluate the degree of patient satisfaction after receiving gut-directed hypnotherapy as treatment in refractory IBS. We hypothesized that there would be a high grade of satisfaction with the intervention and that factors other than GI symptom improvement would also be of importance for patient satisfaction.

Paper IV

The aim of this study was to investigate the possible effects on GI motility by gut-directed hypnotherapy as a treatment for refractory IBS.

The studies

The hypnotherapy project

The hypnotherapy project has in total rendered five papers, of which one has been previously published(169) outside the frame of this thesis. This study investigated the effect on colonic sensorimotor function in IBS patients treated with hypnotherapy.

The project involves three different sites:

1. Sahlgrenska University Hospital, Gothenburg. A highly specialized unit for functional GI disorders.
2. Gävle Hospital, Gävle. A medium-sized county hospital with a small gastroenterology department with two gastroenterologists, serving approximately 100,000 inhabitants.
3. Ersta Hospital, Stockholm. A specialized unit for the clinical treatment of functional GI disorders.

Methodological overview

The results in **Paper I (Trial 1), Paper III and Paper IV** all derives from one large RCT conducted in Gothenburg, where 90 IBS patients were randomized to a 12-week course of hypnotherapy or to a control group, controlled for attention. The control group was later treated with hypnotherapy as well (after 6 months). Results concerning the effects of hypnotherapy on IBS symptoms, quality of life and psychological comorbidity are presented in **Paper I (Trial 1**). Patients in this trial were also evaluated concerning satisfaction with the treatment, effects on cognitive function and sense of coherence. By using this information, factors associated with patient satisfaction with hypnotherapy were investigated in **Paper III**. A sample from this patient population were also investigated pre- and post-treatment, studying possible effects on GI motility by hypnotherapy, using GI transit investigations and antroduodenojejunal manometry, results presented in **Paper IV.**

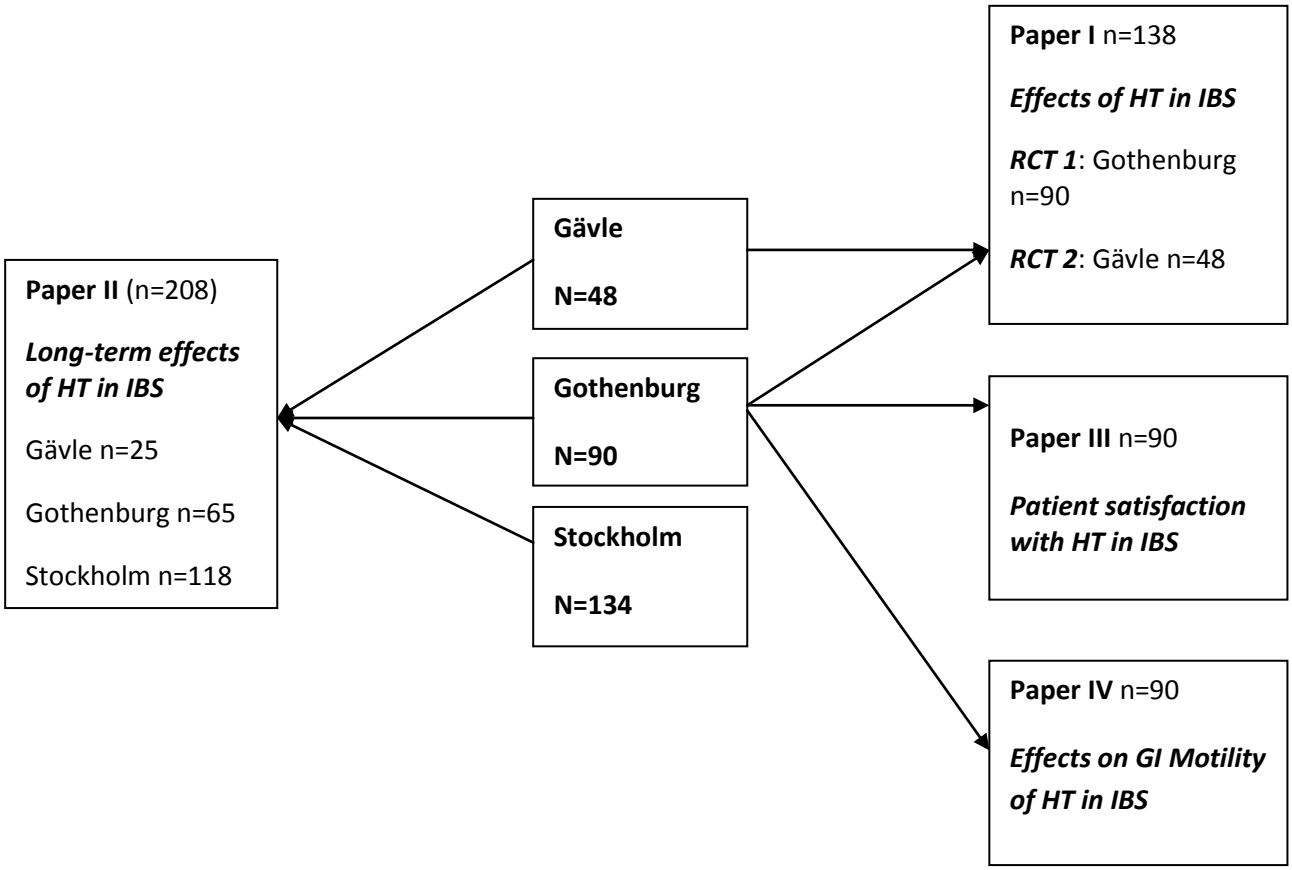
The results in **Paper I (Trial 2)** concerning the effects of hypnotherapy on IBS symptoms, quality of life and psychological comorbidity derive from a RCT in Gävle, where 48 IBS patients were randomized to a 12-week course of hypnotherapy or to a waiting list control group; the control group was later treated with hypnotherapy as well. The results in **Paper II** are based on the retrospectively assessed, subjective, patient-reported long-term effects of hypnotherapy in a sample derived partly from the RCTs described above and partly from a clinical sample treated with hypnotherapy for IBS at Ersta Hospital in Stockholm (n=134).

Subjects **(Figure 1)**

All patients treated with hypnotherapy in the studies included in this thesis had IBS refractory to standard lifestyle advice and medical, symptom-modifying treatment, i.e., these interventions was not sufficient to ease the burden of IBS symptoms adequately. All patients fulfilled the Rome II criteria for IBS(7) and had been adequately investigated in order to rule out organic GI diseases,

possibly explaining the symptoms. In Paper I (Trial 1), Paper III and Paper IV, performed in Gothenburg as well as in Paper I (Trial 2) performed at Gävle Hospital, patients were recruited consecutively among patients referred to the respective gastroenterology department. In Paper II, the subjects included from Gothenburg and Gävle were recruited from the previously treated samples from the RCTs in Paper I and the patients from Stockholm were part of a clinical sample.
All subjects provided written informed consent before inclusion in the studies. The ethics committee of the University of Gothenburg and the local ethics committee of Landstinget Gävle/Dalarna approved the studies performed in Gothenburg and Gävle. The follow-up of the clinical sample from Stockholm was, after discussion with the ethics committee in Stockholm, considered as a clinical follow-up control and no additional approval from the ethics committee was requested.

Figure 1.Patients in the hypnotherapy project (hypnotherapy =HT)



Intervention

The used treatment protocol for gut-directed hypnotherapy is explained below and was identical at all sites (Gothenburg, Gävle and Stockholm). The sample from Gothenburg was treated outside the hospital by three experienced clinical psychologists in their private practices. The sample from Gävle was treated by one experienced clinical psychologist at the gastroenterological outpatient clinic at the hospital. The psychologists from Gothenburg and Gävle had been trained in gut-directed hypnotherapy, but had no earlier clinical experience of this specific intervention. The sample from Stockholm was treated by two psychologists with several years' clinical experience of treating IBS with gut-directed hypnotherapy.

Treatment protocol for gut-directed hypnotherapy

The intervention method used in our studies is based on the Manchester protocol of gut-directed hypnotherapy (175) (Box 2). All patients were individually treated 1 hour/week during a 12-week period. All were treated by clinically experienced psychologists. The psychologists from Gothenburg and Gävle had limited previous experience in gut-directed hypnotherapy, but had received formal training from gut-directed hypnotherapists. The psychologists from Stockholm had both previous clinical experiences from gut-directed hypnotherapy. The patients were told to practice their hypnotic skills at home between the sessions on a regular basis. Audiotapes were used with the patients from Stockholm and Gävle but not with the patients from Gothenburg. The treatment protocol is described in detail by Dr Wendy Gonsalkorale as follows:

First (and Second) Session:
The purpose of the first session in particular is to allow the patient to become familiar with hypnosis and the treatment setting, and the second session may be along similar lines before going on to the gut-directed techniques, if the patient needs more time to become accustomed to hypnosis. A typical first session includes a straightforward hypnotic induction, usually involving progressive relaxation and further focusing or deepening of the hypnotic state by the usual means, such as going to a special place. This is then followed by suggestions for ego-strengthening, confidence-building, and general well-being. Of course, there are any number of examples available, but one that many of our patients have enjoyed is the tree metaphor—thinking of oneself as a tree, the unconscious mind being its roots, providing strengths and resources that are needed, anchoring the person safely so they can "bend and be flexible in the storms and struggles of life," the leaves being "doubts and worries falling away" or experiences that enrich the soil to promote further development. Patients are also reminded in trance that through this experience they are learning (a) the skills of relaxation and hypnosis and, like other skills, these will improve with practice, and (b) to tap into and direct the unconscious mind's ability to regulate bodily functions to control the gut, but also each time they practice hypnosis, they are already creating conditions for the mind and body to reset the balance in bodily functions.

The procedure for hypnotic induction is often combined with asking the patient to repeat the word calm to themselves silently on each out-breath, which also helps slow down the rate of breathing. This is something that has proved very popular with patients and the idea of "calm" is elaborated on in all sorts of ways to help promote relaxation, calm, and well-being, e.g., the patient can envisage the calm in some way and can then breathe it into each cell in the body. Alternatively, each cell is bathed in a sea of calm, the rhythm of each breath can help the calm to gently circulate around the body, with each cell soaking up the calm, taking what it needs—just as the blood gently circulates with the rhythm of each heartbeat, and cells take what they need, the nutrients, oxygen etc. A posthypnotic suggestion is given later in the session that they can use calm in the same way whenever they want to feel more calm and relaxed. The patient is given a recording on audiocassette or CD and is expected to listen to it and to practice on a daily basis. This is normally a standardized hypnosis session based on the first session and copied for each patient, but occasionally the patient's session is recorded for a more individualized approach.

Gut-Directed Sessions:
From the second or third session onward, more specific techniques aimed at controlling and normalizing gut function are introduced. A gut-directed session involves hypnotic induction and deepening as usual, is typically followed by these suggestions:
Ability to control gut. This suggests as the patients drift deeper into the hypnotic state, they are now "tapping into the potential of your unconscious mind, which is now becoming stronger and more powerful, to harness this power and energy to begin to channel and to direct it to gain more control over the gut," and so they can "imagine a surge of control from your mind over your gut," and the gut responding to this.
Hand warmth on abdomen. The patient is asked to move one hand onto the abdomen and, after a count to three as an anticipatory signal, to induce a feeling of warmth and/or comfort, which signifies "the power of the mind being channelled into the gut, soothing it and comforting it, developing control over it and putting it back to normal," and encouraging the patient to let the mind draw on any personal experience of warmth and comfort, e.g., a hot-water bottle or the warmth of the sun. This can be checked and reinforced by asking the patient for a signal, e.g., lifting a finger when one can feel the warmth of the hand on the abdomen. (This warmth is to be expected, since relaxation will promote hand warmth and this sensation will generally increase as the hand remains on the abdomen.) On a second count of three, the patient is then asked to move the other hand onto the abdomen to reinforce the warmth and sense of control.
An image of a normal gut. The patient is asked to let his or her mind "create an image or some way of imagining the gut that represents the gut working normally," in order to communicate these instructions to the gut. This could be suggested by the therapist or patients may readily develop their own that is either entirely self-generated or based on ideas given by the therapist, which in turn may be examples of what other patients have used. Whether the imagery used is literal or whether it is symbolic or metaphorical does not seem to matter, so long as it is meaningful to the patient. For instance, the gut may be thought of as a river, which, for diarrhoea, would be rushing and turbulentor, for constipation, sluggish and stagnant. The patient could then envisage it moving steadily and smoothly instead. Some patients have developed quite interesting images. For example, one woman envisaged her gut as a long, smooth, soft, and multi-coloured silk scarf. Another saw the

problematic gut as a train whose driver had gone to sleep, rushing out of control, so she imagined herself being the driver and slowed the train down to a comfortable speed. Again, one can check by asking the patient to signal when something has come to mind and, when it has, suggest that "by allowing this to be as strong and clear as possible, the more influence this will have over the gut."

Imaginal rehearsal. The patient imagines him- or herself in any previously feared or avoided situations—such as making a journey—but now with the gut working normally.

Posthypnotic suggestions. These consist of reminding patients that:

• by practising these techniques, they will gradually gain more control over the gut, so there are fewer symptoms, and any symptoms will be less intense and bothersome, e.g., "less and less pain, less and less discomfort, less and less bloating, and you have a more normal and satisfactory bowel habit";

• the process naturally takes time and practice, patience, and persistence, but they will do it and "you are now becoming in control of your gut, rather than your gut controlling you. It's not going to control you anymore";

• they can reduce symptoms and more readily settle the gut when needed, by putting the hands on the abdomen, and they will feel the warmth and comfort, and to bring to mind the image of the gut working normally, and that "these are signals to your mind to take control, to take away pain, to take away discomfort, to take away any bloating, and to make your bowel habit more normal." Although the exact content and wording of a session will differ, depending on the therapist, the patient and his or her needs, and the particular session.

Box 2. Gut-directed hypnotherapy—Outline of treatment

1. Consultation
- Clinical history to assess IBS symptoms and impact on patient
- Explanation of IBS symptoms and hypnotherapy
2. Treatment sessions
- 1st (and 2nd) sessions:
- Relaxation/hypnotic induction
- Relevant ego-strengthening
- From 2nd or 3rd sessions
- Inclusion of gut-directed techniques for control and normalization of gut function, e.g., hand warmth on abdomen, imagery, imaginal rehearsal, direct suggestions
- Suggestions and techniques modified as necessary
- Daily practice with audiotape

Control groups

In Paper I (Trial 1, Gothenburg), Paper III and Paper IV, the control group were controlled for attention under the 12-week treatment phase. Patients in this group met with a dietician once for one hour where they received general food advice and with a physiotherapist for one hour, who provided information about relaxation training. Furthermore, a gastroenterologist with special interest in functional GI disorders individually met the patients in the control group for one hour and informed them about GI physiology, with emphasis on the pathophysiologic mechanisms in IBS. Moreover, a study nurse telephoned the subjects in the control group regularly during the treatment period for extra support. All patients in the control group knew that they would receive hypnotherapy after the study was completed.

In Paper 1 (Trial 2, Gävle), the patients in the control group were informed that they would receive hypnotherapy after 1 year but after the randomization they did not receive any extra support, but served as waiting list controls.

Outcome measures (Figure 2)

IBS symptoms

GI-symptom questionnaire *(169)*.

Used in Paper I (Trial 1) and Paper III. This questionnaire evaluates the perceived severity of symptoms related to IBS and was created specifically for this study. It uses a seven-point Likert scale ranging from no symptoms (=1) to very severe symptoms (=7). The symptoms included are bloating, gas, pain, loose stools, urgency, hard stools, and incomplete evacuation. Scores of the individual symptoms are summarized into a total symptom severity score ranging from 7 to 49 and two different domains: sensory symptoms score (pain, bloating, gas) and bowel habit score (loose stools, urgency, hard stools and incomplete evacuation).

Gastrointestinal symptom rating scale - IBS version (GSRS-IBS)*(176)*

Used in Paper I (Trial 2). The Gastrointestinal Symptom Rating Scale (GSRS)-IBS is a validated, IBS specific questionnaire assessing the pattern and severity of IBS-related GI symptoms during the past week using a 7-point Likert scale (1, no discomfort; 2, minor discomfort; 3, mild discomfort; 4, moderate discomfort; 5, moderately severe discomfort; 6, severe discomfort; 7, very severe discomfort) The GSRS-IBS consists of 13 questions divided into 5 domains or syndromes: pain, bloating, constipation, diarrhoea, and satiety. The higher the score the more severe are the symptoms.

Quality of life

Irritable Bowel Syndrome Quality of Life (IBSQOL)*(28)*

Used in Paper I (Trial 1) and Paper III. This disease-specific, health-related QoL instrument includes 30 items measuring 9 dimensions of health: emotional functioning, mental health, sleep, energy, physical functioning, diet, social role, physical role and sexual relations. Raw scores are transformed into a scale of 0-100, with 100 representing the best possible quality of life score.

Short form 36 (SF-36)*(177)*

Used in Paper I (Trial 2). This is a widely used generic HRQOL measure with eight multi-item subscales (36 items), including physical functioning, role limitations caused by physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health. Raw scores are transformed into a scale ranging from 0 (worst possible health state) to 100 (best possible health state) on each of the eight subscales. A physical component score (PCS) and a mental component score (MCS) can be calculated and used as summary scores, and these were used in this study.

Psychological comorbidity

The Hospital Anxiety and Depression Scale (HAD)*(178)*

Used in Paper I and III. This scale was developed for non-psychiatric medical patients to detect anxiety and depression. It consists of 14 items, with 7 items relating to anxiety and 7 items relating to depression. Each item is scored on a 4-point Likert scale, giving a range from 0 to 21 on the anxiety and depression subscales with higher scores indicating more severe symptoms.

Cognitive function

Cognitive scale for functional bowel disorders (CSFBD) *(162)*.

