Hypnotherapy in the management of Irritable Bowel Syndrome

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Colophon

Hypnotherapy in the management of irritable bowel syndrome
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Hypnotherapie in de behandeling van het prikkelbaredarmsyndroom

(met een samenvatting in het Nederlands)

Proefschrift

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Chapter 1

General introduction

IRRITABLE BOWEL SYNDROME

Mrs. de Vries is 53 years old. She is married and has three adult children and two grandchildren. Since ten years she has been suffering from irritable bowel syndrome (IBS) diarrhoea type, after she had a gastroenteritis during a holiday in Egypt. Before that, she was a very active woman, participating in different social clubs. She used to go to a sport club twice a week, liked to play cards and to go shopping with her friends. She did not have any major life events and describes her marriage as good. Her son recently divorced, which caused her sorrow, but the relationship with the daughter-in-law remained good and she is allowed to see the grandchildren. After the onset of the IBS complaints, she found it more difficult to continue with her social activities, because she always wanted to be near a toilet due to the risk of unexpected diarrhoea. She had a severe diarrhoea attack once when she was shopping and after that she gradually refrained from social activities. She does not go to her clubs anymore, does not dare to go to a restaurant, and the worst for her is that she cannot visit one of her daughters anymore, because she is afraid to go by train. Because her world is getting smaller and smaller, she has become depressed. During the ten years of her complaints, she frequently visited her general practitioner, who advised her dietary changes and prescribed different types of medication, but without sufficient effect. She consulted a gastroenterologist twice, who reconfirmed the diagnosis made by the general practitioner. Now she recently read an article on hypnotherapy in the magazine of the IBS patient organisation. Although she always thought this was some kind of complementary medicine, she is desperate and visits the general practitioner to discuss if that is an option for her…

PRESENTATION AND EPIDEMIOLOGY

IBS is a chronic functional gastrointestinal disorder, characterised by recurrent periods of abdominal pain, discomfort, altered bowel habits, and/or symptoms of bloating and distension, not explained by structural or biochemical abnormalities.[1] The diagnosis is based on consensus-based criteria, known as the Rome IV criteria:[2]

Recurrent abdominal pain, on average, at least one day per week in the last three months, associated with two or more of the following criteria:

1 Related to defecation
2 Associated with a change in frequency of stool
3 Associated with a change in form (appearance) of stool

Criteria fulfilled for the last three months with symptom onset at least six months before diagnosis.

Three types of IBS can be distinguished: IBS with predominant constipation, IBS with predominant diarrhoea, or IBS with alternating periods of diarrhoea and constipation.

Worldwide, the estimated prevalence of IBS in the open population is 11.2%[3], varying from 14-24% for women and 5-19% for men.[4] IBS can affect all age groups, but the incidence of IBS symptoms peaks in the third and fourth decade. However, symptoms are also reported by a substantial proportion of individuals in their seventh or eighth decade.[5] IBS is the most frequently diagnosed functional gastrointestinal disease in primary care, with an annual incidence of 4-13/1000 patients.[6] In secondary care, 20-70% of patients referred to gastroenterologists are diagnosed with IBS.[7] The disorder is frequently associated with extra colonic symptoms (for example fatigue and headache) and psychiatric comorbidity.[8] Referred IBS patients are known to have a longer disease history, more psychosocial comorbidity, and higher stress and depression scores.[7-9]

IBS complaints can severely affect daily functioning, resulting in high direct and indirect healthcare costs. The number of days that the patient is not able to work varies between 8.5 and 21.6 days per year[10], resulting in annual loss of labour productivity in the United States of USD 205 million.[11]

Estimated societal costs for IBS per patient per year in the United States and the United Kingdom vary between USD 348 and 8750 for direct costs and from USD 355 to 3344 for indirect costs.[10]

PATHOPHYSIOLOGY

Several pathophysiological mechanisms underlying IBS have been proposed, including disturbance in intestinal motility and increased visceral sensitivity. Most widely accepted at this time is a bio-psycho-social model[5,7] with different interacting aetiological factors: visceral hypersensitivity, disturbances in gastrointestinal

motility, disturbed stress responses, psychological factors, and environmental influences.[5]

Traditionally, IBS was regarded as a gastrointestinal motor disorder, but no motility pattern specific to IBS has been identified.[12] Studies on motoric activity of the colon conclude that this is rarely abnormal in patients with IBS.[5] After a landmark study by Ritchie *et al.*[13], the interest in the research field shifted from the motility to the sensitivity of the colon.[14,15] Most studies confirmed the presence of increased visceral sensitivity in IBS patients.[5,15] Different mechanisms are supposed to play a role in visceral hypersensitivity: an increased sensitivity of both the peripheral and central nervous system and a difference in pain processing on the central level and in the spinal cord. It is suggested that in IBS patients, there is a persistent disruption in the interaction of the enteric nervous system and the central nervous system (the so called "brain-gut axis"). This may translate in an increased signalling from the peripheral gut itself, amplification of a normal intestinal signal during its journey through the spinal cord and brainstem, abnormalities in central pain processing, or defects in the descending inhibitory mechanisms modulating pain transmission from the periphery to the brain.[15,16]

PSYCHOLOGICAL MECHANISMS

Psychological mechanisms may affect health status, clinical outcome, and illness behaviour in IBS.[5,17] Psychological stress exacerbates gastrointestinal symptoms[18], affects gastrointestinal motility, even in healthy controls[19], and influences consultation behaviour.[7,18] Adverse life events, such as emotional, sexual, or physical abuse, are major predisposing factors for the development of IBS later in life.[20] Stress-related disturbances with a decreased parasympathetic activity and increased sympathetic activity can often be observed in IBS patients[21] and these are probably caused by a different endocrine regulatory mechanism.[5] Lowered parasympathetic activity can also be responsible for many extra colonic symptoms in IBS patients.[22] Psychological stress can influence the cognitive, motivational, and emotional components that are connected with the processing of noxious stimuli.[23]

Pain, the main symptom of IBS, is influenced by affective-emotional, cognitive, and behavioural components, which means that when a noxious stimulus enters the central nervous system from the periphery, it is modulated by a series of complex cognitive, affective, and motivational processes. This process is influenced by memories of previous sensory events.[15,24] Specific cognitions which are associated with IBS are hyper vigilance, somatisation, and catastrophising.

Hypervigilance can be described as, in the case of IBS, an increased awareness of bowel sensations. Somatisation is seen in approximately 50% of IBS patients and can be described as the abnormal somatic translation of psychological stress. Catastrophising means that IBS patients have abnormal, catastrophic cognitions about functional and social consequences of the symptoms they experience.[25] Psychiatric comorbidity may be present in 20-50% of IBS patients with the most common disorders being depression, anxiety, and hypochondriasis.[5] A study by Koloski *et al.*[9] in a random population showed that those who had higher levels of anxiety at baseline were significantly more likely to develop IBS in the following 12 years, and that subjects who had no heightened level at baseline but were suffering from IBS 12 years later had higher levels of anxiety and depression. This suggests that the relationship between the nervous system and the gut is bi-directional. The associated psychiatric comorbidity may be a characteristic of the disorder itself, but it may also be the reason for the patient to consult a doctor.[26]

TREATMENT

According to most evidence based multidisciplinary guidelines[27,28] adequate management of IBS starts with proper explanation and education. Many patients are poorly informed and have misconceptions about the aetiology and prognosis of IBS.[29] In the next step, lifestyle interventions and dietary advice can be given.[30,31] Many IBS patients do benefit from addition of soluble fibre, but not from insoluble fibre.[30] Recently, low short-chain sugar diet (FODMAP) has been proposed as an effective dietary intervention.[31] In patients with persistent symptoms, pharmacotherapy can be considered. There is a wide spectrum of drugs being used in IBS: analgesics, laxatives, anti-diarrhoeal agents, antispasmodics (among which peppermint oil), anti-depressants, and the antibiotic rifaximin. Evidence for effectiveness of pharmacotherapy is generally poor, however, and the placebo effect is high. Most guidelines advise a restricted use of drugs for IBS.[2,32]

Since 1984[33], there has been an increasing interest in psychological treatment for IBS. A wide range of psychotherapeutic interventions has been studied, including relaxation therapy, biofeedback, cognitive behavioural therapy, short psychodynamic therapy, and hypnotherapy.[4,34] The quality of studies is generally poor, and studies are heterogeneous in design, patient population, control intervention, and outcomes. Systematic reviews concluded that cognitive behavioural therapy, short psychodynamic therapy, and hypnotherapy are probably effective treatments for IBS and can be a useful option for patients with refractory symptoms.[4,32,34]

HYPNOTHERAPY FOR IBS

Since the 1950s, hypnosis is officially recognised as a legitimate medical treatment by the British Medical Association (1955) and the American Medical Association (1958).[35]

The psychological theory most widely used to explain the effect of hypnosis on the brain is the neo-dissociation theory, which states that hypnosis creates a (temporary) separation between different cognitive control structures in the brain. The fact that a hypnotised patient can undergo a painful procedure without experiencing pain is caused by dissociation between the cognitive structures responsible for the perception of pain and the central control structures responsible for conscious awareness.[36] Several studies in population samples have provided evidence that hypnotic analgesia can modulate central nociceptive processes that originate from the anterior cingulate cortex, the area of the brain where the emotional content of pain is processed.[37,38] Pain unpleasantness ratings improved during hypnotic modulation. Two PET brain imaging studies suggest that the effect of hypnosis on pain is brought about by affecting the central modulation of pain.[38,39] Two studies assessing the physiological effect of hypnotherapy in IBS patients both reported a beneficial effect on motility, but symptom improvement was not investigated.[40,41] Research on the effect of hypnotherapy on rectal sensitivity has generated diverging results, varying from improved sensitivity[42-44] to no effect.[45,46] So far only one study has tested the effect of hypnosis on the autonomic nervous system, suggesting a small reduction in sympathetic activity and a stress lowering effect.[45] Hypnosis was demonstrated to have a beneficial effect on a number of psychological features in IBS, such as somatisation and psychological distress[47], anxiety and depression[47], and IBS related disease cognitions.[48]

EVIDENCE FOR EFFECTIVENESS OF HYPNOSIS FOR IBS

Since the first publication of prof. Whorwell in the Lancet in 1984[33], there has been much research on the use of hypnosis as treatment option for IBS. Although many thought hypnotherapy was a promising intervention for patients with IBS, the evidence for effectiveness was considered limited[3] and the quality of the trials often inadequate.[3,28] A more recent study on the efficacy of hypnotherapy from 2012 concluded that gut-directed hypnotherapy in refractory IBS is an effective treatment option with long-lasting effects (follow-up 2-7 years) and that, apart from the clinical benefits, it may reduce healthcare costs.[49] Based on meta-analysis in 2014, Schaefert *et al.*[50] concluded that hypnosis is safe and provides adequate

and sustained symptom relief in 54% of patients with refractory IBS. A systematic review by Ford *et al.*[32] in 2014 concluded that hypnotherapy is effective in IBS, but recommended more research in the future, with randomised controlled trials and larger sample sizes. In addition, many point at the fact that the applicability of hypnosis in daily practice is hampered by the limited number of therapists experienced in treating IBS. Until now, only one study comparing the effectiveness of individual with group application was published.[51] The study is from 1989 and involved only 33 patients. The results indicated there was no significant difference in effectiveness between the two groups.

OBJECTIVES AND OUTLINE OF THIS THESIS

Hypnotherapy is a promising psychological intervention for IBS patients, but high-quality studies in large population samples from both primary and secondary care are needed to confirm its effectiveness. In addition, the optimal way of delivery of hypnotherapy needs to be assessed. Group therapy could be an alternative to individual sessions, once the non-inferiority is demonstrated. A major advantage of group sessions is that, given the low number of therapists with experience in IBS, it would make hypnotherapy more widely accessible for IBS patients, and save intervention related costs.

Therefore the aim of this thesis is twofold:
1. To assess the effectiveness of hypnotherapy compared to a control intervention in patients with IBS from primary and secondary care.
2. To compare the effectiveness of group versus individual delivery of hypnotherapy.

In **chapter 2** we report on the design of the randomised control trial (RCT) and describe the specific methodological challenges commonly encountered in studies on functional gastrointestinal diseases, such as selection of the study population, diagnostic inclusion criteria, a valid control intervention, the placebo effect, and outcome assessment. A good control intervention needs to have all components of the experimental intervention with the exception of the active treatment component under study, i.e., hypnotherapy should be missing but all other components are retained: time, attention, active intervention, and contact with a therapist. In this chapter we explain why we chose for an educational program as the control intervention in our RCT.

To make the content of this educational program match with the needs of IBS patients, we performed a systematic review on the knowledge and conceptions of IBS patients about their disorder. In **chapter 3**, the results of this systematic review are described. We used these to design our educational program.

In **chapter 4** we describe the results of a study on the medical costs generated by IBS patients in primary and secondary care. Obtaining detailed insight in the healthcare costs of a specific illness is important because of the possibility to determine the economic burden of the disease for the community. Furthermore, it enables estimates on the cost-effectiveness of existing and of new treatments, and could thus facilitate choices in treatment policy.[53] In the present study, the aim was to compare the costs and magnitude of healthcare consumption for patients diagnosed with IBS in primary and secondary care, compare these costs with the average health care expenditure for patients without IBS, and describe these costs in further detail.

The placebo response increases as the result of a positive relationship of the patient with the therapist, an increased number of office visits, and duration of the treatment. Thus, a high placebo response may arise from the therapeutic contact and can be used as an additional beneficial factor in psychological therapeutic interventions. In **chapter 5** we describe the results of a systematic review on the placebo effect of psychological interventions in the treatment of IBS. We presumed that the placebo response would be larger in trials on psychological interventions than in drug trials and trials on dietary fibre and herbal medicine.

To position hypnotherapy in the context of other possible psychological therapies for IBS, we performed a systematic review on psychological treatments other than hypnosis. The results of this review and the recommendations are described in **chapter 6**.

In **chapter 7** we describe the results of our RCT on the effectiveness of hypnotherapy in a large sample of IBS patients, including follow-up data gathered nine months after treatment. Our pre-set hypotheses were (1) that hypnotherapy would be more effective than an educational supportive therapy and (2) that hypnotherapy delivered in a group would be as effective as individual hypnotherapy.

Finally, in **chapter 8**, we discuss the implications of our findings for clinical practice and future studies.

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Chapter 2

A Randomised Controlled Trial on hypnotherapy for Irritable Bowel Syndrome: design and methodological challenges (the IMAGINE study)

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ABSTRACT

Background: Irritable Bowel Syndrome (IBS) is a common gastrointestinal disorder in primary and secondary care, characterised by abdominal pain, discomfort, altered bowel habits, and/or symptoms of bloating and distension. In general the efficacy of drug therapies is poor. Hypnotherapy as well as Cognitive Behaviour Therapy and short Psychodynamic Therapy appear to be useful options for patients with refractory IBS in secondary care and are cost-effective, but the evidence is still limited. The IMAGINE study is therefore designed to assess the overall benefit of hypnotherapy in IBS as well as comparing the efficacy of individual versus group hypnotherapy in treating this condition.

Methods/Design: The design is a randomised placebo-controlled trial. The study group consists of 354 primary care and secondary care patients (aged 18-65) with IBS (Rome III criteria). Patients will be randomly allocated to either six sessions of individual hypnotherapy, six sessions of group hypnotherapy, or six sessions of educational supportive therapy in a group (placebo), with a follow-up of nine months post treatment for all patients. Ten hospitals and four primary care psychological practices in different parts of the Netherlands will collaborate in this study. The primary efficacy parameter is the responder rate for adequate relief of IBS symptoms. Secondary efficacy parameters are changes in the IBS symptom severity, quality of life, cognitions, psychological complaints, self-efficacy, as well as direct and indirect costs of the condition. Hypnotherapy is expected to be more effective than the control therapy, and group hypnotherapy is expected not to be inferior to individual hypnotherapy.

Discussion: If hypnotherapy is effective and if there is no difference in efficacy between individual and group hypnotherapy, this group form of treatment could be offered to more IBS patients, at lower costs.

Trial registration number: ISRCTN: ISRCTN22888906.

BACKGROUND

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder, characterised by recurrent episodes of abdominal pain, discomfort, altered bowel habits, and/or symptoms of bloating and distension, not explained by structural or biochemical abnormalities.[1] The estimated prevalence is 14-24% for women and 5-19% for men.[2] The consultation rate is relatively low: only 20-25% of IBS patients seek medical advice[3] but because the prevalence is so high this still represents a substantial number of patients. The reported incidence of IBS in primary care is 4-13/1000 patients a year.[4] General practitioners see on average 1-2 new IBS patients a week. In the Netherlands, about 10% of the patients seen by a general practitioner are referred to a medical specialist, e.g., gastroenterologists[5], in the United Kingdom 44%.[1] The estimated number of patients who are diagnosed with IBS after referral to the gastroenterologists, varies from 20-70%.[6] Patients with IBS can have severe and often incapacitating complaints, resulting in as much annual absence from work as, for instance, from the flu.[7] The diagnosis can only be considered if there are no other indications of organic pathology and there are now consensus based criteria, the most recent of which are the so called Rome III criteria.[8]

Irritable Bowel Syndrome

Diagnostic criterion*

Recurrent abdominal pain or discomfort** at least three days/month in the last three 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 three months with symptom onset at least six months prior to diagnosis.*

*** Discomfort means an uncomfortable sensation not described as pain.*

In pathophysiology research and clinical trials, a pain/discomfort frequency of at least two days a week during screening evaluation is recommended for subject eligibility

Three types of IBS can be distinguished: IBS with either predominant constipation, predominant diarrhoea, or alternating periods of diarrhoea and constipation. Several pathophysiological mechanisms underlying IBS have been proposed, including a disturbance in intestinal motility and enhanced visceral sensitivity

which, according to the bio-psycho-social model of IBS, interact with other factors such as environmental influences, parent-child interactions, and disturbed stress responses to result in symptoms.[9]

Effective therapy of IBS is lacking. A recent review on pharmacological treatment for IBS concluded that in general the efficacy of drug therapies is poor.[10] Bulking agents, antispasmodics, and antidepressants can be tried but the response is often suboptimal.

Since 1984[11], there has been an increasing research interest on the effectiveness of psychological treatment for IBS. A wide range of psychotherapeutic interventions have been studied including relaxation therapy, biofeedback, cognitive behavioural therapy (CBT), short psychodynamic therapy, and hypnotherapy. Two Cochrane reviews on the efficacy of hypnotherapy[2] and other psychological therapies[12] support effectiveness. In England, the NICE guideline (2008) on IBS was published, with a special section on the psychological interventions which concluded that "CBT as well as short Psychodynamic and Hypnotherapy can be a useful option for patients with refractory IBS".[13] Hypnosis is officially recognised as a legitimate medical treatment by the British Medical Association (1955) and the American Medical Association (1958). There has been much research on the use of hypnosis in the treatment of (chronic) pain[14] and, as pain is the main symptom of IBS, it is understandable that therapists have applied hypnosis in treatment of IBS patients. Pooled results of research about the effectiveness of hypnotherapy for IBS patients are described in three reviews/ meta-analysis. The NICE guideline concludes that hypnotherapy may be considered a promising intervention for IBS, but judges the evidence as still too limited.[13] Further investigation is recommended, with special interest in the potential of this intervention as a primary care therapy option with long-term follow-up. The Cochrane review on hypnotherapy for treatment of IBS concludes that "The quality of the included trials was inadequate to allow any conclusion about the efficacy of hypnotherapy for irritable bowel syndrome." And, "More research with high-quality trials is needed".[2]

In a more recent meta-analysis, Ford *et al.* conclude that hypnotherapy leads to less persistence of complaints than usual care or control therapy.[15]

On the basis of these publications one can conclude that hypnotherapy is a promising and possibly cost-effective intervention for IBS in secondary care. Further investigation with high-quality trials and long-term follow-up is needed, especially with regard to its efficacy in a primary care setting.

To improve cost-effectiveness, group application of hypnotherapy could be considered. So far, there has only been one study on a group application, indicating no significant difference in effectiveness in a population of only 33 patients.[16]

We have designed a randomised controlled trial (RCT), comparing the effectiveness and costs of individual and group hypnotherapy with a control intervention in patients with IBS. In this paper, we describe the aim, design, and methodological challenges of the study protocol.

METHODS/DESIGN

Aims

The primary objectives of this study are twofold. The first aim is to assess the efficacy of hypnotherapy in IBS treatment. The second aim is to compare the efficacy of group hypnotherapy with individual hypnotherapy in IBS treatment. Secondary objectives are to assess the effect of individual or group hypnotherapy on symptom severity, quality of life, dysfunctional cognitions, psychological complaints, self-efficacy, and IBS related costs.

Design

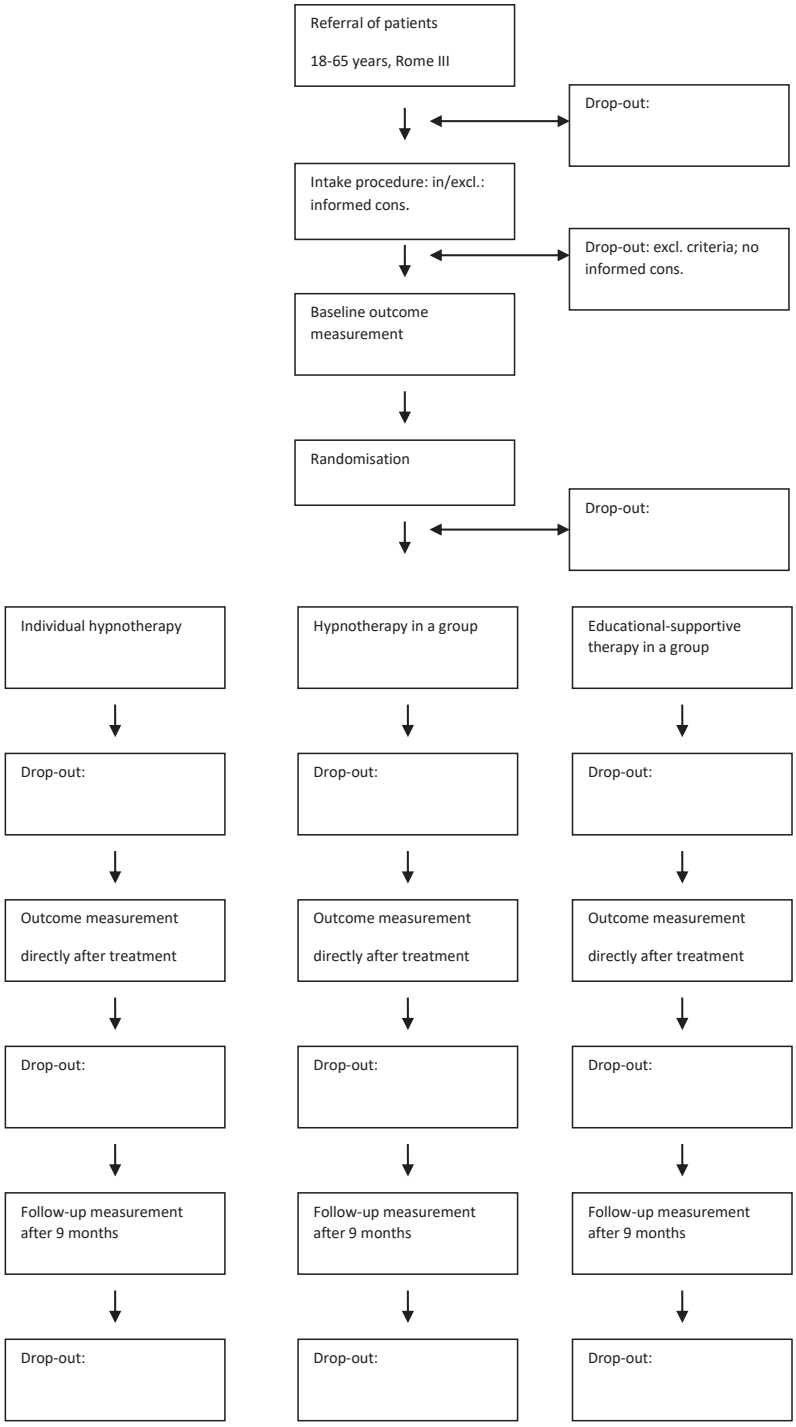
The study is designed as a comparative and a non-inferiority 12-weeks single blind controlled parallel-group trial. The trial will involve IBS patients in primary and secondary care, who will be randomly allocated to either six sessions of individual hypnotherapy, six sessions of hypnotherapy in group format, or six sessions of educational supportive therapy in a group format (control condition) (flowchart Figure 1). Starting May 2011, the inclusion of patients will take approximately two years, with a follow-up of nine months.

Ethical considerations

The study is conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO). The study protocol has been approved by the Medical Ethics Committee of the University Medical Centre of Utrecht, the Netherlands.

Patient data will be coded and analysis and publication of the results will be anonymous.

Figure 1. Design of the RCT



Hypotheses

The primary hypotheses assessed in this study are:

1. At the end of therapy, more patients in the hypnotherapy condition will report adequate relief than in the educational supportive therapy condition (control treatment).
2. Hypnotherapy offered in a group format is as effective as individual hypnotherapy.

Study population

The study population consists of patients with IBS referred by a general practitioner or medical specialist. Ten general hospitals and four psychological practices in primary care collaborate in the study.

Inclusion criteria

- Age 18-65 years.
- Diagnosis of IBS according to the Rome III criteria. The Dutch translated version of the IBS Module of the Rome Foundation is used to check criteria.[8]

Exclusion criteria

- Inability to understand the content of the sessions, because of insufficient command of the Dutch language.
- Inability to fill out the questionnaires.
- Inability (for example: too aggressive) or unwillingness to function in a group.
- A psychiatric condition that requires attention first (for example: severe depression, PTSS, or psychosis).
- A combination of IBS and other chronic bowel diseases, as far as they are already diagnosed, such as ulcerative colitis, Crohn's disease, or coeliac disease.
- Major surgery to the lower gastrointestinal tract, such as partial or total colectomy, small bowel resection, or partial or total gastrectomy.
- Past or present radiotherapy to the abdomen (for example: carcinoma of the cervix).

Procedure

Cooperating general practitioners and specialists are asked to give each eligible patient an invitational letter explaining the goal of the study and describing the interventions. The patient fills in the IBS questionnaire to confirm the diagnosis. If the patient is interested in participating in the trial, the general practitioner or specialist hands the patient study information with the Informed Consent letter and a brochure from the government explaining the law and the rights of

patients participating in medical research. After confirmation of the intention to participate, the patient is referred to the collaborating psychologist, either in the hospital or in primary care practice. The psychologist checks the in- and exclusion criteria and explains the study. If the patient is willing to participate, he/she signs the Informed Consent letter, completes the questionnaires, and sends them, together with the IBS-criteria checklist in a reply-envelope to the investigator. After randomisation the patient is invited to the therapy he/she is randomised to.

Randomisation

After inclusion, patients are randomly allocated to one of the three treatment conditions by means of a computer-based, six-block random number tables procedure. Because for group treatment six patients are required, the randomisation is done block-wise to prevent prolonged waiting time for the individual patient. The researcher performs randomisation.

Intervention

Patients will be randomised to one of the three treatment arms.

1. Individual hypnotherapy is delivered in a series of six individual, bi-weekly 45-minute sessions in which patients receive a structured hypnotherapy treatment. The treatment procedure is developed by the investigator (CF) based on the hypnotherapy protocol for IBS from the research group of Whorwell in Manchester, the United Kingdom.[17] Basically, hypnotic suggestions are given to normalise motility of the gut and reduce pain and feelings of discomfort. The precise wording is adjusted to the individual patient. Treatment is given by qualified psychologists educated as hypnotherapists and specifically trained for the intervention.
2. Group hypnotherapy is delivered in a series of six bi-weekly 60-minute group sessions, with a maximum of six IBS patients per group. The group hypnotherapy is based on the same principle as the individual hypnotherapy but is adapted for the group format. Group hypnotherapy will be given by the same psychologists who deliver the individual therapy.
   Both individual and group hypnotherapy patients are given homework assignments consisting of CD-recorded hypnotherapeutic exercises. Carrying out these exercises takes 15-20 minutes, at least once daily.
3. Educational supportive therapy is delivered in a series of six bi-weekly 60-minute group sessions, with a maximum of six patients per group. In the sessions topics are discussed that are of importance to IBS patients, as determined by research.[18-22] The topics include: information about IBS, the role of food and

life regulation, and dealing with stress in managing IBS. Homework assignments are given that take about 15-20 minutes per day.

Educational supportive therapy will be performed by nurse practitioners or psychological assistants who are specifically trained for the intervention.

Treatments are carried out according to a detailed therapy protocol in which all sessions are described (verbatim). Therapists receive this verbatim protocol, the CD with the hypnotherapeutic exercises, and homework assignments.

All therapists are trained in the protocol they carry out and subsequent treatment is supervised by the principal researcher.

To prevent contamination of groups, therapists giving hypnotherapy will not give educational supportive therapy and vice versa.

Other treatments during the study

Patients may continue usual care as instructed by their physicians but are asked not to change it during the research, except on doctor's advice. They are free to seek other treatment. This will be recorded in their questionnaire.

Study parameters/endpoints

As yet, it is not known what makes hypnotherapy an effective treatment. We assume that hypnotherapy has a direct influence on visceral hypersensitivity (pain processing and pain perception) and an indirect influence on pain perception through relaxation and changing cognitions.[14] Furthermore, gut motor activity (motility) can be influenced by hypnotherapy.[14] Finally, hypnotherapy can have an effect on psychological factors such as self-efficacy and feelings of depression that can play a role in IBS. Our choice for outcome measures has been influenced by these assumptions.

Main study parameter/endpoint

In line with previous conclusions on optimal outcome assessment in trials on functional gastrointestinal disease[23,24], we chose the number of weeks with adequate symptom relief as the primary outcome. This measure addresses weekly symptom improvement in IBS with treatment using a single question ("Did you have adequate relief of IBS related abdominal pain or discomfort in the past week?") scored on a dichotomous scale (Yes/No). This instrument is a well validated simple outcome assessment for IBS treatment[25] with a positive responder being defined as someone with more than two weeks adequate relief per month which has determined to indicate a clinically significant improvement.[26]

The first primary outcome is the difference in the percentage of positive responders between group hypnotherapy and group educational therapy. Group

hypnotherapy is expected to be substantially more effective than educational therapy.

The second primary outcome is the difference in percentage of positive responders between group hypnotherapy and individual hypnotherapy. Group hypnotherapy is expected not to be inferior to individual hypnotherapy.

Secondary study parameters/endpoints

Irritable Bowel Syndrome Symptom Severity

IBS symptoms will be monitored using the IBS-symptom severity score (IBS-SSS).

The IBS-SSS assesses five features of IBS (pain severity, pain frequency, abdominal distension, bowel satisfaction, interference with life in general) and their intensity, using visual analogue scales.[27] The IBS-SSS has been validated and its use is recommended in an overview on outcome measures.[25]

Irritable Bowel Syndrome Quality of Life

Disease-specific quality of life will be assessed using the Irritable Bowel Syndrome Quality of Life scale (IBS-QOL).[28] It has been validated in different populations. This instrument includes 30 items and consists of nine scales (dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexuality, relationships, and overall scale).

Other measurements

Psychological symptoms

Psychological symptoms are assessed with the Dutch version of the Symptom Checklist (SCL-90). It was originally published by Derogatis[29] and translated and validated for the Dutch population by Arrindell & Ettema.[30] The SCL-90 is a 90-item multidimensional self-report inventory, designed to evaluate a broad range of psychological problems and symptoms of psychopathology. It has nine subscales: Agoraphobia, Anxiety, Depression, Somatisation, Insufficiency of thought and action, Distrust and Interpersonal Sensitivity, Hostility, Sleeping problems, and Psychoneuroticism (total score).

The SCL-90 is an internationally accepted, widely used questionnaire with good psychometric qualities.[29]

Dysfunctional cognitions

The Cognitive Scale for Functional Bowel Disorders (CS-FBD) has been developed by Toner[32] and translated with permission from the author by Y. van Rood. The CS-FBD consists of 31 items to measure a patient's level of dysfunctional cognitions concerning his or her IBS. It is a valid and reliable scale that can be used as an outcome measure in evaluating the efficacy of psychotherapeutic interventions for functional bowel disorders.[31]

Self-efficacy

The Self-Efficacy Scale (SES) is a seven-item questionnaire to measure the confidence of patients about their capacity to influence their somatic complaints. It was originally developed for patients suffering from chronic fatigue[32] and adapted with permission of the author by C. Flik and Y. van Rood for patients with IBS.

Costs

The Trimbos/iMTA Questionnaire (TiC-P) for costs associated with psychiatric illness measures direct medical costs due to healthcare utilisation during the past four weeks and indirect non-medical costs due to productivity loss during the past two weeks.[33] It can be adapted for other conditions as well and for this study was adapted for IBS.

Timeline and follow-up

Enrolment started May 2011. The inclusion of patients will take approximately two years. After the active treatment period of 12 weeks, all patients will be followed for an additional period of nine months to assess the sustainability of the effects of the interventions. The primary outcome will be measured weekly during the first four weeks after finishing treatment and again weekly during four weeks nine months post treatment. The secondary endpoints will be assessed prior to intervention, immediately after the intervention, and at nine months after finishing the intervention (see Table 1).

Table 1. Overview of assessments

	Weeks					
Visit (time point)	0 (start of treatment)	12 (end of treatment)	12+4 (every four weeks after treatment)	12+ (every week after treatment)	52 (nine months after treatment)	52+4 (four weeks after nine months)
Assessments						
IBS-Mode	X				X	
Informed consent	X					
Inclusion exclusion criteria	X					
Demographic data	X					
Status report	X					
Adequate relief			X			X
IBS-SSS	X	X			X	
IBS-QOL	X	X			X	
SCL-90	X	X			X	
CS-FBD	X	X			X	
SES	X	X			X	
TiC-P	X	X			X	
CD-diary		X		X		

Other study parameters

Patients are given a "CD use" diary in which they can record the number of times they used the CD or did the hypnotherapeutic exercises in the last week. The homework assignments in the educational supportive therapy are not registered separately.

Sample Size Calculation

Assuming an individual hypnotherapy response rate of 57%[2], a maximum acceptable level of difference of 15% between individual and group hypnotherapy, an alpha of 0.05, and power (1-beta) of 0.80, 135 patients are required in both arms of the non-inferiority trial to show that group hypnotherapy is not inferior to individual hypnotherapy.

Spiller[34], in an overview of 25 randomised controlled trials, states that when the placebo response is plotted against the length of study, placebo response will be maximum of 75% at around 6-8 weeks, falling to 25% at 24 weeks and zero at 12 months. Our follow-up period will be nine months. To test whether group hypnotherapy is more effective than group placebo therapy, we will have more than sufficient power assuming a placebo response rate of 25% and a group

hypnotherapy response rate of 57% using the proposed 135 patients in both arms.[13] Powering the study for only the comparison between hypnotherapy and the control intervention would require only 44 patients in both arms assuming an alpha of 0.05, a power (1-beta) of 0.80, a cluster size of six patients per therapist, and an intra-class correlation coefficient of 0.05. Assuming at least 10% of loss to follow-up, 354 patients need to be included in the study (150+150+54 (placebo-arm)).

Recruitment

The 354 patients are recruited in primary and secondary care.

Primary care: Assuming an estimated mean incidence of IBS in primary care in eight of every 1000 patients, 20 newly diagnosed patients per practice per year, and an expected inclusion rate of 25%, 30 general practitioners, each referring five patients each year, will be able to refer the total required number of patients (354) in 2.5 years.

Secondary care: The estimation of the number of consultations for IBS in gastroenterology practice varies between 20-70% of all referrals per year. Using a conservative estimate, about 25% of all referrals will be because of IBS. Thus, in a normal gastroenterologist's practice of a general hospital, with 500 new patients for each gastroenterologist each year, there will be 125 new IBS patients each year. Assuming that 10% of the patients will be interested in taking part in the trial, each gastroenterologist can refer 12 patients a year. Therefore ten hospitals with at least two referring specialists to cooperate in this study for 1.5 years (354 patients) are needed.

Ten hospitals and four primary care psychological practices (working with several referring general practitioners), in different parts of the Netherlands, have agreed to collaborate in the trial. This ensures that the study population will be representative of the whole Dutch population.

When combining the expected referral rates from the primary and secondary care practices, two years of recruitment will be sufficient to attain the required number (354) of participants.

Statistical analysis

General remarks

All statistical analyses will be based on the intention to treat principle, i.e., patients will be analysed according to their initial assignment to one of the randomisation arms.

Uni- & bivariate analysis

The percentage of patients with a positive response will be calculated post-treatment and at nine months after treatment and differences between the three randomisation arms will be tested with the chi-square test.

In addition, the adequate relief scores and secondary outcomes (IBS-SSS, IBS-QOL, SCL-90, CS-FBD, SES and TiC-P scores) will be estimated by time point of assessment and arm of randomisation using a statistical model for repeated measurements (preferably a random effects model). To assess the difference between the arms of randomisation by time point of assessment, terms for interaction of {arm x time point} will be included in the statistical model.

Multivariate analysis

Subgroup analyses

The analyses described above will also be performed separately for patients who fulfil the Rome III IBS diagnostic criteria for constipation-predominant, diarrhoea-predominant, and mixed-type IBS. In a study of Gonsakorale *et al.*[35] one of the conclusions was that hypnotherapy was less useful for males with diarrhoea. If males with diarrhoea-predominant bowel habit are overrepresented in one of the conditions, adjustment in multivariate regression analysis is indicated.

Analyses will be performed separately for those referred from primary and secondary healthcare. In secondary care, IBS patients have a longer disease history, more psychosocial comorbidity, and higher stress and depression scores. It is possible that these differences may influence the effect of the intervention.

Adjustment for confounders

In the case of (unexpected) differences in relevant baseline characteristics between the three comparison groups, adjustment for the possible confounding effect of these differences will be performed in multivariate regression analyses.

Benefit/Risk for patients

Benefit: Research indicates that hypnotherapy is a promising intervention for IBS which could potentially be of considerable benefit to the patients participating in the study. Research also indicates that patients want to be informed more about IBS. Patients randomised to the placebo condition receive this information and thus can also benefit from participating in the study.

Risk: In all the research that has been evaluated by the Cochrane study, no adverse effects for patients have been reported. This treatment is symptom-oriented

with care taken to exclude those individuals with contra-indications and treatment is always carried out by experienced therapists educated in hypnotherapy.

Discussion; Methodological challenges

In planning this study, a number of challenges commonly encountered in studies on functional gastrointestinal diseases needed to be overcome: selection of the study population, diagnostic inclusion criteria, a valid control intervention, placebo effect, and outcome assessment.

Selection of the study population

Lack of heterogeneity among IBS patients can affect the generalisability of trial results.[36] To overcome this problem, patients will be recruited from primary and secondary care populations. The NICE guideline (2008) recommends the inclusion of patients from primary care to enhance the generalisability of the results. Cooperating hospitals and primary care practices are situated all over the Netherlands, so the population participating in the study will be representative of the whole Dutch population.

Although attention to the study was drawn by announcements to both physicians in primary and secondary care and patients by the Dutch IBS Patient Foundation website, there will always be a selection bias, because only patients who are motivated are included in this study. It cannot be ruled out that they differ in some respects from those who do not want to participate on the effect of hypnotherapy.

Diagnostic inclusion criteria

The selection of the diagnostic inclusion criteria were a second challenge in the study. A taskforce of the American Journal of Gastroenterology[37] conducted a systematic review on the accuracy of symptom-based criteria in the diagnosis of IBS. They summarise the diagnostic criteria that have been used over the years which are those reported by: Manning (1978), Kruis (1984), Rome I (1990), Rome II (1999), and Rome III (2006). The main differences are in the number of symptoms included as well as their duration, which is important as they should be been present for a considerable period of time before the diagnosis is considered.

The accuracy of the Rome II and Rome III criteria has not been formally evaluated yet and the ACG task force chose their own pragmatic definition: "abdominal pain or discomfort that occurs in association with altered bowel habits over a period of at least three months".

Because of the problem of the absence of a specific diagnostic test for IBS, the Rome committee developed the IBS module, a short questionnaire (ten questions)

with a scoring device. It is applicable in primary and secondary care and takes only a few minutes for patients to complete. For standardisation and to facilitate comparison of research populations in the future, in this RCT the questionnaire was chosen to confirm the diagnosis of IBS.

The Rome committee has started a translation project to make it possible for this questionnaire to be used worldwide. Following official translation guidelines[38] and with the official consent of the Rome III committee, the module has been translated into Dutch and will be of use to every specialist in the field of IBS in the Netherlands.

Optimal control intervention

To design a good control intervention is notoriously difficult in research on the effectiveness of psychological treatments.[39] "Care as usual" is not a good control-option since it does not exclude the possibility that treatment effect is due to differences in therapist attention rather than to the intervention.[23] A good placebo condition needs to have all components of the experimental intervention, except the active component. This is very difficult to realise with psychotherapeutic interventions. A "sham" intervention with the same time investment for patient and therapist but with a nontherapeutic intervention potentially generates a negative effect. Consequently, an intervention was designed in which hypnotherapy was missing but all other components were retained: time, attention, active intervention, and contact with therapist. The intervention, an informative educational programme, covers topics IBS patients like to have more knowledge about.[18-22] The informative educational programme will be given by nurse practitioners or welfare workers and not by hypnotherapists because it is anticipated that hypnotherapists will automatically use the suggestive language they use in the hypnotherapy. To emphasise the supportive and educational character of this control-intervention, the deliberate use of nurse practitioners or welfare workers was felt to be the most appropriate to deliver this intervention. Furthermore, the effects of the doctor-patient relationship will be controlled for by using multiple experienced therapists.[39]

Placebo effect

The placebo response causes serious problems for the design of RCTs in IBS. Spiller (1999) describes on the basis of 25 RCTs on medication and fibre from 1976-1998 a median placebo response of 47%.[34] Ford & Moayyedi (2010) estimated a response rate of 37.5% across all RCTs on pharmacological therapies in adult IBS patients.[40] Spiller claims that the placebo response diminishes after

approximately 12 weeks and was lost altogether by six months. Recommendations to diminish the effect of placebo response on outcomes of RCTs are:

- lengths of the therapy should be more than eight weeks and follow-up for more than six months; diagnosis should be based on the Rome criteria and not on clinical judgement;
- patient-reported endpoints are better than physician-reported outcomes; it is important to be able to distinguish between subgroups of IBS-C, IBS-D, and IBS-M.

In the design of this RCT these recommendations were met in terms of: the length of therapy is three months, follow-up will be nine months after ending the therapy, and we chose for the Rome III IBS module to diagnose the cases and distinguish the subgroups.

Outcome assessment

As no objective standards for diagnosing functional gastrointestinal diseases exist, outcome assessments have to be based on subjective criteria. According to Irvine[23], the "adequate relief" questionnaire[25] is the current standard primary outcome measurement in treatment trials of Functional Gastrointestinal Disorders. For a more detailed IBS symptom assessment the IBS-Severity Scoring System[27] is recommended.[24] Furthermore, IBS related Quality of Life is an important secondary outcome measure.[23] At present, the IBS Quality of Life measurement[28] is the best choice "because it has been the most extensively validated and shows appropriate psychometric quality".[24] Mangel (outcome measure: "adequate relief"[25]) and Whorwell (IBS-SSS[27]) gave their consent for translating these questionnaires into Dutch.

IBS complaints can have an episodic course and in accordance with the recommendation on measuring severity during episodic symptoms by the research design of the Rome committee[23], patients will fill in the assessments on two occasions: immediately at the end of treatment and after nine months. Also the "adequate relief" question is asked every week, for a period of four weeks.

It is possible that the patients in the control group with educational supportive therapy also will experience some improvement in their complaints, but the expectation is that treatment with hypnotherapy will be superior.

Conclusion

The results of this primary and secondary care based randomised placebo-controlled trial, evaluating the efficacy of individual and group hypnotherapy treatment in IBS, will contribute to the scientific basis of IBS management. The

trial intends to include the greatest population of patients of all the trials in psychological treatments for IBS to date.[2,12]

If the results of the study show that (group) hypnotherapy for IBS is effective, implementation into clinical practice will be the next aim.

The authors declare that they have no competing interests.

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Chapter 3

Systematic review: knowledge and educational needs of patients with Irritable Bowel Syndrome

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ABSTRACT

Background: Educational programs have been used as a control condition in trials on psychological therapies for irritable bowel syndrome (IBS). An optimal control condition should have all logistic features of the experimental intervention, except the active component, but also have basic therapeutic benefit for the patient.

Aim: To systematically determine patients' educational needs on the basis of the (mis)conceptions that they have of their disease and their reported desire for information to optimise the control intervention in IBS research.

Methods: A systematic review of studies on the knowledge and educational needs of IBS patients in terms of their condition was performed. Studies published as full-text in the English language in peer-reviewed journals and that included adult IBS patients diagnosed according to the Manning or Rome I, II, or III criteria were selected.

Results: Eight studies involving 2132 patients were included. When focusing on misconceptions of patients, the most prevalent are that (i) IBS is caused by dietary factors, food allergies and food intolerance (37-90%), heredity (52%), or a lack of digestive enzymes (52%), (ii) IBS is a form of colitis (43%), (iii) IBS will last a lifetime (31-54%), (iv) IBS will develop into cancer (15-49%), or (v) IBS worsens with age (48%). Patients are "unhappy" with their level of knowledge or feel poorly informed (65%). They want information about the diagnostic process, which foods to avoid (63%), causes (62%), coping strategies (59%), new medications (55%), course (52%), and the role of psychological factors (51%).

Conclusions: IBS patients have a large variety of educational needs. Educational programs optimally addressing these needs can be used adequately as a placebo control condition in research on psychological interventions.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterised by recurrent periods of abdominal pain, discomfort, altered bowel habits, and/or symptoms of bloating and distension that are not explained by structural or biochemical abnormalities.[1] The diagnosis can only be considered if there are no other indications for organic pathology and is made based on consensus-based criteria, known as the Rome III criteria.[2] The estimated prevalence is 14-24% for women and 5-19% for men.[3] IBS is one of the functional somatic syndromes. Functional somatic syndromes are characterised by patterns of persistent bodily complaints for which adequate examination does not reveal sufficiently explanatory structural or other specified pathology.[4]

Psychological treatments for IBS have been shown to be effective compared with waiting list or care as usual.[2,5] However, to establish specific therapeutic effectiveness, psychological treatment should be compared with a placebo. Designing a good placebo control condition for psychological interventions in IBS is notoriously difficult.[6] Adequate control conditions need to have all logistic features of the experimental intervention, except the active therapeutic component. In the optimal control condition, the therapeutic intervention is missing, but all nonspecific components have to be retained: amount of time and attention and number of contacts with the therapist. Furthermore, the control intervention must be attractive for patients by having at least some therapeutic benefit. Therefore, an intervention that is part of normal clinical practice can be used as placebo intervention. Providing basic information about IBS is one of the fundamental parts of normal clinical practice; thus, educational programs do fulfil the criteria for a good placebo intervention if the programs offer information that satisfies the educational needs and desires of patients.

We performed a systematic review to identify what (mis)conceptions patients have about IBS, and what their informational needs are about the disease.

METHODS

Design

Systematic review.

Eligibility criteria

Studies on empirical research on the knowledge and educational needs of IBS patients in terms of their disease were included. The studies had to be published

as full-text in the English language in peer-reviewed journals. The patients in the study had to be 18 years or older and be diagnosed with IBS according to the Manning or Rome I, II, or III criteria and there were no restrictions on the setting in which the patients were recruited, whether primary, secondary, or tertiary care. Also there were no restrictions on the study design. Explorative studies, observational prospective surveys using questionnaires, focus groups, and interviews were all accepted.

Search

An extensive literature search was performed for research until 21-5-2014 using five databases: Medline, Cochrane, Embase, PsycINFO, and CINAHL. The search used both text words and subject headings (where applicable). The following free-text search terms were used to search for the IBS concept in all databases: irritable bowel syndrome, IBS, irritable colon, and spastic colon. The following terms were used to search the knowledge/conceptions concept: perception*, knowledge*, cognition, information*, attitude*, participation, question*, conception*, misconception*, education, expectation*, understand*, view*, and satisfaction in combination with patient*.

The subject headings used to search the databases, information on the search interfaces and the exact searches for each database are presented in the supplementary document available from the corresponding author.

Study selection

Two authors (CF and YvR) independently reviewed the selected papers for suitability for inclusion. If no agreement could be reached, the third author (NdW) made a decision.

Data extraction

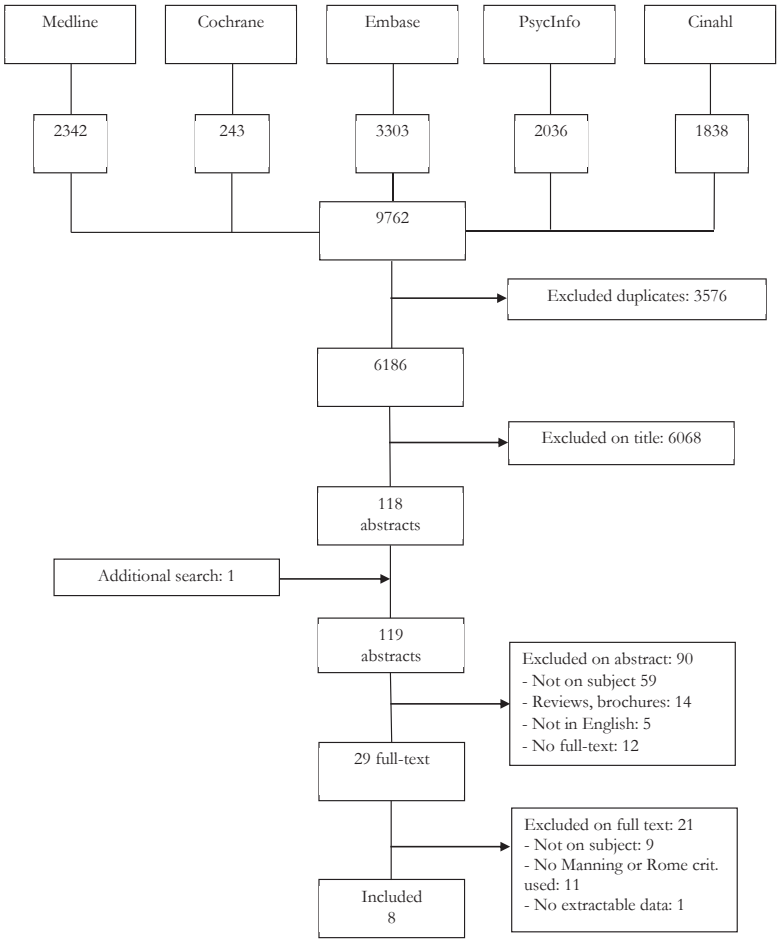
The following data were extracted: the name of the first author, the year of publication, the country in which the study was carried out, the setting in which the patients were found, the sample size, sex, age, illness duration, the criteria for IBS diagnosis, the study method used, and the topics of research. The results of the studies were summarised into two topics: conceptions about IBS and reported desire for information.

RESULTS

Study selection

The literature search identified 6186 unduplicated studies. After screening the titles, 118 studies were potentially eligible (see flowchart Figure 1). After reviewing the abstracts, 90 more studies were discarded because they did not meet the inclusion criteria (see Figure 1 for the reasons). Review of the reference sections of the remaining 28 articles resulted in one additional article. From the 29 articles that were reviewed in full-text, 21 articles were also discarded for not fulfilling the inclusion criteria (see flowchart). Finally, eight studies fulfilled the inclusion criteria and were included in this review: Bijkerk *et al.*[7], Casiday *et al.*[8], Halpert *et al.*[9], Hayes *et al.*[10], Lacy *et al.*[11], Lacy *et al.*[12], O'Sullivan *et al.*[13], and Riedl *et al.*[14]

Figure 1. Flowchart



Characteristics of the studies included

General characteristics of studies

All of the studies were published between 2000 and 2014. Three were carried out in the United States[9,11,12], two in the Netherlands[7,8] of which one was also carried out in the United Kingdom[8], one in Germany[14], and two in Ireland[10,13]. The patients were treated in primary, secondary, and tertiary settings (Table 1).

Method of data collection

One study used qualitative semi-structured interviews[8] and one study used open-ended questions[13]. All other studies used structured questionnaires for the collection of their data.

Patient characteristics

The included studies involved 2132 patients. The mean age of the patients was between 39.3 and 53.7 years (standard deviations ranging from 11-17.4). The majority of the patients were women (range: 65.9-91.1%) and the mean duration of IBS symptoms reported ranged from 4.5-14.2 years. All studies, except that of Bijkerk *et al.*[7], used the Rome I, II, or III criteria to confirm the diagnosis.

Synthesis of results

Conceptions

In the qualitative study of Casiday and colleagues patients considered diet and stress as the principal causes of IBS and were afraid of the long term effects of IBS (such as developing cancer) (Table 2). Table 2 presents an overview of the outcomes of the structured questionnaires for the most important conceptions of patients about their IBS. The most important conceptions about aetiology are that food allergies and food intolerance are the main causes of IBS, followed by psychological factors (anxiety, depression, and stress), heredity, and lack of digestive enzymes. In terms of conceptions of the state of IBS, more than 40% believed that it is a form of colitis, whereas the most important ideas about the prognosis are that IBS will never go away and worsens with time and that it will develop into cancer, colitis, or inflammatory bowel disease and also that it will lead to malnutrition, that surgery will be needed in the future, and that it will shorten one's life.

Reported desire for information

Patients in the qualitative study of Casiday and colleagues indicated they did not understand the diagnostic process; in the study of O'Sullivan and colleagues, patients indicated that they have many unanswered questions about their disease (77%), were "very unhappy" with their level of disease knowledge (38%), and considered themselves as poorly informed (27%).

From the quantitative studies, Halpert and colleagues explicitly asked the patients about the information that they most desired. The main topics that most patients want information about are which foods to avoid (63.3%), the causes of IBS (62%), effective coping strategies (59.4%), and the role of psychological factors (50.8%). For prognosis, patients wanted to know whether they have to live with IBS for life (51.5%) and whether the condition can worsen (46.7%). Finally, IBS patients wanted information on medication and research (55.2 and 48.6%, respectively).

Table 1. Characteristics of the included studies

	Year	*Country*	*Setting*	*Percentage female*	*Mean age (SD)*	*Mean disease duration (SD)*	*Number of patients*	*Diagnostic criteria*	*Method of research*	*Topics of research*
Bijkerk et al.[7]	2003	NL	PC	-	44.5 (17.4)	49% > 10 years	79	62% Manning	structured questionnaire	Aetiology of IBS
Casiday et al.[8]	2008	UK, NL	PC	68%	43	-	51	Rome II	semi-structured interviews	Impact on daily life; aetiology; diagnosis; treatment; patient-doctor interactions; triggers
Halpert et al.[9]	2007	US	PC, SC, TC	85%	39.3 (12.5)	6.9 (4.2)	1242	Rome II	on line survey	Perception of patients on their condition; knowledge gaps; subgroup differences health- care seekers/non health care seekers; users/ non users internet
Hayes et al.[10]	2014	IRL	TC	91.1%	41.9 (12.0)	-	155	Rome III	postal questionnaire	Perception of patients on whether food affected IBS symptoms and with specific foods or food in general
Lacy et al.[11]	2007	US	PC, SC	83%	53.7 (16.9)	14.2 (12)	261	Rome II	questionnaire	Knowledge, fears and concerns
Lacy et al.[12]	2012	US	PC, SC, TC	85%	48 (15)	13.6 (11.1)	186	Rome III	Structured questionnaire	Fears and concerns regarding diagnosis of IBS

Table 1. Characteristics of the included studies (*continued*)

	Year	*Country*	*Setting*	*Percentage female*	*Mean age (SD)*	*Mean disease duration (SD)*	*Number of patients*	*Diagnostic criteria*	*Method of research*	*Topics of research*
O'Sullivan et al.[13]	2000	IRL	SC	84%	42 (11)	4.5	70	Rome I	open-ended questions	Perceived level of knowledge; satisfaction with level of knowledge; educational needs; association with age, sex, consultation, anxiety and depression
Riedl et al.[14]	2009	GER	TC	65.9%	43 (15.4)	-	88	Rome III	questionnaire	Patients subjective theories of illness

Abbreviations:

***NL**: Netherlands, **UK**: United Kingdom, **US**: United States, **IRL**: Ireland, **GER**: Germany*

***PC**: Primary Care, **SC**: Secondary Care, **TC**: Tertiary Care*

Table 2. Conceptions of IBS patients on aetiology, state, and prognosis of their IBS

Conceptions		Bijkerk *et al.*[7]	Halpert *et al.*[9]	Hayes *et al.*[10]	Lacy *et al.*[11]	Lacy *et al.*[12]	Riedl *et al.*[14]
	Food allergies and intolerance	37%		89.6%	47.9%		
	Anxiety is the cause				80.5%		
	Intrapsychic cause (at least partial)						78%
	Depression is the cause				63.2%		
Aetiology	Interpersonal cause						59%
	heredity				52.1%		
	Lack of digestive enzymes		52%				
	Somatic cause	39%					
	Family factor (parental influence and upbringing)	11%			29.9%		
State	It is a form of Colitis		42.8%				
	It will never go away				31.4%	54%	
	It will develop into cancer or increase the risk of cancer		21.4%		15.3%	49%	
	It worsens with age/time		47.9%			9%	
	It will develop into Colitis		43%				
Prognosis	It will lead to malnutrition		37.2%				
	Surgery will be needed in the future		34.3%				
	It will shorten one's life				4.6%	30%	
	It increases the risk on Irritable Bowel Disease				29.9%		
	It will always stay the same					22%	

DISCUSSION

The results of this systematic review show that IBS patients do have a large variety in informational needs. Several of the conceptions and views that patients have about aetiology, state, and the prognosis are irrational and not supported by the current state of scientific knowledge.[15-17] The exact cause of IBS is unknown, but studies suggest it is not caused by one factor but by a combination of factors, such as abnormal motility and increased sensitivity of both the peripheral and the central nervous systems.[17] Many patients consider food and dietary factors as the most significant causes, but relevant evidence is lacking.[15-17] Gluten intolerance is slightly more prevalent among IBS patients (4.67 versus 0.25-1%[18]), whereas lactose malabsorption is not increased[18], and there is insufficient evidence that food allergy testing or exclusion diets are effective in IBS.[15] Twin studies suggest "a strong environmental contribution to IBS and possibly a minor genetic contribution".[17]

Prognostically, there is no evidence that IBS will worsen with age or will never go away.[19] IBS patients rarely develop other gastroenterological diseases, and IBS is not associated with the development of any serious disease in the long term and will not shorten one's life.[16,17]

In the studies, patients' informational needs varied considerably and were dependent on the way in which the issue was discussed. When individuals are asked open questions[8,12], topics are less often mentioned than when these topics can be ticked off a list.[9] This phenomenon might be interpreted as a sign that patients are not always aware of what information they wish to have. The fact that the number of patients with misconceptions exceeds the number of patients who consider themselves as poorly informed might indicate that patients overestimate their level of knowledge.

In one study, 65% of the patients were unhappy with their level of knowledge or thought that they were poorly informed.[11] Compared with patients with inflammatory bowel disease (Crohn's disease and ulcerative colitis) more than twice as many patients with IBS felt poorly informed and were unhappy with their disease knowledge[13] which makes the need to inform IBS patients better more urgent.

Most patients (67%) prefer to receive medical information from their doctor, 55% from the internet, 38% from brochures, 38% from books, and 14% from a nurse.[20] Only written information seemed sufficient for primary care patients but was not enough for a group of mainly secondary/tertiary care patients.[21] As Thompson[22] states, "No listing of statistics, no hand out, no internet chat room can substitute for a reassuring discussion between the individual patient and caring physician about the nature of the disease and how it will affect him or her".

The strength of the present study is the systematic literature search, the use of strict selection criteria for IBS, and the fact that the studies were carried out in primary care and hospital settings in different countries, which increases the generalisability of the results.

The use of strict inclusion criteria to ensure that the review involved IBS patients resulted in the exclusion of articles in which patients were self-declared IBS patients or in which the criteria used by doctors were unclear. As a result, eight studies, which were good studies from other perspectives, were excluded from the review.

A limitation of the review is the fact that most results reported are based on one study only, which does not contribute toward the strengths of the evidence. This is caused by the fact that in different researches, the structured questionnaires did not use the same answer possibilities.

From the eight eligible studies, a disproportionate number of patients (58%) were from the study by Halpert *et al.*[9] This factor might have affected the results. However, the questions asked in the different studies overlapped, and there appeared to be no contradictory results, although the figures on the different topics differed considerably. Where the figures are higher on the same topics, patients were from a setting of care for more severe problems (for example tertiary versus primary care).

Our review provides insight into the educational needs of patients. An educational program should contain information on the functioning of the digestive system, a basic explanation of IBS, its causes, and its prognosis, and information on dietary measures that can be obtained and on adequate ways of coping with stress and symptoms. Such a program not only corrects existing misconceptions of IBS patients but also corresponds to their need for information.

Educational programs optimally addressing the informational needs can be adequately used as a placebo control condition for intervention studies on psychological therapies for IBS.

Conclusion

Patients with IBS do have several misconceptions about their disease and a large variety of educational needs in terms of the background of their disease, its prognosis, and its management. An educational program fulfilling the educational needs of patients could act as an adequate placebo control condition in clinical trials on psychological interventions for IBS.

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Chapter 4

Comparison of medical costs generated by Irritable Bowel Syndrome patients in primary and secondary care in the Netherlands

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ABSTRACT

Background: Irritable Bowel Syndrome (IBS) is a functional somatic syndrome characterised by patterns of persistent bodily complaints for which thorough diagnostic workup does not reveal adequate explanatory structural pathology. Detailed insight into disease-specific healthcare costs is critical because it codetermines the societal impact of the disease, enables the assessment of cost-effectiveness of existing and new treatments, and facilitates choices in treatment policy.