Used in Paper III. The CSFBD is a scale designed to access cognitions in patients with functional bowel disorders. It includes statements derived from the typical thoughts of IBS patients, subdivided into themes relating to bowel function and personal characteristics relevant to IBS. The patients are asked to rate to which extent each statement applies to them, using a 7-point scale, ranging from *Strongly Disagree* (scoring 1) to *Neither Agree/Disagree* (scoring 4) to *Strongly Agree* (scoring 7). The final version of the scale consists of 25 items, but an additional 6 items were used in this study, as was the case in a previous study assessing cognitive change in patients with IBS who underwent gut-directed

hypnotherapy (161). Scores for eleven individual themes can be calculated, but in this study we only used a total score (range 31-217), with higher scores indicating more negative IBS-related cognitions

Sense of coherence

Sense of coherence scale (SOC) *(179)*

Used in Paper III. Sense of coherence reflects the ability a person has to cope with difficult situations in life. The SOC includes 29 items measuring three aspects of this ability: manageability, comprehensibility and meaningfulness. The scale uses a 7-point response format, where 1 represents the weakest and 7 the strongest sense of coherence. A high score indicates successful coping abilities and increased likelihood of having a good health and quality of life.

Patient satisfaction

Patient satisfaction scale

Used in Paper III. This scale was developed specifically for this study and was used to evaluate the degree of satisfaction with the intervention. The patients were asked to score their satisfaction with the gut-directed hypnotherapy immediately after the end of the 12-week treatment period on a Likert scale, ranging from 1 (specified as “not at all satisfied”) to 5 (“very satisfied”), with the scale steps 2, 3 and 4 not specified. Moreover, the patients were also asked if they would start with gut-directed hypnotherapy again if they had had the knowledge and experience about this intervention that they possessed after the treatment period.

Subjective assessment questionnaire (SAQ) (158)

Used in Paper II. The SAQ is a questionnaire constructed and validated for the use of retrospectively measuring changes after hypnotherapy. It is a simple questionnaire developed in the hypnotherapy unit in Manchester, UK. The results from this questionnaire are comparable to using the widely spread IBS-SSS (irritable bowel syndrome symptom severity scale) in a prospective manner. The questionnaire consists of 7 questions concerning the degree of IBS-symptoms directly after treatment and at present, healthcare consumption, use of symptom-modifying drugs, present use of hypnotherapy, the use of other types of treatment for IBS and the general meaningfulness of gut-directed hypnotherapy, using Likert-type responses.

GI transit measurements

Gastric emptying, small bowel transit and colonic transit were assessed by use of a one-visit radiological method developed at our unit (66). For colonic transit measurement, the patients ingested 10 radiopaque rings daily for 6 days. On the sixth day, the dose was divided; five rings in the morning and five rings at 8 p.m. This was done to enhance accuracy in measuring rapid colonic transit. All measurements were made on the seventh day. After an overnight fast, the patients arrived in the morning at the laboratory and the radiopaque rings still present in the bowel were counted by use of fluoroscopy (Exposcop 7000 Compact,Ziehm GmbH, Nüremberg, Germany). Colonic transit time expressed in days was calculated by dividing the number of retained radiopaque rings by the daily dose, i.e. 10. The patients then had a 400-kcal test meal of oatmeal porridge, one cheese sandwich and a glass of a lactose-free drink (Solhavre, producer: Scanian Farmers AB, SE-170 85 Solna, Sweden) made out of 10% oat, rapeseed oil and water. Twenty radiopaque spherical markers were added to the meal. These type of markers have been shown to empty from the stomach before and without relation to the antral phase III (180). Fluoroscopy was used to count the number of radiopaque spherical markers in the stomach, the small bowel and the colon directly after the meal and then every 30 min. The patients were observed until at least 10 markers reached the colon or for a maximum time of 8 h. By plotting the number of markers against time, the area under the curve was used to calculate gastric emptying time and small bowel transit time as described and validated previously (66). The radiation exposure for the whole gut transit test is about 2 mS (66).

Small bowel manometry

Equipment: Motility was recorded with an eight-channel assembly for pressure recording (Zinetics, Salt Lake City, Utah, USA), as has been described in detail previously (181). The water-perfused catheter had an outer diameter of 4.8 mm, a central lumen of 1.8 mm for the guide wire, and eight lumens with a diameter of 0.8mm each for pressure recording. The pressure recording side ports were situated 2, 17, 30, 32, 34, 45.5, 47, and 48.5 cm from the tip of the catheter. Thus, three ports were situated in the antrum 1.5 cm apart, three in the descending part of the duodenum 2 cm apart, one in the distal duodenum close to the ligament of Treitz, and one in the proximal jejunum. The eight channels were connected to capillaries and perfused with water at 0.3 ml/min. The catheter was connected to pressure transducers and recordings made with a polygraph (PC Polygraph, Synectics, Stockholm, Sweden), which converted the pressure data to digital information at 4 Hz. This information was transferred to an IBM-compatible computer via a fibre-optic interface. The individual recording was displayed on the computer screen and stored for later analysis

Experimental design: Motility was recorded starting either in the morning after an overnight fast or in the afternoon after at least a six-hour fasting period. The catheter was placed under fluoroscopic guidance with the tip in the proximal part of the jejunum. The subjects were placed in a semi-reclining position and fasting motility was recorded for 5 hours, followed by intake of a

standard meal and a continued recording for one hour. The test meal consisted of porridge made from 200 ml water and 50 g rolled oats, 150 ml milk; white bread (50 g) and butter (10 g); and about 13 g of cheese (16% fat). The total energy content of the meal was 500 kcal.

Analysis: Analysis of the different phases of interdigestive motility as well as the meal-related motility response was performed by direct visual inspection on the computer screen by one of the investigators. Quantitative measures were calculated in order to aid in the interpretation of pathology and the possible effect of the study intervention. The numbers of phase III activities of the migrating motor complex (MMC) were counted and the duration of full MMC cycles were measured when possible. Small bowel MMC phase III activity was defined as a sequence of regular pressure waves, 10.5–14/min, for at least 2 minutes, followed by motor quiescence (phase I). Phase III duration in individual channels and its propagation velocity were interpreted. A motility index (MI), expressed as the area under the curve (mmHg*s), was used. This parameter was calculated during fasting motility for each 30 min period preceding a MMC phase III activity when possible, or when this was absent or the measurement not technically possible, during the 30 min preceding meal intake ("Fasting MI"). The MI was also calculated for the last 30 min of fed motility before the end of the study ("Fed MI"). In order to minimize the effects of slightly varying catheter position during the registrations, all quantitative variables were calculated in the two distal small bowel channels only. All analyses was made by use of a commercially available software (Polygram, version 5.06 X1, Synectics Medical, Stockholm, Sweden), where the basic menu of the program was used for calculations.

Criteria for abnormal small bowel motility

1. a) *Aberrant propagation of MMC phase III* (non-or retrograde propagation, too slow (<1.0 cm/min) or too rapid (>25 cm/min)propagation)

b) *Aberrant configuration of MMC phase III* (baseline elevation>30 mmHg for more than 3 min) At least two phase-III abnormalities had to be present for fulfilment of this criterion.

2. *Bursts of non-propagated phasic pressure activity* in the fasting or fed states. Bursts were periods with a duration of >2 min with high amplitude (>20 mmHg) and high frequency (>9/min) phasic pressure activity that was neither propagated nor followed by motor quiescence. At least two bursts had to be present for fulfilment of this criterion.

3. *Sustained (>30 min) and intense, uncoordinated phasic pressure activity* in one segment of the intestine and normal or reduced activity at the same time at other levels.

4. *Inability of an ingested meal to change fasting intestinal activity into a fed pattern*.

5. *Severe hypomotility,* absence of contractions or mainly low-amplitude (<20 mmHg) contractions throughout the recording irrespective of fed status(182, 183).

Outcome measurements: flowchart Paper I, III and IV

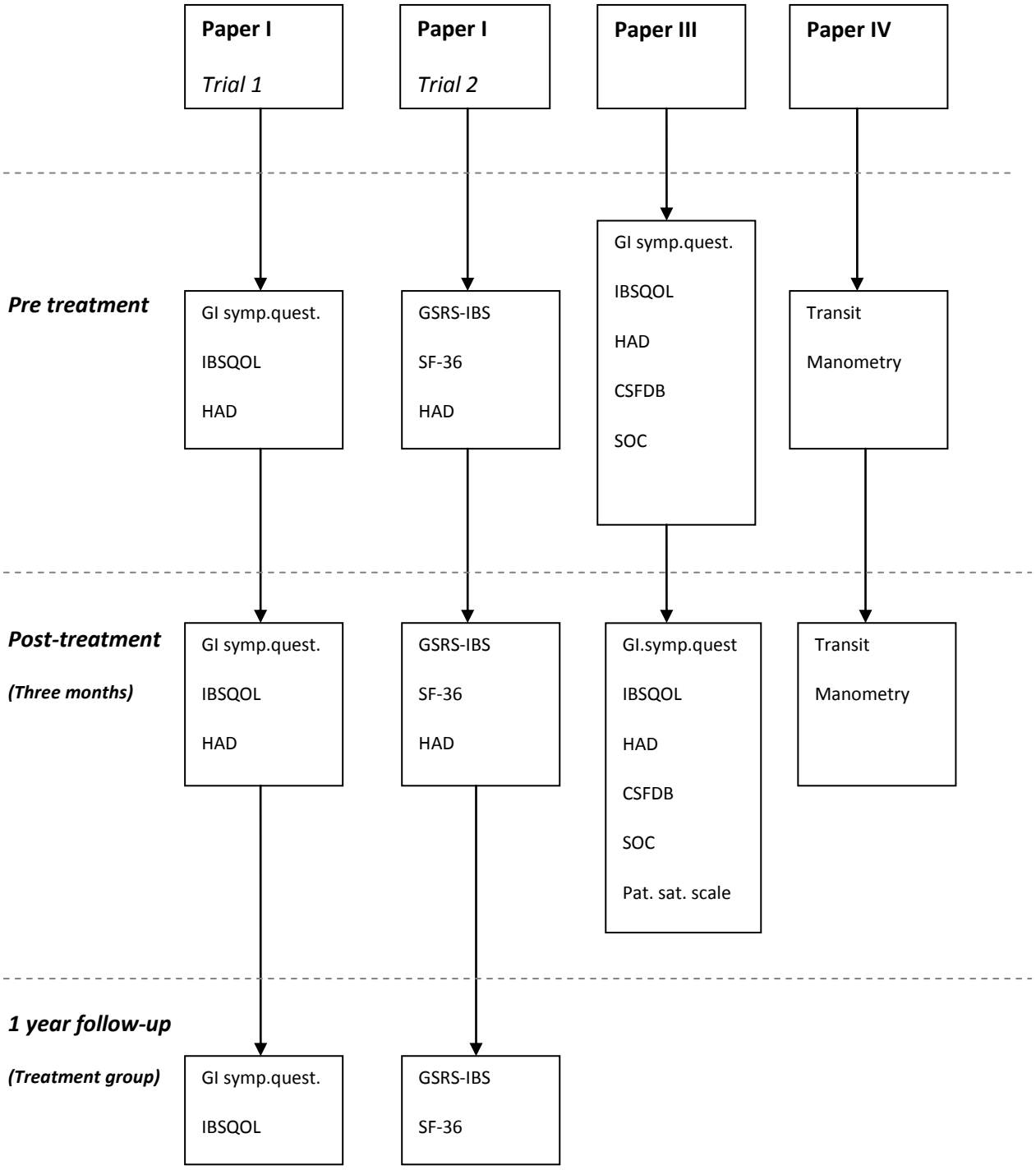


Fig. 2 Outcome measurements Paper I, III and IV

Statistical methods

Patient data and results from questionnaires were entered into a database by persons otherwise not included in the conduct of studies. The scores from the questionnaires and demographics are reported as mean±standard deviation, unless otherwise stated. Statistical significance was accepted at the 5% level. The data analyses were performed with SPSS version 19.

Paper I: All analyses were performed on an intention-to-treat basis, including all patients who were randomized and started the study. For drop-outs, we used the principle of last observation carried forward technique and the data missing post-treatment were imputed from baseline assessments and included in the final analyses. Analyses of the results from the questionnaires were made with parametric methods (*t*-tests for paired and independent samples). The proportion of responders in the hypnotherapy group vs. the control group was compared using Pearson χ^2test.

Paper II: As ordinal data were obtained from the questionnaire, between-group comparisons of continuous variables were performed with the nonparametric Mann–Whitney U test. Categorical variables were compared with the χ^2 test.

Paper III: Pre- to post-treatment changes were assessed using Wilcoxon signed-rank tests. Results from the patient satisfaction scale are presented as the proportion of individuals with the different scores (1-5) and the bivariate correlations with age and results from questionnaires, were assessed with the Spearman Rank Correlation Test. Associations between patient satisfaction and gender, IBS subtype and IBS symptom response status ("responder" or "non -responder"), were explored with Pearson χ^2 test. Thereafter, in an attempt to find factors independently associated with patient satisfaction, factors bivariately associated with patient satisfaction at $p<0.05$ were entered into a multiple linear regression analysis. Before entering variables into the logistic regression analysis, multicollinearity was excluded by testing correlations between the independent variables and highly inter-correlated independent variables were removed (≥0.7), and collinearity diagnostics were performed to rule out low tolerance values (≤0.1). All variables included in the regression analysis are displayed in a table, i.e. the full model is shown.

Paper IV: Means were compared between two groups using the Student´s *t*-test, whereas nominal data were compared by use of the Pearson χ^2 test. Comparisons of numerical data before and after the intervention were done by Wilcoxon signed rank test or by paired t-test as appropriate.

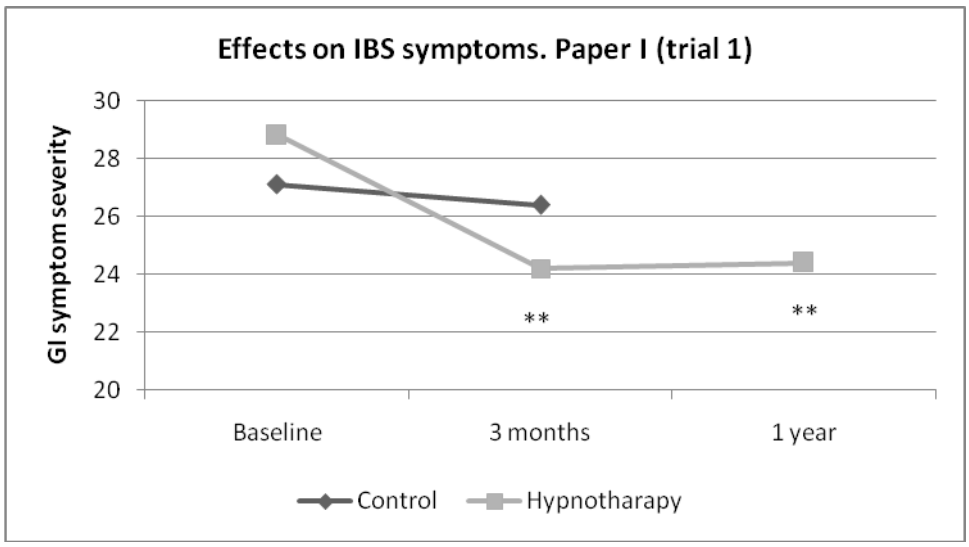
Results

Effects of hypnotherapy on IBS symptoms

Paper I: To evaluate the short time effects of gut-directed hypnotherapy on refractory IBS when treating patients outside specialized hypnotherapy research centres, we conducted two RCTs (Trial 1 in Gothenburg and Trial 2 in Gävle). The change in IBS symptom severity at three months (post-treatment) relative to baseline was compared between the hypnotherapy and control group in the two studies separately, and constituted our primary endpoint (demonstrated as mean difference and 95% confidence interval (CI)). We also performed within-group comparisons, comparing results at three months with baseline for both groups and results from the one-year follow-up evaluation relative to baseline in the hypnotherapy groups. To demonstrate the treatment response more clearly, we defined a responder as a subject with a post-treatment reduction of ≥25% on the total symptom score.

***Trial 1*:** The severity of GI symptoms was reduced in the gut-directed hypnotherapy group at 3-month follow-up vs. baseline ($p< 0.01$), and this was true for both sensory symptoms ($p<0.01$) and bowel habit ($p<0.05$), whereas, no significant improvement of GI symptoms was seen in the control group ($p=0.7$). When comparisons were made between the gut-directed hypnotherapy and the control group, there was a significantly greater improvement in total severity of GI symptoms in the gut-directed hypnotherapy group (3.7 (0.3 – 7.2), (mean difference (95% CI); $p=0.03$) (Figure 3), and this was also seen for sensory symptoms (2.2 (0.5 – 3.1); $p=0.01$), but not significantly so for bowel habit (1.6 (− 0.6– 3.7); $p=0.15$), even though the trend was in the direction of a greater reduction of the perceived severity of bowel habit disturbance in the gut-directed hypnotherapy group. The symptom reduction in the gut-directed hypnotherapy group was maintained 1 year after treatment ($p<0.01$). Using the responder definition, i.e., reduction of the total symptom score ≥ 25% on the GI-symptom questionnaire, 17 patients were responders in the gut-directed hypnotherapy group (38%) compared with five in the control group (11%) ($p<0.01$) (Figure 5). At the one-year follow-up, 19 patients met the responder definition in the gut-directed hypnotherapy group (42%). There were no differences in the results obtained by the three therapists (data not shown).