Aim: To compare the costs and magnitude of healthcare consumption for patients diagnosed with IBS in primary and secondary care, compare these costs with the average healthcare expenditure for patients without IBS, and describe these costs in further detail.

Methods: Reimbursement data for patients diagnosed with IBS by a general practitioner or specialist between 2006 and 2009 were extracted from a healthcare insurance company and compared to an age and gender matched control group of patients without IBS. Using a case-control design, direct medical costs for general practitioner consultations, specialist care, and medication prescriptions were calculated.

Results: Data of 326 primary care and 9274 secondary care IBS patients were included in the analysis. For primary care patients, the mean total annual healthcare costs for the three years after diagnosis compared to the three years before diagnosis increased with EUR 486 after IBS was diagnosed, whereas for secondary care patients these costs increased with EUR 2328. Total healthcare costs remained higher in the three years after the initial diagnosis when the patient is treated in secondary care, compared to primary care. This increase was significant for hospital specialist costs and medications, but not for general practitioner contacts. For controls, there was no significant difference in mean total annual health costs in the three years before and the three years after the diagnosis and also no significant difference in cost increases between both primary and secondary care control patients.

Conclusion: Total healthcare costs per patient substantially increase after a diagnosis of IBS and IBS related costs are significantly higher when patients are treated in secondary care compared to primary care. IBS patients should be treated in primary care where possible, not only because guidelines recommend this from a quality of care viewpoint, but also to optimise use of healthcare resources. Referral should be restricted to those patients with alarm symptoms, with ill-matching symptoms, or other cases of diagnostic uncertainty.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional somatic syndrome (FSS) characterised by patterns of persistent bodily complaints for which a thorough diagnostic workup does not reveal adequate explanatory structural pathology.[1] IBS is one of the most prevalent gastrointestinal disorders in Western countries[2] and is reported to frequently co-occur with other chronic and functional diseases.[3] Similar to individuals with other FSS, IBS patients who seek consultations utilise healthcare services more frequently than non-IBS patients.[4] IBS causes a substantial economic burden. In two systematic reviews, total direct costs for IBS in the United States and the United Kingdom are estimated between USD 348 and USD 8750 per patient per year[5] with total annual costs of GBP 45.6 million in the United Kingdom and USD 1.35 billion in the United States.[6] Detailed insight into disease-specific healthcare costs is critical because it codetermines the societal impact of the disease, enables the assessment of the cost-effectiveness of existing and new treatments, and facilitates choices in treatment policy.[7]

Societal costs for healthcare can be divided into several categories: direct medical costs associated with diagnosis and treatment, indirect costs related to production losses, and intangible costs related to the impact of the disease on the patient's quality of life.[8]

Although guidelines suggest that in the absence of alarm symptoms the majority of IBS patients can be adequately managed in primary care[9], there are substantial differences in referral rates across Europe, ranging from 10% in the Netherlands[10] to 44% in the United Kingdom.[5] If disease-related medical costs for IBS management substantially differ between primary and secondary care, variation in referral rates will have important economic consequences.

In the present study, we aimed to obtain insight into the economic consequences of referral in IBS management by comparing direct medical costs for IBS when patients are diagnosed and treated in primary or secondary care. We hypothesised that IBS management in secondary care is more costly than that in primary care because of increased comorbidity, more intensive use of diagnostic tests, and frequent cross-referral to other specialists.

METHODS

Design

We performed a retrospective case-control study using reimbursement anonymised data from Achmea Health Insurance, one of the largest health insurance

companies in the Netherlands, and anonymised routine care data from the primary care database of the Julius Primary Care Network (JPCN) of the University Medical Centre, Utrecht. In the Netherlands all patients have a compulsory healthcare insurance. The use of the data was approved by the research committees of both Achmea and JPCN. Patients from the JPCN database were linked to an Achmea policy holder by means of chance linking based on date of birth, gender, and postal code. As the data were delivered to the researchers anonymously, no informed consent from the insurees was necessary.

Databases

The Achmea database contains reimbursement data for more than one million patients. Achmea facilitates the use of anonymised reimbursed healthcare consumption data for scientific research under strict scientific and ethical conditions. These data include medications, general practitioner and specialist consultations, diagnostic and therapeutic procedures, and hospital admissions. The reimbursement for diagnostic and therapeutic procedures is standardised using Diagnostic Treatment Codes (Dutch: DBC), which include the first and last dates of treatment, the treating specialist, the type of treatment, and the diagnosis. Medications are registered in the database using anatomical therapeutic codes (ATC) detailing the daily defined dosages, the date, and the costs of the medication reimbursements. The general practitioner contacts are registered using the date, type of contact, International Classification for Primary Care (ICPC) -coded diagnosis, and reimbursed costs.

The JPCN database contains anonymous routine healthcare data extracted from the electronic medical records (EMR) of 140 general practices with approximately 240,000 patients. The JPCN population represents an average Dutch urban population. Approximately 50% of JPCN patients are insured by Achmea. In addition to the demographic information, the database contains the ICPC base diagnoses, diagnostic results, and ATC-based prescription data.

Patient selection

We selected patients from 23 JPCN practices that accurately registered the insurance companies used by their patients. Four groups were selected. The first group was drawn from these 23 practices and consisted of all patients who were diagnosed with IBS (ICPC-code) between 2006 and 2009 who were not referred to secondary care and who were insured with Achmea healthcare. This group will be referred to as primary care patients.

The second group consisted of all patients from the Achmea database who were diagnosed with IBS by hospital specialists (DBC-codes) between 2006 and

2009. This group will be referred to as secondary care patients. The IBS diagnosis in primary and secondary care is generally made in accordance with the Rome III criteria, in the absence of red flag risk factors. The third and fourth groups consisted of frequency matched on age- and gender-matched control group without IBS, twice the size of the first and second group, who were randomly drawn from the Achmea database: the third group matched the primary care patients, the fourth group matched the secondary care patients. Control-group subjects all had one or more medical diagnoses registered by either a general practitioner or specialist, for any medical condition but IBS. Patients from the JPCN database were linked to an Achmea policyholder based on their date of birth, gender, and postal code.

Study period

For secondary care, we allowed the diagnosis of IBS to be made anywhere between 2006 and 2009. To ensure that a primary care patient was not subsequently referred to a hospital, we excluded all the primary care patients who were diagnosed during the last year of study. For the control subjects, the date of diagnosis of their matched case was used as an index date.

Outcome

The primary outcomes were the direct medical costs for diagnosis and management of IBS, generated in primary and secondary care. The secondary outcomes were direct total medical costs for comorbid chronic, functional, and all other disorders of the IBS patients in the present study.

Cost specifications

The number of contacts with the general practitioner were divided both in primary and in secondary care for: consultations and home visits during office hours, consultations and home visits outside office hours, and repeat prescriptions.

Total costs for specialist care for IBS were calculated and the specified costs for the following three diagnostic groups were calculated both for primary and secondary care: chronic disorders, all other functional disorders, and all other disorders.

For chronic disorders, the list of the ten most prevalent chronic diseases in the Netherlands was used (RIVM 2010): diabetes mellitus, arthritis, coronary diseases, noise- and old-age-related deafness, visual disturbances, asthma, contact eczema, chronic obstructive pulmonary disease (COPD), stroke, and constitutional eczema. Ten specialists were asked to select the DBC codes that were used to register these disorders. For the functional disorders, the same procedure was

followed: specialists on different clinical topics were asked to determine which of the DBC codes concerned functional disorders. A functional disorder was defined according to the definition of Henningsen *et al.*[1] The group of all other disorders excluded all previously specified groups, including psychiatric disorders (in the Netherlands these were not registered using the same system).

We included total medication costs and specified the costs both for primary and secondary care for the following subgroups of medications associated with functional (gut) disorders: laxatives, spasmolytics, anti-depressants, and hypnotics.

Analysis

For IBS patients diagnosed in primary and secondary care as well as for their respective controls, the reimbursement data for IBS management and relevant comorbidity were extracted and the direct medical costs were calculated; all observed years before and after the diagnosis between 2006 and 2009 were analysed as separate observations. Total costs were divided into three subgroups: general practitioner costs, hospital or specialist costs, and medication reimbursement costs. For the cases and their controls, we calculated the average annual costs before and after IBS diagnosis.

Data analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). We described the differences between primary and secondary care IBS patients and their controls and tested the differences in mean costs between primary and secondary care IBS patients before and after the IBS diagnosis was determined using Student's *t*-tests.

Table 1. Study population, number, and characteristics

		Primary care patients	Primary care controls	Secondary care patients	Secondary care controls
Total number	N	326	652	9274	18548
Female gender	N/%	230/70%	460/70%	6506/70%	13012/70%
Patients with data before diagnosis	N	133	266	5972	11944
Patients with data after diagnosis	N	326	652	7538	15076
Age	Average (SD)	49 (17)	49 (17)	53 (18)	53 (18)

RESULTS

Patients

Among the 20,000 Achmea insured primary care persons in the JCPN population we identified 326 patients diagnosed with IBS and only treated in primary care. From the 1,000,000 Achmea insured persons we were able to select 9274 IBS patients diagnosed in secondary care. We included 652 primary care and 18548 secondary care non-IBS patients as controls. For the percentages of females and mean age and for a breakdown of the number of cases per year before and after IBS diagnosis, see Table 1.

Nine primary care control patients and one primary care IBS patient were excluded from the analysis because their annual average healthcare costs exceeded five standard deviations (SD) above the average.

Total annual health care costs before and after IBS diagnosis

Mean total annual healthcare costs for primary care IBS patients increased after the diagnosis by EUR 486 (± 3192) and for secondary care IBS patients by EUR 2328 (± 5888). The difference in total cost increase between primary and secondary care patients was significant ($p<0.01$). We did not find a significant difference in the total change in cost between the two control groups ($p=0.26$) (Table 2).

This increase was primarily explained by the increase in hospital specialists' costs and in medication costs. These costs increased and remained high over each of the three years after diagnosis. There was a slight increase in costs for general practitioner care for primary and secondary care patients, whereas general practitioner costs in the two control groups minimally changed over time. The increase in costs was significantly greater for secondary care patients compared to primary care patients for medications, hospital specialist costs, and total costs, while there was no significant difference for general practitioner costs (Table 2).

Number of contacts with the general practitioner before and after IBS diagnosis

The mean annual number of consultations and home visits during office hours increased by two visits for primary care and one visit for secondary care IBS patients after the IBS diagnosis (Table 3). For control patients these numbers did not change. Consultations outside of office hours and home visits increased only for secondary care IBS patients, whereas for controls there were no consultations.

For primary and secondary care IBS patients the mean annual number of repeat prescriptions increased by two, whereas for controls this remained at the same level (Table 3).

Table 2. Mean healthcare costs per patient per year (mean (SD) in Euro) (including both total and specific costs) for primary and secondary care IBS patients and matched controls in the years before and after the diagnosis of IBS.

		T = -3 Mean(SD)	T = -2 Mean(SD)	T = -1 Mean(SD)	Mean annual before Mean(SD)	T = +1 Mean(SD)	T = +2 Mean(SD)	T = +3 Mean(SD)	Mean annual after Mean(SD)	Mean dif Mean(SD)	P value difference
GPs	**Primary care patients**	-	98 (103)	104 (103)	102 (103)	129 (120)	125 (130)	127 (127)	127 (125)	25 (121)	0.15
	Secondary care patients	93 (90)	102 (97)	142 (119)	122 (110)	147 (165)	155 (158)	168 (181)	154 (166)	32 (146)	
	Primary care controls	-	67 (67)	74 (94)	72 (87)	68 (78)	68 (75)	75 (95)	70 (81)	-2 (82)	0.13
	Secondary care controls	74 (88)	77 (99)	78 (98)	77 (97)	78 (96)	80 (95)	83 (96)	80 (2)	3 (96)	
Hospital specialists*	**Primary care patients**	-	1168 (2645)	1087 (2520)	1111 (2551)	1345 (2572)	1391 (2932)	1544 (2822)	1409 (2758)	298 (2719)	<0.01×
	Secondary care patients	1139 (3780)	1063 (2763)	1500 (3713)	1303 (3450)	3695 (6400)	2678 (6198)	2815 (5783)	3173 (6230)	1870 (5269)	
	Primary care controls	-	591 (1812)	874 (2504)	792 (2325)	822 (2328)	1048 (2882)	1051 (2553)	955 (2585)	164 (2537)	0.16
	Secondary care controls	1259 (4742)	1319 ±4806)	1342 (6006)	1322 (5457)	1294 (8598)	1333 (4987)	1441 (5071)	1337 (5149)	15 (5277)	

Table 2. Mean healthcare costs per patient per year (mean (SD) in Euro) (including both total and specific costs) for primary and secondary care IBS patients and matched controls in the years before and after the diagnosis of IBS. (*continued*)

		T = -3 Mean(SD)	T = -2 Mean(SD)	T = -1 Mean(SD)	Mean annual before Mean(SD)	T = +1 Mean(SD)	T = +2 Mean(SD)	T = +3 Mean(SD)	Mean annual after Mean(SD)	Mean dif Mean(SD)	P value difference
Medication	**Primary care patients**	-	401 (657)	448 (680)	434 (672)	522 (792)	580 (911)	751 (2087)	598 (1269)	164 (1177)	<0.01×
	Secondary care patients	477 (992)	545 (1143)	630 (1227)	579 (1169)	939 (1707)	999 (1797)	1163 (2087)	1005 (1822)	426 (1587)	
	Primary care controls	-	398 (783)	481 (1360)	457 (1220)	449 (1252)	471 (1231)	490 (1435	466 (1291)	10 (1278)	0.97
	Secondary care controls	525 (1398)	555 (1390)	558 (1452)	552 (1434)	561 (1597)	558 (1346)	561 (1304)	560 (1459)	8 (1445)	
Total*	**Primary care patients**	-	1667 (2922)	1640 (2898)	1648 (2898)	1996 (2923)	2096 (3269)	2423 (3746)	2134 (3258)	486 (3192)	<0.01×
	Secondary care patients	1708 (4080)	1710 (3204)	2272 (4145)	2003 (3863)	4781 (7058)	3832 (6951)	4146 (6670)	4331 (6958)	2328 (5888)	
	Primary care controls	-	1056 (2236)	1429 (3052)	1320 (2840)	1338 (2872)	1586 (3369)	1616 (3156)	1492 (3120)	171 (3068)	0.26
	Secondary care controls	1858 (5295)	1950 (5376)	1978 (6501)	1951 (6002)	1933 (5893)	1971 (5490)	2086 (5558)	1976 (5692)	26 (5812)	

**: Excluding psychiatric care; ×, significant difference at alpha = 0.05*

T=-3 indicates Three years before diagnosis, T=+1 one year after diagnosis and so forth

Annual hospital specialist care costs before and after IBS diagnosis

Mean overall costs for specialist care for secondary care IBS patients rose by EUR 1870 (± 5269) annually after the IBS diagnosis was made. For primary care IBS patients this increase was EUR 298 (±2719). This difference between primary and secondary care patients was significant ($p<0.01$) (Table 2).

For secondary care IBS patients, the mean IBS specific, annual specialists' care costs increased with EUR 427 (±572).

Mean annual costs for all other chronic disorders increased with EUR 100 (±1299) for primary care IBS patients and with EUR 282 (±2337) for secondary care patients. The cost increase was significantly higher in secondary care ($p <0.01$).

The difference in the increase of costs between primary and secondary care patients was significant ($p<0.01$) (Table 4). These costs remained high over each of the three years after diagnosis. The disease groups contributing to the cost increase were: angina pectoris, arthritis, and stroke in primary care patients and coronary diseases, COPD, asthma, and visual disturbances in secondary care patients.

In both IBS patient groups, no substantial change in costs related to all other functional disorders after the diagnosis (-23 and +21 respectively) was found, though this difference in the increase of costs between primary and secondary care patients was significant ($p<0.01$).

There was a considerable increase in the mean annual costs for "all other disorders" after IBS was diagnosed in primary care patients (EUR 221 (± 2351)). These costs also increased and remained high over each of the three years after diagnosis. Highest increases were observed in costs for hernia cicatricles, endometriosis, and ileus. For secondary care patients, the costs increased by EUR 1139 (±4395). The largest increases were observed for diverticulosis, colon cancer, breast cancer, and urinary bladder tumours. This difference between primary and secondary care patients was significant ($p<0.01$) (Table 4).

Medications before and after IBS diagnosis

The total costs for medications increased significantly by EUR 426 (±1587) in the group of secondary care patients and EUR 164 (±1177) for primary care patients (Table 2). This difference between primary and secondary care patients was significant ($p<0.01$). Table 5 shows the change in medication costs in medication subgroups. There was a sharp increase in antacid use among the secondary care patients. The main contribution to the medication costs increase came from "all other drugs", not related to any specific type of gastrointestinal medication. In this group, the difference in the cost increase between primary and secondary care patients was significant ($p=0.02$).

Table 3. Annual number of GP contacts (mean (SD)) for primary and secondary care IBS patients and matched controls specified per year before and after the diagnosis of IBS.

		T = -3 Mean(SD)	T = -2 Mean(SD)	T = -1 Mean(SD)	Mean annual before Mean(SD)	T = +1 Mean(SD)	T = +2 Mean(SD)	T = +3 Mean(SD)	Mean annual after Mean(SD)	Mean dif Mean (SD)
1. Consults and home visits during office hours	**Primary care patients**	-	6 (6)	7 (6)	6 (6)	8 (6)	8 (7)	8 (7)	8 (6)	2 (6)
	Secondary care patients	6 (6)	7 (6)	10 (7)	8(6)	9 (8)	9 (8)	10 (9)	9 (8)	1 (7)
	Primary care controls	-	4 (4)	5 (5)	4 (5)	4 (5)	4 (5)	5 (6)	4 (5)	0 (5)
	Secondary care controls	5 (5)	5 (6)	5 (5)	5 (5)	5 (5)	5 (5)	5 (6)	5 (5)	0 (5)
2. Consults and home visits outside office hours	**Primary care patients**	-	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (0)	0 (1)	0 (1)
	Secondary care patients	0 (1)	0 (1)	0 (1)	0 (1)	1 (2)	1 (1)	1 (2)	1 (2)	0 (1)
	Primary care controls	-	0 (0)	0 (1)	0 (1)	0 (0)	0 (1)	0 (1)	0 (1)	0 (1)
	Secondary care controls	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)
3. Repeat prescriptions	**Primary care patients**	-	4 (6)	4 (5)	4 (6)	5 (7)	5 (7)	6 (8)	5 (7)	2 (7)
	Secondary care patients	4 (6)	5 (6)	5 (6)	5 (6)	6 (7)	7 (8)	7 (8)	7 (7)	2 (7)
	Primary care controls	-	4 (6)	4 (6)	4 (6)	4 (5)	4 (5)	4 (6)	4 (5)	0 (5)
	Secondary care controls	4 (5)	4 (6)	4 (6)	4 (6)	4 (6)	4 (6)	4 (6)	4 (6)	0 (6)

All p-values for the difference in means were not significant (p>0.5).

T=-3 indicates three years before diagnosis, T=+1 one year after diagnosis and so forth

Table 4. Mean healthcare costs per patient per year for primary and secondary care IBS patients and their matched controls specified per year before and after diagnosis for IBS, chronic disorders, functional disorders, and all other disorders (mean (SD) in Euro).

		T = -3 Mean(SD)	T = -2 Mean(SD)	T = -1 Mean(SD)	Mean annual before Mean(SD)	T = +1 Mean(SD)	T = +2 Mean(SD)	T = +3 Mean(SD)	Mean annual after Mean(SD)	Mean dif Mean(SD)	p value difference[a]
Irritable bowel syndrome	**Primary care patients**	-	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<0.01*
	Secondary care patients	0 (0)	0 (0)	0 (0)	0 (0)	725 (866)	174 (520)	175 (468)	427 (745)	427 (572)	
	Primary care controls	-	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.99
	Secondary care controls	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Chronic disorders	**Primary care patients**	-	332 (2074)	161 (543)	211 (1213)	289 (1151)	271 (1063)	407 (1819)	312 (1319)	100 (1299)	<0.01*
	Secondary care patients	318 (2373)	326 (1649)	379 (2017)	352 (1967)	600 (2659)	652 (2522)	684 (2407)	635 (2564)	282 (2337)	
	Primary care controls	-	189 (1095)	236 (1295)	222 (1239)	212 (1137)	309 (1600)	413 (1924)	294 (1523)	72 (1473)	0.38
	Secondary care controls	385 (2120)	398 (2314)	354 (1783)	373 (2021)	395 (2926)	379 (2187)	411 (2500)	393 (2611)	20 (2386)	
Functional disorders	**Primary care patients**	-	21 (83)	67 (390)	54 (330)	30 (236)	41 (228)	17 (141)	31 (214)	-23 (241)	<0.01*
	Secondary care patients	27 (242)	32 (262)	40 (289)	36 (274)	55 (346)	58 (478)	60 (365)	57 (399)	21 (353)	
	Primary care controls	-	42 (440)	6 (57)	17 (242)	12 (134)	9 (96)	13 (112)	11 (117)	-6 (149)	0.32
	Secondary care controls	17 (214)	18 (218)	17 (182)	17 (199)	19 (223)	16 (151)	15 (136)	17 (185)	0 (191)	

Table 4. Mean healthcare costs per patient per year for primary and secondary care IBS patients and their matched controls specified per year before and after diagnosis for IBS, chronic disorders, functional disorders, and all other disorders (mean (SD) in Euro). (*continued*)

		T = -3 Mean(SD)	T = -2 Mean(SD)	T = -1 Mean(SD)	Mean annual before Mean(SD)	T = +1 Mean(SD)	T = +2 Mean(SD)	T = +3 Mean(SD)	Mean annual after Mean(SD)	Mean dif Mean(SD)	p value difference∂
All other disorders*	**Primary care patients**	-	815 (1752)	860 (2382)	847 (2210)	1026 (2312)	1080 (2585)	1120 (2215)	1067 (2384)	221 (2351)	<0.01×
	Secondary care patients	794 (2863)	705 (2064)	1081 (2828)	915 (2616)	2315 (5429)	1794 (5322)	1896 (4882)	2054 (5292)	1139 (4395)	
	Primary care controls	-	360 (954)	633 (2005)	553 (1767)	598 (1880)	730 (2234)	625 (1407)	650 (1911)	97 (1885)	0.26
	Secondary care controls	857 (4107)	903 (3968)	971 (5630)	932 (4925)	880 (4197)	937 (4294)	1016 (4212)	927 (4233)	5 (4530)	

T=-3 indicates three years before diagnosis, T=+1 one year after diagnosis and so forth

**Excluding irritable bowel syndrome, chronic disorders, functional disorders and psychiatric disorders; ×, significant difference at alpha = 0.05; ∂: p value for the difference in increase of costs between primary and secondary care subjects.*

Table 5. Mean costs per patient per year for medication subgroups (mean euro (SD)) of primary and secondary care IBS patients and their matched controls specified per year before and after diagnosis.

		T = -3 Mean(SD)	T = -2 Mean(SD)	T = -1 Mean(SD)	Mean annual before Mean(SD)	T = +1 Mean(SD)	T = +2 Mean(SD)	T = +3 Mean(SD)	Mean annual after Mean(SD)	Mean dif Mean(SD)	p value difference
1. Laxatives	**Primary care patients**	-	10 (38)	13 (41)	12 (40)	32 (105)	34 (107)	39 (123)	34 (110	23 (101)	
	Secondary care patients	9 (48)	9 (40)	18 (45)	14 (44)	46 (76)	33 (76)	36 (83)	39 (78)	25 (66)	0.72
	Primary care controls	-	1 (7)	3 (14)	2 (12)	3 (17)	2 (13)	4 (22)	3 (17)	1 (17)	
	Secondary care controls	5 (28)	5 (28)	5 (29)	5 (28)	5 (30)	6 (31)	6 (32)	6 (31)	0 (30)	
2. Spasmolytics	**Primary care patients**	-	6 (24)	6 (24)	6 (24)	11 (31)	7 (25)	9 (33)	10 (29)	4 (28)	0.25
	Secondary care patients	12 (70)	13 (75)	14 (76)	13 (75)	14 (73)	16 (77)	16 (76)	15 (75)	2 (75)	
	Primary care controls	-	0 (0)	0 (2)	0 (2)	0 (6)	0 (3)	0 (3)	0 (4)	0 (4)	0.99
	Secondary care controls	6 (52)	7 (53)	7 (52)	7 (52)	7 (52)	8 (53)	7 (47)	7 (51)	0 (52)	
3. Anti-depressants	**Primary care patients**	-	7 (45)	10 (45)	9 (45)	15 (84)	17 (100)	20 (100)	16 (94)	7 (86)	0.66
	Secondary care patients	2 (13)	2 (16)	5 (20)	3 (18)	9 (29)	8 (29)	9 (32)	8 (30)	5 (25)	
	Primary care controls	-	2 (11)	4 (38)	4 (33)	8 (49)	10 (67)	8 (51)	9 (56)	5 (53)	0.02*
	Secondary care controls	1 (9)	1 (9)	1 (10)	1 (10)	1 (9)	1 (9)	1 (11)	1 (10)	0 (10)	
4. Antacids	**Primary care patients**	-	83 (229)	72 (181)	75 (196)	76 (184)	70 (155)	60 (138)	70 (164)	-5 (171)	<0.01*
	Secondary care patients	47 (132)	56 (139)	70 (153)	62 (146)	117 (214)	113 (204)	115 (204)	115 (209)	54 (186)	
	Primary care controls	-	26 (98)	22 (78)	23 (84)	27 (115)	30 (112)	29 (106)	28 (112)	5 (107)	0.16
	Secondary care controls	36 (120)	37 (115)	36 (114)	36 (115)	36 (116)	35 (110)	33 (106)	35 (112)	-1 (113)	
5. Hypnotics	**Primary care patients**	-	12 (38)	8 (29)	10 (32)	8 (32)	7 (29)	4 (19)	7 (28)	-3 (29)	<0.01*
	Secondary care patients	8 (30)	9 (33)	9 (34)	9 (33)	12 (41)	13 (42)	11 (40)	12 (41)	3 (38)	
	Primary care controls	-	6 (23)	5 (22)	5 (22)	6 (27)	5 (25)	3 (19)	5 (25)	0 (24)	0.99
	Controls to referred	6 (29)	6 ±27)	6 (27)	6 (27)	6 (28)	6 (28)	5 (26)	5 (28)	0 (28)	

Table 5. Mean costs per patient per year for medication subgroups (mean euro (SD)) of primary and secondary care IBS patients and their matched controls specified per year before and after diagnosis. (*continued*)

		T = -3 Mean(SD)	T = -2 Mean(SD)	T = -1 Mean(SD)	Mean annual before Mean(SD)	T = +1 Mean(SD)	T = +2 Mean(SD)	T = +3 Mean(SD)	Mean annual after Mean(SD)	Mean dif Mean(SD)	p value difference
6. Other ATC group N drugs[a]	**Primary care patients**	-	55 (139)	45 (152)	48 (148)	53 (144)	71 (234)	75 (274)	64 (214)	16 (203)	0.40
	Secondary care patients	83 (309)	82 (305)	90 (357)	86 (334)	106 (397)	115 (410)	120 (412)	112 (404)	26 (377)	
	Primary care controls	-	28 (79)	56 (311)	47 (265)	64 (456)	65 (359)	65 (352)	65 (400)	17 (378)	0.29
	Secondary care controls	55 (246)	60 (292)	60 (319)	59 (300)	64 (354)	58 (306)	58 (293)	61 (327)	1 (316)	
7. Other ATC group A drugs[b]	**Primary care patients**	-	44 (183)	42 (194)	43 (191)	40 (178)	41 (134)	46 (141)	42 (155)	-1 (163)	<0.01×
	Secondary care patients	20 (97)	22 (95)	28 (125)	25 (112)	64 (223)	75 (257)	99 (304)	75 (253)	50 (207)	
	Primary care controls	-	29 (97)	35 (146)	33 (133)	32 (170)	36 (195)	24 (120)	32 (169)	-2 (163)	0.88
	Secondary care controls	42 (182)	45 (193)	45 (186)	45 (188)	43 (182)	45 (188)	42 (185)	44 (185)	-1 (186)	
8. All other drugs[c]	**Primary care patients**	-	182 (321)	252 (454)	232 (419)	287 (508)	333 (649)	497 (1944)	354 (1085)	123 (992)	0.02×
	Secondary care patients	296 (830)	352 (1009)	397 (1065)	367 (1015)	570 (1504)	627 (1565)	757 (1859)	627 (1604)	261 (1392)	
	Primary care controls	-	306 (678)	356 (1263)	341 (1124)	308 (1082)	322 (1070)	356 (1320)	325 (1140)	-17 (1137)	0.57
	Secondary care controls	373 (1258)	393 (1235)	397 (1295)	392 (1270)	399 (1464)	401 (1202)	410 (1152)	402 (1320)	9 (1299)	

T=-3 indicates three years before diagnosis, T=+1 one year after diagnosis and so forth

[a]*ATC group N drugs: drugs typically aimed at the neurological system, excluding anti-depressants and hypnotics*

[b]*ATC group A drugs: Drugs typically aimed at the alimentary tract, excluding laxatives, spasmolytics and antacids*

[c]*Excluding ATC group A and group N drugs*

×*Significant difference at alpha = 0.05.*

DISCUSSION

Summary of findings

Total healthcare costs for IBS patients increased substantially in the years after the diagnosis, 29% for primary and 116% for secondary care patients. In secondary care this increase was primarily attributed to costs for hospital specialists (+144%) and medications (+74%). The most remarkable is that for all three kinds of medical costs these remain high all three years after diagnosis.

The additional specialist-associated costs for the primary care IBS patients were primarily due to chronic disorders other than IBS (nearly 50%) and by other disorders (25%). This observation is consistent with the results from a study by Levy *et al.*[11], in which the majority of the excess healthcare costs between IBS patients and population controls was attributed to care unrelated to lower gastrointestinal problems. The increase in costs related to hospital specialist care for secondary care patients is, for the most part, due to costs for other chronic disorders (+80%) and "all other disorders" (+124%). Patients with functional gastrointestinal diseases consult their doctors more often for non-gastrointestinal complaints[12] and for other somatic and psychiatric disorders.[3] We hypothesise that gastroenterologists are more likely to refer IBS patients to other hospital specialists than general practitioners, thus explaining the differences in increased costs. In the Netherlands, as in many other countries with a strong primary care, the general practitioner acts as the "case manager" of the patient, coordinating the diagnostic and treatment process. The longitudinal relation with the patient and the knowledge of medical history and psychosocial system facilitates an integral approach to IBS and helps to prevent unnecessary referral and diagnostic procedures. This benefits both disease outcome and patient's quality of life and reduces healthcare costs.

Comparison with similar studies

It is remarkable that in our study the costs for other functional disorders (e.g., fibromyalgia, fatigue, and unexplained pain) in IBS patients are not very high, although high rates of co-occurrence of IBS with other functional diseases have been reported.[3] In the Netherlands, both in primary and secondary care, only one diagnosis per specialty can be designated per treatment. The general practitioner and specialist may be inclined to select the diagnosis with the highest reimbursement value as a result of this policy. Because the reimbursement value for functional disorders is relatively low, this result might lead to an under-diagnosis.