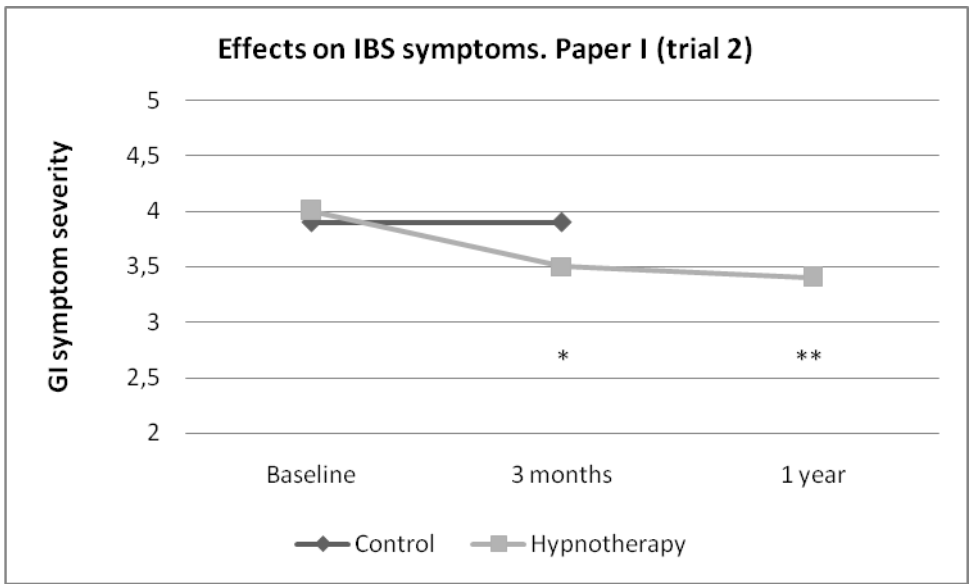
Figure 3



** p<0.01 vs. baseline. Comparison between groups at three months: p= 0.03.

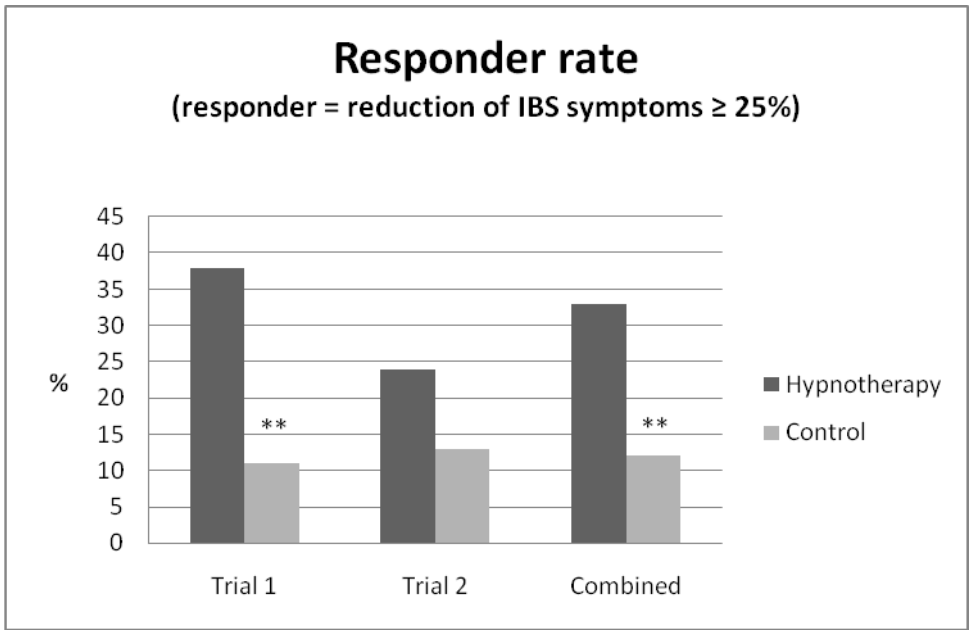
Trial 2**:** At the three-month follow-up, there was a significant reduction in the total GI-symptom severity (p<0.05) in the gut-directed hypnotherapy group, whereas no significant reduction was seen in the control group (p=0.7)(Figure 4). The symptom reduction in the gut-directed hypnotherapy group was more obvious and statistically significant for sensory symptoms, such as pain and bloating, than for the perceived severity of diarrhoea and constipation. When we compared the change in the severity of total GI symptoms between the gut-directed hypnotherapy group and the control group, this did not reach statistical significance (0.33 (− 0.22– 0.91) (mean diff (95% CI); p=0.22), even though the trend was in the direction of numerically greater improvement in the gut-directed hypnotherapy group. The same was true for the GSRS domains, with no significant between-group comparisons, except for a greater reduction of bloating in the gut-directed hypnotherapy group (0.82 (0.30 – 1.3); p=0.003). The reduction of GI-symptom severity in the gut-directed hypnotherapy group was maintained one year after treatment (p<0.01). Using the responder definition, i.e., reduction of the total symptom score ≥ 25% on the GI-symptom questionnaire, six patients were responders in the gut-directed hypnotherapy group (24%) compared with three in the control group (13%) (p=0.3) (Figure 5). At the one-year follow-up, seven patients met the responder definition in the gut-directed hypnotherapy group (28%).

Figure 4



** p<0.01 vs. baseline, * p<0.05 vs. baseline. Comparison between groups at three months p=0.22 (n.s).

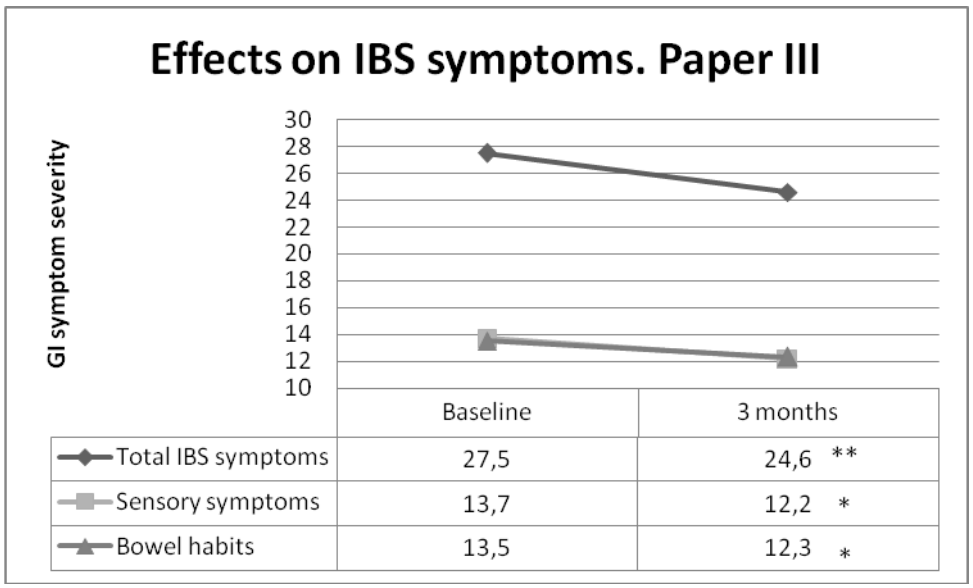
Figure 5.



** p<0.01

Paper III: In this study we evaluated the effect of hypnotherapy on IBS symptoms by comparing results from the GI-symptom questionnaire after the treatment period (three months) with baseline scores in an uncontrolled fashion in the total population of treated patients from Gothenburg (n=83). There was a significant reduction in the overall IBS symptom (p=0.005) severity and this was true for both sensory symptoms (p=0.012) and bowel habit (p=0.03) (Figure 6).

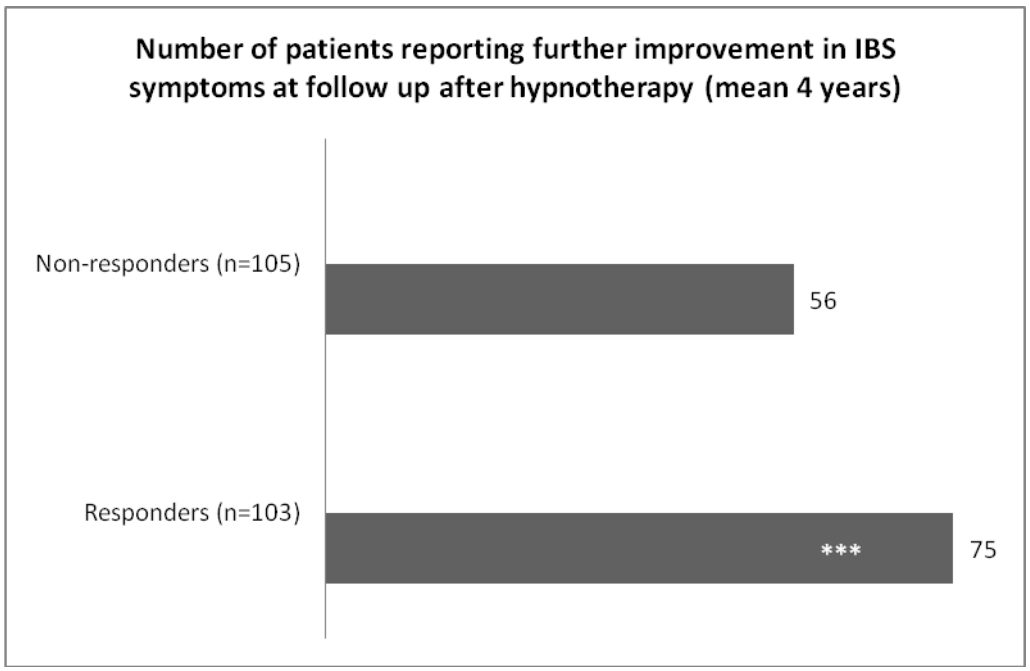
Figure 6



** p<0.01 vs. baseline, * p<0.05 vs. baseline.

Paper II: To evaluate the long-term effects of gut- directed hypnotherapy on refractory IBS, we conducted a retrospective study, investigating the long-term perceived efficacy of gut-directed hypnotherapy. This was made by distributing the "subjective assessment questionnaire (SAQ)" to 244 IBS patients that had been treated with gut-directed hypnotherapy because of refractory IBS in three different clinics. In total 208 patients responded (overall response rate 85%). This long-term follow-up was conducted 2-7 (mean 4) years after treatment. A responder was defined as a patient who reported that his or her IBS symptoms at the end of the course of hypnotherapy compared with before the treatment started were "very much better" or "moderately better". With this definition, 103 of 208 patients (49%) were considered as responders. With a less strict responder definition, i.e., patients reporting that their IBS symptoms were "very much better," "moderately better," or "slightly better," 159 of 208 (76%) patients would have been considered to be responders. However, all analyses in the study were based on the stricter definition. In the responder group, 75 patients (73%) reported that they had improved further at the follow-up compared with 56 patients (53%) in the non-responder group (p<0.0001) (Figure 7). Ten percent of the responders reported that the symptoms were unchanged at follow-up compared with after the treatment and 18 percent reported worsened symptoms at follow-up. The corresponding numbers for the non-responder group was 35 and 13 percent respectively.

Figure 7

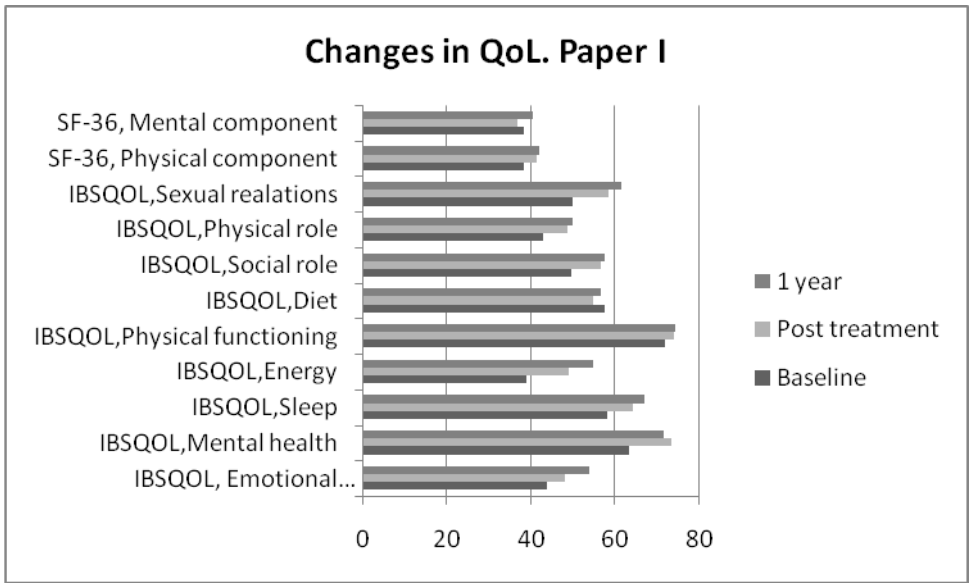


*** p<0.001

Effects of hypnotherapy on quality of life

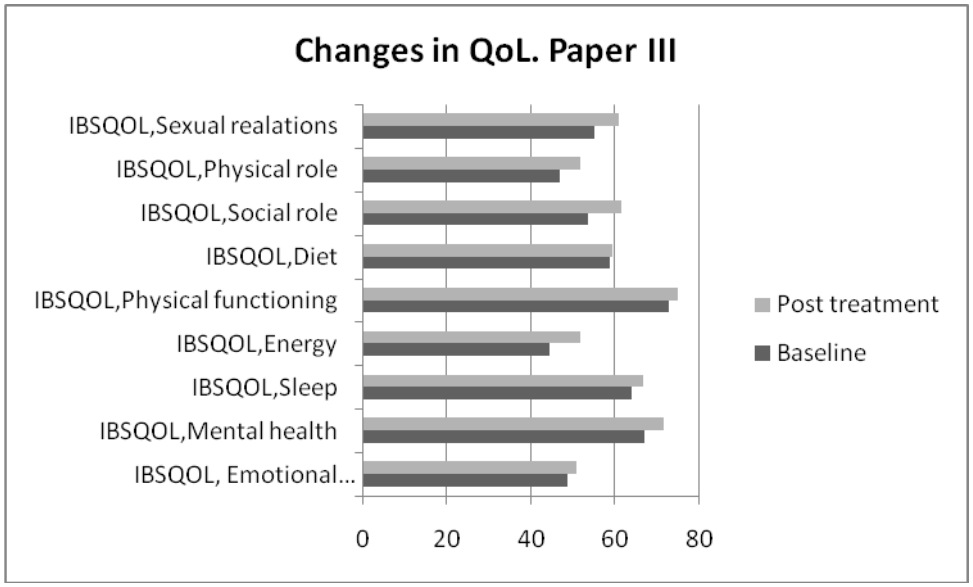
Paper I (Trial 1), IBSQOL was used to evaluate the effect of hypnotherapy on quality of life. Measurements were made pre- vs. post-treatment and in the treatment group after one year. When comparing measurements before and after the treatment, a significant improvement was seen in the gut-directed hypnotherapy group in the dimensions of mental health (p<0.01), sleep (p<0.05), energy (p<0.01), and social role (p<0.05) (Figure 8). Also, in the control group, there was a significant improvement in the energy dimension (p< 0.01). The improvement in QOL was maintained significantly for the same domains at the one-year follow-up in the gut-directed hypnotherapy group, but additionally there was also a significant improvement in the dimension of emotional functioning (p<0.01) vs. baseline. However, there were no significant differences in any of the dimensions in IBSQOL when comparing changes in QOL at the three-month follow-up relative to baseline between the gut-directed hypnotherapy group and the control group (p>0.20). **In Paper I (Trial 2)**, we used SF-36 to evaluate QOL. When comparing the measurements at baseline to post-treatment assessment, a significant improvement (p<0.05) was seen in the gut-directed hypnotherapy group in the physical component score, whereas no change in the mental component score was observed (Figure 8). No significant changes in the physical or mental component summary scores were seen in the control group. There were no significant differences in any of the component scores when comparing between the gut-directed hypnotherapy group and the control group. At the one-year follow-up, there was still an improvement in the physical component score in the gut-directed hypnotherapy group, but this did not reach statistical significance (p=0.07).

Figure 8



Paper III: In this study, we evaluated the effect of hypnotherapy by comparing results from IBSQOL after the treatment period with baseline scores in an uncontrolled fashion in the total population of treated patients from Gothenburg (n=83). The domains of mental health (p=0.02), energy (p=0.008) and social role (p<0.0001) were significantly improved after hypnotherapy (p=0.002) (figure 9).

Figure 9

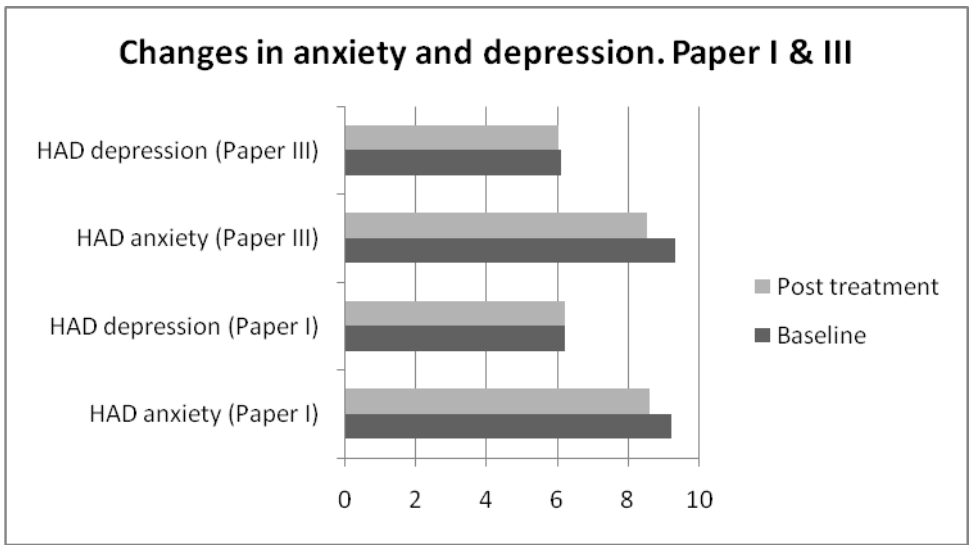


Effects of hypnotherapy on psychological comorbidity (figure 10)

Paper I: We used HAD in both trials at the same time points, and therefore data from both studies were combined. The anxiety scores tended to be lower after gut-directed hypnotherapy (p=0.07), indicating less severe anxiety, whereas no changes in the anxiety scores could be detected in the control group, and the severity of depressive symptoms remained unchanged in both groups. When between-group comparisons of the changes in HAD scores were performed, a greater reduction for anxiety was seen in the gut-directed hypnotherapy group than in the control group (p<0.05).

Paper III: In this study we evaluated the effect of hypnotherapy by comparing results from HAD after the treatment period with baseline scores in an uncontrolled fashion in the total population of treated patients from Gothenburg (n=83). Anxiety scores were significantly improved after hypnotherapy (p=0.002), but no significant reduction in depressive symptoms was seen (p=0.88).

Figure 10

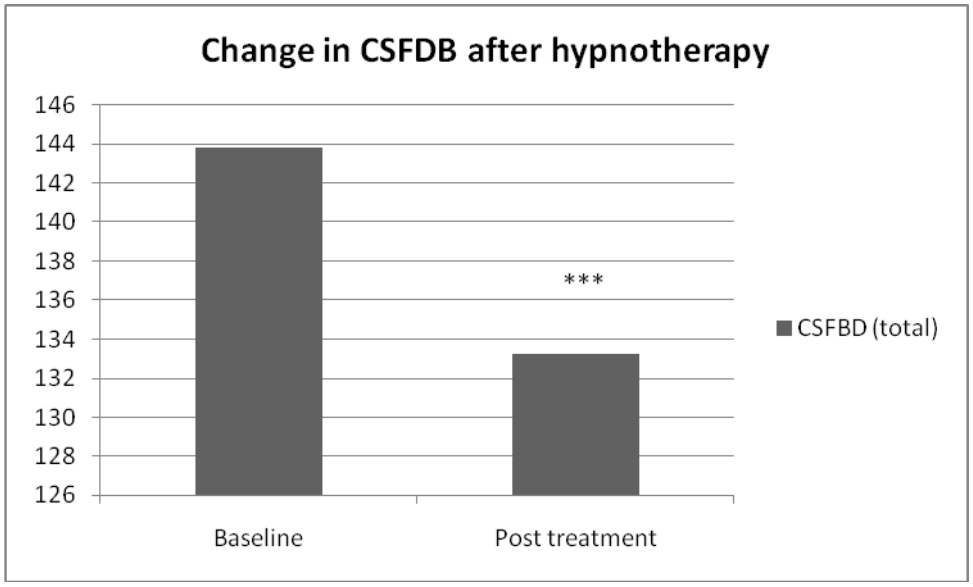


Effects of hypnotherapy on cognitive functioning

In Paper III we evaluated the effect of hypnotherapy on cognitive function by comparing results from the CSFBD scale after the treatment period with baseline scores in an uncontrolled fashion in the

total population of treated patients from Gothenburg (n=83). The total score of the scale were used. The CSFBD scores were significantly improved after hypnotherapy (p<0.0001) (Figure 11).

Figure 11



*** p<0.001

Effects of hypnotherapy on sense of coherence

In **Paper III** we evaluated the effect of hypnotherapy on sense of coherence by comparing results from the SOC scale after the treatment period with baseline scores in an uncontrolled fashion in the total population of treated patients from Gothenburg (n=83). We found no significant effects on either of the subscales (comprehensibility, manageability, meaningfulness).

Long-term effects of hypnotherapy

For methodological background and results concerning the long-term effect on IBS symptoms see; page 40 “Effects on IBS symptoms, Paper II”.

Healthcare utilization at follow-up (Figure 12)

When comparing the consultation rates reported after hypnotherapy in the responder and non-responder group, 69% of patients who were responders reported reduction of visits to a GP for GI symptoms after the end of the hypnotherapy compared with 31% among non-responders (p<0.0001). For visits to a GP for other symptoms, these figures were 19% vs. 12% (p=0.19). Regarding visits to a gastroenterologist, 64% of the responders reported that they had consulted less

often after the hypnotherapy vs. 32% of the non-responders (p <0.0001). Among the non-responders, the healthcare consumption for GI symptoms was more frequently unchanged and few patients in both the responder and non-responder group reported an increase in healthcare consumption at follow-up.

Figure 12

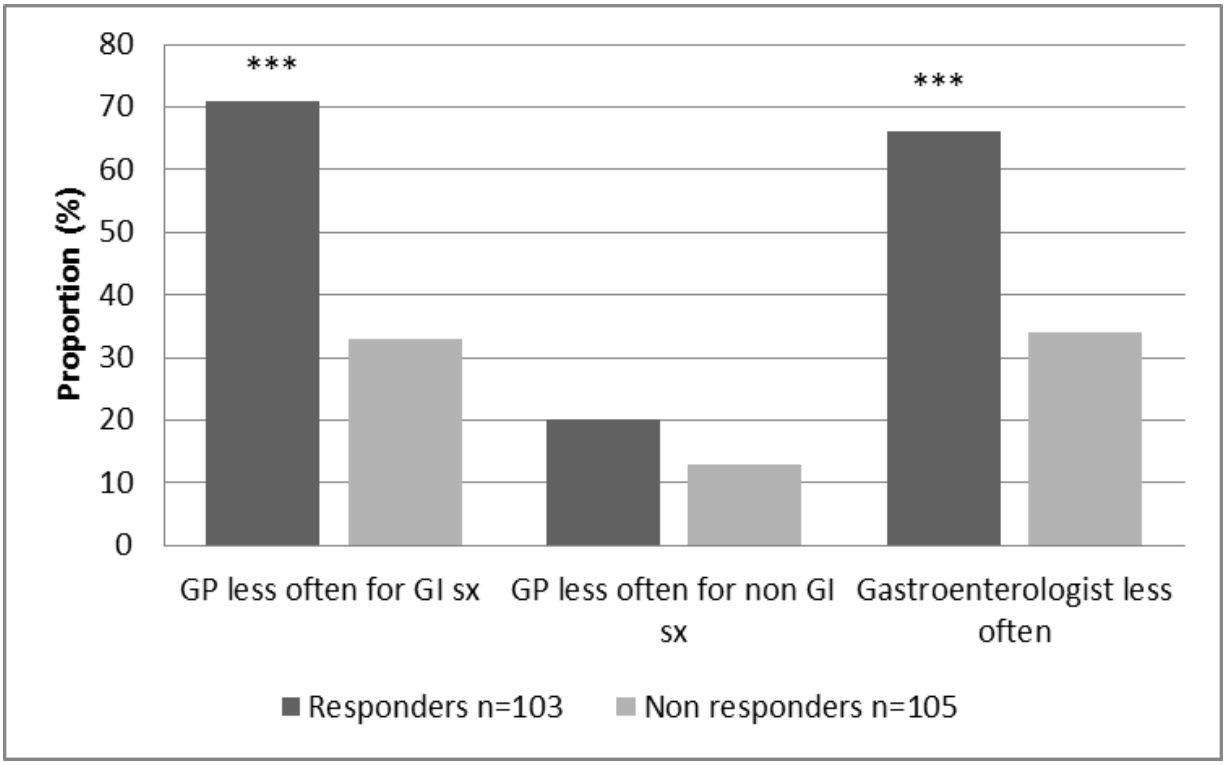


Figure 12. Self reported healthcare consumption at follow-up. Responders vs. non-responders *** p<0.001

Use of IBS symptom modifying drugs at follow-up

At follow-up, 54 patients (52%) in the responder group and 54 patients (51%) in the non-responder group reported active use of drugs for IBS symptoms (NS). There were numerically more responders that reported using pharmacological treatment alternatives less often (26 vs. 20%) and a numerically higher proportion of non-responders reported an increase in the use of medication after the course of hypnotherapy (15 vs. 7%), but these differences did not reach statistical significance

Use of alternative treatments at follow-up

In the responder group, 28 patients (27%) had tried other treatment options after the hypnotherapy treatment and 18 found these helpful, compared with the non-responder group, where 33 patients (31%) had tried other treatment options and 20 found them helpful (NS). The most common types of treatment options reported were acupuncture, complimentary alternative medicine (CAM), and yoga.

Continued hypnotherapy practice at follow-up

In the responder group, 75 patients (73%) reported that they still actively used the hypnotherapy technique on a regular basis at follow-up, compared with 51 patients (47%) in the non-responder group (p <0.001). Most patients in the responder group that still actively used gut-directed hypnotherapy reported that they used it several times a month, whereas it was more common to use hypnotherapy on a daily basis in the non-responder group. Among patients who still used hypnotherapy actively, 47 of 75 in the responder group (63%) still used their taped session compared with 24 of 51 patients (47%) in the non-responder group (p=0.19).

Patient satisfaction with hypnotherapy

In Paper II we used the subjective assessment questionnaire to evaluate the long-term effects of hypnotherapy as treatment in severe IBS. When patients were asked: "Has the course of hypnotherapy been worthwhile?", 87% of the patients reported that they considered the gut-directed hypnotherapy to have been worthwhile. In the responder group, all 103 patients reported the hypnotherapy as being worthwhile, compared with 78 of the 105 patients (74%) in the non-responder group (p<0.0001). Although there is a significant difference between responders and non-responders, this confirms our clinical observation that treatment with hypnotherapy often is associated with a high degree of satisfaction even among "non-responders" in terms of effect on IBS symptoms. To further investigate this, the study described in Paper III was performed.

Paper III: In this study 83 patients, treated with hypnotherapy due to severe IBS were investigated to evaluate factors associated with patient satisfaction after hypnotherapy for IBS. Patients reported their degree of satisfaction after the treatment period on a five-point scale, ranging from 1= not at all satisfied to 5= very satisfied. Questionnaires assessing IBS symptom severity, quality of life, cognitive function, sense of coherence, depression and anxiety were completed before and after treatment (for results concerning questionnaires see above). Thirty patients (36%) were very satisfied and 57 (69%) scored 4 or 5 on the patient satisfaction scale. Only 4 patients (4.8%) reported that they were not at all satisfied with the treatment (Figure 13). Sixty-four patients (77%) also reported that they would start the treatment with hypnotherapy again if they had had the knowledge and experience about this intervention that they possessed after the treatment period. Baseline characteristics or scores on the questionnaires before treatment were not significantly correlated with patient satisfaction after hypnotherapy. Scores on the patient satisfaction scale were bivariately associated with post-treatment scores on GI symptom severity (p<0.05), the IBSQOL domains sleep (p<0.05), physical function (p<0.05), physical role (p<0.05) and sexual relations (p<0.001). Factors bivariately associated with patient satisfaction at p<0.05 were entered into a multiple linear regression analysis with the patient satisfaction as the dependent variable. The model explains 22.4% of the variance in the dependent variable, but only the domain of sexual relations in the IBSQOL scale made a unique statistically significant contribution to the model (p=0.018). To further evaluate the association between the degree of patient satisfaction and change in symptom severity and quality of life, we compared the baseline and post-treatment scores for GI symptom severity and the IBSQOL domain sexual relations with each of the scale steps on the patient satisfaction scale. Only the patients that

scored 5 (very satisfied) reported a significant improvement in GI symptom severity (p=0.008) and IBSQOL, sexual relations (p=0.004). When using the responder definition "25% reduction in total IBS symptom severity at post-treatment evaluation", 52% of the responders were "very satisfied" with hypnotherapy and the corresponding number for non-responders were 31% (Figure 14).

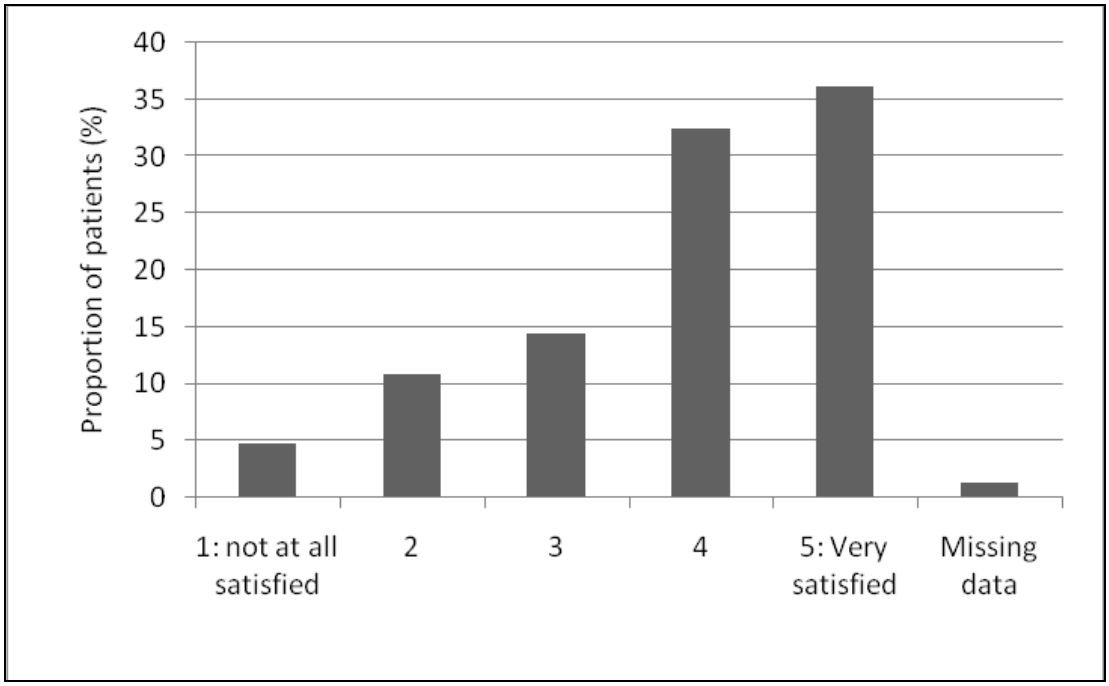


Figure 13. Results from the patient satisfaction scale after gut-directed hypnotherapy: "Are you satisfied with the gut-directed hypnotherapy?"

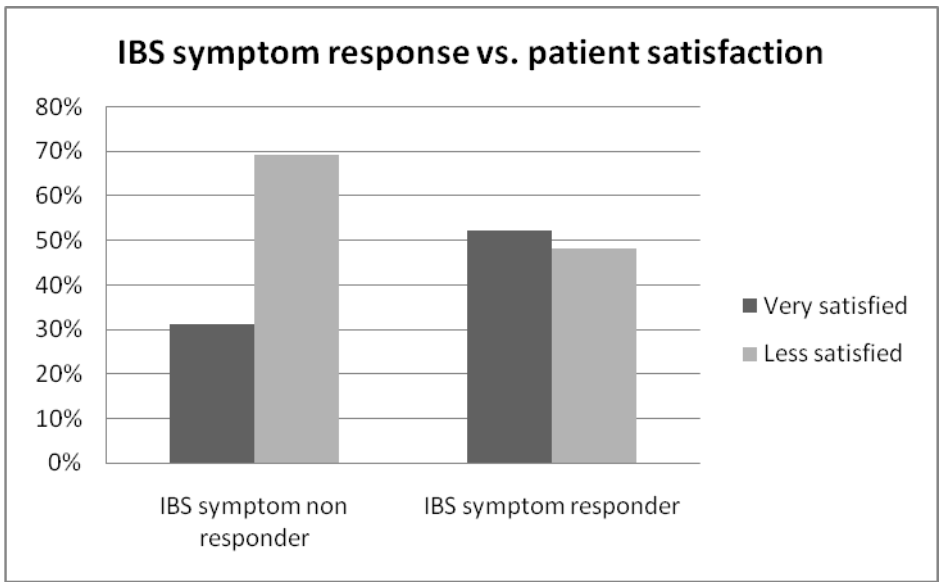


Figure 14. IBS symptom response vs. patient satisfaction (p=0.07)

Effects of hypnotherapy on GI physiology

Ninety patients with IBS, refractory to standard management, were randomized to receive gut directed hypnotherapy or to serve as a control group, controlled for attention (for details see page 25). All patients were planned for investigation with gastric emptying test, small bowel and colonic transit investigation. A subgroup (n=35) was also invited to be investigated with antroduodenojejunal manometry. In the treatment group, 40 patients accepted to undergo GI physiological investigations; in the control group this was true for 41 patients. Ten patients in hypnotherapy group and 14 patients in the control group underwent small bowel manometry before and after the treatment period. In the treatment group, 37, 33 and 38 patients respectively had interpretable gastric emptying tests, small bowel transit and colonic transit investigations. The corresponding numbers in the control group was 40, 31 and 41 patients.

Small bowel manometry: At baseline two patients in the treatment group had pathological manometries (criteria 2); after the intervention one of the patients still had burst activity but now also fulfilled criteria 1b for pathological small bowel manometry which was also true for one patient in the control group at the second investigation. No significant differences were found after the intervention compared to before in any of the groups but a numerical trend towards a higher number of MMC after hypnotherapy, with an increase of the median number of MMCs pre vs. post treatment of 2 (0-4) vs.3 (2-6) (median (range); p= 0.14) .

Gastrointestinal transit: No significant differences concerning gastric emptying time, small bowel transit time or colonic transit time was found when comparing the baseline and post intervention measurements in the hypnotherapy group or in the control group, and no differences between the groups. The only trend that was noted was an acceleration of the gastric emptying after gut-directed hypnotherapy (3.0±2.0 vs. 2.6±1.6 hours; p=0.14).

Methodological considerations

Paper I: The primary endpoint was improvement of IBS symptoms and we did not use "adequate relief of IBS symptoms" - a commonly used endpoint in IBS trials -, which could have been interesting, due to the fact that many treated patients expressed a high grade of satisfaction with the treatment - even subjects where the improvement in IBS symptoms was minimal. In **Trial 1** we did not include audiotapes for the patients' training in between sessions. This may have affected the results, but the therapist instructed the patients thoroughly to train their hypnotic skills at home between sessions without using audiotapes. In **Trial 2,** no significant difference between the groups regarding our primary endpoint could be detected, even though the trends were clearly in favour of the intervention group. This is possibly due to a relatively small number of participants, potentially leading to a type II error. Several domains in the QoL measurements improved in the hypnotherapy groups compared to baseline but did not reach significant differences compared with the control groups, which may also be due to a type II error. The SF-36, used in **Trial 2** is also rather insensitive to changes, which may explain the smaller effect on QoL in this trial. The one-year follow-up results were uncontrolled, due to the fact that it was considered unethical to keep the subjects in the control arm from receiving hypnotherapy for more than six months which must be taken into consideration when interpreting the results. However, in studies of psychological treatment options it is notoriously difficult to create a valid control group and blinding is of course impossible. In **Trial 1** the control group condition was designed to control for attention and included educational and supportive elements. In **Trial 2** the control group was a pure waiting list control, which has to be considered as suboptimal. However, no obvious differences in the results were seen between the control group conditions.