The increase in antacid use after the IBS diagnosis in secondary care may be explained by the fact that more than in primary care, gastroenterologists are aware

of the overlap between IBS and upper gastrointestinal symptoms. This results in frequent co-prescription of antacids, H2 blockers, and proton pomp inhibitors (PPI's) in patients diagnosed with IBS.

Strengths and limitations

The extrapolated incidence of IBS in our study population was 5.4/1000/year, which is in line with the IBS incidence reported for primary care in the Netherlands. This indicates that the patients sample we extracted is representative for primary care IBS patient group in the Netherlands.

A strong point of this study is the long observation period. Whereas the majority of previous studies have gathered information for up to one year[7,13-17], we gathered total costs over four years. Because data from the insurance company are based on reimbursement, the dataset provides insight into valid medical costs and not proxy costs calculated from medical file research or questionnaire data.

The demographic characteristics of our IBS population are notable. The Achmea population is slightly older than the mean Dutch population. In the Netherlands, approximately 15% of the population is 65 years or older; for the Achmea population, this is 18%.[18] In the studies of Akehurst *et al.*[7], Creed *et al.*[13], and Hillillä *et al.*[16], the mean ages of the studied populations were 47, 39, and 42 years, respectively. The mean age of our IBS population (i.e., 49 for primary care and 53 for secondary care) is higher. Total healthcare costs increase with age and decrease with a higher educational level.[19] College-educated subjects incur significantly lower healthcare costs through their insurance program.[19] The Achmea population has a lower educational level (as measured by the postal code) compared to the average Dutch population.

Costs observed in the present study were highly skewed towards the lower end of the cost spectrum, as reflected in the high standard deviations relative to the average costs. One might argue that the median values would be more suitable for presenting numbers in highly skewed distributions. However, we chose not to do so because in healthcare, a small group of people are often responsible for a large share of the costs. The medians might result in values that are very low or even zero, underestimating the actual financial burden of IBS on society.

Not all patients in our study had data available for the year before the IBS diagnosis. Nevertheless, we calculated averages for these patients for the period after the initial diagnosis because the number of primary care patients with IBS was low. One could argue that this observation may have generated a bias because, theoretically, patients for whom data are only available after diagnosis have different characteristics than those who were analysed both in the years before and after diagnosis. To test this possibility, we examined only the cases for whom data

were available before and after the diagnosis, and we did not arrive at different conclusions.

Another limitation is the fact that, although multidisciplinary guidelines in the Netherlands recommend the use of Rome criteria to diagnose IBS, we did not check if the physicians in our study actually used these criteria. Although this may have resulted in diagnostic uncertainty in some, we think that the diagnosis was valid in the majority of IBS patients included.

One might argue that there is a difference in IBS symptom severity and disease impact between patients attending primary and secondary care, which explains the bigger increase in IBS costs in secondary care. We do not share this viewpoint. A study by Smith *et al.*[20] showed no difference in IBS symptom severity between patients treated in primary and secondary care. In addition, our results demonstrate that the difference in costs between primary and secondary care is not so much due to direct IBS related costs but due to costs for other disorders.

CONCLUSION

Healthcare costs substantially increase after the diagnosis of IBS is made, and costs increase significantly more and remain higher over the years for patients who are treated in secondary care compared to patients treated by a general practitioner. IBS patients should be treated in primary care where possible, not only because guidelines recommend this from a quality of care viewpoint, but also to optimise use of healthcare resources. Referral should be restricted to those patients with alarm symptoms, with ill-matching symptoms, or other cases of diagnostic uncertainty.

Ethics

The use of the study data was approved by the research committees of both Achmea and the Julius Primary care Network.

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Chapter 5

Systematic review: the placebo effect of psychological interventions in the treatment of Irritable Bowel Syndrome

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ABSTRACT

Aim: To determine the placebo response rate associated with different types of placebo interventions used in psychological intervention studies for irritable bowel syndrome (IBS).

Methods: Randomised controlled trials comparing psychological interventions (stress management/relaxation therapy, (cognitive) behavioural therapy, short-term psychodynamic therapy, and hypnotherapy) for the treatment of adult patients with IBS diagnosed with the Manning or Rome criteria with an adequate placebo control treatment and reporting data on IBS symptom severity were identified by searching PubMed, Embase, the Cochrane Library, CINAHL, and PsycINFO databases. Full-text articles that were written in English and published between 1966 and February 2016 in peer-reviewed journals were selected for the present review. Placebo interventions were considered to be adequate if the number of sessions and the amount of time spent with the therapist were the same as in the active treatment. The placebo response rate (PRR) was computed for IBS symptom severity (primary outcome measure) as well as for anxiety, depression, and quality of life (secondary outcome measures).

Results: Six studies, with a total of 555 patients, met the inclusion criteria. Four studies used an educational intervention, whereas two studies used a form of supportive therapy as the placebo intervention. The PRR for IBS symptom severity ranged from 25% to 59%, with a pooled mean of 41.4%. The relative PRR for the secondary outcome measures ranged from 0% to 267% for anxiety, 6% to 52% for depression, and 20% to 125% for quality of life. The PRR associated with pharmacological treatments, treatment with dietary bran, and complementary medicine ranged from 37.5% to 47%. Contrary to our expectations, the PRR in studies on psychological interventions was comparable to that in studies on pharmacological, dietary, and alternative medical interventions.

Conclusion: The PRR is probably determined to a larger extent by patient-related factors, such as expectations and desire for the treatment to be effective, than the content of the placebo intervention.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterised by recurrent episodes of abdominal pain, discomfort, and altered bowel habits that are not explained by structural or biochemical abnormalities.[1] Several pathophysiological mechanisms underlying IBS have been proposed. According to the bio-psycho-social model of IBS, a disturbance in intestinal motility and enhanced visceral sensitivity interact with other factors, such as environmental influences, parent-child interactions, and disturbed stress responses.[2]

Because of the limited effect of pharmacotherapy[3,4], there has been increasing interest in psychological treatments for IBS. Two Cochrane reviews provided evidence for the effectiveness of cognitive behavioural therapy (CBT), interpersonal psychotherapy (IPT)[5], and hypnotherapy.[6] Another review[3] concluded that CBT, IPT, and hypnotherapy, not relaxation therapy, were more effective than typical care in relieving IBS symptoms. In 2014, a systematic review showed that relaxation therapy was effective in reducing IBS symptoms.[7]

In the research on psychological treatment methods, it is possible that the treatment effect is the result of increased attention and time investment on the patient rather than the therapy itself. In randomised controlled trials (RCTs), a placebo group should be used to control for this effect. The placebo group is defined as a "matched control group participating in an activity regarded therapeutically inert from the theoretical perspective of the therapy under study".[8]

Although a placebo control is different in pharmacological studies than in psychological studies, they are equally important in both cases for achieving a methodologically valid comparison. In pharmacological research the placebo response rate (PRR) is variable and may be affected by the type, dosage, size, colour, frequency, and route of administration of the placebo medication.[9] In psychological interventions, the PRR may result from the consultation itself and the relationship with the physician/therapist.[10] IBS patients experienced greater benefits from augmented, positive interaction with a practitioner than from limited or no interaction at all (i.e., being put on a waiting list).[10] They also benefitted more from an increased number of office visits and a longer duration of treatment[11,12], suggesting that supportive and empathic interaction with a practitioner might influence clinical outcomes. Placebo effects can be defined as "the beneficial effects that are attributable to the responses of the patient to the context in which the treatment is delivered, rather than to specific actions of the treatment".[13] In RCTs in which psychological interventions are studied, a control intervention with an equal number and length of sessions, using an individual or a group format and with comparably trained therapists should be used to control

for these effects.[8] Currently, researchers who examine psychological interventions debate whether and to what degree the effects of psychotherapy are based on placebo effects or therapeutic factors.[8,14,15]

From a methodological perspective, the PRR is viewed as an effect that needs to be corrected for. However, from a clinical perspective, a high PRR and a good treatment response are considered to be equally positive outcomes. From this perspective, when the PRR associated with psychological interventions is larger than associated with pharmacological interventions, the psychological placebo treatment may be of greater clinical relevance. The positive relationship with the therapist can be used as an additional beneficial factor.

We presumed that the placebo response would be greater in psychological interventions than in drug trials. So far, studies on the PRR in IBS have focused primarily on pharmacological treatments, treatment with dietary bran, and complementary medicine. PRR rates in these studies ranged from 37.5% to 47%.[11,16-18]

One systematic review of alternative therapies for IBS included a meta-analysis of psychological therapies.[19] A separate evaluation of the results of four of the 17 included studies that used a "true placebo group" was reported. The PRR of these four studies was 30.4%. This study searched the MEDLINE database for articles published through 2001, sample sizes were low and the IBS criteria for the inclusion of studies were not defined. Since then, results of a number of new studies have been published.

The present study aims to review systematically the PRR associated with different types of placebo control interventions in studies on psychological interventions in IBS and compare them to the PRR of placebo control interventions of drug trials.

METHODS

Inclusion and exclusion criteria

Types of studies

RCTs comparing psychological interventions for the treatment of IBS with a placebo control treatment that were written in English and published as a full-text in a peer-reviewed journal, were eligible for inclusion. Cross-over studies were excluded, as were studies comparing two types of psychological therapeutic interventions without a placebo control.

Types of participants

Studies including male or female patients over the age of 18 years with IBS diagnosed according to Manning or Rome I, II, or III criteria were included in the analysis.

Types of interventions

In accordance with earlier Cochrane reviews[5,6], the following psychological interventions for the treatment of IBS were considered: stress management/relaxation therapy, (cognitive) behavioural therapy, short-term psychodynamic therapy, and hypnotherapy.

Types of placebo treatments

Because of the potential impact of the format of the placebo intervention on the outcome, only studies with placebo-controlled interventions using the same number of sessions and therapeutic time as the active treatment were considered to be eligible for inclusion (for Baskin's other criteria, see Table 1).[8] Studies using a waiting list, usual care, symptom monitoring, and therapeutic contact by phone or internet, were excluded.

Types of outcome measures

Studies were eligible for inclusion if they reported improvement in IBS symptoms and/or abdominal pain (measured with a validated IBS questionnaire), and/or adequate relief of abdominal pain and discomfort, and/or satisfactory relief of IBS symptoms, as recommended by the Rome III classification system for the design of IBS treatment trials.[20]

Studies were excluded if no information on the effectiveness of the psychological interventions was available or if the proportion of patients in each group with overall symptom improvement after therapy was not reported.

Search methods to identify studies

Electronic searches

We performed a systematic search of RCTs published from 1966 to February 2016 that were available in PubMed, Embase, the Cochrane Library, CINAHL, and PsychINFO databases. The following search terms were used:

- "irritable bowel syndrome" [MeSH] OR "colonic diseases, functional" [MeSH: NoExp] OR "irritable bowel syndrome" [tiab] OR "irritable bowel syndromes" [tiab] OR "irritable colon" [tiab] OR "mucous colitis" [tiab] OR "ibs" [tiab] OR "functional colonic disease" [tiab] OR "functional colonic diseases" [tiab] OR "spastic colon" [tiab],

combined with:

- ((cognitive[tiab] OR psychological[tiab] OR psychologic[tiab] OR psychodynamic[tiab] OR psychoanalytic[tiab] OR "psycho analytic"[tiab] OR stress[tiab] OR relaxation[tiab] OR conditioning[tiab] OR "problem solving"[tiab] OR interpersonal[tiab] OR "hypno analytic"[tiab] OR behavioral[tiab] OR behavioural[tiab] OR behavior[tiab] OR behaviour[tiab]) AND (therapy[tiab] OR therapies[tiab] OR treatment[tiab] OR treatments[tiab] OR intervention[tiab] OR interventions[tiab] OR management[tiab])) OR (psychotherapy[tiab] OR psychotherapies[tiab] OR psychoeducation[tiab] OR "psycho education"[tiab] OR psychoeducational[tiab] OR psychotherapy[tiab] OR hypnotherapy[tiab] OR hypnosis[tiab] OR hypnoses[tiab] OR hypnotism[tiab] OR hypnoanalysis[tiab] OR mesmerism[tiab] OR "hypno analysis"[tiab] OR autohypnosis[tiab] OR "auto hypnosis"[tiab] OR psychoanalyses[tiab] OR psychoanalysis[tiab] OR "psycho analysis"[tiab] OR biofeedback[tiab]) OR ("Behavior Therapy"[MeSH] OR "Psychoanalysis"[MeSH] OR "Psychoanalytic Therapy"[MeSH])

No filters or limits were used.

Data collection and analysis

Study selection

Two authors (CF and LB) reviewed the title and abstract of each identified article to determine the extent to which it met eligibility criteria, such as type of study, participants, interventions, placebo treatments, and outcome measures, as described previously. A manual search of the references listed in the articles retrieved from the online search was performed to identify additional studies. The full texts of the selected articles were then reviewed by the same authors to assess eligibility based on the same criteria. Discrepancies between the selections made by CF and LB were resolved by a third author (NdW).

Data extraction

From the resulting selection of papers, information on the number of patients, patient characteristics (sexe, mean age, and mean duration of illness), criteria for diagnosis (Rome I, Rome II, Rome III, or Manning), treatment setting, intervention (type, group or individual delivery format, number of sessions, training of therapists, and use of treatment/placebo manual), placebo control (type, group or individual delivery format, number of sessions, training of therapists, and use of treatment/placebo manual), duration of treatment, duration of the follow-up period, and results relating to the primary and secondary outcome measures were extracted.

Assessment of Risk of Bias

The risk of bias assessment tool developed by the Cochrane Collaboration for RCTs was used.[21] The following sources of bias can be assessed with high, low, or unclear bias ratings: adequate generation of the allocation sequence, concealment of allocation to conditions, blinding of participants and personnel, handling of incomplete outcome data, and selective outcome reporting. The percentage of patients who dropped out of the intervention and placebo control group as well as the results of the intention to treat (ITT) analysis (when provided) were added.

Outcome measures

In this review, the post-treatment IBS symptom severity score was the primary outcome measure. Most studies presented the results of the ITT analysis, although only one study included the results of the per protocol (PP) analyses. Secondary outcome measures were improvement of symptoms of anxiety and depression as well as quality of life. Quality of life was recommended as an outcome measure by the Rome III committee, whereas anxiety and depression were chosen as secondary outcome measures due to their high rates of comorbidity.[22]

Statistical analyses

The response rate of the primary outcome measures was calculated by dividing the percentage of patients who responded according to the study criteria by the number of patients in the ITT analysis or who completed treatment. Relative placebo responses (Rel-PR) with 95% confidence intervals (95%CI) were calculated as the ratio of placebo response to active treatment response. Additionally, the mean Rel-PR across all studies was calculated.

The weighted average PRR was calculated by adding up the PRR per study multiplied by the number of patients in the placebo control group of that study and dividing the product by the total number of control patients in all of the studies.

Criteria for response evaluation were not available for the secondary measures; therefore, PRRs for the secondary outcome measures of anxiety, depression, and quality of life were calculated by setting the response rate for these measures in the active arm at 100% and computing the response rate in the placebo arm as a relative percentage of the active arm. A relative response rate >100% indicated that the placebo intervention was more effective than the treatment intervention. To allow for comparison of the PRR between the primary and secondary outcome measures, we recalculated the rates for the primary outcome measures in this way.

For the secondary outcome measures, the PRR for the different types of placebo interventions were calculated by adding up the PRR per study multiplied with the

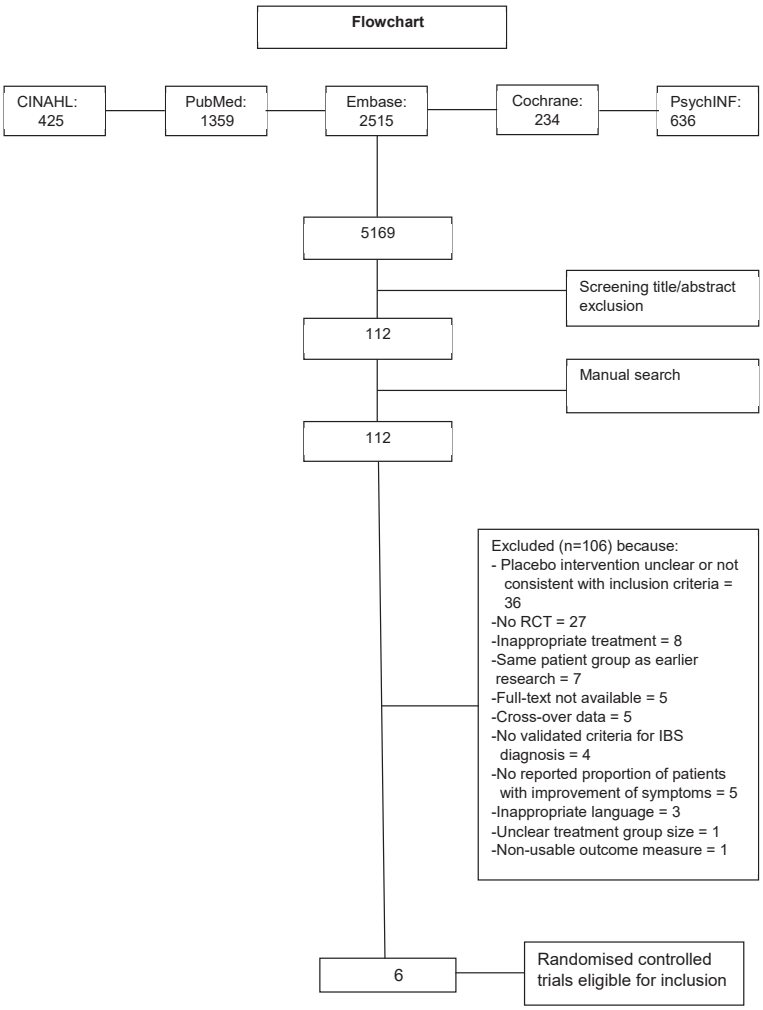
number of patients in the placebo control group of that study and dividing the product by the total number of control patients in all of the studies.

RESULTS

Description of studies

The literature search resulted in the identification of 5169 studies. After screening the titles and abstracts, 112 studies were potentially eligible (see flowchart Figure 1). The manual search yielded no additional studies.

Figure 1. Flowchart



After reviewing the full manuscripts of these studies, 106 studies were excluded for various reasons (see flowchart Figure 1), leaving six eligible trials[23-28] that were included in the analysis. The characteristics of the included studies are shown in Table 1. Sample sizes ranged from 21 to 215. Patients were recruited from primary, secondary, and tertiary care institutions, although they were also partially recruited through advertisements in three studies.[23-25] The treatment setting was unclear in two of the selected studies.[25, 27]

The mean age of the study populations ranged from 31.6 to 45.5 years. The proportion of female participants ranged from 52.4% to 100%. Only one study reported the duration of IBS[26]: a median of four years for the intervention group and 10.5 years for the placebo group. The duration of treatment and the placebo intervention ranged from eight weeks to three months. The duration of the follow-up period ranged from three months to 12 months.

Quality assessment

Four of the six studies fulfilled almost all quality criteria (Table 2).

Type of placebo interventions

Four studies used an educational program as the placebo intervention.[23,24,27,28] In these studies, educational materials were provided and discussed with a therapist. In the study by Payne and Blanchard[27], individual cognitive therapy was compared to an educational placebo intervention delivered in a group format. The other studies compared individual CBT (with interceptive exposure to visceral sensations) or stress management[23], individually delivered CBT[24], and autogenic training[28] to an individual educational placebo intervention.

Two studies, on mindfulness and hypnotherapy delivered in a group format used support therapy as the placebo intervention.[25,26] In the study by Gaylord *et al.*[25], the placebo intervention sessions were facilitated by social workers who served as group leaders, focussing on specific predesigned topics and promoting open group discussions. The placebo intervention in the study by Moser *et al.*[26] consisted of doctor's visits of the same duration as the treatment.

Placebo response

Primary outcome measure

One of the six studies investigated the effects of two separate psychological interventions and compared them with the effect of one placebo intervention[23], which brings the total number of outcomes to seven (see Table 3). All studies reported a significant reduction in IBS symptoms for at least one of the treatment

Table 1. Descriptive Statistics for Characteristics of Included Studies

First Author	Year	Country	N	Mean Age (yrs)	Female_Sex	Recruitment	Years of illness	Criteria	Therapy	Control	Format	Ses-sions	Trained Therapist Intervention/ Placebo	Protocol Inter-vention/Placebo
Craske *et al.*[23]	2011	US	110	39.4	74	Community advertisement; university clinic		RII;	Cognitive-behavioral therapy	Psycho-educational support	Individual	10	unclear/ unclear	yes/yes
Drossmann *et al.*[24]	2003	US and Canada	215	37.3	100	Community and hospital advertisement; physician referral in comm unity or university-based practices		R1	Cognitive-behavioral therapy	Psycho-educatio-nal support	Unclear	12	yes/yes	yes/yes
Gaylord *et al.*[25]	2011	US	75	42.7	100	Local advertisement; physician care		RII;	Mindful-ness	Support	Group	9	yes/yes	yes/yes
Moser *et al.*[26]	2013	Austria	100	45.5	79	Primary, secondary care and university clinic	4/10.5	RIII	Hypno-therapy	Support	Group	10	yes/yes	yes/no
Payne *et al.*[27]	1995	US	34	40.1	85	Personal physician	16	RI	Cognitive therapy	Psycho-educational support	Therapy: individual control group	10	yes/ unclear	yes/yes
Shinozaki[28]	2010	Japan	21	31.6	52	University clinic			Relax	Psycho-educational support	Individual	8	yes/ unclear	yes/yes

Table 2. Risk of Bias Ratings for Included Studies

First Author	Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	% Dropout Treatment /Placebo Control	ITT or PP
Craske et al.[23]	2011	low	low	low	low	low	low	Interoceptive Exposure:34; Stress Management:36 /16	ITT
Drossmann *et al.*[24]	2003	low	low	low	low	low	low	13/24	ITT
Gaylord *et al.*[25]	2011	low	low	low	low	low	low	6/18	ITT
Moser *et al.*[26]	2013	low	low	low	low	low	low	0/2	PP
Payne & Blanchard[27]	1995	unclear	unclear	low	unclear	low	low	0/0	ITT
Shinozaki[28]	2010	unclear	unclear	High	high	low	low	0/0	ITT

Possible ratings were low, high or unclear risk of bias. Studies with 2 control groups were rated twice for risk of bias because of lack of blinding (rated or active control groups appear in parentheses).ITT indicates that the analysis was intent to treat (analysed as randomised). PP: per protocol

interventions. For the response rate for the primary outcome measure of the placebo and active intervention arms, see Table 3. We performed the calculations using post-treatment figures. However, for the study by Craske *et al.*[23], we used the figures at three-month follow-up because only they were reported.

Rel-PRs ranged from 0.33 (95%CI: 0.12–0.94) in the study by Payne and Blanchard[27] to 1.1 (95%CI: 0.7-1.73) in the study by Craske.[23] For details on the Rel-PRs, see Figure 2.

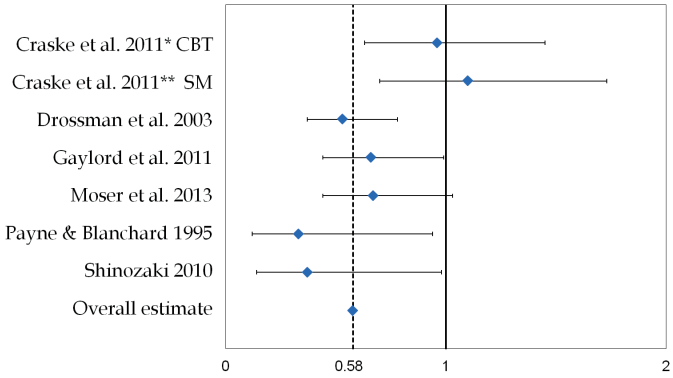
After adjusting for study sample size, the weighted average PRR for all studies was 41.4%. In subgroup analysis, after adjusting for study sample size, the pooled PRR was 39.5% for the educational programs and 42.9% for the supportive interventions, including doctor's visits.[26]

Table 3: Placebo treatment and placebo response rate

Study	Placebo Treatment	Primary Outcome Measure	Duration of Treatment[1]	Follow-up	Placebo Response	Treatment Response
Craske *et al.*[23] 2011	Psycho-educational support	BSS index[a]	10 weeks	3 months	59% (13/22)	62% (29/47)[1] 54% (22/41)[2]
Drossman *et al.*[24] 2003	Psycho-educational support	Composite score[b]	12 weeks		37.3% (19/51)	70% (77/110)
Gaylord *et al.*[25] 2011	Support group	IBS-SSS[c]	8 weeks	3 months	45.2% (17.6/39) 53.1% (20.7/39)	68.8% (27.4/36) 75% (27/36)
Moser *et al.*[26] 2013	Supportive talks	IBS-IS[d]	12 weeks	12 months	40.9%(18/44) 25% (11/44)	60.8%(28/46) 54.3% (25/46)
Payne & Blanchard[27] 1995	Psycho-educational support	CPSR[e]	8 weeks	3 months	25% (3/12) 18% (2/12)	75% (9/12) 83% (10/12)
Shinozaki[28] 2010	Psycho-educational support	AR[f]	8 weeks		30% (3/10)	81.8% (9/11)

[1]Cognitive behavioral treatment; [2]Stress management; [a] Bowel syndrome severity index (BSS); [b] Composite score: Mc-Gill Pain Questionnaire; IBS-QOL; satisfaction with treatment; global well-being; [c] IBS-Symptom Severity Score (IBS-SSS); [d] IBS-Impact Scale (IBS-IS); [e] Composite primary symptom reduction (CPSR); [f] Adequate relief (AR)

Figure 2. Relative placebo responses (Rel-PR) were defined as the ratio of placebo response to active treatment response in the individual studies.



*The mean relative placebo responses (Rel-PR) and 95% confidence intervals are shown. *Cognitive Behavioral therapy, contingency management; **Cognitive Behavioral therapy, stress management*

Secondary outcome measures

Data on anxiety were presented in five studies[23,25-28], whereas data on depression were provided in three studies.[25,27,28] Five studies assessed quality of life using the IBS-QOL or SF-36 as the outcome measure.[23-26,28] The relative PRR for anxiety ranged from 0%[23,27] to 267%.[28] The relative PRR for depression ranged from 6%[27,28] to 52%.[25] For quality of life, it ranged from 20%[26] to 125%.[23] The relative placebo responses are presented in Table 4.

With regard to the different types of placebo interventions, after adjusting for sample size, the weighted average sizes for the educational placebo interventions were 27.8% for state anxiety, 65.1% for trait anxiety, 6% for depression, and 72.7% for quality of life. For the supportive interventions, they were 27.2% for anxiety, 52% for depression, and 20.8% for quality of life.

Table 4. Comparison of outcome measurements

Author	Symptoms	Anxiety	Depression	Quality of life
Craske CBT-IE	Bowel Symptom Severity (BSS)	Visceral Sensitivity Index (VSI)	-	IBS-QOL (FA and IF)
	56%/89% = 63%	0%/44% = 0%	-	FA: 31/25 = 125% IF: 9/10 = 84%
Craske SM	BSS	VSI	-	IBS-Qol (FA and IF)
	56%/82% = 68%	0%/23% = 0%	-	FA: 31/17 = 184% IF: 9/14 = 64%
Drossman	McGill pain Questionnaire	-	-	IBS-QOL
	2.77/4.58 = 60%	-	-	4.8/9.35 = 51%
Gaylord	IBS-Symptom Severity Score (IBS-SSS)	VSI Brief State Inventory-anxiety	Brief State Inventory-depression	IBS-QOL
	42.2/68.8 = 61%	1.16/5.78 = 20% 1.64/3.86 = 42%	0.78/1.49 = 52%	3.7/0.19 = 36%
Moser	IBS-Impact Scale (IBS-IS)	HADS Hospital Anxiety and Depression Scale	-	SF-36
	40.9/60.8 = 67%	0.5/3.7 = 14%	-	24/117.9 = 20%
Payne & Blanchard	Composite Primary Symptom Reduction (CPSR)	STAI (state) STAI (trait)	Beck's Depression Inventory (BDI)	-
	25%/75% = 33%	-0.1/5.3 = 0% -0.4/8.1 = 0%	0.4/6.3 = 6%	-

Table 4. Comparison of outcome measurements (*continued*)

Author	Symptoms	Anxiety	Depression	Quality of life
Shinozaki	Adequate Relief Self Reported IBS Questionnaire (SIBSQ) 30/81.8 = 37% 19.6/3.2 = 612%	State Trait Anxiety Inventory (state) STAI (trait) 3.2/2.8 = 114% 4/1.5 = 267%	Self Rating Depression Scale (SDS) 0.1/1.8 = 6%	SF-36 15.5/58.2 = 27%

The percentages were calculated by dividing the treatment effect in the placebo group by the treatment effect in the intervention group and multiplying the quotient by 100. FA: Food avoidance; IF: Interference ; VSI: Visceral sensitivity index.

DISCUSSION

Summary of findings

Our results showed that the PRR in six studies investigating the effect of psychological treatment on IBS for the primary outcome varied from 25.0% to 59.0%. The pooled adjusted mean PRR was 41.4%, which is comparable to the PRR reported in studies on pharmacological therapy (37.5%)[16], medication and dietary fibre (47%)[18], medication and alternative medicine (40.7%)[17], and complementary medicine (42.6%).[11] Our presumption that the response to placebo interventions in studies on psychological treatment for IBS would be greater than that to pharmacological interventions, was not confirmed by our results.

Explanation of findings

Compared to the placebo medication used in the pharmacological studies, the placebo interventions used in the psychological studies involved extensive patient-professional contact. It has been proposed that the personality of and empathy exhibited by the therapist during the placebo intervention are responsible for the placebo effect.[10,29] Furthermore, the more time that the therapist spends with a patient, the greater the placebo response. Hence, one would expect that the PRR in psychological studies would be higher. The fact that we found comparable PRR to those reported in pharmacological studies is obviously inconsistent with this hypothesis. Other factors may need to be considered. Vase *et al.*[30] showed that the combination of expected pain relief and desire for pain relief accounted for up to 81% of the variance in the effect of active treatment. They concluded that "adding a verbal suggestion for pain relief in drug treatment can increase the magnitude of placebo analgesia to that of an active agent." Kirsch[14] also argued that the placebo effect is generally dependent on the activation of response expectancy in the patient. From this perspective, the PRR is determined by the expectation of and desire for symptom relief of the patient, which is influenced by the way that the therapy is introduced and executed by the nurse, doctor, or therapist. A positive interpersonal encounter with affective communication and adequate information from the health professional can positively influence the patient's expectations and result in an improvement in health status.[31] Therefore, the words that a general practitioner uses to create expectations within the patient are important, in both pharmacotherapy and psychological interventions.[32] The fact that we did not find a difference in placebo response in our study supports the idea that contextual factors and cognitive and emotional changes, such as expectancy, desire, and memory play a role in the development of the placebo response.[33]

Strengths and limitations

An important strength of the present study is the use of strict inclusion criteria to define IBS, psychological treatment, and placebo control conditions.[5,6] Although this approach also resulted in a small number of studies and a relatively low number of patients, we consider the comparability of the format of psychological and placebo intervention to be essential for a valid assessment of the "true" placebo effect.

Comparison to the literature

After adjusting for sample size, the pooled PR in the previous systematic review by Spanier *et al.*[19] was 30.4%. Three of the four studies included in that analysis were excluded in this study, which involved different inclusion and exclusion criteria. Specifically, Blanchard *et al.*[34] had no strict diagnostic criteria for IBS and Shaw *et al.*[35] used usual care as the control intervention, which was not an appropriate control group according to our definition.

In a recent meta-analysis by Ford *et al.*[36], 31 studies were included. Five of them were also included in our review, but we excluded the remaining 26 studies for the following reasons: the IBS criteria were not clear (two studies) or Latimers criteria were used (one study), it was not an RCT (one study), the intervention used was inappropriate according to our criteria (self/management by a nurse (one study), not by a therapist (two studies), by e-mail (one study)), or the control group did not fulfil the Baskin criteria (symptom monitoring (seven studies), care as usual (six studies), waiting list (one study), medication (one study), or not having the same number of therapeutic sessions (three studies)).

It would be interesting to compare the PRR of the psychological interventions for IBS to that in studies on psychological interventions for other diseases. In the systematic review entitled "Psychological Interventions for treatment of inflammatory bowel disease" located in the Cochrane database and published in 2011[37], none of the control groups in the included studies met our criteria for control groups. In a study by Keefer *et al.*[38] on gut-directed hypnotherapy for ulcerative colitis published in 2013, a control group that met our criteria was used. The placebo rate was 40%, which was comparable to the placebo rate found in our research. In a systematic review published in 2005, Enck & Klosterhalfen[12] compared the PRRs for functional bowel disorders with those of non-intestinal diseases and other organic gastrointestinal diseases. Most of the studies focused on drug treatment. The authors stated that the placebo effects in functional bowel disorders were similar to those in non-intestinal diseases (depression, pain, and Parkinson's disease) and not too dissimilar to those in other gastrointestinal diseases (duodenal ulcer, inflammatory bowel disease).

Secondary outcome measures

The placebo effect on the secondary outcome measures differed considerably across studies. However, the overall trends showed the greatest effects on symptom scores and the smallest effects on quality of life, anxiety, and depression, which is aligned with the findings reported by Vase *et al.*[30] Pain is the main complaint of IBS patients, and almost invariably these patients possess the hope and desire that treatment will bring relief of their IBS related pain. The combination of expected pain relief and desire for pain relief generates the largest placebo effect and, consequently, the effect on symptom scores is likely to be the greatest.

The relatively high PRR for anxiety in the study of Shinozaki *et al.*[28] (267%) may have been caused by the content of the educational program, which was completely focused on dietary education. Most IBS patients have considerable anxiety surrounding the potential for dietary substances to act as complaint-inducing agents. A program with this content is apparently helpful in reducing this anxiety. In the study by Craske *et al.*[23], the educational program had a positive impact on the patients' food avoidance. Additionally, the effect on the Food Avoidance scale of the IBS-QOL scale was greater than the effects in the two treatment arms (125% and 184%). The results of these studies suggest that it may be worthwhile to include an educational module in IBS treatments.

In the study by Shinozaki *et al.*[28], the PRR>100% of the Self-Reported IBS Questionnaire (SIBSQ) indicated that the placebo intervention was more effective than the treatment intervention. It is not clear why this study found a significant positive treatment effect of autogenic training on the primary outcome measure of "adequate relief" and a significant positive effect of the placebo intervention on the primary symptom measure SIBSQ.

Conclusions and clinical implications

In conclusion, despite the more extensive patient-professional contact, the PRR in the placebo arm of RCTs with psychological treatment interventions is comparable to that of RCTs on drug interventions. This finding does not support the hypothesis that the personality and empathy of the professional are the main determinants of the placebo effect. Most likely, the PRR is determined to a greater extent by patient- than doctor-related factors. Particularly important is the combination of expectations about and desire for symptom relief, both of which are influenced by the way that the therapy is introduced and executed. Thus, for optimal control group comparison in studies investigating psychological treatment for IBS, patients in the control group should have similar expectations from the control intervention as patients in the active intervention arm. Therefore,

future RCTs should map the expectations of patients in both RCT arms before starting the intervention.

In clinical practice, the placebo response can be used optimally by enhancing the expectations of the patient through the provision of realistic but positive information about the expected effect of the treatment. The preference of patients for a certain treatment might be related to the expected benefit, although it could also be the result of other contextual factors, such as the way in which the treatment is delivered (group versus individually). Future research should investigate the effect of patients' preference for a certain treatment arm on the treatment outcome.

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Chapter 6

Effectiveness of psychological treatments for Irritable Bowel Syndrome when compared to high-quality placebo control conditions: a systematic review

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This study is part of the preparation of the update of the Cochrane review by Zijdenbos et al. *(2009), in collaboration with the Cochrane Collaboration.*

ABSTRACT

Aim To evaluate the effectiveness of psychological treatments for irritable bowel syndrome (IBS) when compared to high-quality placebo control conditions.

Methods Randomised controlled trials comparing psychological interventions for the treatment of adult patients with IBS, with the exception of hypnosis, were identified by searching the Cochrane Library, Medline, Embase, and PsycInfo from the first available data until March 2017. Those studies using high-quality placebo control interventions, i.e., therapist-delivered interventions focused on IBS with direct contact with a trained therapist (live or via internet) in a comparable number of sessions, with similar length and frequency as the treatment under study, were considered to be eligible for inclusion. Only full-text articles published in English and in peer-reviewed journals were selected for the present review.

Results The literature search resulted in 1211 studies, of which 110 studies were potentially eligible. 105 studies did not meet inclusion criteria and were excluded, leaving five eligible trials: three on cognitive behavioural therapy (CBT), one on mindfulness, and one on relaxation therapy. Four studies used psychoeducation and support as the placebo intervention and one used a support group. Mindfulness and relaxation therapy were more effective than placebo control interventions in the treatment of IBS whereas CBT was not.

Conclusion When considering only studies with high-quality control interventions, of all psychological interventions only mindfulness and relaxation therapy were found to be effective in patients with IBS. In contrast to CBT, which is directed at IBS related thoughts and behaviour, these interventions aim at body and mind relaxation. This might reduce the physiological stress response that provokes and maintains IBS symptoms.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder, characterised by recurrent episodes of abdominal pain, discomfort, altered bowel habits, and/or symptoms of bloating and distension, in the absence of structural or biochemical abnormalities.[1] IBS affects up to 15% of the population in Western countries and leads to a reduced quality of life and high healthcare utilisation.[2,3,4] The diagnosis is based upon consensus-based criteria, the most recent of which are the Rome IV criteria.[5] Although spasmolytic and antidepressants may work for some patients, evidence for effectiveness is generally weak and most guidelines advise a restricted use of pharmacotherapy in IBS.[5,6] Psychological interventions have been investigated as an alternative therapeutic intervention in IBS. In 2009, the Cochrane Collaboration published a systematic review on the effectiveness of available psychological treatments for IBS, i.e., cognitive behavioural therapy (CBT), interpersonal psychotherapy, and relaxation/stress management.[7] The review was based on 25 studies and concluded that psychological interventions may be slightly superior to usual care or waiting list control conditions. However, the meta-analysis was significantly limited by quality issues, such as validity, heterogeneity, small sample size, and inadequate outcomes. A separate Cochrane review on the effectiveness of hypnotherapy in IBS was published in 2007.[8] This review was based on four studies, and concluded that no conclusion about the efficacy of hypnotherapy for IBS could be drawn because of inadequate quality of the trials. Since 2009, three new meta-analyses and systematic reviews on the efficacy of psychological interventions for improvement of IBS symptoms were published.[5,6,9] Laird *et al.* (2016) performed a meta-analysis of 41 trials investigating the effectiveness of psychotherapy for reducing IBS symptoms. Compared with a heterogeneous group of control conditions, psychological therapies had a significant effect on IBS symptom improvement immediately after treatment. The effect size was intermediate, but remained significant in 1-12 months follow-up.[5] Li *et al.* (2014) focused on the use of CBT to improve symptomatology, quality of life (QOL), and psychological state of patients with IBS. In a meta-analysis of eighteen randomised control trials (RCTs), CBT proved more effective in reducing bowel symptoms, QOL, and psychological state than waiting list controls, both immediately after intervention and in short-term follow-up. CBT was not superior to other psychological treatments.[9] Ford *et al.* (2014) performed a systematic review and meta-analysis of RCTs comparing antidepressants with placebo, and psychological therapies with control therapy or usual care in patients with IBS. 48 RCTs were found eligible, 31 of which compared psychological therapies with control therapy or usual care. The authors concluded that CBT, hypnotherapy,

multicomponent psychological therapy, and dynamic psychotherapy were all beneficial in the management of IBS.[6]

Although the results of these meta-analyses suggest that psychological therapies are superior, most of the included studies used inactive control conditions such as care as usual, waiting list, or symptom monitoring. For adequate comparison, however, control interventions must be comparable to the psychological intervention, except for the therapeutic component. This means that control interventions must have an active component, with content relevant to the IBS patient. The intervention must be therapist-delivered, in a comparable format (individual or group) with a comparable number of sessions of equal length.[10] The placebo response rate depends on the type of control intervention. We recently assessed the placebo effect in studies on psychological treatment for IBS.[11] The pooled placebo response rate was 41.4%, with 39.5% for educational programs (four studies) and 42.9% for supportive interventions (two studies). Recently new psychological interventions for IBS have been developed, such as mindfulness therapy and emotional awareness training, and new formats, such as internet-delivered therapies. In addition, there is increased attention for the importance of an adequate control intervention in studies on psychological interventions, to safeguard valid comparison.[10] The aim of the present study is to systematically review the effectiveness of psychological interventions for IBS using only high-quality control conditions.

METHOD

Design

Systematic review.

Search method

According to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[13], we did an electronic search in the Cochrane Library, Medline, Embase, and PsycInfo for RCTs published from the first available date until March 2017. A combination of MeSH and free-text words for IBS and psychotherapy was used to identify relevant articles. See Appendix for the detailed search strategies. Finally, a manual search of the references listed in the articles retrieved from the online search was performed to identify additional studies.

Inclusion and exclusion criteria

Types of studies

RCTs comparing psychological interventions for the treatment of IBS with a placebo control treatment, published full text in an English peer-reviewed journal, were eligible for inclusion. Cross-over studies were excluded, as were studies comparing two types of psychological therapeutic interventions without adequate placebo control intervention.

Patients

Studies including patients 18 years of age or older diagnosed with IBS according to Manning or Rome I, II, or III criteria were considered for analysis.

Types of interventions

Therapies delivered in direct contact with the therapist (live or via internet), included in the medical subject heading (MeSH term) of Psychotherapy were considered eligible for inclusion. Hypnotherapy was excluded from the present review because there is a separate Cochrane review on hypnotherapy.

Types of placebo control interventions

Studies with a placebo control condition consisting of an active intervention, executed by a trained therapist, with an equal number of sessions of equal length and delivered in an equal number of weeks as the active psychological intervention were considered eligible for inclusion. Studies using a control group consisting of waiting list, usual care, symptom monitoring only, and those with only indirect contact with the therapist (by telephone or internet) were excluded.

Types of outcome measures

Studies were eligible if the primary outcome measure was improvement in IBS symptoms or abdominal pain only (measured with a validated IBS questionnaire), or adequate relief of IBS symptoms, following recommendations of the Rome III committee.[12] Studies were excluded if no information on the effectiveness of the psychological interventions was available or if the proportion of patients in each group with overall symptom improvement after therapy was not reported.

Data collection and analysis

Study selection

Three authors (CF, OQ, and YvR) reviewed the title and abstract of the electronically selected articles to determine if they matched the eligibility criteria. The full-text of the selected articles was then reviewed by the same authors to confirm their eligibility using the same criteria. In the case of discrepancies between the reviewers these were to be resolved by a fourth author (NdW).

Data extraction

From the selected papers, the following data were extracted: country, information on the number of patients, patient characteristics (mean age, percentage female, and mean duration of illness), recruitment procedure and treatment setting, criteria for diagnosis (Rome I, Rome II, Rome III or Manning), intervention type, delivery format (group or individual), number and length of sessions, number of weeks in which sessions were delivered, training of therapists in the treatment protocol, use of treatment/placebo manual, duration of the follow-up period, and results of the primary outcome measure (mean and standard deviation or response rate). Also, the type of statistical analysis, intention to treat (ITT), and/or per protocol (PP) was added.

Assessment of risk of bias

The risk of bias assessment tool developed by the Cochrane Collaboration for RCTs was used.[14] With this tool, the following sources of bias can be assessed and scored (high, low, or unclear level of bias): adequate generation of the allocation sequence, concealment of allocation to conditions, blinding of participants and personnel, blinding of outcome assessment, handling of incomplete outcome data, and selective outcome reporting. Because of the importance of the relationship with the therapist in psychological treatment, we defined the use of one single therapist for the intervention as a potential risk of bias. In addition, drop-out rates for intervention and placebo control groups were added.

Statistical analyses

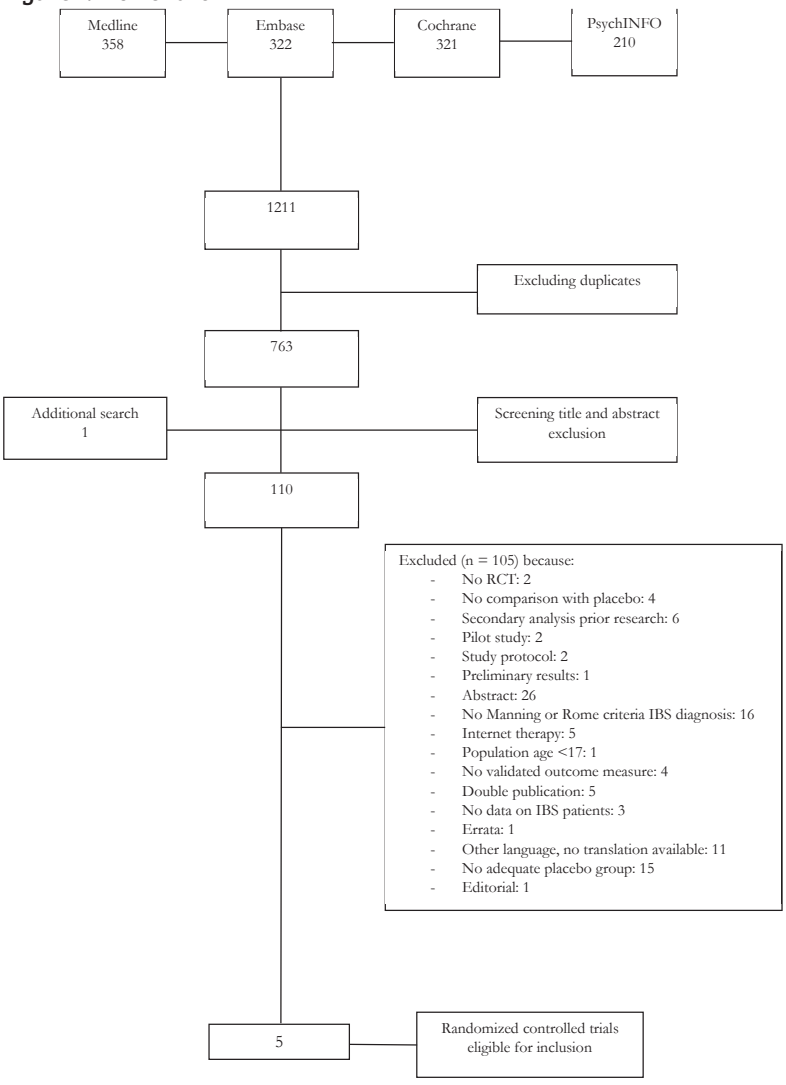
For the continuous outcome measures the standardised mean difference (SMD) with 95% confidence intervals (CI) was calculated using a random effects model for each outcome. For the dichotomous outcome measures we calculated the odds ratio (OR) (Mantel-Haenszel method).

RESULTS

Description of studies

The electronic literature search resulted in the identification of 1211 studies. Manual search of the references yielded one additional study. After screening the titles and abstracts, 110 studies were deemed potentially eligible (see Figure 1).

Figure 1. Flowchart



After reviewing the full manuscripts of these 110 studies, 105 studies were excluded for various reasons (see Figure 1), leaving five trials with a total of 406 patients that were included in the analysis: Blanchard *et al.* (2007), Craske *et al.* (2011), Gaylord *et al.* (2011), Payne & Blanchard (1995), and Shinozaki *et al.* (2010).[15-19] The characteristics of the included studies are shown in Table 1. Sample sizes ranged from 21 to 166.[15,19] Patients were recruited by local advertisement, or from the population consulting a general practitioner (primary care), a gastroenterologist or internist in a general hospital (secondary care), or medical specialist in a university hospital (tertiary care).
The mean age of the study populations ranged from 31.6 to 49.0 years.[15,19] The proportion of female participants ranged from 52% to 100%.[15,17] Only two studies reported on the duration of IBS, which was 19 and 16 years respectively.[15,18] The number of sessions for the psychological treatment and placebo intervention ranged from eight to ten sessions.[19,15-18]

Type of interventions

The five articles described three types of psychological therapies: CBT (three studies)[15,16,18], mindfulness (one study)[17], and relaxation therapy (one study)[19]. Four of the five studies used an educational program as the placebo control intervention.[15,16,18,19] In these studies, educational materials were provided and discussed with the therapist. One study used a support group.[17] Four studies used the same delivery format (individual or group) for the intervention as for the control condition. In the study by Payne and Blanchard[18], individual cognitive therapy was compared to an educational placebo intervention delivered in group setting. In the study of Craske *et al.* two types of cognitive behavioural interventions were used.[16] One intervention used interoceptive exposure to visceral sensations and the other stress management. Results will be described separately.

Quality assessment

Risk of bias due to inadequate random sequence generation and allocation concealment was high in the study of Blanchard *et al.*[15] and unclear in the studies of Payne & Blanchard[18] and Shinozaki *et al.*[19] In psychological intervention studies, it is not possible to blind participants and professionals for the type of treatment (active or control) that they will receive. All studies therefore scored high on bias for this criterion. Apart from this, there was only one study for which all types of bias were rated low.[17] In the studies of Payne & Blanchard[18] and Shinozaki *et al.*[19] therapy and control intervention were delivered by one therapist, which increases the risk of bias. Craske *et al.*[16] did not report on the number of therapists, so the risk of bias is unclear. The percentage of dropouts was highest in the study

of Craske *et al.*[16] In the treatment conditions interoceptive exposure and stress management, 34% and 36% of the patients dropped out respectively. Because

Table 1. Systematic review of studies on the effectiveness of psychological interventions for IBS using high-quality control interventions. Characteristics and quality criteria of included studies (N=5)

First author	Blanchard *et al.*[15]	Craske *et al.*[16]	Gaylord *et al.*[17]	Payne & Blanchard[18]	Shinozaki *et al.*[19]
Year	2007	2001	2001	1995	2010
Country	US	US	US	US	Japan
Number of patients	166	110	75	34	21
Mean age (yrs)	49.0	39.4	42.7	40.1	31.6
Female (%)	81	74	100	85	52
Mean illness duration (yrs)	19	n.r.	n.r.	16	n.r.
Recruitment / Treatment setting [a]	3/3	0/3	0;2/3	1/3	3/3
IBS criteria	Rome II	Rome II	Rome II	Rome I	Rome II
Intervention [b]	CT	CBT	MT	CT	RT
Placebo control [c]	PES	PES	S	PES	PES
Format Intervention / Control	Group/ Group	Individual/ Individual	Group/ Group	Individual/ Group	Individual/ Individual
Number of sessions	10	10	9	10	8
Duration of session (min)	90	50	120 [d]	60	30-40
Intervention period (wks)	10	10	8	8	8
Trained therapist intervention/ placebo	Yes/yes	Unclear/ unclear	Yes/yes	Yes/unclear	Yes/unclear
Protocol intervention/placebo	Yes/yes	Yes/yes	Yes/yes	Yes/yes	Yes/yes
Intention to treat (ITT) or per protocol (PP) analysis	ITT and PP	ITT	ITT	ITT	ITT

n.r. not reported

a: 0 = local (advertisement), 1 = primary care, 2 = secondary care; 3 = tertiary care

b: CT = cognitive therapy; CBT = cognitive behavioural therapy; MT = mindfulness therapy; RT = relaxation therapy

c: PES = Psychoeducational support; S = support

d: 120 minutes plus one half-day retreat

of this, the risk of bias due to incomplete outcome data was rated high. Payne & Blanchard[18] and Shinozaki *et al.*[19] had no dropouts (see Table 2).

Table 2. Systematic review of studies on psychological interventions in IBS quality assessment and risk of bias ratings for included studies (N=5)

First author	Blanchard *et al.*[15]	Craske *et al.*[16]	Gaylord *et al*[17]	Payne & Blanchard[18]	Shinozaki *et al.*[19]
Year	2007	2011	2011	1995	2010
Random sequence generation	high	low	low	unclear	unclear
Allocation concealment	high	low	low	unclear	unclear
Blinding of participants and personnel	high	high	high	high	high
Blinding of outcome assessment	low	low	low	unclear	unclear
Incomplete outcome data	low	high (high dropout)	low	low	low
Selective reporting	low	low	low	low	low
Number of therapists	low	unclear	low	high	high
% Dropout of treatment /Placebo control	9/13	IE[1] 34/16; SM[2] 36/16	6/18	0/0	0/0

Note: Possible ratings were low, high, or unclear risk of bias. Studies with two control groups were rated twice for risk of bias because of lack of blinding (rated or actice control groups appear in parentheses).

[1]*IE = interoceptive exposure*

[2]*SM = stress management*

Effectiveness of psychological interventions

Cognitive Behavioural Therapy

Two studies on cognitive therapy Blanchard *et al.* (2007) and Payne & Blanchard (1995) used the same endpoint: the Composite Primary Symptom Reduction Score (CPSR), a composite score of reduction in pain and tenderness, bloating, and diarrhoea and/or constipation.[15,18] Payne & Blanchard (1995) found cognitive therapy to be more effective than the psychoeducational support group (SMD: 1.02 [95%CI 0.16, 1.88]). However, Blanchard *et al.* (2007) did not find a significant effect for cognitive therapy. The combined effect of these studies is not significant (SMD: 0.11 [95%CI -0.36, 0.57]). In the study of Craske *et al.* CBT with interoceptive exposure and CBT with stress management were compared with a psychoeducational support group.[10] As primary endpoint the Bowel Severity Index (BSS) was used, which is a composite score of individual symptom ratings of overall gastrointestinal symptoms, lower abdominal pain,

Table 3. Systematic review of studies on psychological treatment of IBS. Outcome measures and intervention effect of included studies (N=5)

Comparison	Author	Outcome measure	Intervention			Control			SMD [95%CI]
			Mean	SD	N total	Mean	SD	N total	
Cognitive therapy versus psychoeducational support	Blanchard *et al.*	Composite primary symptom reduction score (CPSR)[a]	0.132	0.44	120	0.246	0.4	46	-0.26 [-0.61, 0.08]
Cognitive therapy versus psychoeducational support	Payne & Blanchard	Composite primary symptom reduction score (CPSR)[a]	0.67	0.24	12	0.31	0.42	12	1.02 [0.16, 1.88]
Cognitive behavioural therapy versus psychoeducational support	Craske *et al.* IE[1] Craske SM[2]	Bowel symptom severity index (BSS)[b]	0.54 0.25	0.74 0.83	47 41	0.25 0.25	0.98 0.98	22 22	-0.35 [-0.86, 0.16] 0.00 [-0.52, 0.52]
Mindfulness versus support group	Gaylord *et al.*	IBS-symptom severity score (IBS-SSS)[b]	204	25	36	269	30	39	-2.32 [-2.91, -1.73]
			Positive treat-ment effect		Total	Positive treatment effect		Total	Odds ratio
Relaxation therapy versus psychoeducational support	Shinozaki *et al.*	Adequate relief	9		11	3		10	10.50 [1.36, 81.05]

a: high score is better

b: low score is better

SMD: Standard Mean Difference

CI: Confidence Interval

[1]*Craske IE = Interoceptive Exposure*

[2]*Craske SM = Stress Management*

lower abdominal bloating, and lower abdominal discomfort. Both interventions proved equally effective as a psychoeducational support group. For an overview of all the outcomes, see Table 3.

Mindfulness

Gaylord *et al.* (2011) compared mindfulness with a support group control intervention, using the IBS-symptom severity score (IBS-SSS) as primary outcome measure. They included only women and found mindfulness to be more effective than support group in reducing IBS symptoms (SMD: -2.32 [95%CI -2.91, -1.73]).[17]

Relaxation therapy

Shinozaki *et al.* (2010) studied the effectiveness of relaxation therapy as compared to an educational support intervention, using adequate relief (AR) as primary outcome measure. This dichotomous outcome measure consists of a single question ("did you experience adequate relief of IBS symptoms in the past week?"). The proportion of AR after the last session of the relaxation therapy group was significantly higher than in the psychoeducational support intervention (Odds ratio: 10.50 [95%CI 1.36, 81.05]).[19]

DISCUSSION

Summary of findings

We identified only five studies evaluating the effectiveness of psychological interventions in IBS that used high-quality placebo interventions. In three out of five studies the psychological intervention was found to be superior.[17,18,19] Based on the combined results of the three studies, cognitive therapy is not superior to educational control intervention. Based on single studies, both mindfulness and relaxation therapy were found to be superior to placebo, with a difference large enough to be clinically relevant.

Quality of the included studies

The study of Shinozaki *et al.* used AR as the outcome measure.[19] Although AR has been recognised as an easy to apply and validated instrument, its reliability (internal consistency) has not been established and its responsiveness to change has not been empirically tested. To obtain a reliable estimate, the AR question should be posed once a week for four consecutive weeks.[20] In the study of Shinozaki *et al.* this was only asked once, so it cannot be ruled out that the findings are

the result of chance, rather than of the therapy. The study of Shinozaki *et al.* and the study of Payne & Blanchard did carry additional risks of bias. In both studies the randomisation procedure was unclear as was the allocation concealment. As treatment was delivered by only one therapist it cannot be ruled out that the observed effect is therapist-dependent. Finally, the number of patients in both studies was small.

The study of Gaylord *et al.*[17] was considered the study with the lowest risk of bias. Furthermore, it used support as the placebo control intervention, which might be even more potent as a placebo than psychoeducation.

Outcome measures needed to be validated instruments to assess IBS symptoms or relief of symptoms. The five studies used four different outcome measures as their primary endpoint. Four studies were excluded because they either did not use an IBS specific score, or a non-validated one.[22-25] Drossman *et al.*[22], for instance, used as primary outcome measure a composite score consisting of satisfaction with treatment, global wellbeing, pain intensity (2-week diary), and health-related quality of life. All these topics were recommended by the Rome committee, but the questionnaire was not validated.

It is important for the field that consensus is reached about the best outcome measures to be used in future IBS intervention studies. Bijkerk *et al.* started this process by reporting expert opinions on five IBS symptom scales.[26] Empirical study on the reliability and responsivity as a specific aspect of validity of these instruments is necessary and might help to select the most suitable instruments for measuring intervention-induced changes in IBS symptoms.

Explanation of findings

Even after selecting studies with only well-designed control comparisons, we still found psychological interventions to be superior to placebo control. This may be somewhat surprising, as Baskin *et al.*[10] found in their meta-analysis that the effectiveness of well-designed placebo interventions was comparable to that of the interventions with which they were compared.

The results show that mindfulness and relaxation are more effective than support or psychoeducation and support. Both interventions induce a relaxed state of body and mind and, as such, reduce the physiological stress response which can provoke and maintain IBS symptoms.[27] Their point of action is very different from CBT which is directed at IBS related thoughts and behaviours. Irrational disease-related thoughts and behaviour might help to sustain IBS symptoms and, as such, we would have expected CBT to result in a decrease of IBS symptom severity. However, CBT was not more effective than psychoeducation and support intervention. This could be explained by the fact that CBT and psychoeduca-

tion have the same point of action, i.e., both result in a change in IBS related thoughts and behaviours. In that case, both CBT and control intervention result in a decrease of IBS symptom severity. If psychoeducation is indeed as important as it now seems[28], then it might be worthwhile to develop psychoeducational interventions that are easily available for all patients.

Although we did not include studies using hypnotherapy in IBS, we expect that the effect of hypnosis is comparable to that of mindfulness and relaxation, because one of the working mechanisms is lowering stress.[29]

Strengths and limitations

One of the strengths of the present systematic review is the use of strict inclusion criteria for both the placebo control conditions and the outcome measures. According to Baskin *et al.*[10] we included only control conditions which were structurally equivalent to the intervention, i.e., treatment and placebo provided participants with an equal number and length of sessions and the sessions were delivered in an equal number of weeks, and therapists had generally equivalent skill and training. In addition, Baskin *et al.*[10] advise that an identical format (e.g., group or individual) should be used for the experimental and control intervention. If we had also adhered to that advice, Payne & Blanchard[18] would have been excluded as well because they used different format for the experimental and control intervention. However, exclusion would not have changed the conclusions concerning the effectiveness of CBT. Furthermore, we did not formally assess the criterion that the placebo control intervention should allow participants to discuss their IBS associated problems. However, since supporting each other was part of all control conditions it is most likely that this criterion was also met.

Conclusion

Only five studies compared the effectiveness of psychological interventions in IBS with that of a high-quality control intervention such as psychoeducation and support. Of those, only mindfulness and relaxation therapy, and not CBT, proved to be more effective than the placebo control intervention. In contrast to CBT, which is directed at IBS related thoughts and behaviours, these interventions induce a relaxed state of body and mind and may reduce the physiological stress response which can induce and maintain IBS symptoms.

Replication of studies on relaxation and mindfulness in IBS is needed to confirm these effects, as are studies investigating the psychometric qualities of IBS outcome measures.