Paper II: This is a retrospective study, reporting the patients' subjective assessments, which methodologically has its limitations when interpreting the results: the risk for recall bias is obvious. The subjective assessment scale (SAQ) has however been validated previously against the widely used questionnaire IBS-SSS, and this strengthens the validity of our results. The result emanates from three different sites; Gothenburg and Gävle, where the patients were treated within the RCTs in Study 1, and Stockholm, where the patients were treated as part of the clinical routine. The therapists in the RCTs were previously inexperienced in gut directed hypnotherapy, whereas the therapists in Stockholm had longstanding clinical experience of this specific intervention. However, no significant differences in the results from the different sites were noted.

Paper III: The use of a non-validated, single- item question when assessing the degree of satisfaction after hypnotherapy treatment, is a weakness in this study. This approach could be unreliable due to the fact that patient satisfaction is a multidimensional construct. However, since our evaluation of patient satisfaction was part of a clinical trial (Study I (Trial 1)) with several other assessments, the use of a single item assessment was considered to be a valid compromise to obtain the results without too many questions for the patients. When the study was performed, no IBS-specific multidimensional satisfaction scale existed but since a recently developed scale now is available (184), and this should be used in future studies when assessing patient satisfaction in IBS.

Paper IV: The sample size was rather small in the group investigated with small bowel manometry which limits the possibility of detecting changes in these type of measurements. There was a significant drop-out in the hypnotherapy group concerning the post-treatment assessment with small bowel manometry, probably due to the bothersome investigation and the fact that this group already had been treated, which may have affected the results. However, except for a numerical, but not statistical, tendency towards an increased number of MMCs after hypnotherapy, no clear trends in the effect on small bowel manometry was evident. Based on this, we consider it unlikely that a larger sample size would have detected clinically meaningful effects of hypnotherapy on small bowel manometry. All subjects did not have interpretable transit data but this did not differ between the groups. The group that underwent transit investigations was quite large and no tendency towards effects on small bowel transit was seen, so it is unlikely that an even larger group would have affected the results.

General discussion

The overall aim of this thesis was to evaluate the effects of gut-directed hypnotherapy as treatment in refractory IBS, when the intervention was given outside specialized hypnotherapy research centres, aiming to motivate a wider spread of this intervention as possible part of IBS care in clinical practice. We also aimed to investigate the effects of hypnotherapy on GI motility. The first two studies investigated the short and long-term result of delivering hypnotherapy in this context. The third study investigated factors associated with the high degree of patient satisfaction often reported by patients treated with hypnotherapy, a field previously unexplored. The fourth study evaluated possible permanent effects on small bowel manometry and GI transit investigations after treating IBS patients with hypnotherapy.

IBS is the most common of the functional GI diseases (12) but the degree of symptoms varies considerably between patients, leading to the fact that patients with a low burden of symptoms never or infrequently consult healthcare providers due to IBS symptoms (185, 186). This group can often be managed by giving lifestyle advice, symptom modifying drugs targeting the individual symptoms, and reassurance concerning the benign nature of the condition (116). For patients with more intrusive symptoms, often associated with a substantial reduction of quality of life (25, 26), psychological comorbidity (42, 45), extraintestinal symptoms (24) and high societal costs (37, 38), very few treatment options are available. Effective pharmacological treatments for this group of patients have been difficult to develop. Although several new drugs have been investigated in RCTs, there are usually moderate differences in effect on IBS symptoms compared to placebo (10-15%) (116). These drugs are expensive and there are no long-term beneficial effects after stopping the medication and they have also in some cases been associated with serious side effects, which is unacceptable when treating a benign condition (118, 119).

Psychological treatment in different contexts, psychodynamic short term therapy, cognitive behavioural therapy and gut-directed hypnotherapy, have proven to be effective in treating IBS, both in the short- and long-term perspective (125, 145, 148, 149, 156, 158). Effects of gut-directed hypnotherapy and CBT have been investigated in several studies and the NNT by those interventions has in meta-analyses been established to be 2-3 (138).

The vast majority of earlier studies concerning the effects of gut-directed hypnotherapy as treatment in IBS have been conducted in a specialized hypnotherapy research centre in Manchester, England. The reported results are impressive with highly significant effects on IBS symptoms, quality of life, psychological comorbidity and extraintestinal symptoms (148, 149, 156, 161). Also the long-term effects of hypnotherapy have been evaluated and confirmed(158). However, in spite of these impressive results, the treatment modality has not been widely spread as a part of IBS care in clinical practice, probably due to the fact that the results from such specialized centres are difficult to translate into a clinical situation where therapists with expertise and experience of gut-directed hypnotherapy are rare. To evaluate the results of gut-directed hypnotherapy as treatment of IBS in a setting closer to standard clinical routine, with therapists previously inexperienced with this specific intervention, is therefore of value in order to motivate an increased clinical use of gut-directed hypnotherapy as treatment of patients with severe and refractory IBS.

Effects on IBS symptoms

The results from our RCTs (Paper I) confirm the effectiveness in treating refractory IBS with hypnotherapy in a clinical setting, with a significant reduction in IBS symptoms in both studies in the treatment groups. The effect was more pronounced for sensory symptoms such as abdominal pain and bloating and the effect was sustained at the one-year follow-up of the treatment groups. No effects on IBS symptoms were seen in the control groups when comparing baseline measurements to the post treatment evaluation. When comparison was made between the treatment and control groups, the difference in IBS symptoms reached statistical significance in Trial 1, but not in Trial 2, potentially due to a smaller sample in Trial 2 leading to a potential type II error. In Paper III, when investigating the effects of hypnotherapy in all IBS patients treated in the Gothenburg study in an uncontrolled fashion, we also found a statistically significant effect on IBS symptoms when comparing pre vs. post treatment measurement. This is also in line with the results in Paper II, where the patients, based on retrospective and subjective assessments of the effect of hypnotherapy, were divided into responders and non-responders, 49% were considered as responders directly after the intervention. In Paper I, we defined a responder to hypnotherapy as an individual with at least 25% reduction in IBS symptom scores post treatment. In Trial 1 the responder rate in the hypnotherapy group vs. the control group was 38% vs. 11% ($p<0.01$) and in Trial 2 the corresponding numbers were 24% vs. 13% ($p=0.3$). When calculating a combined response rate using the results from both trials in Paper I, we found a response rate of 33% vs. 12% ($p<0.01$) in the hypnotherapy vs. the control groups. The long-term effect of gut-directed hypnotherapy when delivered outside specialized hypnotherapy was confirmed in Paper II, where at follow-up (mean 4 years after treatment) 73% of the responders had continued to improve and 10% had unchanged IBS symptoms compared with the post treatment evaluation. The continued improvement in the responder group could not be explained by the use of other treatments after hypnotherapy, since there was no difference in the use of alternative treatments in responders vs. non –responders after hypnotherapy.

We therefore consider gut-directed hypnotherapy to be an effective treatment option for refractory IBS symptoms, also when delivered outside specialized hypnotherapy centres. The response rate in our studies is between 24-50% which is a considerably lower treatment effect compared to the reports from the Manchester group (148, 149, 156), but in line with results from other groups (152-154). This probably reflects that the expertise and experience of the therapists in a specialized hypnotherapy centre influences the results substantially. The differences in results could also be influenced by unspecific, psychological effects such as higher treatment expectations when treated in a specialized unit. The therapeutic effects may increase gradually if the intervention is introduced in a clinical context, as the therapeutic experience increases at the specific site. Compared with pharmacological treatments under development, which do not have better effect on IBS symptoms (187-189), are expensive, short lasting and associated with potential side-effects, gut-directed hypnotherapy is an important treatment alternative without these shortcomings and in the long run, may also be cost effective (116, 158). Another psychological treatment option is cognitive

behavioural treatment which has also been proven to be effective in treating IBS. When delivered over the internet (ICBT), RCTs evaluating this treatment modality have recently reported a response rate of around 50% (adequate relief of IBS symptoms) (145, 190). This is in line with our results in Paper II, where the endpoint was also a subjectively, assessed measurement of the treatment effect, although not in a randomized, controlled fashion. When instead using a validated questionnaire (GSRS-IBS) to prospectively validate ICBT, the response rate is between 40 and 50% (144) which is higher than the response rates in our studies. A possible reason for this could be that the patient population in these studies was a self-referred sample, whereas in our studies the study population was defined as patients with refractory IBS, where all other previous treatments had failed.

Effects on quality of life and psychological parameters

Results from the RCTs in Paper I reveal a positive effect on several dimensions in QOL in the hypnotherapy groups. This reached statistical significance in the mental component of SF-36 (Trial 2) and the dimensions of mental health, sleep, energy and social role in IBS QOL (Trial 1). The same pattern was also seen in Paper III. The effects were sustained at the one-year follow-up in Paper I. These results are in line with previously reported results from the Manchester group but the effect size is lower (156, 158), and between-group comparisons did not yield significant results. There was a significant reduction in anxiety within the hypnotherapy group in Paper I, but no effect on depressive symptoms, and the same was seen in Paper III. This is in line with the earlier reports from Galovski et al (152) and Palsson et al (153). The Manchester group has however, reported significant effects on both anxiety and depression in several studies (156, 158, 161). Also the difference in effects on quality of life and psychological comorbidity when comparing our results with the results from the Manchester group, probably reflects the fact that the expertise and experience of the therapists in a specialized hypnotherapy centre influences the results substantially. In Paper I, Trial 2, we used SF-36 when measuring QoL which is rather insensitive in detecting changes. This study is also probably underpowered. These factors could also affect the results in this trial. The effect of hypnotherapy on IBS related cognitions, as reflected by a reduced total score on the Cognitive scale for functional bowel diseases (CSFBD), was evaluated in Paper III, where there was a highly significant effect on IBS related cognitions after the intervention, compared to baseline. This effect has earlier been reported in a study from the Manchester group, where improvement in this scale was found to be directly correlated to the improvement in IBS symptoms. The authors concluded that the improvement of cognition could be a mechanism behind the effect of hypnotherapy in treating IBS (161). This type of analysis was not performed in our study.

Patient satisfaction

In the long-term follow-up of the effects of hypnotherapy (Paper II), we could report that a total of 87% of the treated patients considered gut-directed hypnotherapy to be worthwhile; this was true not only for 100% of the responders but also in 74% of the non-responders. The same pattern has also been reported by the Manchester group (158). This indicates that, even though not all responded to the treatment in terms of reduction of IBS symptom, there is a high degree of patient satisfaction associated with gut-directed hypnotherapy. These observations encouraged us to study factors of importance for patient satisfaction after gut-directed hypnotherapy in IBS patients (Paper

III). Factors of importance for patient satisfaction in general are incompletely understood, and studies measuring predictors of patient satisfaction have explained only a small proportion of the variance in satisfaction, often less than 20% (191), indirectly indicating that patient satisfaction is relatively complex. In a recent study by Dorn et al (184), satisfaction with IBS care was conceptualized as a multidimensional construct related to patient characteristics, illness characteristics, the health care setting, and the health care encounter. This model was confirmed in the process of developing a questionnaire to assess satisfaction with IBS care. Different factors seemed to be of importance for satisfaction, and GI symptoms and IBS-related quality of life were only modestly associated with satisfaction (184). Unfortunately, this scale was not developed at the time of the performance of our study, so we used a non-validated single-item question when assessing the degree of satisfaction after treatment with hypnotherapy. The use of a single question may be unreliable, given the fact that patient satisfaction is a multidimensional construct. We found a high degree of patient satisfaction after gut-directed hypnotherapy. Patient satisfaction was associated with improvement of GI symptoms and quality of life, but these factors only explained 22% of the variance. The only factor independently associated with patient satisfaction was the IBS-QOL domain sexual relations, which is interesting, since IBS is associated with a high degree of sexual dysfunction (192). Other factors are probably also of importance, since a substantial proportion of the patients in this study reported that they were satisfied with this treatment option despite no/minor improvement of GI symptoms. Other factors of potential importance for patient satisfaction not measured in our study may be gastrointestinal-specific anxiety, factors related to the health care setting, prior healthcare experiences, expectations, interaction with the therapist and social factors (184, 191, 193). IBS patients often report that previous contacts with healthcare providers have been inadequate in terms of not “being taken seriously” (194). This feeling is probably not present when treated with this type of intervention and could also affect the level of satisfaction. A high grade of individual satisfaction is probably in itself an important goal when treating this often very bothersome but benign condition. Factors associated with patient satisfaction besides improvement in IBS symptoms and quality of life remain to be established and further research to better understand these processes is needed, preferably by using the recently developed multidimensional Irritable Bowel Syndrome satisfaction with care scale.

Other long-term results of gut-directed hypnotherapy

The subjective assessment questionnaire (SAQ) has been developed by the Manchester group to evaluate long-term effects of gut-directed hypnotherapy (158). The results concerning the long-term effects on IBS symptoms reported in Paper II is discussed above. The consultation rates for GI symptoms in the responder group were significantly reduced after hypnotherapy, both with GPs and gastroenterologists, but no reduction in visits with GPs for other symptoms was detected. This is in line with the long-term follow-up study from Manchester, but in this study there was also a significant reduction reported by responders concerning consultations with GPs for non-GI symptoms after the intervention (158). The use of medications targeted towards IBS symptoms was also reported to be significantly decreased after hypnotherapy in the Manchester study. In our study, there was a numerical trend towards non-responders taking symptom modifying drugs more often and responders doing so less often after hypnotherapy, but no statistical significant difference was seen. These results indicates a potential to reduce health care costs when treating IBS patients with

hypnotherapy, which is of great importance given the fact that the direct and indirect health care costs in this group of patients is substantial (40). In the SAQ, patients also reported whether they still used the hypnotherapy technique actively. In the Manchester study 85% of the responders and 58% of the non-responders still used the technique regularly; in our study the corresponding numbers were 73% and 47%. The fact that a high proportion of responders continued to actively use the technique was expected but the finding that about half of the non-responders used the technique continuously at follow- up is striking. The reason for this could be that in spite of their non-responder status based on effects of hypnotherapy on GI symptoms, other positive effects have been gained, such as the ability to cope with the GI symptoms even though the symptoms were unchanged.

Effects of gut-directed hypnotherapy on GI Motility

The effects of gut-directed hypnotherapy on GI motility have previously been sparsely investigated. The current knowledge concerns effects of hypnotherapy on GI motility during the hypnotic state. In this context hypnotic relaxation has been found to prolong orocaecal transit time and reduce colonic motility (164). Induced emotions under the hypnotic state (anger and excitement) have also been found to increase the colonic motility (165). In our study we aimed to evaluate if there are permanent, long-standing effects on GI motility after a course of hypnotherapy that could explain the effect on IBS symptoms. In Paper IV, patients were randomized to hypnotherapy or supportive care; measurement with small bowel manometry and GI transit investigations were made before and after the intervention. No differences in the results in either of the measurements were obtained in any of the groups, explaining the effects of hypnotherapy on IBS symptoms. A possibility could be that the effect of hypnotherapy on GI motility in IBS patients is of short duration and may serve to temporarily affect the severity of IBS symptoms when patients are actively using the technique. However, our results imply that it is unlikely that the main mechanism behind the effect on IBS symptoms after course of gut-directed hypnotherapy is mediated through permanent changes in GI motility.

General comments

Gut-directed hypnotherapy is an expensive intervention: in this protocol, 1 hour/ week over a period of 12 weeks, with treatment delivered by licensed psychologists (175). Probably it is cost effective in its present form (158), but there is a need to investigate if there are any ways of further developing the effectiveness and availability of the intervention. In one previous study, group-therapy has been found to be equally effective as individual treatment (150) and, in a recent abstract from Dr Moser et al from Vienna, this is further supported in a randomized, controlled study (195). Another way to make the treatment more effective is to reduce the number of sessions and standardize the treatment even further. The group from North Carolina has developed a protocol with a seven-session hypnosis-treatment approach, designed for verbatim delivery (196). This protocol reduces the interaction time between therapist and patients. Because it is delivered via a verbatim protocol, where the specific skills of a psychologist are less important, it has the possibility of being delivered by specially trained nurses instead of psychologists, which could contribute to increasing the availability and cost effectiveness of the intervention. An abstract reporting the results of nurse-administered hypnotherapy has recently been presented from our group and a full paper is in

progress (197). In the field of cognitive behavioural therapy, internet delivered treatment has successfully been developed to treat a variety of different conditions, among them IBS (142, 145). This is another way of increasing the availability of a certain intervention. If this is a possible path for the delivering of gut-directed hypnotherapy is not known and remains to be investigated. Today there are mainly two psychological IBS treatment alternatives available in clinical practice: gut-directed hypnotherapy and cognitive behavioural therapy. Both interventions have proven to be effective, but there is no knowledge if one is superior to the other or if certain patients would benefit more from one of the interventions. This is a field that needs further investigation and head to head comparisons are needed.

Conclusions

Gut-directed hypnotherapy is an effective treatment for refractory IBS even when delivered outside specialized hypnotherapy research centres. Besides effects on GI symptoms, there are positive effects on quality of life parameters, anxiety and IBS-related cognitions. The effect on GI symptoms is long-lasting and the intervention is generally associated with a high grade of patient satisfaction, even in subjects with no or minor effect on GI symptoms. Patient satisfaction is associated with improvement in GI symptoms and quality of life, but other factors are probably also of importance and need to be further investigated. The effect size is generally lower than those reported from specialized hypnotherapy centres, but at least as effective as some of the drugs currently under development for the treatment of IBS. The result also implicates a potential to reduce health care costs when treating IBS patients with hypnotherapy.

The results of this thesis support the introduction of gut-directed hypnotherapy as a part of clinical care in treating patients with IBS, refractory to lifestyle advice and treatment with symptom modifying drugs. Our belief is that the treatment effects of gut-directed hypnotherapy are correlated with the degree of expertise and experience of the hypnotherapist and have the ability to increase over time once the intervention is introduced at a specific site. We also think that there are possibilities to further develop the intervention and by this increase its availability to this large group of patients.

Acknowledgements

Besides all IBS patients who took part in our studies, I would like to express my sincere gratitude to:

Professor Magnus Simrén, my main supervisor, who believed in me and my project and took me under his protective wings when others expressed doubts about combining medicine and behavioural science. I could not have wished for better guidance in the noble art of academic work. Magnus, besides from being a role model in science, you are also a great friend and I look forward to further collaboration in the future.

Peter Unge, my co-supervisor. You are the main reason why I became a gastroenterologist in the first place. We started this together and it really has not turned out too bad at all. Your great enthusiasm, supporting me in my early years of gastroenterological training, has meant a lot to me, both clinically and in my academic work.

Henry Nyhlin, my co-supervisor. You are one of the best clinicians I have ever met; working with you has inspired me in many ways, but most of all in developing my clinical skills in the patient-doctor relationship which is the greatest skill of all in medical practice. You have also been a great academic companion and have a unique way of looking at matters from a novel perspective.

Brjánn Ljótsson, my great friend. You have acted as a sort of informal co-supervisor during the last years. Without your help in statistics I would probably have flushed my SPSS software down the cybertoilet and given up! You are such a gifted clinical psychologist and your scientific achievements are utterly impressive: you will become a professor before you turn forty! Thank you for all the good times we have spent together in various locations around the world.

Patrik Arvidsson, my first partner in crime, who treated all the patients in the Gävle project. Without you, this would not have happened. I often think of our enthusiastic conversations and wild plans.

Hans Törnblom, the wizard of GI motility investigations! Thank you for sharing your expertise in this field. It still warms my heart when I think of how you, without hesitation, laid the last touch on our paper when my focus was elsewhere.

Hasse Abrahamsson, Einar Björnsson and Riadh Sadik, my co-writers. Thank you for all your valuable comments and general support. Research is certainly teamwork!

All my dear coworkers at Gastrocentrum Sabbatsberg: Karin Öhman, Pirjo Halunen, Marita Fischer, Maud Hansén, Maria Gustavsson, Sara Rydh, Andreas Aly, Bosse Kollberg and Anne Cornett. You are the best gastroteam in the world and my second family. Thank you for being so supportive and understanding during the last year when my main focus has been on this thesis.

Lasse Kjellström, my college and dear friend. Working with you is a privilege. I am so happy that we escaped to Sabbatsberg together.

Tom Lindfors, my brother from another mother. You are a very good friend and my private IBD consultant. I don't know have many DDWs we spent together, but it is always great to travel (and party) with you, we must keep this tradition alive for many years to come.

Arnold Söderlind, the only specialist in “endoscopic diseases” I have ever met. You are a dear friend and the “silverback” at Sabbatsberg and we could not manage without you!

Barbro Lebrun, my friend and college. Without you, Gastrocentrum would be a boot camp. You bring style, finesse and a great knowledge to our group.

Despina Stålberg, my friend and college. Thank you (and Erik) for the assistance with the PDFs.

Anette Prytz, my sister in crime. To administrate Gastrocentrum with me is probably not an easy task and I could never find a better partner than you. You are such a gifted manager and your efforts have really made a difference! But most of all, thank you for all the fun moments we shared.

Lisa Falk, my dear friend. You have become the psychological backbone at Gastrocentrum and it is a pleasure working with you. Thank you for all the good times and interesting conversations about life and how to live it.

Gunilla Wirström, thank you for guiding me in the dimensions of quality of life.

Martha Sjöberg, thank you for sharing your clinical expertise in the noble art of gut-directed hypnotherapy.

Annika Stenman and Ann-Cristine Persson, the team at Gastromottagningen, Gävle. Thank you for all great assistance in performing the Gävle project.

Gary Watson, my dear brother in law. Thank you for optimizing the language.

Yvonne Haglund and Magnus Dahl, my present and former directors at Sabbatsberg. Thank you for being so supportive, understanding the importance of performing clinical research in the context of private healthcare.

Berit and Arne Lindfors, dear mum and dad, no one could wish for finer parents, you have always believed in me. I love you!

Pernilla Watson, my loving sister, you are always there when I need you.

My beautiful daughters, Elvira, Embla and Malva, without you, life would not be worth living. I am very proud of you and I love you all so very much.

Last but not least, my wonderful, beautiful wife Airene. It is quite an achievement to start a private healthcare centre at the same time as your husband is “on another planet”, finishing his thesis. I am really proud of you! I love you - BTBMB!

Populärvetenskaplig sammanfattning

Bakgrund

Irritabel tarm syndrom (IBS) är en funktionell tarmstörning där symtomen beror på en störd funktion och ökad känslighet i mag-tarmkanalen. Vad som orsakar detta är till stora delar idag okänt. Symtomen består av obehag/ smärta i magen och störd tarmfunktion, ledande till förstoppning och/eller diarré. Diagnosen ställs framförallt utifrån de typiska symtomen, men ofta behövs en del utredning göras för att utesluta andra bakomliggande sjukdomar. IBS är i sig ofarligt men kan vara mycket besvärligt. Behandlingen av IBS bygger på en bra konsultation med en tydlig förklaring av sjukdomen, dess ofarlighet samt generella livsstilsråd gällande t.ex. kost, motion och stresshantering. Hos patienter med liten symtomgrad är ovanstående regim ofta tillfredställande, men hos patienter med svårare symtom, nedsatt livskvalitet, psykiatrisk samsjuklighet och hög grad av associerade symtom (t.ex. trötthet, huvudvärk, muskelvärk och urinträngningar) behövs ytterligare behandling.

Läkemedelsbehandling av IBS bygger idag på att försöka minska de individuella typerna av symtom (smärta, diarré, förstoppning etc.), men en effektiv läkemedelsbehandling med effekt på samtliga delsymtom saknas idag.

Psykologisk behandling av IBS har studerats sedan tidigt 80-tal. Studier med psykodynamisk korttidsterapi, hypnoterapi och kognitiv beteendeterapi har alla visat en gynnsam effekt på IBS-symtom, men psykologisk behandling har så här långt ej fått något brett genomslag som behandlingsalternativ.

”Gut-directed hypnotherapy” (tarminriktad hypnoterapi) beskrevs första gången 1984 i en studie från Manchester. I denna studie förbättrades upp till 85 % av patienterna gällande sina IBS symtom. Manchestergruppen har sedan publicerat en rad artiklar som påvisar en god långtidseffekt av hypnoterapi, med en positiv effekt på både mag-tarm- symtom och associerade symtom, samt förbättrad livskvalitet och minskad sjukfrånvaro.

Studier från andra forskargrupper har sedan konfirmerat en god behandlingseffekt av hypnoterapi, men resultaten har inte varit lika imponerande. Av de studier som så här lång presenterats kommer merparten från andra specialiserade ”hypnoterapicenter” och väldesignade studier med behandlingen given i en miljö utanför sådana center saknas.

Hypnoterapi bygger på mental och muskulär avslappning där patienten får använda hypnotiska suggestioner för att avleda eller fokusera på symtomen. Efter återkoppling från terapeuten utnyttjas individuellt anpassade suggestioner för att uppnå en djup känsla av möjligheten att kunna kontrollera sina symtom. Specifika suggestioner ledande till ökad kontroll över mag-tarmkanalen utvecklas (t.ex. ”en flod som flyter lugnt och stilla”). Patienten får först öva på att ta kontroll över yttre stimuli som t.ex. ljud, tryckkänsla från stolen för att sedan fortsätta övningarna med att ta kontroll över inre fenomen som t.ex. andning och slutligen IBS-symtom. Behandlingen utgår från ett protokoll utformat av Manchestergruppen och behandlingen ges 1 timme per vecka under 12 veckor. Mellan sessionerna uppmanas patienten till aktiva övningar med hjälp av inspelat individualiserat behandlingsmaterial.

Övergripande syfte med avhandlingsarbetet

I. Att undersöka effekten av hypnoterapi på IBS-symtom, psykologisk samsjuklighet och livskvalitet när behandlingen ges utanför högspecialiserade ”hypnoterapicenter”.
II. Att undersöka långtidseffekter av hypnoterapi gällande effekt på IBS-symtom samt självrapporterad sjukvårdskonsumtion och läkemedelsanvändning när behandlingen ges utanför högspecialiserade ”hypnoterapicenter”.
III. Att undersöka patientnöjdheten med hypnoterapi som behandling vid IBS.
IV. Att undersöka om det finns effekter på tarmarnas rörelsemönster när patienten får behandling med HT för IBS.

Resultat

Artikel I: Två randomiserade (lottade), kontrollerade (jämförelse med kontrollgrupp som inte får behandlingen som undersöks) behandlingsstudier presenterade i samma artikel (Trial 1, Trial 2).

Trial 1, genomförd på Sahlgrenska sjukhuset med behandlingen given hos psykologer på deras privata mottagningar. 90 patienter randomiserades till hypnoterapi eller kontrollgrupp. Inom hypnoterapigruppen minskade symtomen signifikant vid uppföljning men inte inom kontrollgruppen. Även mellan grupperna fanns en signifikant skillnad i symtomen efter behandlingen. Effekten i behandlingsgruppen höll i sig upp till 1 år efter behandlingen. Bättre livskvalitet och minskad grad av ångest sågs också i behandlingsgruppen men skillnaden uppnådde inte statistisk signifikans jämfört med kontrollgruppen

Trial 2, genomförd på Gävle sjukhus gastroenterologiska mottagningen där också behandlingen gavs. 48 patienter randomiserades till hypnoterapi eller kontrollgrupp. Inom hypnoterapi gruppen minskade symtomen signifikant vid uppföljning men inte inom kontrollgruppen. Skillnaden mellan behandlingsgrupp och kontrollgrupp uppnådde dock inte statistisk signifikans, vilket kan bero på att patientantalet i studien var för litet. Effekten inom behandlingsgruppen höll i sig upp till 1 år efter behandlingen. Bättre livskvalitet och minskad grad av ångest sågs också i behandlingsgruppen, men skillnaden uppnådde inte statistisk signifikans jämfört med kontrollgruppen

Dessa studier visar således att hypnoterapi är en effektiv behandlingsform för IBS-patienter, men effekten av behandlingen är lägre när den ges utanför högspecialiserade hypnoterapicenter.

Artikel II: 208 patienter som behandlats med hypnoterapi mellan 2000-2006 följdes upp avseende långtidseffekt av behandlingen på IBS-symtom samt självrapporterad förändring av sjukvårdskonsumtion och bruk av läkemedelsbehandling mot IBS symtom. Patienterna delades upp i ”responders”(49%) och ”icke responders” (51%), baserat på den självrapporterade effekten på IBS symtomen efter behandlingens avslutande (responders= patienter som rapporterade lindring av IBS symtom, icke responders= patienter som inte upplevde lindring av sina IBS symtom efter behandlingen). Behandlingen hade givits utanför ”högspecialiserade hypnoterapicenter”. Vid uppföljningen 2-7 år efter behandling (medel 4 år) hade 73 % av patienterna i responder-gruppen förbättrats ytterligare och rapporterade en signifikant minskning av sjukvårdskonsumtion jämfört

med icke responders. 87 % av alla patienter angav att hypnoterapibehandlingen varit viktig och meningsfull (100 % av responders och 74 % av icke responders). Ingen skillnad i användandet av läkemedel mot IBS symtom efter hypnoterapin kunde ses mellan grupperna.

Denna studie är att hypnoterapi vid IBS är en effektiv behandling med goda långtidseffekter även om den ges utanför ”högspecialiserade hypnoterapi-center”. Behandlingen har även potential att spara sjukvårdsresurser i denna patientgrupp

Artikel III: Patientnöjdheten med hypnoterapi som behandling av IBS är hög, även hos patienter som inte svarat på behandlingen med avseende effekt på mag-tarmsymtom (se artikel II). Vi undersökte 83 patienter med IBS som genomgått hypnoterapi i studie Ia. Efter behandlingen skattade patienterna sin ”grad av nöjdhet med behandlingen” på en 5- gradig skala där 1= inte alls nöjd och 5= mycket nöjd. Även formulär gällande IBS symtom, livskvalitet, kognitiv funktion, känsla av sammanhang, depression och ångest fylldes i före och efter behandlingen. Efter behandlingen sågs signifikant minskade IBS symtom, förbättrad livskvalitet, minskad ångest och förbättrad kognitiv funktion. Trettio patienter (36 %) skattade sig som ”mycket nöjda med behandlingen”. Femtiosju patienter (69 %) skattade 4 eller 5 på ”nöjdhetsskalan”. Patientnöjdhet var kopplat till minskade IBS symtom och ökad livskvalitet efter behandlingen. När patienterna delades upp utifrån om de svarat tillfredställande på behandlingen (lindring av IBS symtom), var 52 % av responders ”mycket nöjda” med behandlingen men även i non-responder gruppen var 30 % ”mycket nöjda”.

Denna studie visar att hög patientnöjdhet med hypnoterapi är associerat med förbättrad livskvalitet och minskade IBS symtom, men även andra faktorer ligger bakom den höga patientnöjdheten, eftersom även en stor del av non-responders var mycket nöjda med behandlingen.

Artikel IV: Effekten på tarmarnas rörelsemönster av hypnoterapi vid behandling av IBS är ofullständigt känd. 90 IBS patienter randomiserades till hypnoterapi eller en till en kontrollgrupp (som en del i Trial 1, Artikel I). 81 patienter utvärderades med undersökningar av tarmarnas rörelsemönster före och efter hypnoterapi behandlingen. Det var inga signifikanta skillnader före och efter behandling i någon av grupperna.

I denna studie kunde vi inte finna någon kvarstående effekt på tarmarnas rörelsemönster efter genomgången hypnoterapi för IBS. Fortsatt forskning för att förstå hur effekten av hypnoterapi medieras är nödvändig

Slutsatser

Hypnoterapi som behandling vid IBS är en effektiv behandling även om den ges utanför specialiserade ”hypnoterapi center”. Effektstorleken är dock lägre. Behandlingseffekten håller i sig över tid och behandlingen är förenad med en mycket hög patientnöjdhet som delvis förklaras av effekter på IBS symtom och livskvalitet, men även andra faktorer verkar spela roll. Behandlingen har också en potential att spara sjukvårdsresurser i denna patientgrupp. Hur effekten av hypnoterapibehandling vid IBS medieras är okänt men den beror sannolikt inte på en påverkan av tarmarnas rörelsemönster.

References

1. Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. BMJ (Clinical Research Ed). 1978;2(6138):653-4.
2. Ford AC, Talley NJ, Veldhuyzen van Zanten SJO, Vakil NB, Simel DL, Moayyedi P. Will the history and physical examination help establish that irritable bowel syndrome is causing this patient's lower gastrointestinal tract symptoms? JAMA. 2008;300(15):1793-805.
3. Spiegel BM, Farid M, Esrailian E, Talley J, Chang L. Is irritable bowel syndrome a diagnosis of exclusion?: a survey of primary care providers, gastroenterologists, and IBS experts. Am J Gastroenterol. 2010;105(4):848-58.
4. Cash BD, Schoenfeld P, Chey WD. The utility of diagnostic tests in irritable bowel syndrome patients: a systematic review. Am J Gastroenterol. 2002;97(11):2812-9.
5. Thompson WG. The road to rome. Gastroenterology. 2006;130(5):1552-6.
6. Thompson WG, Creed F, Drossman DA, Heaton KW, Mazzacca G. Functional bowel disease and functional abdominal pain. Gastroenterology International. 1992;5(2):75-91.
7. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. Gut. 1999;45 Suppl 2:II43-7.
8. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology. 2006;130(5):1480-91.
9. Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome in general practice: prevalence, characteristics, and referral. Gut. 2000;46(1):78-82.
10. Harvey RF, Salih SY, Read AE. Organic and functional disorders in 2000 gastroenterology outpatients. Lancet. 1983;1(8325):632-4.
11. Switz DM. What the gastroenterologist does all day. A survey of a state society's practice. Gastroenterology. 1976;70(6):1048-50..
12. Lovell RM, Ford AC. Global Prevalence of and Risk Factors for Irritable Bowel Syndrome: A Meta-analysis. Clin Gastroenterol Hepatol. 2012..
13. Olafsdottir LB, Gudjonsson H, Jonsdottir HH, Thjodleifsson B. Stability of the irritable bowel syndrome and subgroups as measured by three diagnostic criteria - a 10-year follow-up study. Aliment Pharmacol Ther. 2010; 32(5):670-80..
14. Bommelaer G, Poynard T, Le Pen C, Gaudin A-F, Maurel F, Priol G, et al. Prevalence of irritable bowel syndrome (IBS) and variability of diagnostic criteria. Gastroenterol Clin Biol. 2004;28(6-7 Pt 1):554-61.
15. Choung RS, Locke GR. Epidemiology of IBS. Gastroenterol Clin North Am. 2011;40(1):1-10.
16. Spiller R, Aziz Q, Creed F, Emmanuel A, Houghton L, Hungin P, et al. Guidelines on the irritable bowel syndrome: mechanisms and practical management. Gut. 2007;56(12):1770-98.
17. Lovell RM, Ford AC. Effect of Gender on Prevalence of Irritable Bowel Syndrome in the Community: Systematic Review and Meta-Analysis. Am J Gastroenterol. 2012;107(7):991-1000.
18. Agreus L, Svardsudd K, Nyren O, Tibblin G. Irritable bowel syndrome and dyspepsia in the general population: overlap and lack of stability over time. Gastroenterology. 1995;109(3):671-80.