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APPENDIX SEARCHES

	Medline	Results
1	Irritable Bowel Syndrome/	5,516
2	("Irritable Bowel Syndrome" or "colonic diseas*" or "gastrointestinal syndrom*" or ((spas* or irritable or functional) adj (colon or colitis or bowel or gastrointestinal))).ti,ab,kf.	14,212
3	1 or 2	14,980
4	exp Psychotherapy/	171,914
5	(psychotherap* or (psych* adj (therap* or treatment* or intervention* or approach*)) or ((bahavio* or cognitive) adj2 (therap* or intervention*)) or (exposure adj2 treatment*) or cbt or interoceptive exposure or mindful* or relaxation or "stress reduction" or "stress management" or "integrative therapy" or "acceptance and commitment therapy" or ACT or FAP).ti,ab,kf.	408,209
6	4 or 5	526,787
7	3 and 6	1,066
8	(randomized controlled trial or controlled clinical trial).pt. or (random* or placebo or trial or groups).ab.	2,508,553
9	7 and 8	325

	Psycinfo	Results
1	exp Irritable Bowel Syndrome/	972
2	("Irritable Bowel Syndrome" or "colonic diseas*" or "gastrointestinal syndrom*" or ((spas* or irritable or functional) adj (colon or colitis or bowel or gastrointestinal))).ti,ab.	1,488
3	1 or 2	1,651
4	exp placebo/ or crossover.mp. or exp treatment effectiveness evaluation/ or exp mental health program evaluation/ or ((random* or ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$))).mp. or placebo$).mp.	200,981
5	3 and 4	207

	Cochrane	Results
ID	Search	
#1	[mh "Irritable Bowel Syndrome"]	
#2	("Irritable Bowel Syndrome" or "colonic diseas*" or "gastrointestinal syndrom*" or ((spas* or irritable or functional) near/2 (colon or colitis or bowel or gastrointestinal))):ti,ab,kw	
#3	#1 or #2	
#4	[mh Psychotherapy]	
#5	(psychotherap* or (psych* near/2 (therap* or treatment* or intervention* or approach*)) or ((bahavio* or cognitive) near/3 (therap* or intervention*)) or (exposure near/3 treatment*) or cbt or interoceptive exposure or mindful* or relaxation or "stress reduction" or "stress management" or "integrative therapy" or "acceptance and commitment therapy" or ACT or FAP):ti,ab,kw	
#6	#4 or #5	
#7	#3 and #6	
#8	in Trials	251

Chapter 7

Group-delivered versus individual hypnotherapy for Irritable Bowel Syndrome: results from the IMAGINE study

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Prepared for submission

ABSTRACT

Background: Irritable Bowel Syndrome (IBS) is the most common gastrointestinal disorder in the population. The effectiveness of hypnotherapy in IBS has been demonstrated but mainly for patients with refractory symptoms, delivered in specialised departments, in an individual setting. We designed the IMAGINE study to assess the effectiveness of hypnotherapy, delivered in a group and individual setting in patients with IBS referred from primary and secondary care.

Methods/Design: In a multi-centred randomised placebo-controlled trial, 354 primary and secondary care patients (aged 18-65 years) with IBS (Rome III criteria) from 13 hospitals in the Netherlands were randomly allocated to either six sessions of individual hypnotherapy (IHT), six sessions of group hypnotherapy (GHT) or six sessions of educational supportive therapy in a group (control group, EST). Outcomes were measured prior to treatment, immediately after treatment (at three months), and nine months after treatment (at 12 months). The primary outcome parameter was the responder rate for adequate relief (AR) of IBS symptoms. Secondary outcome measurements were changes in the IBS symptom severity, quality of life, disease cognitions, psychological complaints, self-efficacy, and direct and indirect costs. We hypothesised that hypnotherapy was more effective than the educational control intervention, and that group hypnotherapy was not inferior (<15%) to individual hypnotherapy.

Results: After finishing therapy, three months from baseline, the primary outcome AR was met in 40.2% of the patients in the IHT group, in 34.1% in the GHT group, and in 17.1% in the EST group. At 12 months the figures were 41.8%, 50.0%, and 22.6% respectively. In the intention to treat (ITT) analysis, hypnotherapy was more effective than EST, both at three months (OR 2.9, 95%CI 1.2-7.4, p=0.02), and at 12 months (OR 2.8, 95%CI 1.2-6.7, p=0.02). To test the non-inferiority hypotheses, a per protocol analysis was performed. At three months 49.9% (95%CI 39.2-60.6%) of IHT and 42.7% (95%CI 32.3-53.8%) of GHT patients showed adequate relief, and at 12 months 55.5% (95%CI 43.4-67.1%) of IHT and 51.7% (95%CI 40.2-63.0%) of GHT patients. Difference at both time points were not significant.

Patients in all three groups improved in symptom severity (IBS-SSS), in quality of life (IBS-QOL), in psychological complaints (SCL-90), in cognitions (CS-FBD), and in self-efficacy (SES), with slightly better outcomes for the hypnotherapy interventions, but in the ITT analysis differences were not significant. Direct and

indirect costs (TiC-P) improved in all three groups with no statistically significant differences in favour of hypnotherapy groups.

Conclusion: Hypnotherapy is an effective treatment for patients with IBS both from primary and secondary care, and can be effectively delivered in both group and individual setting. Group delivery may facilitate widespread use of hypnotherapy in daily practice.

Trial registration:
Trial register: Current Controlled Trials
Registration number: ISRCTN22888906

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder, characterised by recurrent episodes of abdominal pain, discomfort, altered bowel habits, and/or symptoms of bloating and distension, in the absence of structural or biochemical abnormalities.[1] The diagnosis is based upon consensus-based criteria, the most recent of which are the Rome IV criteria.[2] Patients with IBS can have severe incapacitating complaints resulting in an impaired quality of life[3] and a substantial economic burden for society.[4-6] Pharmacotherapy for IBS has limited effectiveness, although spasmolytics and antidepressants may work in some patients.[7] Psychological interventions, like cognitive behaviour therapy (CBT) and short psychodynamic therapy, have demonstrated effectiveness in IBS, but their application is thwarted due to the limited availability of therapists.[7,8]

Since 1984[9], there has been an increasing scientific interest in hypnotherapy for IBS. So far, most research was done in tertiary care patients with refractory complaints, and meta-analyses of these studies show that the evidence for effectiveness is still limited.[7,10-14] More high-quality trials are needed, with long-term follow-up, in larger patient groups, including primary care.[7,10,11] Special attention should be paid to adequate control group comparison. Most studies so far used inactive control conditions such as care as usual, waiting list, or symptom monitoring. For adequate comparison, however, control interventions must be comparable to the psychological intervention, except for the therapeutic component. They must have an active component, with content relevant to the IBS patient and the intervention must be therapist delivered, in a comparable format.[15]

So far, hypnotherapy is usually delivered in individual setting. Group application may, once proven equally effective, contribute to more widespread use in clinical practice, as fewer therapists are needed. The only comparative study so far showed no difference in effectiveness between individual and group treatment, but the study sample was small (N=33) and patients were referred from secondary and tertiary care.[16]

We designed a randomised controlled trial (RCT) assessing the effectiveness of hypnotherapy, delivered in both individual and group setting, in primary and secondary care patients with IBS in comparison to a control group with educational supportive therapy.[17] We hypothesised that hypnotherapy would be more effective than educational supportive therapy and that hypnotherapy in a group setting would be non-inferior to individual therapy.

METHODS

Design

Non-inferiority 12-week controlled parallel-group randomised clinical trial with three arms (Trial Registration number: ISRCTN22888906). Details on the study design are reported elsewhere.[17]

Study population

The study population consisted of patients with IBS aged between 18 and 65 years referred by primary care physicians and hospital specialists from 13 hospitals in the Netherlands. All patients met the Rome III criteria for IBS. We used the Dutch version of the IBS Module of the Rome Foundation[18] officially translated by two authors (CF and YvR). Patients with insufficient command of the Dutch language, those unwilling to participate in group sessions, those with a psychiatric condition, those with comorbid chronic bowel diseases, and those with a history of major gastrointestinal surgery or radiotherapy were excluded.

Randomisation

After an intake session with the hospital-based psychologist/hypnotherapist, in which in- and exclusion criteria were checked and informed consent was signed, patients were randomly allocated to one of the three study arms: (1) individual hypnotherapy (IHT), (2) group hypnotherapy (GHT), or (3) control intervention with educational supportive therapy (EST). Randomisation with a ratio of 3:3:1 (see sample size calculation) was carried out by means of a computer-based, six-block random number tables procedure performed by staff not involved in the treatment. As group treatment required six patients, randomisation was done block-wise to prevent prolonged waiting time for the individual patient.

Intervention groups

For IHT, patients were offered six bi-weekly 45-minute sessions in which they received hypnotherapy following a structured protocol with the same content for each session. After introduction and explanation of the therapy, the first step was the hypnotic induction, followed by suggestions, illustrated by images described in the protocol, to normalise motility of the gut and reduce pain and feelings of discomfort. Finally possible questions concerning the hypnotic process were discussed and the importance of practising the exercises at home was emphasised. The treatment procedure was developed by the investigator (CF) based on the Manchester protocol for hypnotherapy in IBS previously developed and validated by Whorwell *et al.*[19]

In GHT, patients participated in six bi-weekly 60-minute group sessions, with a maximum of six IBS patients per group. The group hypnotherapy used the same protocol as the individual hypnotherapy. Both patient groups were given homework assignments consisting of CD-recorded hypnotherapeutic exercises that required 15-20 minutes daily.

Group and individual hypnotherapy were given by the same therapists. All therapists were qualified psychologists who were trained as hypnotherapists, but without specific experience with IBS patients. Before the start of the study they were instructed on the intervention by one of the authors (CF).

Control group

According to earlier recommendations, optimal control interventions for the evaluation of psychological therapies require a comparable number of contacts and lengths of sessions with the therapist as the treatment under study, and content that is relevant for patients.[15] We developed an EST consisting of six bi-weekly 60-minute group sessions, with a maximum of six patients per group. In this EST, IBS related topics were discussed: general information about the condition, food and lifestyle and dealing with stress in IBS. Details of the EST are described elsewhere.[20] Homework assignments were given that took about 15-20 minutes per day. EST was provided by nurse practitioners or psychological assistants who were specifically trained by the author (CF) for the control intervention.

Other treatments during the study

Patients were allowed to continue medical care as given by their physicians but were asked not to change medication during participation, except on doctor's advice.

Outcome measurements

Primary outcome

In line with previous recommendations on optimal outcome assessment in trials on functional gastrointestinal disorders, we chose adequate relief (AR) of IBS symptoms as the primary outcome.[21,22] AR is a validated outcome in IBS research, consisting of a single question ("Did you have adequate relief of IBS related abdominal pain or discomfort in the past week? (Yes/No)"). The question is asked once weekly during four consecutive weeks.[23,24] Responder is defined as patients answering "yes" three or four out of four weeks. With consent of the authors, an official Dutch translation was made by the authors (CF and YvR).

Secondary outcomes

Irritable Bowel Syndrome Symptom Severity

IBS symptoms were measured using the IBS-symptom severity score (IBS-SSS), which assesses five features of IBS (pain severity and frequency, abdominal distension, bowel satisfaction, and interference with life in general) and their intensity, using visual analogue scales.[25] The IBS-SSS is a validated and recommended outcome measure for IBS symptomatology. With consent of the authors, an official Dutch translation was made by the authors (CF and YvR).

Irritable Bowel Syndrome Quality of Life

Disease-specific quality of life was assessed using the Irritable Bowel Syndrome Quality of Life scale (IBS-QOL).[26] This scale has been validated in various populations and includes 30 items on nine scales: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexuality, relationships, and an overall scale. The sum score is used as outcome.

Psychological symptoms

Psychological symptoms were assessed with the Dutch version of the Symptom Checklist (SCL-90).[27,28] The SCL-90 is a 90-item multidimensional self-reported inventory, designed to evaluate psychological problems and psychopathology on nine subscales: agoraphobia, anxiety, depression, somatisation, insufficiency of thought and action, distrust and interpersonal sensitivity, hostility, sleeping problems, and psychoneuroticism (total score). The sum score is used as outcome. The SCL-90 is a validated and widely used questionnaire with good psychometric qualities.[27]

Dysfunctional cognitions

The Cognitive Scale for Functional Bowel Disorders (CS-FBD) has been developed by Toner[29] and was translated with permission by one of the authors (YvR). The CS-FBD consists of 31 items which measure a patient's level of dysfunctional cognitions concerning his or her IBS. It is a valid and reliable scale that can be used as an outcome measure in evaluating the efficacy of psychotherapeutic interventions for functional bowel disorders.[29]

Self-efficacy

The Self-Efficacy Scale (SES) is a seven-item questionnaire designed to measure the confidence patients have in their capacity to influence their somatic com-

plaints. It was originally developed for patients suffering from chronic fatigue[30] and adapted by CF and YvR with permission from the authors.

Costs

The Trimbos/iMTA Questionnaire (TiC-P) measures direct medical costs due to healthcare utilisation for psychiatric illness during the past four weeks and indirect nonmedical costs due to productivity loss during the past two weeks.[31] It was adapted to IBS for this study. Direct medical costs included the total costs for visits to the primary care doctor and specialist and the costs for medication in the past four weeks.

Other study parameters

Patients were requested to record the number of times they used the CD or did the hypnotherapeutic exercises in the last week for 52 consecutive weeks.

Timeline and follow-up

Enrolment started May 2011 and ended in April 2016. Prior to intervention the secondary outcome measures were assessed at baseline. After the active treatment period of three months, the primary outcome measure was assessed and the secondary outcome measures were assessed again. Finally, nine months after end of the intervention, 12 months from baseline, the primary and secondary measures were assessed again.

Sample size calculation

For the first comparison between hypnotherapy and EST we assumed a 32% difference between hypnotherapy and control intervention, based on an earlier reported response rate for individual hypnotherapy of 57%[10] and a placebo response rate of 25%.[32] Powering the study for only this comparison would require 44 patients in both arms, assuming an alpha of 0.05, a power (1-beta) of 0.80, a cluster size of six patients per therapist, and an intra-class correlation coefficient of 0.05.

For the second comparison on non-inferiority between group and individual hypnotherapy the maximum acceptable difference for non-inferiority was set on 15%. With an alpha of 0.05 and power (1-beta) of 0.80, 135 patients in both arms were required to demonstrate that GHT is not inferior to IHT. Combining the sample size of both comparisons, assuming 10% loss to follow-up, using six patients per group, inclusion of a total of 354 patients (150 (IHT) +150 (GHT) +54 (EST)) was required.

Statistical analysis

The main analysis (hypnotherapy versus control group) was performed based on the intention to treat (ITT) principle. In line with the recommendations from the CONSORT statement, analysis of the non-inferiority comparison was based on the per protocol (PP) principle.[33]

The primary outcome (AR) at both three and 12 months was analysed with logistic regression, incorporating a residual covariance (i.e., Generalised Estimated Equations (GEE) type) matrix[34] in the regression model to correct for repeated measurements. Under the presumption of non-inferiority between IHT and GHT which was tested in a PP analysis, we analysed the combined results of IHT and GHT versus EST, reporting the odds ratios (with 95% CIs and p-values). To evaluate the non-inferiority hypothesis, we estimated the proportion of AR (with 95% CIs) within each group.

Secondary continuous outcomes (IBS-SSS, IBS-QOL, SCL-90, CS-FBD, SES, and TiC-P scores) at three and 12 months were analysed with a linear regression model that also incorporated a residual covariance matrix. From these models, we estimated the mean of the outcomes for all treatment groups and differences between these means, all with 95% CIs. In all analyses, we included the time of visit (three months and 12 months), the type of treatment (IHT, GHT, or EST), and the time of visit by treatment interaction. Visit by treatment interactions were included to obtain the comparison between treatment groups for each visit separately. Baseline measurements, available for all secondary outcomes, were included to correct for any imbalance between groups and to optimise power.

Based on Gonsalkorale *et al.*[12], we performed an additional analysis to evaluate the effect of the treatment for different types of IBS (constipation-predominant, diarrhoea-predominant, and mixed type). Additionally, we performed analyses for subgroups according to referral (general practitioner or hospital specialist) and symptom severity (IBS-SSS).

Subsequently, we performed an additional analysis to evaluate any potential bias due to missing outcome measurements. In line with recent recommendations[35], we performed analyses for primary outcome with correction for IBS-QOL, SCL-90, and IBS-SSS at baseline.

We observed few missing values on baseline measurements, mainly due to patients skipping individual questions in otherwise filled-out questionnaires. To avoid any risk of bias and loss of statistical power, we decided to use multiple imputation techniques.[35,36] No outcome measures were imputed. Missing data were imputed 10 times, when applicable, analyses were performed for each imputation separately. The results were pooled with Rubin's rule. Multiple imputation was performed with SPSS 21. All analyses were performed with SAS v9.4.[37]

Patient involvement

Patients were not involved in the development of the design or conduct of the study, nor were they asked for advice on the interpretation or writing up of the results. The study was communicated to patients by a presentation at a meeting of the Dutch association of IBS patients and a publication in the association's journal.

RESULTS

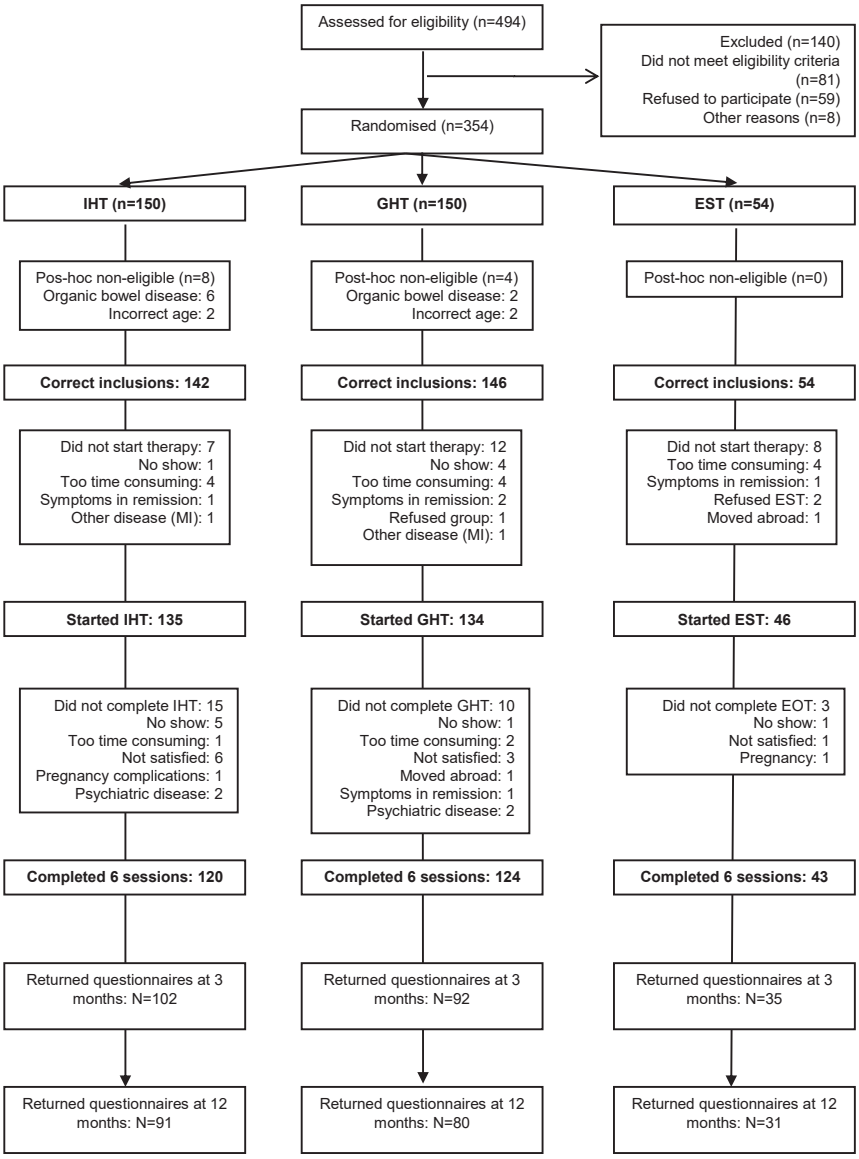
Patients

Between May 2011 and April 2016, 494 patients referred for hypnotherapy were assessed for eligibility. Of these, 140 patients were non-eligible: 81 patients refused participation, 16 patients did not meet the Rome III criteria, five patients had insufficient command of the Dutch language, one patient was unwilling to participate in group treatment, 25 patients had a psychiatric condition, seven patients had comorbid bowel disease, and five patients had had major surgery to the lower gastrointestinal tract. In total, 354 patients met the inclusion criteria and were allocated to IHT (N=150), GHT (N=150), and EST (N= 54) (see flowchart in Figure 1).

Of those randomised, eight patients (six in IHT and two in GHT group) had to be excluded from analysis because after randomisation they were diagnosed with a somatic disease that explained their symptoms (one colorectal cancer, one pancreatic cancer, two inflammatory bowel disease, one neuralgia, and two unknown other disease)[38]. Four patients were excluded after randomisation because in retrospect the participants were older than 65 years (two in IHT and two in GHT). This resulted in a total number of patients for ITT analysis of 142 patients in the IHT group, 146 in the GHT group, and 54 in the EST group.

Of the 300 patients randomised to hypnotherapy, 19 patients did not start the therapy for various reasons, seven in IHT and 12 in GHT group. Of the patients randomised to the EST group, eight patients did not start the therapy for various reasons (see Figure 1).

Figure 1. Flowchart Imagine RCT



Of the 135 patients that started IHT, 120 (88.9%) completed it. In the GHT group, 134 patients started with the therapy and 124 (92.5%) completed it. In the EST group, 46 patients started with the therapy and 43 (93.5%) completed it. The drop-out rate during therapy was 15.5%, 15.1%, and 20.3% for IHT, GHT, and EST respectively. The baseline characteristics of all patients are shown in Table 1. There were no remarkable differences between groups. The patients' compli-

Table 1. Baseline characteristics of the intention to treat population

	Individual hypnotherapy N=142	**Group hypnotherapy** N=146	**Educational supportive therapy** N=54
Dutch nationality	143 (98.6%)	142 (97.9%)	52 (98.1%)
female	113 (77.9%)	109 (75.2%)	47 (88.7%)
Age	N=141	N=142	N=51
mean (years) (SD)	37.3 (13.2)	37.4 (13.2)	34.5 (12.5)
Marital status:	N=144	N=144	N=53
single	31.9%	34.7%	39.6%
married	61.8%	59.0%	58.5%
divorced	5.6%	5.6%	1.9%
widowed	0.7%	0.7%	0.0%
Educational level:	N=130	N=138	N=51
primary and secondary	46.9%	39.9%	52.9%
high school A level	9.2%	23.2%	9.8%
academic	43.8%	37.0%	37.3%
Duration of symptoms:	N=145	N=145	N=52
0.5 - 3 years	32.4%	28.3%	37.7%
3 - 10 years	30.3%	32.4%	28.3%
> 10 years	37.2%	39.3%	34.0%
IBS subtype:	N=144	N=141	N=52
IBS-Constipation	16.7%	12.8%	15.4%
IBS-Diarrhoea	20.8%	24.8%	34.6%
IBS-Mixed type	61.1%	60.3%	44.2%
IBS-Unspecified	1.4%	2.1%	5.8%
IBS symptom severity score (range:0-500)	N=131	N=141	N=47
mean (SD)	300.7 (76.5)	286.0 (73.3)	305.8 (75.1)
IBS-QOL Total score (range:0-100)	N=146	N=146	N=53
mean (SD)	61.70 (17.98)	63.72 (14.84)	61.73 (19.25)
SCL-90 Total score (range:90-450)	N=146	N=145	N=53
mean (SD)	155.40 (47.79)	152.79 (43.27)	159.59 (60.38)
CS-FBD (range:31-217)	N=146	N=146	N=53
mean (SD)	117.14 (39.95)	113.70 (34.67)	118.74 (42.28)
Self-efficacy score (SES) (range:7-28)	N=142	N=144	N=52
mean (SD)	19.78 (3.84)	19.31 (3.03)	18.62 (3.82)
Absence of work in past 2 weeks	N=111	N=111	N=42
yes	14.4%	21.6%	19.0%
Work hindrance in past 2 weeks	N=102	N=98	N=39
yes	82.4%	82.7%	74.4%
Work efficiency in past 2 weeks	N=96	N=95	N=38
mean scale (0-10) (SD)	7.03 (1.86)	6.49 (1.88)	6.68 (2.11)
Medical costs in past 4 weeks	N=147	N=149	N=53
mean (€) (SD)	117.3 (114.4)	127.4 (113.6)	138.6 (184.8)

ance in reporting the use of the CD was low. After 12 months, only 44 patients returned their list of CD use, which was considered insufficient for analysis.

No adverse effects of the therapies were reported.

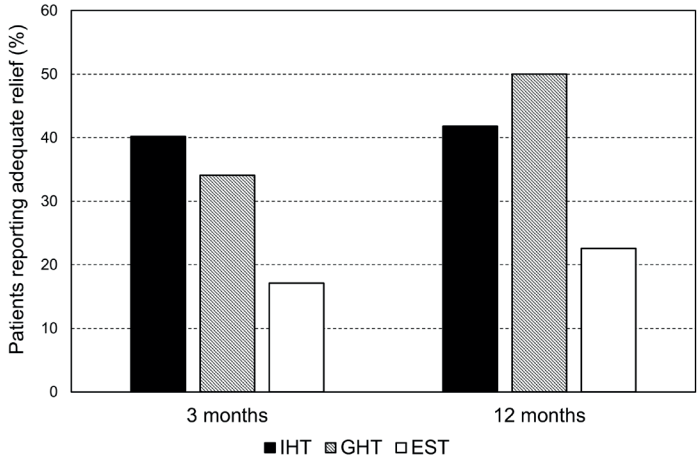
Primary outcome

At the end of therapy, after three months, AR questionnaires were available for 102 of the IHT patients (75.6% of those who started therapy), 92 of the GHT patients (68.7%), and 35 of the EST patients (76.1%). Of these patients, 40.2% in the IHT, 34.1% in the GHT, and 17.1% in the EST groups were responders. AR results at twelve months were available for 91 IHT (67.4% of those who started therapy), 80 of the GHT (59.7%) and 31 of the EST patients (67.4%). Of these, 41.8%, 50.0%, and 22.6% respectively, were responders (see Figure 2 and Table 2A).

In ITT analysis (Table 3), the percentage of patients with AR was significantly higher in patients treated with hypnotherapy than in those treated with EST, both after three months (odds ratio (OR) 2.9 (95%CI 1.2-7.4)), and after 12 months (OR 2.8 (95%CI 1.2-6.7)). The number needed to treat for hypnotherapy versus EST was 4.9 after three months and 4.4 after 12 months.

In PP analysis, the responder rate was 49.9% (95%CI 39.2-60.6%) in the IHT and 42.7% (95%CI 32.3-53.8%) in the GHT intervention arm at three months. At 12 months, 55.5% (95%CI 43.4-67.1%) of IHT and 51.7% (95%CI 40.2-63.0%) of GHT patients reported AR. Treatment response did not differ between individual and group hypnotherapy, neither at three months (OR 1.3 (95%CI 0.7-2.4)), nor at 12 months (OR 0.7 (95%CI 0.4-1.2)) (Table 3).

Figure 2. Percentage of patients reporting adequate relief of symptoms, at 3 and at 12 months after the start of the treatment.



IHT: individual hypnotherapy, GHT: group hypnotherapy, EST: educational supportive therapy.

Table 2A. Primary and secondary outcome parameters of patients in IHT, GHT, and EST group; scores at baseline, three, and 12 months

	Adequate relief IBS-SSS		**IBS-QOL**			**SCL-90**			**CS-FBD**			**SES**					
	N %		N mean total (SD)			N mean total (SD)			N mean total (SD)			N mean total (SD)			N mean total (SD)		
	3 m	**12 m**	**BL**	**3 m**	**12 m**	**BL**	**3 m**	**12 m**	**BL**	**3 m**	**12 m**	**BL**	**3 m**	**12 m**	**BL**	**3 m**	**12 m**
IHT	102	91	131	91	74	146	103	90	146	103	90	146	103	90	142	103	90
	40.2%	41.8%	300.7	250.2	250.4	61.90	70.77	73.60	155.40	141.35	137.32	116.77	100.76	92.04	19.78	20.25	20.57
			(76.5)	(95.1)	(100.6)	(18.12)	(18.37)	(18.01)	(47.79)	(45.71)	(45.17)	(39.90)	(43.77)	(43.37	(3.84)	(4.41)	(4.91)
GHT	91	80	141	84	74	146	93	84	145	93	84	146	93	84	144	93	83
	34.1%	50.0%	286.0	258.7	219.2	63.76	69.32	73.52	152.79	151.17	141.50	113.93	103.04	95.21	19.31	19.97	20.24
			(73.3)	(89.3)	(106.6)	(14.94)	(15.66)	(16.82)	(43.27)	(49.90)	(44.74)	(34.81)	(41.29)	(45.19)	(3.03)	(4.96)	(6.67)
EST	35	31	47	31	28	53	34	31	53	34	31	53	34	31	52	34	31
	17.1%	22.6%	305.8	269.4	263.3	61.93	70.78	69.04	159.59	141.42	148.81	118.93	98.53	104.91	18.62	19.41	19.87
			(75.1)	(83.4)	(108.1)	(19.38)	(18.39)	(21.25)	(60.38)	(53.52)	(59.35)	(44.69)	(41.66)	(46.80)	(3.82)	(3.23)	(4.20)

Table 2B. Socioeconomic outcome parameters of patients in IHT, GHT, and EST group; scores at baseline, three, and 12 months.

	Medical costs N mean total (EUR) (SD)			**Absence of work in past 2 wks** N percentage 'yes'			**Work hindrance in past 2 wks** N percentage 'yes'			**Efficiency of work in past 2 wks** N mean scale (SD)		
	Baseline	**3 m**	**12 m**	**Baseline**	**3 m**	**12 m**	**Baseline**	**3 m**	**12 m**	**Baseline**	**3 m**	**12 m**
IHT	147 117.3 (114.4)	104 133.7 (144.2)	90 101.2 (78.28)	111 14.4%	76 6.6%	69 10.1%	102 82.4%	74 73.0%	66 62.1%	96 7.03 (1.86)	72 7.42 (1.81)	64 8.59 (7.64)
GHT	149 127.4 (113.5)	96 119.5 (130.7)	86 102.5 (97.73)	111 21.6%	73 13.7%	67 6.0%	98 82.7%	69 81.2%	64 56.3%	95 6.49 (1.88)	70 7.09 (1.89)	62 7.66 (1.90)
EST	53 138.77 (184.8)	35 112.01 (114.7)	30 126.91 (158.0)	42 19.0%	23 0%	23 8.7%	39 74.4%	23 69.6%	20 70%	38 6.75 (1.92)	22 7.41 (1.47)	19 7.42 (2.01)

Secondary outcomes

Patients in all three groups improved in IBS symptoms, quality of life, psychological complaints, IBS related cognitions, and self-efficacy, with slightly better outcomes for the hypnotherapy treatments (Table 2A). In all groups the total medical costs diminished between baseline and 12 months. At three and 12 months patients in all groups reported less IBS related work absence, less work hindrance and a better work efficiency, with no significant differences between groups (Table 2B). However, in ITT analysis no significant differences between the combined hypnotherapy treatments and placebo control condition were found (Table 4) and PP analysis showed no differences between the mean scores at three and 12 months in the two hypnotherapy groups (Table 5).