19. Agréus L, Svärdsudd K, Talley NJ, Jones MP, Tibblin G. Natural history of gastroesophageal reflux disease and functional abdominal disorders: a population-based study. Am J gastroenterol. 2001;96(10):2905-14.
20. Ford AC, Forman D, Bailey AG, Axon AT, Moayyedi P. Irritable bowel syndrome: a 10-yr natural history of symptoms and factors that influence consultation behavior. Am J Gastroenterol. 2008;103(5):1229-39.
21. Halder SL, Locke GR, 3rd, Schleck CD, Zinsmeister AR, Melton LJ, 3rd, Talley NJ. Natural history of functional gastrointestinal disorders: a 12-year longitudinal population-based study. Gastroenterology. 2007;133(3):799-807.
22. Marshall JK. Post-infectious irritable bowel syndrome following water contamination. Kidney Int Suppl. 2009(112):S42-3.
23. Marshall JK, Thabane M, Garg AX, Clark WF, Moayyedi P, Collins SM. Eight year prognosis of postinfectious irritable bowel syndrome following waterborne bacterial dysentery. Gut. 2010;59(5):605-11.
24. Whorwell PJ, McCallum M, Creed FH, Roberts CT. Non-colonic features of irritable bowel syndrome. Gut. 1986;27(1):37-40.
25. Glia A, Lindberg G. Quality of life in patients with different types of functional constipation. Scand J Gastroenterol. 1997;32(11):1083-9.
26. Hahn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. Digestion. 1999;60(1):77-81.
27. Talley NJ, Weaver AL, Zinsmeister AR. Impact of functional dyspepsia on quality of life. Dig Dis Sci. 1995;40(3):584-9.
28. Hahn BA, Kirchdoerfer LJ, Fullerton S, Mayer E. Patient-perceived severity of irritable bowel syndrome in relation to symptoms, health resource utilization and quality of life. Aliment Pharmacol Ther 1997;11(3):553-9.
29. Testa MA, Simonson DC. Assesment of quality-of-life outcomes. N Engl J Med. 1996;334(13):835-40.
30. Creed F, Ratcliffe J, Fernandez L, Tomenson B, Palmer S, Rigby C, et al. Health-related quality of life and health care costs in severe, refractory irritable bowel syndrome. Ann Intern Med. 2001;134(9 Pt 2):860-8.
31. Gralnek IM, Hays RD, Kilbourne A, Naliboff B, Mayer EA. The impact of irritable bowel syndrome on health-related quality of life. Gastroenterology. 2000;119(3):654-60.
32. Patrick DL, Drossman DA, Frederick IO, DiCesare J, Puder KL. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. Dig Dis Sci. 1998;43(2):400-11.
33. El-Serag HB, Olden K, Bjorkman D. Health-related quality of life among persons with irritable bowel syndrome: a systematic review. Aliment Pharmacol Ther. 2002;16(6):1171-85.
34. Simren M, Brazier J, Coremans G, Dapoigny M, Muller-Lissner SA, Pace F, et al. Quality of life and illness costs in irritable bowel syndrome. Digestion. 2004;69(4):254-61.
35. Drossman DA, Li Z, Andruzzi E, Temple RD, Talley NJ, Thompson WG, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. Dig Dis Sci. 1993;38(9):1569-80.
36. Dean BB, Aguilar D, Barghout V, Kahler KH, Frech F, Groves D, et al. Impairment in work productivity and health-related quality of life in patients with IBS. Am J Manag Care. 2005;11(1 Suppl):S17-26.
37. Longstreth GF, Wilson A, Knight K, Wong J, Chiou C-F, Barghout V, et al. Irritable bowel syndrome, health care use, and costs: a U.S. managed care perspective. Am J Gastroenterol. 2003;98(3):600-7.

38. Talley NJ, Gabriel SE, Harmsen WS, Zinsmeister AR, Evans RW. Medical costs in community subjects with irritable bowel syndrome. Gastroenterology. 1995;109(6):1736-41.
39. Hillila MT, Farkkila NJ, Farkkila MA. Societal costs for irritable bowel syndrome--a population based study. Scand J Gastroenterol. 2010;45(5):582-91.
40. Nyrop KA, Palsson OS, Levy RL, Korff MV, Feld AD, Turner MJ, et al. Costs of health care for irritable bowel syndrome, chronic constipation, functional diarrhoea and functional abdominal pain. Aliment Pharmacol Ther. 2007;26(2):237-48.
41. Mykletun A, Jacka F, Williams L, Pasco J, Henry M, Nicholson GC, et al. Prevalence of mood and anxiety disorder in self reported irritable bowel syndrome (IBS). An epidemiological population based study of women. BMC Gastroenterolol. 2010;10(1):88.
42. Whitehead WE, Palsson OS, Levy RR, Feld AD, Turner M, Von Korff M. Comorbidity in irritable bowel syndrome. Am J Gastroenterol. 2007;102(12):2767-76.
43. Drossman DA, McKee DC, Sandler RS, Mitchell CM, Cramer EM, Lowman BC, et al. Psychosocial factors in the irritable bowel syndrome. A multivariate study of patients and nonpatients with irritable bowel syndrome. Gastroenterology. 1988;95(3):701-8.
44. Choung RS, Locke GR, 3rd, Zinsmeister AR, Schleck CD, Talley NJ. Psychosocial distress and somatic symptoms in community subjects with irritable bowel syndrome: a psychological component is the rule. Am J Gastroenterol. 2009;104(7):1772-9.
45. Lee S, Wu J, Ma YL, Tsang A, Guo WJ, Sung J. Irritable bowel syndrome is strongly associated with generalized anxiety disorder: a community study. Aliment Pharmacol Ther. 2009;30(6):643-51.
46. Kumano H, Kaiya H, Yoshiuchi K, Yamanaka G, Sasaki T, Kuboki T. Comorbidity of irritable bowel syndrome, panic disorder, and agoraphobia in a Japanese representative sample. Am J Gastroenterol. 2004;99(2):370-6.
47. Gros DF, Antony MM, McCabe RE, Swinson RP. Frequency and severity of the symptoms of irritable bowel syndrome across the anxiety disorders and depression. J Anxiety Disord. 2009;23(2):290-6.
48. Kellow JE, Phillips SF. Altered small bowel motility in irritable bowel syndrome is correlated with symptoms. Gastroenterology. 1987;92(6):1885-93.
49. Kellow JE, Gill RC, Wingate DL. Prolonged ambulant recordings of small bowel motility demonstrate abnormalities in the irritable bowel syndrome. Gastroenterology. 1990;98(5 Pt 1):1208-18.
50. Kellow JE, Eckersley GM, Jones M. Enteric and central contributions to intestinal dysmotility in irritable bowel syndrome. Dig Dis Sci. 1992;37(2):168-74.
51. Gorard DA, Libby GW, Farthing MJ. Ambulatory small intestinal motility in 'diarrhoea' predominant irritable bowel syndrome. Gut. 1994;35(2):203-10.
52. Schmidt T, Hackelsberger N, Widmer R, Meisel C, Pfeiffer A, Kaess H. Ambulatory 24-hour jejunal motility in diarrhea-predominant irritable bowel syndrome. Scand J Gastroenterol. 1996;31(6):581-9.
53. Cann PA, Read NW, Brown C, Hobson N, Holdsworth CD. Irritable bowel syndrome: relationship of disorders in the transit of a single solid meal to symptom patterns. Gut. 1983;24(5):405-11.
54. Jian R, Najean Y, Bernier JJ. Measurement of intestinal progression of a meal and its residues in normal subjects and patients with functional diarrhoea by a dual isotope technique. Gut. 1984;25(7):728-31.
55. Nielsen OH, Gjorup T, Christensen FN. Gastric emptying rate and small bowel transit time in patients with irritable bowel syndrome determined with 99mTc-labeled pellets and scintigraphy. Dig Dis Sci. 1986;31(12):1287-91.

56. Camilleri M, McKinzie S, Busciglio I, Low PA, Sweetser S, Burton D, et al. Prospective study of motor, sensory, psychologic, and autonomic functions in patients with irritable bowel syndrome. Clin Gastroenterol Hepatol. 2008;6(7):772-81.
57. Chey WY, Jin HO, Lee MH, Sun SW, Lee KY. Colonic motility abnormality in patients with irritable bowel syndrome exhibiting abdominal pain and diarrhea. Am J Gastroenterol. 2001;96(5):1499-506.
58. Clemens CH, Samsom M, Van Berge Henegouwen GP, Smout AJ. Abnormalities of left colonic motility in ambulant nonconstipated patients with irritable bowel syndrome. Dig Dis Sci. 2003;48(1):74-82.
59. Clemens CH, Samsom M, Roelofs JM, van Berge Henegouwen GP, Smout AJ. Association between pain episodes and high amplitude propagated pressure waves in patients with irritable bowel syndrome. Am J Gastroenterol. 2003;98(8):1838-43.
60. Narducci F, Bassotti G, Granata MT, Pelli MA, Gaburri M, Palumbo R, et al. Colonic motility and gastric emptying in patients with irritable bowel syndrome. Effect of pretreatment with octylonium bromide. Dig Dis Sci. 1986;31(3):241-6.
61. Rogers J, Henry MM, Misiewicz JJ. Increased segmental activity and intraluminal pressures in the sigmoid colon of patients with the irritable bowel syndrome. Gut. 1989;30(5):634-41.
62. Welgan P, Meshkinpour H, Hoehler F. The effect of stress on colon motor and electrical activity in irritable bowel syndrome. Psychosom Med. 1985;47(2):139-49.
63. Welgan P, Meshkinpour H, Beeler M. Effect of anger on colon motor and myoelectric activity in irritable bowel syndrome. Gastroenterology. 1988;94(5 Pt 1):1150-6.
64. McKee DP, Quigley EM. Intestinal motility in irritable bowel syndrome: is IBS a motility disorder? Part 1. Definition of IBS and colonic motility. Dig Dis Sci. 1993;38(10):1761-72.
65. McKee DP, Quigley EM. Intestinal motility in irritable bowel syndrome: is IBS a motility disorder? Part 2. Motility of the small bowel, esophagus, stomach, and gall-bladder. Dig Dis Sci. 1993;38(10):1773-82.
66. Sadik R, Abrahamsson H, Stotzer PO. Gender differences in gut transit shown with a newly developed radiological procedure. Scand J Gastroenterol. 2003;38(1):36-42. Epub 2003/03/01.
67. Chang L, Lee OY, Naliboff B, Schmulson M, Mayer EA. Sensation of bloating and visible abdominal distension in patients with irritable bowel syndrome. Am J Gastroenterol. 2001;96(12):3341-7.
68. Lasser RB, Bond JH, Levitt MD. The role of intestinal gas in functional abdominal pain. N Engl J Med. 1975;293(11):524-6.
69. Agrawal A, Houghton LA, Lea R, Morris J, Reilly B, Whorwell PJ. Bloating and distention in irritable bowel syndrome: the role of visceral sensation. Gastroenterology. 2008;134(7):1882-9.
70. Serra J, Azpiroz F, Malagelada JR. Impaired transit and tolerance of intestinal gas in the irritable bowel syndrome. Gut. 2001;48(1):14-9.
71. Serra J, Azpiroz F, Malagelada JR. Gastric distension and duodenal lipid infusion modulate intestinal gas transit and tolerance in humans. Am J Gastroenterol. 2002;97(9):2225-30.
72. Dainese R, Serra J, Azpiroz F, Malagelada JR. Effects of physical activity on intestinal gas transit and evacuation in healthy subjects. Am J Med. 2004;116(8):536-9.
73. Accarino A, Perez F, Azpiroz F, Quiroga S, Malagelada JR. Abdominal distention results from caudo-ventral redistribution of contents. Gastroenterology. 2009;136(5):1544-51.
74. Simren M. Bloating and abdominal distention: not so poorly understood anymore! Gastroenterology. 2009;136(5):1487-90.
75. Mertz H, Naliboff B, Munakata J, Niazi N, Mayer EA. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. Gastroenterology. 1995;109(1):40-52.

76. Whitehead WE, Palsson OS. Is rectal pain sensitivity a biological marker for irritable bowel syndrome: psychological influences on pain perception. Gastroenterology. 1998;115(5):1263-71.
77. Posserud I, Syrous A, Lindstrom L, Tack J, Abrahamsson H, Simren M. Altered rectal perception in irritable bowel syndrome is associated with symptom severity. Gastroenterology. 2007;133(4):1113-23.
78. Chang L, Mayer EA, Labus JS, Schmulson M, Lee OY, Olivas TI, et al. Effect of sex on perception of rectosigmoid stimuli in irritable bowel syndrome. Am J Physiol . 2006;291(2):R277-84.
79. Simren M, Abrahamsson H, Bjornsson ES. An exaggerated sensory component of the gastrocolonic response in patients with irritable bowel syndrome. Gut. 2001;48(1):20-7.
80. Posserud I, Agerforz P, Ekman R, Bjornsson ES, Abrahamsson H, Simren M. Altered visceral perceptual and neuroendocrine response in patients with irritable bowel syndrome during mental stress. Gut. 2004;53(8):1102-8.
81. Mayer EA, Gebhart GF. Basic and clinical aspects of visceral hyperalgesia. Gastroenterology. 1994;107(1):271-93.
82. Naliboff BD, Berman S, Suyenobu B, Labus JS, Chang L, Stains J, et al. Longitudinal change in perceptual and brain activation response to visceral stimuli in irritable bowel syndrome patients. Gastroenterology. 2006;131(2):352-65.
83. Naliboff BD, Derbyshire SW, Munakata J, Berman S, Mandelkern M, Chang L, et al. Cerebral activation in patients with irritable bowel syndrome and control subjects during rectosigmoid stimulation. Psychosom Med. 2001;63(3):365-75.
84. Naliboff BD, Munakata J, Fullerton S, Gracely RH, Kodner A, Harraf F, et al. Evidence for two distinct perceptual alterations in irritable bowel syndrome. Gut. 1997;41(4):505-12.
85. Silverman DH, Munakata JA, Ennes H, Mandelkern MA, Hoh CK, Mayer EA. Regional cerebral activity in normal and pathological perception of visceral pain. Gastroenterology. 1997;112(1):64-72.
86. Tillisch K, Mayer EA, Labus JS. Quantitative Meta-Analysis Identifies Brain Regions Activated during Rectal Distension in Irritable Bowel Syndrome. Gastroenterology. 2011 Jan;140(1):91-100.
87. Naliboff BD, Berman S, Chang L, Derbyshire SW, Suyenobu B, Vogt BA, et al. Sex-related differences in IBS patients: central processing of visceral stimuli. Gastroenterology. 2003;124(7):1738-47.
88. Larsson MB, Tillisch K, Craig AD, Engstrom M, Labus J, Naliboff B, et al. Brain responses to visceral stimuli reflect visceral sensitivity thresholds in patients with irritable bowel syndrome. Gastroenterology. 2012;142(3):463-72 e3.
89. Levy RL, Cain KC, Jarrett M, Heitkemper MM. The relationship between daily life stress and gastrointestinal symptoms in women with irritable bowel syndrome. J Behav Med. 1997;20(2):177-93.
90. Suls J, Wan CK, Blanchard EB. A multilevel data-analytic approach for evaluation of relationships between daily life stressors and symptomatology: patients with irritable bowel syndrome. Health Psychol. 1994;13(2):103-13.
91. Blanchard EB, Lackner JM, Jaccard J, Rowell D, Carosella AM, Powell C, et al. The role of stress in symptom exacerbation among IBS patients. J Psychosom Res. 2008;64(2):119-28.
92. Mayer EA, Craske M, Naliboff BD. Depression, anxiety, and the gastrointestinal system. J Clin Psychiatry. 2001;62 Suppl 8:28-36.
93. Chapman S, Martin M. Attention to pain words in irritable bowel syndrome: Increased orienting and speeded engagement. Br J Health Psychol. 2011 Feb;16(Pt 1):47-60.

94. Keough ME, Timpano KR, Zawilinski LL, Schmidt NB. The association between Irritable Bowel Syndrome and the anxiety vulnerability factors: Body vigilance and discomfort intolerance. J Health Psychol. 2011 Jan;16(1):91-8.
95. Lackner JM, Quigley BM, Blanchard EB. Depression and abdominal pain in IBS patients: the mediating role of catastrophizing. Psychosom Med. 2004;66(3):435-41.
96. Lackner JM, Quigley BM. Pain catastrophizing mediates the relationship between worry and pain suffering in patients with irritable bowel syndrome. Behav Res Ther. 2005;43(7):943-57.
97. Lackner JM, Lou Coad M, Mertz HR, Wack DS, Katz LA, Krasner SS, et al. Cognitive therapy for irritable bowel syndrome is associated with reduced limbic activity, GI symptoms, and anxiety. Behav Res and Ther. 2006;44(5):621-38.
98. Håkanson C, Sahlberg-Blom E, Ternestedt BM. Being in the Patient Position: Experiences of Health Care Among People With Irritable Bowel Syndrome. Qual Health Res. 2010 Aug;20(8):1116-27.
99. Bertram S, Kurland M, Lydick E, Locke GR, 3rd, Yawn BP. The patient's perspective of irritable bowel syndrome. J Fam Pract. 2001;50(6):521-5.
100. Dancey CP, Backhouse S. Towards a better understanding of patients with irritable bowel syndrome. J Adv Nurs. 1993;18(9):1443-50.
101. Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: long-term prognosis and the physician-patient interaction. Ann Int Med. 1995;122(2):107-12.
102. Larsen JH, Risor O, Putnam S. P-R-A-C-T-I-C-A-L: a step-by-step model for conducting the consultation in general practice. Fam Pract. 1997;14(4):295-301.
103. Noble LM, Kubacki A, Martin J, Lloyd M. The effect of professional skills training on patient-centredness and confidence in communicating with patients. Medical education. 2007;41(5):432-40.
104. Ragnarsson G, Bodemar G. Pain is temporally related to eating but not to defaecation in the irritable bowel syndrome (IBS). Patients' description of diarrhea, constipation and symptom variation during a prospective 6-week study. Eur J Gastroenterol Hepatol. 1998;10(5):415-21.
105. Svedlund J, Sjodin I, Dotevall G, Gillberg R. Upper gastrointestinal and mental symptoms in the irritable bowel syndrome. Scand J Gastroenterol. 1985;20(5):595-601.
106. Young E, Stoneham MD, Petruckevitch A, Barton J, Rona R. A population study of food intolerance. Lancet. 1994;343(8906):1127-30.
107. Manning AP, Heaton KW, Harvey RF. Wheat fibre and irritable bowel syndrome. A controlled trial. Lancet. 1977;2(8035):417-8.
108. Francis CY, Whorwell PJ. Bran and irritable bowel syndrome: time for reappraisal. Lancet. 1994;344(8914):39-40.
109. Evans PR, Piesse C, Bak YT, Kellow JE. Fructose-sorbitol malabsorption and symptom provocation in irritable bowel syndrome: relationship to enteric hypersensitivity and dysmotility. Scand J Gastroenterol. 1998;33(11):1158-63.
110. King TS, Elia M, Hunter JO. Abnormal colonic fermentation in irritable bowel syndrome. Lancet. 1998;352(9135):1187-9.
111. Sullivan MA, Cohen S, Snape WJ, Jr. Colonic myoelectrical activity in irritable-bowel syndrome. Effect of eating and anticholinergics. N Engl J Med. 1978;298(16):878-83.
112. Johannesson E, Simren M, Strid H, Bajor A, Sadik R. Physical activity improves symptoms in irritable bowel syndrome: a randomized controlled trial. Am J Gastroenterol. 2011;106(5):915-22.
113. Saito YA, Prather CM, Van Dyke CT, Fett S, Zinsmeister AR, Locke GR, 3rd. Effects of multidisciplinary education on outcomes in patients with irritable bowel syndrome. Clin Gastroenterol Hepatol. 2004;2(7):576-84.