Table 3. Multivariate comparison of the primary outcome in the combined IHT and GHT group versus EST, and IHT versus GHT, results of intention to treat (ITT) and per protocol (PP) analysis at 3 and 12 months

ITT analysis			
After 3 months **IHT 102** **GHT 92** **EST 35**	**comparison**	**OR (95%CI)**	**p-value**
	IHT[1] and GHT[2] combined versus EST[3]	2.9 (1.2-7.4)	0.02
	IHT versus GHT	1.4 (0.8-2.5)	0.28
After 12 months **IHT 91** **GHT 80** **EST 31**	IHT and GHT combined versus EST	2.8 (1.2-6.7)	0.02
	IHT versus GHT	0.7 (0.4-1.3)	0.25
PP analysis			
After 3 months **IHT 99** **GHT 88** **EST 34**	**comparison**	**OR (95%CI)**	**p-value**
	IHT and GHT combined versus EST	2.9 (1.2-6.9)	0.02
	IHT versus GHT	2.3 (0.9-5.8)	0.07
After 12 months **IHT 89** **GHT 78** **EST 31**	IHT and GHT combined versus EST	3.6 (1.4-9.0)	0.01
	IHT versus GHT	0.7 (0.4-1.2)	0.17

[1]*IHT = individual hypnotherapy*

[2]*GHT = group hypnotherapy*

[3]*EST = educational supportive therapy*

Table 4. Multivariate comparison of secondary outcome measurements in the combined IHT and GHT group versus EST, and IHT versus GHT, results of intention to treat (ITT) analysis at 3 and 12 months

Outcome measure	Time point	Treatment effect	Difference in mean	95%CI	P value
IBS-SSS	**After 3 months**	HT[1] vs. EST[2]	-9.6	-43.8-24.6	0.58
		IHT[3] vs. GHT[4]	-12.7	-39.2-13.9	0.35
	After 12 months	HT vs. EST	-23.2	-59.1-12.8	0.20
		IHT vs. GHT	15.3	-13.5-44.1	0.30
IBS-QOL	**After 3 months**	HT vs. EST	-0.8	-5.4-3.8	0.70
		IHT vs. GHT	2.6	-1.0-6.2	0.20
	After 12 months	HT vs. EST	1.5	-3.2-6.3	0.53
		IHT vs. GHT	1.3	-2.5-5.0	0.51
SCL-90	**After 3 months**	HT vs. EST	3.4	-8.4-15.1	0.57
		IHT vs. GHT	-8.3	-17.4-0.9	0.08
	After 12 months	HT vs. EST	-1.5	-13.7-10.7	0.81
		IHT vs. GHT	-2.6	-12.3-7.0	0.59
CS-FBD	**After 3 months**	HT vs. EST	4.8	-6.7-16.3	0.41
		IHT vs. GHT	-6.1	-15.1-2.9	0.18
	After 12 months	HT vs. EST	-1.9	-13.8-9.9	0.75
		IHT vs. GHT	-6.8	-16.1-2.6	0.16
SES	**After 3 months**	HT vs. EST	0.8	-1.0-2.6	0.39
		IHT vs. GHT	-0.02	-1.4-1.4	0.98
	After 12 months	HT vs. EST	-0.1	-2.0-1.7	0.90
		IHT vs. GHT	0.8	-0.6-2.3	0.26
TiC-P, work efficiency	**After 3 months**	HT vs. EST	-0.2	-1.0-0.6	0.65
		IHT vs. GHT	0.1	-0.5-0.6	0.86
	After 12 months	HT vs. EST	0.1	-0.7-1.0	0.74
		IHT vs. GHT	-0.2	-0.8-0.4	0.50
			OR	**95%CI**	**P value**
TiC-P, work absence (y/n)	**After 3 months**	HT vs. EST	1.1	0.3-4.2	0.94
		IHT vs. GHT	0.8	0.4-1.5	0.49
	After 12 months	HT vs. EST	1.1	0.4-2.8	0.88
		IHT vs. GHT	1.1	0.5-2.5	0.84
TiC-P, work hindrance (y/n)	**After 3 months**	HT vs. EST	1.1	0.5-2.5	0.87
		IHT vs. GHT	0.8	0.4-1.8	0.66
	After 12 months	HT vs. EST	0.8	0.3-2.6	0.74
		IHT vs. GHT	1.0	0.5-2.1	0.95

[1]*HT= hypnotherapy (IHT+GHT combined)*

[2]*EST= educational supportive therapy*

[3]*IHT= group hypnotherapy*

[4]*GHT= group hypnotherapy*

Table 5. Secondary outcome results of patients in IHT and GHT groups, per protocol analysis, mean scores (95%CI) at 3 and 12 months

Outcome measure	Time point	Treatment	mean	95%CI
IBS-SSS	**After 3 months**	IHT[1]	248.3	229.6-267.0
		GHT[2]	260.8	241.2-280.5
	After 12 months	IHT	243.8	223.7-263.9
		GHT	224.5	204.0-245.0
IBS-QOL	**After 3 months**	IHT	71.3	68.8-73.8
		GHT	68.4	65.7-71.0
	After 12 months	IHT	73.9	71.3-76.5
		GHT	72.8	70.0-75.5
SCL-90	**After 3 months**	IHT	140.6	134.1-147.1
		GHT	149.9	142.9-156.8
	After 12 months	IHT	137.8	131.0-144.6
		GHT	141.2	134.0-148.3
CS-FBD	**After 3 months**	IHT	100.0	93.8-106.3
		GHT	105.1	98.5-111.8
	After 12 months	IHT	91.2	84.8-97.7
		GHT	96.5	89.7-103.3
SES	**After 3 months**	IHT	20.2	19.2-21.2
		GHT	20.5	19.4-21.5
	After 12 months	IHT	20.6	19.5-21.6
		GHT	19.9	18.8-21.0
TiC-P, work efficiency	**After 3 months**	IHT	7.3	6.9-7.7
		GHT	7.3	6.8-7.7
	After 12 months	IHT	7.6	7.1-8.0
		GHT	7.7	7.3-8.2
			%	**95%CI**
TiC-P, work absence	**After 3 months**	IHT	24.8	14.4-39.4
		GHT	30.1	18.5-44.9
	After 12 months	IHT	29.5	15.4-49.1
		GHT	25.2	10.5-49.2
TiC-P, work hindrance	**After 3 months**	IHT	65.4	47.2-80.0
		GHT	71.9	52.8-85.4
	After 12 months	IHT	57.2	41.9-71.2
		GHT	54.9	36.1-72.4

[1]*IHT= group hypnotherapy*

[2]*GHT= group hypnotherapy*

In all groups the total medical costs diminished between baseline and 12 months (Table 2B), but there were no statistically significant differences between the groups (Table 4). At three and 12 months patients in all groups reported less IBS related work absence, less work hindrance and a better work efficiency, with no significant differences between groups.

Subgroup analyses

Patients referred from secondary care had a higher chance of being a responder after hypnotherapy compared to those referred from primary care, both at three months and at 12 months (Table 6). Additional analysis showed that the two groups did not differ in IBS subtype, nor in IBS-SSS, IBS-QOL scores at baseline and at three and 12 months, but patients included from secondary care had significantly higher scores on the SCL-90 sub dimensions somatisation, insufficiency of thought and action, distrust, and interpersonal sensitivity (results not shown).

In the subgroup analysis according to IBS symptom severity and IBS subtypes, no statistically significant differences in treatment effect were found for primary and secondary outcome measures at both points in time (Table 6).

Table 6. Multivariate comparison of primary outcome of patients in the two hypnotherapy (IHT and GHT) groups and EST group, grouped according to referral (primary or secondary care) and IBS subtype (constipation, diarrhoea and mixed type). Results of intention to treat (ITT) analysis at 3 and 12 months

subtypes	comparison	timepoint	OR	95%CI	p
Primary care	**HT[1] vs. EST[2]**	3 months	1.8	0.3-11.4	0.52
		12 months	0.9	0.2-5.3	0.92
Secondary care	**HT vs. EST**	3 months	3.5	1.1-10.5	0.03
		12 months	4.11	1.4-11.8	0.01
IBS-constipation	**HT vs. EST**	3 months	2.9	0.7-11.8	0.14
		12 months	2.3	0.5-10.1	0.28
IBS-diarrhoea	**HT vs. EST**	3 months	3.4	0.3-33.3	0.30
		12 months	0.8	0.1-5.6	0.80
IBS-mixed type	**HT vs. EST**	3 months	2.6	0.6-12.5	0.23
		12 months	5.2	1.1-24.7	0.04
IBS-severity Mild[3] (IBS-SSS=175)	**HT vs. EST**	3 months	1.8	0.4-8.2	0.43
		12 months	1.5	0.4-5.7	0.58
IBS-severity Severe[3] (IBS-SSS=300)	**HT vs. EST**	3 months	3.1	1.2-8.3	0.02
		12 months	3.1	1.2-7.9	0.02

[1]HT= hypnotherapy

[2]EST= educational supportive therapy

[3]Odds ratios for IBS-SSS score of 175 and IBS-SSS score of 300 were estimated from an analysis with an interaction between the treatment groups and the (continuous) score.

DISCUSSION

Principal findings

In this RCT with IBS patients referred from primary and secondary care, we found that three months of treatment with hypnotherapy was more effective than an educational control intervention. In addition, hypnotherapy delivered in a group format proved equally effective as individually delivered hypnotherapy. Differences in treatment effect persisted after nine months of follow-up.

Patients in both hypnotherapy groups and in the EST group all improved in quality of life, psychological complaints, cognitions, and self-efficacy, but between groups differences were not significant. Direct and indirect costs diminished, but again, without significant differences in treatment effect between groups.

Treatment effects were more pronounced for patients referred from secondary care, who appeared to have higher psychological problem scores. We found no significant differences in response between subgroups according to symptom severity and IBS subtype.

Strengths and limitations

To date, this is the largest RCT in hypnotherapy for IBS.[7,10] Whereas previous studies may have suffered from a lack of heterogeneity among IBS patients, which can affect the generalisability of the results[39], patients included in our study were recruited from both primary and secondary care across the Netherlands.

In this trial, we did not only assess the effectiveness of hypnotherapy compared to a high-quality control intervention, but also tested whether group-delivered hypnotherapy was not inferior to individual delivered therapy. Given the lack of therapists this may help implementation of hypnotherapy in daily clinical practice.

We chose for the AR questionnaire as the primary outcome measure, as this subjective outcome adequately reflects the impact of IBS symptoms, independent of symptom severity. In functional disorders the perception of symptoms is as important as actual symptom severity.[40] This is supported by the results of our trial, where better adequate relief scores were not accompanied with a significant different improvement in IBS symptom score. The statistical explanation may be that the study was powered for the primary, not secondary outcomes. From a patient's perspective, the explanation maybe that – in contrast to education – hypnotherapy does particularly improve the perception of IBS symptoms, without having a major effect on symptom severity.[41] Thus, the main effect of hypnotherapy may be degrading the symptom impact by changing the mind-set and improving the internal coping mechanism.

The sustainability of treatment effects of psychological interventions has been questioned. Therefore, our trial included a long follow-up period, and we were able to demonstrate that the superiority of hypnotherapy over educational intervention that was present immediately after treatment persisted at 12 months.

In our study, we used a well-designed control intervention. In line with recommendations we constructed a so-called "sham" intervention that lacked hypnotherapy but was comparable for all other treatment components: time, attention, active intervention, and contact with therapis.[16,19,42,43] This informative educational program covered relevant topics and information gaps of IBS patients.[20]

Our study had several limitations. In retrospect, the presumptions used for the power calculation may have been suboptimal. We assumed an individual hypnotherapy response rate of 57% and a placebo response rate of 25%, based on the meta-analysis of four studies, with in total 147 IBS patients.[10] The presumed hypnotherapy response rate may have been too high, and the placebo response estimate too low based on the results of a larger study on placebo effects.[44] The sample size calculation was corrected for potential clustering effects as treatment effects may differ between individual hypnotherapists. In separate analysis we did correct for therapist, but we found no clustering effect due to the hypnotherapists (results not shown).

This study was embedded in routine clinical practice. This increases the validity and generalisability of the results. However, it also resulted in some practical challenges that affected the conduct of the study. In four cases (1.1%) the inclusion proved incorrect, and in eight cases (2.3%) the diagnosis of IBS appeared to be incorrect post-hoc. In total 27 patients (7.6% overall) withdrew from the intervention after randomisation (Figure 1) and a substantial percentage of the questionnaires sent out after three and 12 months was not returned. Therefore, in line with existing recommendations, we imputed missing data and performed extensive sensitivity analyses to ensure the validity of the results.[35] Even though results from these analyses were very similar, a bias due to withdrawal and non-response cannot be fully excluded.

In this study we only calculated the overall direct medical costs related to IBS and we did not detail the specific changes in healthcare consumption. In addition, this cost calculation was based on subjectively reported use of healthcare facilities, which may have been biased.

Although we did include psychological measurements, we did not assess expectations and hopes that patients had regarding the therapy before commencing it. The effect of treatment is determined to a large extent by the combination of expected symptom relief and desire for symptom relief by the patient.[45,46] For optimal comparison in studies investigating psychological treatment for IBS, the

expectations of patients in the control group should be comparable to those of patients in the active intervention arm. We suggest that future RCTs should map the expectations of patients in all RCT arms before starting the intervention.

We did not measure beforehand the hypnotic ability of the eligible patients with a formal hypnotic susceptibility scale. This procedure is time-consuming and therefore augments the costs of the treatment. Previously, no association was found between hypnotic ability and response to treatment.[47,48]

After a year, only few patients supplied data on their actual use of the CD, so compliance to home exercises could not be assessed. Recently, two studies showed that the continued use of the CD after treatment does not contribute to sustaining the improvement.[12,49]

Comparison with other studies

In our study, we chose the number of weeks with adequate symptom relief as the primary outcome. Previous studies that used the IBS-SSS as primary outcome measure reported larger effects on IBS symptomatology compared to ours.[12,14,49] Possible explanations may be that most previous studies lacked an adequate placebo control group. In addition, there may have been underlying causes in patient selection. While previous studies used Rome I criteria (1990), or Rome II criteria (1999), we used the Rome III criteria (2006), which require fewer days with complaints to set the diagnosis. Differences may also be related to the conduct of the intervention itself. In three studies the intervention consisted of 12 hypnotic sessions[12,14,18], one study[49] used seven sessions and in our study six sessions were used. In addition, the experience of the therapists is important. In the Manchester group, therapists have more than five years' experience with IBS focused hypnotherapy, while in our study most of the hypnotherapists did not have specific experience with IBS.

The improvement in the IBS-SSS score for the EST group is in accordance with the research of Ringström *et al.*, who reported that in 38% of the IBS patients in a structured patient education group the score was reduced with at least 50 points.[50]

The scores on the questionnaire investigating IBS cognitions are comparable to the scores of a Dutch population in prior research[51] but lower than in a study with patients from secondary and tertiary care.[52]

The SCL-90 scores of the patients in our study were on the average level of patients in general practice[28], so the psychological status was that of the consulting population in primary care. Compared to mean scores of psychiatric patients, all three groups had below average scores on most SCL-90 dimensions, except for the "somatic scale" and for "sleep disturbance". The high somatisation score was

previously reported in a systematic review.[53] Because the SCL-90 is a measure of psychological complaints and was not designed to set a psychiatric diagnosis, we cannot compare the study population regarding incidence of mood disorders.[54-56]

Some earlier studies on group hypnotherapy demonstrated better results.[15,49,57] We think that this may be related to the fact that we adhered strictly to practicing the hypnotherapy exercises while others combined hypnotherapy with the opportunity to discuss questions as well as share information about IBS. Patients in our GHT group commented that they missed the option to exchange experiences. It might well be that education on IBS and hypnosis both independently contribute to the treatment effect. In clinical practice a stepped-care approach, in which patients receive education as a first and hypnosis as second step, could be the way to further optimise the treatment effect.

In the subgroup analysis, we found a difference in effect between patients referred by a specialist and those referred by their general practitioner. Additional analysis showed a difference in psychological complaints between the groups, but not in symptom severity. Whitehead (2002)[53] suggested a dual-aetiology hypothesis, which divides the IBS patients in "those whose symptoms primarily have a biological basis and others whose symptoms primarily have a psychological basis". Possibly hypnotherapy works best for patients with more psychological complaints. In future research on the effect of hypnotherapy, stratification according to psychological symptoms should be considered.

Conclusion

Our study showed that hypnotherapy is more effective than an educational control intervention and that group hypnotherapy is not inferior to individual hypnotherapy.

Based on these results we recommend considering hypnotherapy as treatment option for all patients with IBS, irrespective of symptom severity and IBS subtype, particularly for patients with severe psychological impact. Our study also demonstrated that hypnotherapy can be effectively administered by hypnotherapists without specific experience with IBS and that group application is as effective as individual hypnotherapy. With group hypnotherapy more patients can be treated at lower costs which could facilitate widespread implementation in clinical practice in the future.

Future research should focus on the optimal number of sessions, on the impact that the patient's expectations have on the final outcome, and on the predictive value of psychological symptoms for the outcome of hypnotherapy.

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Ethical approval

The study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO). The study protocol was approved by the Medical Ethics Committee of the University Medical Centre of Utrecht, the Netherlands (approval number: 10-201/O). All participants gave informed consent before taking part. Patient data were coded and analysis was done blinded.

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Chapter 8

General discussion

INTRODUCTION

Case history; continued

After consulting her general practitioner, Mrs. de Vries decides to visit the psychologist attached to the regional hospital for information on hypnotherapy. Two weeks after consultation she starts a group hypnotherapy program for IBS patients. Already during the first session she felt it as a relief to meet fellow IBS patients and to realise that she was not the only one for whom the disease had such a significant impact on daily life. Although she had to get used to the group format, it soon felt comfortable to jointly follow the hypnotic exercises. She attends every hypnotherapy session and does her homework exercises regularly. After three sessions she notices progression in her complaints and this motivates her to keep on doing CD exercises. After six sessions she experiences that the pain is getting less, and that her bowel action is getting somewhat more regular. She regains self-confidence and starts cautiously taking up her social activities. She visits her friends again and dares to go out for dinner. Four months after finishing therapy she writes the therapist a letter to tell that for the first time in years, she went on holiday to Germany with the family of her daughter.

In the studies described in this thesis we highlighted different medical and societal aspects of IBS: the educational needs of IBS patients, the costs that IBS generates for society, the impact of the placebo effect, and the effectiveness of psychological interventions. Finally, we studied the effectiveness of hypnotherapy in two different formats as compared to educational support.

The main findings of this thesis are:

- In designing studies on IBS, a number of challenges have to be overcome: adequate selection of the IBS patients for the study requires strict diagnostic criteria, a high-quality control intervention must be designed given the high placebo effect, and the selection of the outcome assessment must follow the recommendations of the Rome committee to make comparison of the outcomes of different studies possible. Taking these into account we designed the IMAGINE study (Chapter 2).
- IBS patients have many misconceptions about their disease and often feel poorly informed. Educational programs must be developed to address these informational needs in clinical practice. These can also be used as placebo control condition in studies on psychological interventions in IBS (Chapter 3).
- Total healthcare costs per patient substantially increase after the diagnosis of IBS is made, and IBS related costs are significantly higher when patients are

treated in secondary care. IBS patients should preferably be treated in primary care, not only from a quality of care point of view but also to optimise use of healthcare resources (Chapter 4).

- The placebo response rate in studies on psychological interventions in IBS is high (41.4%) but comparable to that in studies on pharmacological, dietary bran, and complementary medicine interventions. The placebo effect is probably more determined by patient-related factors, such as expectations and desire for the treatment to be effective, than the actual content of the placebo intervention (Chapter 5).
- Of all psychological interventions presently used in IBS, only mindfulness and relaxation therapy and not cognitive behaviour therapy (CBT) were found to be effective, when considering only studies using high-quality control interventions. In contrast to CBT which is directed at IBS related thoughts and behaviour, relaxation and mindfulness aim at body and mind relaxation. This might reduce the physiological stress response that provokes and maintains IBS symptoms (Chapter 6).
- Hypnotherapy is an effective treatment for patients with IBS both from primary and secondary care and can be effectively delivered in both group and individual setting. Group delivery may facilitate widespread use of hypnotherapy in daily practice (Chapter 7).

How to address the information need of IBS patients

The first step in the management of IBS is to provide adequate information and lifestyle advice. As we saw in this thesis, IBS patients have many misconceptions and often feel poorly informed. They want information about the diagnostic process, causes and prognosis of IBS, dietary advice, new medications, psychological factors, and coping strategies. To bring this knowledge within reach of more patients, it would be a step forward to develop an online educational program. More than half of the patients mentioned the internet as a possible source of information. Health information for the public in the Netherlands is provided by the online health information platform 'Thuisarts.nl', created by the Dutch College of General Practice (www.thuisarts.nl). With over a million visits a year it is the best visited health site in the Netherlands. Initiatives to develop an interactive educational program on IBS with different modules are already undertaken. This educational program can be added in future to the 'thuisarts' website as well as to the website of the Dutch IBS patient federation. It is important though to realise that in 2015 two third of patients still preferred to learn about their IBS from their treating physician. Their needs could be adequately met by setting up a short multidisciplinary, informational group program for IBS patients. The

content of our educational supportive therapy (EST) program could be used for this purpose.

The development of hypnotherapy as an evidenced-based treatment

The clinical use of hypnosis has a long tradition. It was officially recognised as a legitimate medical treatment by the British Medical Association in 1955 and the American Medical Association in 1958. In the Netherlands, the "Dutch society for medical hypnosis" was founded in 1965. Around the turn of the millennium hypnotherapy attracted negative public attention, due to discussions on retrieved memories of sexual abuse under hypnotherapy, presentations on stage and television, and malpractice by unregistered therapists. This undermined the legitimacy of practicing hypnotherapy. It was considered more and more as part of the "alternative circuit" without a base of scientific evidence. Officially registered psychotherapists had to defend themselves for using hypnotic techniques, although they were aware of the fact that in clinical practice it was an effective therapeutic intervention for specific medical conditions, such as chronic pain syndrome, nausea resulting from cancer treatment, and medical unexplained physical symptoms and somatoform disorders. In 1990 a handbook was issued about the spectrum of hypnotic exercises that can be used for different medical conditions[1] and two studies were published confirming the effectiveness of hypnotherapy in conversion disorder.[2,3] The International Association for the Study of Pain (IASP) recognised the value of hypnosis. In 2004 a special issue was published on psychological methods of pain control in which the scientific and clinical merits of (cognitive) behavioural therapy and hypnotherapy were extensively described. Since 1984, the research group of Whorwell in Manchester contributed with a series of randomised controlled trials (RCTs) and other studies to the knowledge about the effectiveness of hypnotherapy for treatment of IBS. In 2007, an RCT was published which showed that hypnotherapy was highly effective for symptom control in children with functional abdominal pain, with sustained effects after five years.[4,5] More recently, various systematic reviews were published that demonstrated the effectiveness of psychological treatments, including hypnotherapy, in IBS. The results of the IMAGINE study confirm the effectiveness of hypnotherapy for IBS but demonstrate in addition that hypnotherapy is equally effective when delivered in a group and individual therapy, and that it is effective for both primary and secondary care patients.

Optimal format for hypnotherapy in IBS

Hypnotherapy is effective for all patient groups: children, adults, and older people, referred from primary, secondary, and tertiary care. Previous research showed no

association between hypnotic ability and response to treatment, so no preselection is necessary. In clinical practice, however, special attention must be given to patients with comorbid psychiatric disorders. It must be judged before the start with hypnotherapy, if these disorders must be treated first.

Our study showed that hypnotherapy for IBS can also be practised by trained psychologists/hypnotherapists with little or no experience with IBS (Chapter 7). This facilitates broader application. Therapists in our RCT followed a one-day training on hypnotherapy in IBS by the researcher. In the Netherlands, the Dutch Society for Hypnosis offers a basic course in hypnosis treatment for psychotherapists. This course can be easily expanded with this one-day training for IBS specific treatment.

In our opinion the preferred format should be group therapy, because of the group interaction and because of reasons of cost-effectiveness. Recently, online delivery of hypnotherapy in adult IBS patients has been suggested in the Netherlands. Internet application has already been studied in children, resulting in non-inferiority for the online therapy.[6] However, internet-based application needs to be implemented with caution. In our opinion it would not be wise to make the exercises freely accessible for everyone online. The IBS diagnosis has to be confirmed, and other in- and exclusion criteria must be checked in a "live" interview with a professional. Caution is necessary with patients with certain psychiatric disorders, such as post-traumatic stress disorders. In the study on internet delivery of hypnotherapy in children, all participants were visited after inclusion and randomisation by a nurse to explain the treatment. Probably, a so-called "blended application" with at least one session with a psychologist, who is familiar with hypnotherapy, to check possible exclusion criteria is appropriate before access to the sessions online is given.

It is not clear yet, what the optimum number of sessions is under which as many patients as possible will benefit from hypnotherapy given the expected outcome and costs. From an economic perspective, the number of sessions must be as low as possible. In RCTs so far, the number of sessions varied between six (our study) and 12 sessions, with the possibility for extra sessions on demand (the Manchester group). We suggest a comparative study with different numbers of sessions, delivered by several therapists with comparable experience in IBS and hypnosis.

METHODOLOGICAL CHALLENGES IN STUDIES ON PSYCHOLOGICAL TREATMENT

Control group comparison

Most studies on psychological treatment effectiveness, use waiting list, care as usual, or symptom monitoring by the patients as the placebo control intervention. In research on psychological treatment methods, it is possible that the treatment effect is the result of increased attention and time investment from the therapist rather than the therapy content itself. The supportive and empathic interaction with the therapist is expected to influence clinical outcomes. Therefore, to optimally measure the effect of a psychological treatment in RCTs, a placebo group with an equal number and length of sessions, using an individual or group format and with comparable trained therapists should be used to control for this effect. In addition, the content has to be beneficial for the patient. In our opinion, every placebo group in future RCTs should comply with these conditions. For that purpose, we designed the EST program, based on the informational needs of IBS patients.

The placebo response

In research on IBS treatment and in the clinical treatment of IBS patients, the placebo response is considerable. In pharmacological treatments, treatment with dietary bran and complementary medicine, the placebo response ranged from 37.5% to 47%. Because of the contact with the therapist, we expected the placebo response with psychological treatment methods to be even higher. This hypothesis was not confirmed. The placebo response seems to be determined to a greater extent by patient related factors than by therapist factors. It appears that the combination of treatment expectations and desire for symptom relief are the main patient related factors, and these will of course be influenced by the way the therapy is introduced and executed. This has important implications for the design of RCTs. As patients cannot be blinded to the intervention in research on psychological treatment methods, patients in the control group should have similar expectations of the control arm as of the active intervention arm. This should be measured before starting the interventions.

Content of hypnotherapy sessions

Earlier studies on the effectiveness of group treatment in hypnotherapy yielded better results than in our study. This may have been due to different primary outcome measures used: some used a composite score based on a daily diary of symptoms, bowel actions, pain and distension, and general wellbeing, other

studies used symptoms based scores such as the IBS-SSS. In our study, we chose to use a patient related outcome measure (PROM) for subjective monitoring of IBS outcome: the Adequate Relief questionnaire. Secondly, results may have been better because other studies added education and the opportunity to share information to the hypnotherapy sessions, whereas we adhered strictly to practising the hypnotherapy exercises only. The results of our EST group show that the possibility to talk about one's experiences with companions in distress, exchanging information and giving support to each other has a positive effect on IBS complaints. Future research is required to assess the advantage of combining group hypnotherapy with support and information exchange.

Limitation of practice-based research

The IMAGINE study was embedded in routine clinical practice of thirteen hospitals across the Netherlands. This increases the validity and generalisability of the results and facilitates implementation of the therapy after effectiveness is proven. However, conducting the study in clinical practice also results in some practical issues that affect the conduct of the study. Factors related to the staffing of the department, managements' policy, and the daily work pressure, but also factors concerning the therapists, such as illness, job change, and retirement, have a great impact on the study conduct when so many hospitals are involved. Further, in the daily workflow, emphasis lies on an accurate treatment of individual patients and less on the study protocol. That may explain why inclusion criteria were sometimes not correctly monitored, why the diagnosis of IBS turned out to be incorrect post-hoc, and why patients withdrew from the intervention after randomisation or did not finish therapy.

Implications for clinical practice: place of hypnotherapy in the stepped care for patients

To optimise the quality of IBS care and for cost-effective use of healthcare resources, IBS patients should be treated in primary care as much as possible. In the Netherlands, as in many other countries with a strong primary care, the general practitioner acts as the "case manager" of the patient, coordinating the diagnostic and treatment process. The general practitioner has a longitudinal relation with the patient and has knowledge of the medical history and the patient's psychosocial system. This facilitates an integral approach, which is extremely important in complex functional diseases like IBS. Referral may be needed in case of diagnostic uncertainty, the presence of alarm symptoms, or if specialist consultation is needed to confirm the general practitioner's management. However, it should be incidental and limited to single consultations.

The first step in the management of IBS is to provide adequate information and lifestyle advice. If information and lifestyle advice does not result in symptom improvement, the second step is the prescription of medication. Ford *et al.*[4] summarised the available evidence for the efficacy of pharmacotherapy used to relieve IBS symptoms. Peppermint oil (NNT 3, moderate evidence) the antibiotic rifaximin (NNT 9, moderate evidence), and Linaclotide (NNT 6, high evidence) can be effective. Antispasmodics (NNT 5, low evidence) can give short-term relief but often with troublesome side effects, but there is insufficient evidence to recommend loperamide. Finally, antidepressants may reduce symptoms (NNT 4, high evidence), but they may have side effects.

The third step is psychological interventions. The meta-analysis of Ford *et al.* demonstrated benefit of cognitive behavioural therapy (NNT 3), hypnotherapy (NNT 4), multi-component psychological therapies (NNT 4), multi-component via telephone (NNT 5), and dynamic psychotherapy (NNT 3.5). However, quality of the studies was generally poor, and only four out of 32 included studies used a "sham" control intervention. Using adequate control group comparison we confirmed the effectiveness of hypnotherapy, both at the end of treatment (NNT 4.9) and at nine months follow-up (NNT 4.4). Therefore, we suggest that in the stepped care management of IBS, hypnotherapy be considered as the first step after drug treatment, not only for refractory patients, but also for patients with newly onset symptoms that persist for at least three months.

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Chapter 9

Summary

SUMMARY

The Irritable Bowel Syndrome (IBS) is one of the most common functional gastrointestinal disorders. The estimated prevalence worldwide is 14-24% for women and 5-19% for men. IBS is characterised by recurrent episodes of abdominal pain, discomfort and altered bowel habits, often accompanied by symptoms of bloating and distension. As in the individual patient no structural or biochemical abnormalities can be detected, diagnosis is set on consensus-based criteria, known as the Rome criteria. The latest iteration, Rome IV, dates from 2016.

Recurrent abdominal pain, on average, at least one day per week in the last three months, associated with two or more of the following criteria:

1 Related to defecation
2 Associated with a change in frequency of stool
3 Associated with a change in form (appearance) of stool

Criteria fulfilled for the last three months with symptom onset at least six months before diagnosis.

Three types of IBS can be distinguished: IBS with predominant constipation, IBS with predominant diarrhoea, or IBS with alternating periods of diarrhoea and constipation. IBS patients can have severe complaints, resulting in a low quality of life and a great impact on daily functioning. Not all IBS patients seek medical advice, but those who do have on the average a longer disease history and more psychosocial comorbidity.