114. Colwell LJ, Prather CM, Phillips SF, Zinsmeister AR. Effects of an irritable bowel syndrome educational class on health-promoting behaviors and symptoms. Am J Gastroenterol. 1998;93(6):901-5.
115. Ringström G, Storsrud S, Posserud I, Lundqvist S, Westman B, Simrén M. Structured patient education is superior to written information in the management of patients with irritable bowel syndrome: a randomized controlled study. Euro J Gastroenterol Hepatol. 2010;22(4):420-8.
116. Brandt LJ, Chey WD, Foxx-Orenstein AE, Schiller LR, Schoenfeld PS, Spiegel BM, et al. An evidence-based position statement on the management of irritable bowel syndrome. Am J Gastroenterol. 2009;104 Suppl 1:S1-35.
117. Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. Ann Intern Med. 2000;133(2):136-47.
118. Thompson CA. Alosetron withdrawn from market. Am J Health Pharm 2001;58(1):13.
119. Pasricha PJ. Desperately seeking serotonin... A commentary on the withdrawal of tegaserod and the state of drug development for functional and motility disorders. Gastroenterology. 2007;132(7):2287-90.
120. Evans BW, Clark WK, Moore DJ, Whorwell PJ. Tegaserod for the treatment of irritable bowel syndrome and chronic constipation. Cochrane Database Syst Rev. 2007(4):CD003960.
121. Novick J, Miner P, Krause R, Glebas K, Bliesath H, Ligozio G, et al. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. Aliment Pharmacol Ther. 2002;16(11):1877-88.
122. Johnston JM, Kurtz CB, Macdougall JE, Lavins BJ, Currie MG, Fitch DA, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. Gastroenterology. 2010;139(6):1877-86 e2.
123. Lembo AJ, Schneier HA, Shiff SJ, Kurtz CB, MacDougall JE, Jia XD, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med. 2011;365(6):527-36.
124. Chang JY, Talley NJ. An update on irritable bowel syndrome: from diagnosis to emerging therapies. Curr Opin Gastroenterol. 2011;27(1):72-8.
125. Svedlund J, Sjodin I, Ottosson JO, Dotevall G. Controlled study of psychotherapy in irritable bowel syndrome. Lancet. 1983;2(8350):589-92.
126. Guthrie E, Creed F, Dawson D, Tomenson B. A controlled trial of psychological treatment for the irritable bowel syndrome. Gastroenterology. 1991;100(2):450-7.
127. Creed F, Fernandes L, Guthrie E, Palmer S, Ratcliffe J, Read N, et al. The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. Gastroenterology. 2003;124(2):303-17.
128. Blanchard EB, Schwarz SP. Adaptation of a multicomponent treatment for irritable bowel syndrome to a small-group format. Biofeedback Self Regul. 1987;12(1):63-9.
129. Neff DF, Blanchard EB. A multi-component treatment for irritable bowel syndrome. Beh Ther. 1987;18(1):70-83.
130. Greene B, Blanchard EB. Cognitive therapy for irritable bowel syndrome. J Consult Clin Psychol. 1994;62(3):576-82.
131. Payne A, Blanchard EB. A controlled comparison of cognitive therapy and self-help support groups in the treatment of irritable bowel syndrome. J Consult Clin Psychol. 1995;63(5):779-86.
132. Vollmer A, Blanchard EB. Controlled comparison of individual versus group cognitive therapy for irritable bowel syndrome. Behav Ther. 1998;29(1):19-33.
133. Blanchard EB, Lackner JM, Sanders K, Krasner S, Keefer L, Payne A, et al. A controlled evaluation of group cognitive therapy in the treatment of irritable bowel syndrome. Behav Res Ther. 2007;45(4):633-48.

134. Toner BB, Segal ZV, Emmott S, Myran D, Ali A, DiGasbarro I, et al. Cognitive-behavioral group therapy for patients with irritable bowel syndrome. Int J Group Psychother. 1998;48(2):215-43.
135. Drossman DA, Toner BB, Whitehead WE, Diamant NE, Dalton CB, Duncan S, et al. Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. Gastroenterology. 2003;125(1):19-31.
136. Boyce PM, Gilchrist J, Talley NJ, Rose D. Cognitive-behaviour therapy as a treatment for irritable bowel syndrome: A pilot study. Aust N Z J Psych. 2000;34(2):300-9.
137. Boyce PM, Talley NJ, Balaam B, Koloski NA, Truman G. A randomized controlled trial of cognitive behavior therapy, relaxation training, and routine clinical care for the irritable bowel syndrome. Am J Gastroenterol. 2003;98(10):2209-18.
138. Ford AC, Talley NJ, Schoenfeld PS, Quigley EM, Moayyedi P. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. Gut. 2009;58(3):367-78.
139. Lackner JM, Jaccard J, Krasner SS, Katz LA, Gudleski GD, Holroyd K. Self-administered cognitive behavior therapy for moderate to severe irritable bowel syndrome: clinical efficacy, tolerability, feasibility. Clin Gastroenterol Hepatol. 2008;6(8):899-906.
140. Jarrett ME, Cain KC, Burr RL, Hertig VL, Rosen SN, Heitkemper MM. Comprehensive self-management for irritable bowel syndrome: randomized trial of in-person vs. combined in-person and telephone sessions. Am J Gastroenterol. 2009;104(12):3004-14.
141. Moss-Morris R, McAlpine L, Didsbury LP, Spence MJ. A randomized controlled trial of a cognitive behavioural therapy-based self-management intervention for irritable bowel syndrome in primary care. Psychol Med. 2010;40(1):85-94.
142. Hunt MG, Moshier S, Milonova M. Brief cognitive-behavioral internet therapy for irritable bowel syndrome. Behav Res Ther. 2009;47:797-802.
143. Ljótsson B, Andréewitch S, Hedman E, Rück C, Andersson G, Lindefors N. Exposure and mindfulness based therapy for irritable bowel syndrome - An open pilot study. J Behav Ther Exp Psych. 2010;41(3):185-90.
144. Ljótsson B, Falk L, Wibron Vesterlund A, Hedman E, Lindfors P, Rück C, et al. Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome - a randomized controlled trial. Behav Res Ther. 2010;48(6):531-9.
145. Ljótsson B, Hedman E, Andersson E, Hesser H, Lindfors P, Hursti T, et al. Internet-Delivered Exposure-Based Treatment vs. Stress Management for Irritable Bowel Syndrome: A Randomized Trial. Am J Gastroenterol. 2011;106(8):1481-91.
146. Ljotsson B, Andersson G, Andersson E, Hedman E, Lindfors P, Andreewitch S, et al. Acceptability, effectiveness, and cost-effectiveness of internet-based exposure treatment for irritable bowel syndrome in a clinical sample: a randomized controlled trial. BMC Gastroenterol. 2011;11:110. Epub 2011/10/14.
147. Ljótsson B, Andersson G, Andersson E, Hedman E, Lindfors P, Andréewitch S, et al. Acceptability, effectiveness, and cost-effectiveness of internet-based exposure treatment for irritable bowel syndrome in a clinical sample: a randomized controlled trial. BMC Gastroenterology. 2011;11(1):110.
148. Whorwell PJ, Prior A, Faragher EB. Controlled trial of hypnotherapy in the treatment of severe refractory irritable-bowel syndrome. Lancet. 1984;2(8414):1232-4.
149. Whorwell PJ, Prior A, Colgan SM. Hypnotherapy in severe irritable bowel syndrome: further experience. Gut. 1987;28(4):423-5.
150. Harvey RF, Hinton RA, Gunary RM, Barry RE. Individual and group hypnotherapy in treatment of refractory irritable bowel syndrome. Lancet. 1989;1(8635):424-5.
151. Talley NJ, Owen BK, Boyce P, Paterson K. Psychological treatments for irritable bowel syndrome: a critique of controlled treatment trials. Am J Gastroenterol. 1996;91(2):277-83.

152. Galovski TE, Blanchard EB. The treatment of irritable bowel syndrome with hypnotherapy. Appl Psychophysiol Biofeedback. 1998;23(4):219-32.
153. Palsson OS, Turner MJ, Johnson DA, Burnett CK, Whitehead WE. Hypnosis treatment for severe irritable bowel syndrome: investigation of mechanism and effects on symptoms. Dig Dis Sci. 2002;47(11):2605-14.
154. Roberts L, Wilson S, Singh S, Roalfe A, Greenfield S. Gut-directed hypnotherapy for irritable bowel syndrome: piloting a primary care-based randomised controlled trial.Br J Gen Pract . 2006;56(523):115-21.
155. Webb AN, Kukuruzovic RH, Catto-Smith AG, Sawyer SM. Hypnotherapy for treatment of irritable bowel syndrome. Cochrane Database Syst Rev. 2007(4):CD005110.
156. Gonsalkorale WM, Houghton LA, Whorwell PJ. Hypnotherapy in irritable bowel syndrome: a large-scale audit of a clinical service with examination of factors influencing responsiveness. Am J Gastroenterol. 2002;97(4):954-61.
157. Vidakovic-Vukic M. Hypnotherapy in the treatment of irritable bowel syndrome: methods and results in Amsterdam. Scand J Gastroenterol. 1999;230:49-51.
158. Gonsalkorale WM, Miller V, Afzal A, Whorwell PJ. Long term benefits of hypnotherapy for irritable bowel syndrome. Gut. 2003;52(11):1623-9.
159. Gould RC, Krynicki VE. Comparative effectiveness of hypnotherapy on different psychological symptoms. Am J Clin Hypn. 1989;32(2):110-7.
160. Houghton LA, Heyman DJ, Whorwell PJ. Symptomatology, quality of life and economic features of irritable bowel syndrome--the effect of hypnotherapy. Aliment Pharmacol Ther. 1996;10(1):91-5.
161. Gonsalkorale WM, Toner BB, Whorwell PJ. Cognitive change in patients undergoing hypnotherapy for irritable bowel syndrome. J Psychosom Res. 2004;56(3):271-8.
162. Toner BB, Stuckless N, Ali A, Downie F, Emmott S, Akman D. The development of a cognitive scale for functional bowel disorders. Psychosom Med. 1998;60(4):492-7.
163. Simrén M. Hypnosis for irritable bowel syndrome: the quest for the mechanism of action. Int J Clin Exp Hypn. 2006;54(1):65-84.
164. Beaugerie L, Burger AJ, Cadranel JF, Lamy P, Gendre JP, Le Quintrec Y. Modulation of orocaecal transit time by hypnosis. Gut. 1991;32(4):393-4.
165. Whorwell PJ, Houghton LA, Taylor EE, Maxton DG. Physiological effects of emotion: assessment via hypnosis. Lancet. 1992;340(8811):69-72.
166. Prior A, Colgan SM, Whorwell PJ. Changes in rectal sensitivity after hypnotherapy in patients with irritable bowel syndrome. Gut. 1990;31(8):896-8.
167. Lea R, Houghton LA, Calvert EL, Larder S, Gonsalkorale WM, Whelan V, et al. Gut-focused hypnotherapy normalizes disordered rectal sensitivity in patients with irritable bowel syndrome. Aliment Pharmacol Ther. 2003;17(5):635-42.
168. Houghton LA, Calvert EL, Jackson NA, Cooper P, Whorwell PJ. Visceral sensation and emotion: a study using hypnosis. Gut. 2002;51(5):701-4.
169. Simrén M, Ringstrom G, Bjornsson ES, Abrahamsson H. Treatment with hypnotherapy reduces the sensory and motor component of the gastrocolonic response in irritable bowel syndrome. Psychosom Med. 2004;66(2):233-8.
170. Faymonville ME, Laureys S, Degueldre C, DelFiore G, Luxen A, Franck G, et al. Neural mechanisms of antinociceptive effects of hypnosis. Anesthesiology. 2000;92(5):1257-67.
171. Faymonville ME, Roediger L, Del Fiore G, Delgueldre C, Phillips C, Lamy M, et al. Increased cerebral functional connectivity underlying the antinociceptive effects of hypnosis. Brain Res Cogn Brain Res. 2003;17(2):255-62.
172. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science. 1997;277(5328):968-71.

173. Bonaz B, Baciu M, Papillon E, Bost R, Gueddah N, Le Bas JF, et al. Central processing of rectal pain in patients with irritable bowel syndrome: an fMRI study. Am J Gastroenterol. 2002;97(3):654-61.
174. Mertz H, Morgan V, Tanner G, Pickens D, Price R, Shyr Y, et al. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. Gastroenterology. 2000;118(5):842-8.
175. Gonsalkorale WM. Gut-directed hypnotherapy: the Manchester approach for treatment of irritable bowel syndrome. Int J Clin Exp Hypn. 2006;54(1):27-50.
176. Wiklund IK, Fullerton S, Hawkey CJ, Jones RH, Longstreth GF, Mayer EA, et al. An irritable bowel syndrome-specific symptom questionnaire: development and validation. Scand J Gastroenterol. 2003;38(9):947-54.
177. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.
178. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
179. Antonovsky A. The structure and properties of the sense of coherence scale. Soc Sci Med. 1993;36(6):725-33.
180. Stotzer PO, Abrahamsson H. Human postprandial gastric emptying of indigestible solids can occur unrelated to antral phase III. Neurogastroenterol Motil. 2000;12(5):415-9.
181. Simren M, Castedal M, Svedlund J, Abrahamsson H, Bjornsson E. Abnormal propagation pattern of duodenal pressure waves in the irritable bowel syndrome (IBS) . Dig Dis Sci. 2000;45(11):2151-61.
182. Stanghellini V, Camilleri M, Malagelada JR. Chronic idiopathic intestinal pseudo-obstruction: clinical and intestinal manometric findings. Gut. 1987;28(1):5-12.
183. Wingate D, Hongo M, Kellow J, Lindberg G, Smout A. Disorders of gastrointestinal motility: towards a new classification. J Gastroenterol Hepatol. 2002;17 Suppl:S1-14.
184. Dorn SD, Morris CB, Schneck SE, Hopper TM, Hu YJ, Kelapure R, et al. Development and validation of the irritable bowel syndrome satisfaction with care scale. Clin Gastroenterol Hepatol. 2011;9(12):1065-71 e1-2.
185. Agreus L. Socio-economic factors, health care consumption and rating of abdominal symptom severity. A report from the abdominal symptom study. Fam Pract. 1993;10(2):152-63.
186. Sandler RS, Drossman DA, Nathan HP, McKee DC. Symptom complaints and health care seeking behavior in subjects with bowel dysfunction. Gastroenterology. 1984;87(2):314-8.
187. Camilleri M, Chey WY, Mayer EA, Northcutt AR, Heath A, Dukes GE, et al. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. Arch Intern Med. 2001;161(14):1733-40.
188. Drossman DA, Chey WD, Johanson JF, Fass R, Scott C, Panas R, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome--results of two randomized, placebo-controlled studies. Aliment Pharmacol Ther. 2009;29(3):329-41.
189. Chey WD, Lembo AJ, Lavins BJ, Shiff SJ, Kurtz CB, Currie MG, et al. Linaclotide for Irritable Bowel Syndrome With Constipation: A 26-Week, Randomized, Double-blind, Placebo-Controlled Trial to Evaluate Efficacy and Safety. Am J Gastroenterol. 2012. Epub 2012/09/19.
190. Ljótsson B, Hedman E, Lindfors P, Hursti T, Lindefors N, Andersson G, et al. Long-term follow up of internet-delivered exposure and mindfulness based treatment for irritable bowel syndrome. Behav Res Ther. 2011;49:58-61.
191. Jackson JL, Chamberlin J, Kroenke K. Predictors of patient satisfaction. Soc Sci Med. 2001;52(4):609-20.
192. Fass R, Fullerton S, Naliboff B, Hirsh T, Mayer EA. Sexual dysfunction in patients with irritable bowel syndrome and non-ulcer dyspepsia. Digestion. 1998;59(1):79-85.

193. Jerndal P, Ringstrom G, Agerforz P, Karpefors M, Akkermans LM, Bayati A, et al. Gastrointestinal-specific anxiety: an important factor for severity of GI symptoms and quality of life in IBS. Neurogastroenterol Motil. 2010;22(6):646-e179.
194. Ringström G, Agerforz P, Lindh A, Jerlstad P, Wallin J, Simrén M. What do patients with irritable bowel syndrome know about their disorder and how do they use their knowledge? Gastroenterol Nurs. 2009;32(4):284-92.
195. Moser G TS, Gajowniczek EE, Michalski M, Mikulitis A, Fuhrer M, Ponocny-Seliger E, Kazemi L, Dejaco C, Miehhsler W. . Longterm success of gut directed group-hypnosis for patients with irritable bowel syndrome – first results of a randomized controlled trial. Gut. 2012;2012; 59 (Suppl 59:A40).
196. Palsson OS. Standardized hypnosis treatment for irritable bowel syndrome: the North Carolina protocol. Int J Clin Exp Hypn. 2006;54(1):51-64.
197. Lövdahl J RG, Agerforz P, Asare F, Simrén M. Nurse-administered, gut-directed hypnotherapy in functional bowel disorders: Efficacy and factors predicting a positive response. Gastroenterology. 2012;142 (5) (Suppl 1: S9).