At the moment, IBS is considered a bio-psychosocial disturbance in the brain-gut axis, with an increased sensitivity of both the peripheral visceral and central nervous system and an altered pain processing, disturbances in gastrointestinal motility and abnormal stress response interacting with psycho-social factors.

Optimal management of IBS starts with providing adequate information about the disorder and lifestyle advice. In refractory patients, pharmacotherapy can be considered, but drugs may have side effects which restrict their use. Psychological treatments are an alternative option. Several systematic reviews concluded that cognitive behavioural therapy, short psychodynamic therapy and hypnotherapy can be effective treatment methods for refractory patients. Hypnotherapy has been shown to be effective but more research by randomised controlled trials (RCT) with large heterogeneous sample sizes was recommended. The IMAGINE study was therefore designed to assess the effectiveness of hypnotherapy on

patients of the primary and secondary care and to compare the effectiveness of group delivery to individual treatment.

In **Chapter 2** the design of the IMAGINE study and the methodological challenges are described. The objectives were to assess the efficacy of hypnotherapy in IBS treatment and to compare the efficacy of group hypnotherapy with individual hypnotherapy. Hypotheses tested in this study were that (1) after therapy, more patients in the hypnotherapy condition would report adequate relief of their IBS complaints than in the educational supportive therapy condition (control treatment) and (2) that hypnotherapy offered in a group format is as effective as individual therapy. In the RCT, 354 patients with IBS (aged 18-65) referred from primary and secondary care would be treated with six sessions of individual hypnotherapy, six sessions of group hypnotherapy or six sessions of educational supportive therapy. As primary efficacy parameter, the responder rate for 'adequate relief' of IBS complaints was chosen. Methodological challenges encountered in the study design concerned the selection of the study population, the diagnostic inclusion criteria, the design of an optimal control intervention, the placebo effect, and study outcomes. For an optimal generalisability of the results, IBS patients had to be referred by general practitioners and hospital specialists across the country. To standardise the IBS diagnosis, the questionnaire of the Rome committee was used to confirm the IBS diagnosis. In RCTs on psychological interventions the design of the placebo control intervention is challenging. A placebo condition must have all components of the therapy under study, with the exception of the active treatment component. Therefore: time, equal attention, an active intervention, and the same number of therapist contacts must be included. To that aim, for this RCT an educational program was designed. To be able to measure sustainable effects the follow-up time should be more than six months. Also patient-reported endpoints should be used. For adequate outcome assessment, we used the adequate relief questionnaire, the IBS-symptom severity scale and the IBS quality of life scale.

To optimise the content of the educational program in our RCT we reviewed the available literature. In **Chapter 3** we describe the results of a systematic review of eight studies involving 2132 IBS patients which was performed to determine the educational needs of IBS patients. We looked at the (mis)conceptions that IBS patients have of their disease and at their desire for information. It appeared that most patients were unhappy with their level of knowledge or felt poorly informed. Patients have many misconceptions about IBS: they think food and dietary factors are the most important cause, that IBS will worsen with age and cannot improve, and that IBS will evolve into a serious bowel disease that will shorten their life. We conclude that an educational program should cover a basic

explanation of IBS, of the bio-psycho-social model behind it, and advice on lifestyle measures and ways of coping with stress and symptoms. An educational program that addresses these topics can serve as a good placebo control condition in RCTs on psychological treatment methods.

In the Netherlands, 90 % of IBS patients are treated in primary care. We were interested in the consequences of this basic principle for treatment in terms of health care consumption by IBS patients and related costs. Detailed insight in disease-specific costs can direct specific treatment policy and methods. To that aim, we compared the costs for IBS patients treated solely in primary care with those in secondary care and compared these costs to the healthcare expenditure for patients without IBS. In **chapter 4** we describe the results of this study. We compared annual health care costs made in the three years after the diagnosis of IBS was set with annual health care costs made in the three years before diagnosis and specified these costs in terms of number and contacts with the general practitioner, annual hospital specialist care costs, and costs for prescribed medication. In primary care IBS patients, the mean total health care costs per patient increased by 29% (EUR 486) after IBS diagnosis. For secondary care patients this increase was 116% (EUR 2328). These costs remain high for the three years after diagnosis. The increase was significantly higher for secondary care patients than for primary care patients and were specifically caused by increases for specialist costs and medication. General practitioner related costs did not change. For the non-IBS control group we found no difference between before and after diagnosis, both for primary care and secondary care patients. We concluded that in the absence of alarm symptoms, and diagnostic uncertainty, IBS patients should be treated in primary care, as recommended by guidelines. This optimises cost-effective use of healthcare resources.

It is possible that the effect of a psychological intervention is determined by responses of the patient to the context in which the therapy is delivered and not by the actual content of the psychological treatment. Because of this augmented attention by the therapist, we expected the placebo effect to be greater in psychological interventions than in interventions with medication, dietary fibre or complementary medicine. In **chapter 5** we describe the results of a systematic review on the placebo effect of psychological interventions in the treatment of IBS. We included only adequate placebo interventions, with comparable time being spent with the therapist as in the active treatment. The placebo response rate to treatments with medication, dietary fibre and complementary medicine ranged from 37.5% to 47%. The placebo response rate for the included psychological studies was 41.4%. This was in contrast with our expectations, and we concluded that it may not be the content of the intervention, but patient-related factors,

such as expectations and desire for treatment effectiveness, that determine the placebo response rate.

To position the results of the IMAGINE study we were interested in the effectiveness of other psychological interventions in IBS with, like in our study, only high-quality placebo control conditions. The latter was defined as having an active component, with content relevant to the IBS patient and therapist-delivered in an equal number of sessions of comparable duration. In **chapter 6** the result of a systematic review is described. Of the 110 studies identified, only five studies fulfilled the inclusion criteria; three on (cognitive) behavioural therapy, one on mindfulness and one on relaxation therapy. Only mindfulness and relaxation therapy appeared to be more effective than placebo control. The aim of these interventions is body and mind relaxation, which might reduce the physiological stress responses that play a role in IBS complaints.

In **chapter 7** we describe the results of our RCT in which we compared individual hypnotherapy (IHT) for IBS with group-delivered hypnotherapy (GHT) and educational supportive therapy (EST). In total, 354 patients, referred by primary and secondary care, aged 18-65 years, all meeting the Rome III criteria, were included in the study and treated in 13 hospitals in the Netherlands. After three months, 40.2% in the IHT group, 34.1% in the GHT group and 17.1% in the EST group months reported adequate relief. After 12 months these figures were 41.8%, 50.0% and 22.6%, respectively. An analysis over the entire group of patients included in the treatment showed that the effect of hypnotherapy (IHT and GHT combined) was significantly higher than for EST, both after three and after 12 months, with number needed to treat 4.9 and 4.4, respectively. The per protocol analysis showed that group hypnotherapy was not inferior to individual hypnotherapy. After three months, the responder rate was 49.9% for IHT and 42.7% for GHT. At 12 months these figures were 55.5% for IHT and 51.7% for GHT patients. We concluded that for IBS patients referred from both primary and secondary care, hypnotherapy is an effective treatment and that group hypnotherapy is not inferior to individually delivered hypnotherapy. Group hypnotherapy brings the therapy within reach for more IBS patients at lower costs.

In **chapter 8** we discussed the implications of our main findings. In clinical practice, hypnotherapy can be positioned as the third step in the treatment of IBS patients, after the provision of adequate information and lifestyle advice and a trial of medication. It can be used for patient groups of all ages, both in primary and hospital care.

The placebo effect is more determined by patient-related factors rather than by the content of the intervention itself, therefore, future RCTs should investigate the impact of the patient's expectations on the final outcome. Future research

should also compare the effectiveness of group hypnotherapy alone with that of group hypnotherapy combined with the opportunity to exchange information and discuss questions. We also propose that a comparative study be conducted to assess the optimal number of hypnotherapy sessions. Seeing that the psychological symptoms of the patients as shown in the RCT seemed to be predictive for the outcome of hypnotherapy, we finally suggest to study the effect of hypnotherapy after stratification according to psychological symptom impact.

Samenvatting

SAMENVATTING

Het prikkelbaredarmsyndroom (PDS) is een van de meest voorkomende gastro-intestinale aandoeningen. De geschatte prevalentie is wereldwijd 14-24% voor vrouwen en 5-19% voor mannen. PDS wordt gekenmerkt door terugkerende episodes van buikpijn, ongemak en veranderde stoelgang, meestal samen met symptomen van opgeblazenheid en winderigheid. Daar er bij de individuele patiënt geen structurele of biochemische afwijkingen geconstateerd kunnen worden, wordt de diagnose gesteld op grond van door consensus vastgestelde criteria, bekend als de Rome criteria. De laatste versie, de Rome IV, dateert uit 2016.

> Herhaaldelijk optredende buikpijn, gemiddeld ten minste een dag per week in de laatste drie maanden, samengaand met twee of meer van de volgende criteria:
>
> 1 samenhangend met de stoelgang
> 2 samenhangend met een verandering in frequentie van de stoelgang
> 3 samenhangend met een verandering in de verschijningsvorm van de stoelgang
>
> Aan de criteria moet in de laatste drie maanden voldaan zijn, met het begin van de symptomen ten minste zes maanden voor de diagnose.

Er kunnen drie typen PDS onderscheiden worden: PDS met voornamelijk obstipatie, PDS met voornamelijk diarree en PDS met afwisselende perioden van obstipatie en diarree. PDS-patiënten kunnen ernstige klachten hebben, leidend tot een lage kwaliteit van leven en een grote impact op het dagelijks functioneren. Niet alle PDS-patiënten zoeken medische hulp. De patiënten die hulp vragen, hebben over het algemeen een langere ziektegeschiedenis en meer psychosociale co-morbiditeit.

Op dit moment wordt PDS als een bio-psycho-sociale aandoening van de brein-darm-as beschouwd, met een verhoogde gevoeligheid van zowel het perifere darmzenuwsysteem als het centrale zenuwstelsel, met een andere manier van pijnverwerking, afwijkingen in gastro-intestinale beweging en abnormale stress responsen, die interacteren met psychosociale factoren.

Een goede behandeling van PDS begint met het geven van goede informatie over de aandoening en leefstijladviezen. Bij patiënten bij wie de klachten voortduren, kan medicatie overwogen worden, maar deze kunnen bijwerkingen hebben, welke het gebruik beperken. Psychologische behandelingen zijn ook een optie. Verscheidene systematische literatuuroverzichten concludeerden dat cognitieve gedragstherapie, kortdurende psychodynamische therapie en hypnotherapie ef-

fectieve behandelmethoden kunnen zijn voor moeilijk te genezen patiënten. Van hypnotherapie is aangetoond dat het effectief is maar meer onderzoek door middel van 'randomised controlled trials' (RCTs) met grote patiënten aantallen uit eerste en tweedelijns zorg is werd aanbevolen. Daartoe werd de IMAGINE studie ontworpen om de effectiviteit van hypnotherapie bij PDS-patiënten van de eerste en tweede lijn vast te stellen en de effectiviteit van hypnotherapie in een groep te vergelijken met individuele hypnotherapie.

In **hoofdstuk 2** worden de opzet van de IMAGINE studie en de methodologische uitdagingen die hiermee gepaard gingen, besproken. De hypotheses die in deze studie getest werden waren (1) dat er aan het einde van de therapie meer patiënten die met hypnotherapie behandeld zouden worden voldoende verlichting van hun PDS-klachten zouden hebben dan patiënten in de educatieve ondersteunende therapie (controlebehandeling) en (2) dat hypnotherapie aangeboden in een groep even effectief zou zijn als individueel aangeboden hypnotherapie. In de RCT zouden 354 patiënten met PDS, in de leeftijd van 18-65 jaar en verwezen door de eerste en tweede lijn, in perifere ziekenhuizen of in psychologische eerstelijnspraktijken, behandeld worden met zes sessies individuele hypnotherapie, zes sessies hypnotherapie in een groep of zes sessies educatieve ondersteunende therapie. Als primaire uitkomstmaat werd de mate van respons op de 'adequate klachtenverlichting vragenlijst' voor PDS-klachten gekozen. Methodologische uitdagingen die wij bij de opzet van de studie tegenkwamen betroffen de selectie van de studiepopulatie, de diagnostische inclusiecriteria, het ontwerp voor een goede placebogroep, het placebo-effect en de uitkomstmaten voor de studie. Om de generaliseerbaarheid van de resultaten van de studie zo optimaal mogelijk te maken, moesten PDS-patiënten verwezen worden door eerste en tweedelijnspraktijken verspreid over het land. Om de diagnose PDS te standaardiseren en vergelijking van onderzoekspopulaties mogelijk te maken, werd gekozen voor het gebruik van de vragenlijst van het comité van Rome. In de opzet van een RCT over psychologische interventies is het ontwerpen van een goede placebocontroleconditie heel belangrijk. Deze moet alle componenten van de therapie welke men wil onderzoeken bevatten, behalve het specifieke therapeutische deel. Het moet een activiteit zijn met evenveel therapietijd, aandacht en aantal contacten met de therapeut. Om dat doel te bereiken, werd voor deze RCT een educatief programma ontworpen. Om een blijvend effect te kunnen vaststellen moet de 'follow-up' tijd meer dan zes maanden beslaan. Ook moeten er uitkomstmaten gebruikt worden waarbij de patiënt zelf rapporteert. Voor adequate uitkomstmetingen kozen wij, in lijn met de aanbevelingen van het Rome comité, voor de 'adequate verlichting vragenlijst', de PDS-symptomenlijst en de PDS-kwaliteit-van-leven-vragenlijst.

Om het educatieprogramma, dat wij als placebocontrole in onze RCT gebruikten, optimaal in te richten, onderzochten we de beschikbare literatuur. In **hoofdstuk 3** beschrijven we de resultaten van een systematisch onderzoek van acht studies betrekking hebbende op 2.132 PDS-patiënten, dat werd uitgevoerd om uit te zoeken wat de informatie behoeften van PDS-patiënten waren. We onderzochten de opvattingen (en misvattingen) die PDS-patiënten over hun aandoening hebben en wat hun wensen ten aanzien van informatie waren. Het bleek dat de patiënten veel misvattingen over PDS hebben: ze denken dat dieetfactoren de meest belangrijke oorzaak zijn, dat PDS erger zal worden met het ouder worden en niet kan verbeteren en dat PDS zich zal ontwikkelen tot een ernstige darmziekte en het leven zal verkorten. Wij concluderen dat een educatief programma een basisuitleg over PDS, het bio-psycho-sociale model, leefstijlmaatregelen en manieren van omgaan met stress en symptomen zou moeten bevatten. Een educatief programma dat deze onderdelen bevat kan dienen als een goede placebocontrole in RCTs over psychologische behandelmethodes.

In Nederland wordt 90% van de PDS-patiënten in de eerste lijn behandeld. Wij waren geïnteresseerd in de gevolgen van dit behandeluitgangspunt in termen van omvang van gebruik van de gezondheidszorg voorzieningen en kosten door PDS-patiënten. Gedetailleerd inzicht in ziekte-specifieke kosten kan aanwijzingen geven voor specifieke behandeluitgangspunten en –methoden. Voor dat doel vergeleken wij de kosten voor PDS-patiënten die alleen in de eerste lijn behandeld werden met patiënten die in de tweede lijn behandeld werden en vergeleken deze kosten met de uitgaven voor gezondheidszorg voor patiënten zonder PDS. In **hoofdstuk 4** worden de resultaten van deze studie beschreven. We vergeleken alle jaarlijkse medische kosten die gemaakt werden in de drie jaar nadat de diagnose PDS gesteld werd, met alle jaarlijkse medische kosten die gemaakt werden in de drie jaar voordat de diagnose gesteld werd. We specificeerden deze kosten naar kosten voor de huisarts, de medisch specialistische ziekenhuiskosten en kosten voor voorgeschreven medicatie. Per eerstelijns PDS-patiënt namen de gemiddelde totale gezondheidskosten in de drie jaar na diagnose, vergeleken met de drie jaar voor de diagnose toe met 29% (EUR 486). Voor tweedelijns patiënten bedroeg deze toename 116% (EUR 2.328). Deze kosten bleven hoog gedurende de drie jaren na diagnose. De kosten waren significant hoger voor tweedelijnspatiënten dan voor eerstelijnspatiënten en dit werd specifiek veroorzaakt door hogere kosten geassocieerd met consultatie van de specialist in het ziekenhuis en met de medicatie. Voor de huisarts bleven deze kosten nagenoeg gelijk. In de controlegroep was er geen significant verschil tussen de drie jaar na en voor diagnose en geen significant verschil tussen eerste- en tweedelijnspatiënten. We concludeerden dat als er geen alarmsymptomen zijn en geen diagnostische onzekerheid bestaat,

PDS-patiënten in de eerste lijn behandeld dienen te worden, conform de richtlijnen. Dit bevordert het doelmatig gebruik van gezondheidszorg.

Het is mogelijk dat het effect van een psychologische interventie veroorzaakt wordt door de reactie van de patiënt op de context waarin de therapie geleverd wordt en niet door de inhoud van de psychologische behandeling zelf. Zoals we beschreven in hoofdstuk 2 kan het effect veroorzaakt zijn door de aandacht en tijdinvestering van de therapeut en daarom moet er in RCTs gebruik gemaakt worden van een placebogroep. Vanwege de grotere aandacht in psychologische behandelsessies, verwachtten we dat het placebo-effect groter zou zijn bij psychologische interventies dan bij interventies met medicatie, vezels of complementaire middelen. In **hoofdstuk 5** beschrijven we de resultaten van een systematisch literatuur onderzoek naar het placebo-effect van psychologische interventies bij de behandeling van het prikkelbaredarmsyndroom. We includeerden alleen RCTs met adequate placebo-interventies, waarin men evenveel tijd met de therapeut doorbracht als in de behandeling die onderzocht werd. De grootte van het placebo-effect bij behandelingen met medicatie, vezels of complementaire middelen varieerde tussen 37,5% en 47%. De grootte van het placebo-effect bij de bestudeerde onderzoeken met psychologische behandelmethoden bedroeg 41,4%. Kennelijk is het niet de inhoud van de interventie, maar zijn het patiëntgerelateerde factoren zoals verwachtingen m.b.t. de werkzaamheid van de behandeling, die de grootte van het placebo-effect bepalen.

Om de resultaten van onze interventiestudie met hypnotherapie in de context van de resultaten van andere psychologische interventies voor PDS te plaatsen, waren we geïnteresseerd in de effectiviteit van deze interventies wanneer ze, zoals in onze studies, als vergelijking gebruik hadden gemaakt van een placebo-controlegroep van hoge kwaliteit. Dat laatste hebben we gedefinieerd als hebbende een actieve component, met inhoud relevant voor de PDS-patiënt en gegeven door een therapeut in een vergelijkbaar aantal sessies van gelijke duur. In **hoofdstuk 6** worden de resultaten van een systematisch literatuuronderzoek naar deze effecten beschreven. Van de 110 studies die in aanmerking kwamen, voldeden er maar vijf aan de vastgestelde criteria; drie over (cognitieve) gedragstherapie, een over 'mindfulness' en een over ontspanningstherapie. Alleen 'mindfulness' en ontspanningstherapie bleken effectiever dan de placebocontrole. Het doel van deze interventies is de ontspanning van lichaam en geest, welke mogelijk de fysiologische stressreacties verminderen die een rol spelen bij PDS-klachten.

In **hoofdstuk 7** beschrijven we de resultaten van onze RCT waarin we individuele hypnotherapie (IHT) voor PDS vergeleken met hypnotherapie in een groep (GHT) en educatieve ondersteunende therapie (EOT). In totaal werden 354 patiënten van 18-65 jaar, die voldeden aan de Rome III criteria en waren

verwezen vanuit de eerste en tweede lijn, geïncludeerd in de studie. Zij werden in 13 ziekenhuizen in Nederland behandeld. Na drie maanden had 40,2% van de patiënten in de IHT, 34,1% in de GHT en 17,1% in de EOT een positief resultaat op de primaire uitkomstmaat 'adequate klachtenverlichting'. Na 12 maanden waren dat respectievelijk 41,8%, 50,0% en 22,6% van de patiënten. De analyse over alle patiënten die voor de behandeling geïncludeerd waren, liet zien, dat het behandeleffect van hypnotherapie significant beter was dan voor de EST, zowel na drie als na 12 maanden. Het aantal patiënten dat behandeld moet worden opdat er een verbetert, is na drie maanden 4,9 en na 12 maanden 4,4. Analyse van de resultaten van diegenen die de behandeling ook daadwerkelijk hebben afgemaakt, liet zien dat hypnotherapie in een groep niet inferieur was aan de individuele hypnotherapie. Na drie maanden hadden 49,9% van de IHT-patiënten en 42,7% van de GHT-patiënten voldoende verlichting van hun klachten. Na 12 maanden waren deze cijfers: 55,5% voor de IHT en 51,7% voor de GHT-patiënten. Wij concludeerden dat hypnotherapie voor patiënten uit de eerste en tweede lijn een effectieve behandelmethode is en dat hypnotherapie in een groep niet inferieur is aan individuele hypnotherapie. Hypnotherapie in een groep maakt de therapie bereikbaar voor meer patiënten, tegen lagere kosten.

In **hoofdstuk 8** bespraken we de implicaties van onze bevindingen voor de klinische praktijk en voor toekomstig onderzoek. In de klinische praktijk kan hypnotherapie, na het geven van adequate informatie en leefstijladvies en het voorschrijven van medicatie, de derde stap in de behandeling voor PDS-patiënten zijn. Het kan ingezet worden voor patiënten uit alle leeftijdsgroepen, verwezen vanuit eerste, tweede en derde lijn.

Het placebo-effect wordt meer bepaald door patiënt-gerelateerde factoren dan door de inhoud van de therapie en daarom zouden in toekomstig onderzoek de verwachtingen van patiënten in alle RCT-armen gemeten moeten worden om zo de invloed van deze verwachtingen op de uitkomsten van behandeling te onderzoeken. Ook kan in toekomstig onderzoek het effect van hypnotherapie in een groep vergeleken worden met het effect van een combinatie van groepshypnotherapie en informatie en uitwisseling over PDS. We stellen ook een vergelijkende studie voor naar de uitkomsten van behandeling met wisselende aantallen sessies hypnotherapie. Daar in onze RCT de ernst van de psychologische symptomen voorspellend leek te zijn voor de uitkomst van de hypnotherapie, zou in toekomstig onderzoek stratificatie naar de ernst van de psychologische symptomen overwogen kunnen worden.

Dankwoord

DANKWOORD

Aan een lang traject gaat nu een einde komen. Een traject, waar ik enorm van genoten heb. Na mijn jarenlange arbeid op de afdeling Psychiatrie en Psychologie, waar ik altijd met plezier gewerkt heb, weer geheel nieuwe ervaringen opdoen, dingen leren, inspirerende, op hun vakgebied kundige mensen ontmoeten, op congressen moeten spreken, terwijl Engels niet mijn 'fort' is en als 'computer-immigrant' ook daar de wonderen van ontdekken. Het is niet meer voor te stellen, maar de eerste computer werd op mijn werk geïntroduceerd toen ik 44 jaar was. Hiernaast het overwinnen van tegenslagen. Promoveren betekent ook een test voor frustratietolerantie en doorzettingsvermogen.

Allereerst wil ik de raad van bestuur van het St Antoniusziekenhuis en speciaal ook het toenmalige managementteam Lucie Blaauw (helaas overleden) en Henk Koers bedanken, dat zij het mij mogelijk hebben gemaakt dit traject aan te vangen; al mijn collega's van de afdeling Psychiatrie en Psychologie, in het bijzonder mijn vakgroep, die, zonder morren, mij deze werkdag gegund hebben en de medewerkers van het secretariaat en in het bijzonder Arthur Girmscheid die, meestal in zijn vrije tijd, met veel geduld de 'flowcharts' en tabellen een goede lay-out wist te geven.

Prof. Niek de Wit, mijn promotor, die mij uitnodigde om aan dit traject te beginnen. Dank voor de begeleiding waarmee je mijn wetenschappelijke overdenkingen en producten van nijvere arbeid, altijd weer op een hoger plan wist te tillen. Immer de grote lijn vasthoudend en op het juiste moment weer een nieuwe stap introducerend. Je gaf me veel vrijheid en vertrouwen en altijd positief commentaar. Daar heb ik, zeker in mijn begeleiding van eigen opleidelingen, een voorbeeld aan genomen. Gelukkig was er naast de bespreking van het werk, ook altijd tijd om 'het leven' door te nemen.

Prof. Andre Smout, ik was geloof ik nog geen week begonnen, toen je aankondigde van het UMCU naar het AMC te gaan. Het heeft de begeleiding nooit in de weg gestaan. Of je nu op weg was naar Parijs, op de Bahama's of op een ander tropisch eiland bivakkeerde, altijd had ik binnen de kortste keren antwoord op mijn mails en becommentarieerde je met een humorvolle mildheid mijn artikelen. Hiernaast was 'met pensioen gaan' later een thema wat ons verbond.

Mijn co-promotor Dr. Yanda van Rood. Ik had je gevraagd vanwege je zeer gedegen kennis en werkwijze op het gebied van de Klinische Psychologie. Gedegen was je. Minutieus beoordeelde je mijn schreden op het gebied van het schrijven van wetenschappelijke artikelen. Soms werd ik moedeloos van het vele commentaar, maar als ik me hier weer overheen zette, bleek je altijd gelijk te hebben, mij te behoeden voor onvolkomenheden en het niveau aanzienlijk te verbeteren. Dank

voor de gastvrije manier waarop je mij ook een aantal keren thuis hebt ontvangen om samen rustig te kunnen werken.

Mijn co-promotor Dr. Ing. Wijnand laan. Samen hebben we de methodologie en statistiek opgezet. Hierna bleven we samen gestaag doorwerken, ondanks al jouw escapades van wereldreis, baan in het buitenland en andere banen. Alle andere kandidaat co-promotoren heb ik me van het lijf weten te houden, want ik wist dat ik niemand zou kunnen vinden, die met zoveel geduld mij alles uitlegde en met hetzelfde gemak over de computer zou dansen als jij. Ook persoonlijk konden en kunnen we het goed vinden en ik prijs me gelukkig dat Lijne en jij tot mijn vriendenkring zijn toegetreden en ik zo nu en dan op jullie kleine mannetjes mag passen.

The members of my Project-group, Prof. Whorwell form Manchester and Prof. Weusten from The St Antonius hospital, thank you for your support for my PhD study and your positive comments on the study protocol and articles. Prof. Weusten a long time ago, asked me if I could contribute from my experience, to the solution of the problems of all those patients who came to their department of Gastroenterology in a lot of pain. They were diagnosed with IBS and he and his colleagues had often so little to offer them to relieve their complaints. I searched for psychological treatment methods and found the treatment with Hypnosis developed by Prof. Whorwell, which I later adapted for the Dutch population. This was where all my work with IBS patients started.

Bedankt alle collega's van de andere ziekenhuizen en eerstelijns-praktijken, die voldoende vertrouwen hadden in mij en de door mij opgezette behandelingen om mee te willen doen aan het onderzoek. Daar hebben jullie veel tijd in willen steken en ik hoop dat we met dit traject heel veel patiënten een eind verder hebben kunnen helpen. Bedankt dus Detty van der Beek, Erik te Biesebeke, Edith Blommerde, Kees Denissen, Yvette van Dokkum, Marieke Fonk, Tanja Hengel-Schouten, Pieter de Heuvel, Ingrid Hoelsgens, Carla van de Kloet-Quak, Judith Koopman, Floris Kuiperi, Paul Mangus, Marieke van Meeteren, Suzanne Noldus, Ruth Overtoom-Corsmit, Arpina Pogosian, Gerdien Schuitemaker, Ernst Strubbe, Leo Timmermans, Willem Venenendaal, Rolf Wijvekate en collega's.

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Bovenal prees en prijs ik mij gelukkig met het contact met Nienke Bleijenberg. Samen koffie drinken of lunchen en dan even de belangrijke dingen werktech-

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Zoals altijd, is ook in deze lange jaren, het leven in al zijn, helaas ook vaak moeilijke facetten, langs gekomen. Mijn vrienden Joke Kleykamp en Kees Koning kunnen de promotie helaas niet meer meemaken.

En dan het gezin van herkomst. Studeren was bij ons een vanzelfsprekendheid. Een verschil tussen man en vrouw hierin, was totaal niet aan de orde. Mijn ouders volgden met duidelijke trots onze onderwijsvorderingen. Het is vreemd om als enige van een gezin over te zijn. Pappa en Peter, jullie zouden niet veel gezegd hebben, maar van anderen zou ik dan gehoord hebben dat jullie trots op me waren. Mamma, de toenemende zorg voor jou was, naast het werken aan de promotie, mijn voornaamste levenstaak. Je hebt reusachtig je best gedaan om er tot de voltooiing bij te zijn, maar dat het zo lang ging duren, hadden we niet kunnen bevroeden. Tot je 103 de levensjaar heb je het volgehouden en wat zou je hebben genoten, op die eerste rij. Ik draag deze promotie dan ook aan jullie drie op.

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En dan ga ik nu eindelijk echt met pensioen!

Curriculum Vitae

CURRICULUM VITAE

Carla Flik was born on July 12, 1951 in Laren (N-H) in the Netherlands. After her graduation from high school, she studied psychology at the University of Utrecht. She worked for forty years as a clinical psychologist-psychotherapist in various functions at the department of Psychiatry and Psychology of the St Antonius Hospital in Utrecht, at the University of Wageningen, was a teacher at the post-graduate education for colleagues (RINO) and had a private practice. She specialised in Gestalt-therapy, Group-psychotherapy, Family and Relations (System) Therapy, Hypnotherapy, was practitioner in EMDR (trauma therapy) and is supervisor in System-therapy and Hypnotherapy. At the St Antonius Hospital, besides her work at the clinic and policlinic of the Psychiatry and Psychology, she was a member and co-founder of the multidisciplinary teams of the heart-revalidation, pain policlinic, the chronic obstructive pulmonary Disease (COPD), and Gynecology. She also started cooperation with the gastroenterologists on the treatment of Irritable Bowel Syndrome (IBS) patients. She was co-founder and coordinator of the Psychosomatic sub-department of the Psychiatry and Psychology department and was for many years a member of the board of an association of organisations with programs for patients with persistent medically unexplained symptoms (NOLK). She wrote several articles about the treatment of chronic pain and on useful questionnaires for COPD patients. She is co-author of the Dutch multidisciplinary guidelines on 'Somatic unsatisfactorily explained complaints (SOLK) and somatoform disturbances' and on 'Irritable Bowel Syndrome'.

Prof. Niek de Wit of the Julius Centre for Health Sciences and Primary Care of the University Medical Centre in Utrecht, the Netherlands, invited her to start with a PhD study on the treatment of IBS patients. She has dedicated two days a week to this study which officially started on first of October 2009. The board of the St Antonius Hospital granted one day for the study; the other day she worked in her spare time. On 1 January 2016 she retired from her work at the St Antonius Hospital, but has continued to work on this thesis.

List of Publications

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