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COGNITIVE BEHAVIOR THERAPY IN THE TREATMENT OF IRRITABLE BOWEL SYNDROME

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all work and no play

ABSTRACT

Background: Irritable bowel syndrome (IBS) is a disorder characterized by abdominal pain or discomfort combined with altered bowel habits and is associated with impaired quality of life. The prevalence of IBS in the general adult population is approximately 10%. Psychological factors have been implicated in IBS because of high rates of comorbidity with psychiatric diagnoses and the fact that stress can cause IBS symptoms. Several studies have been conducted on psychological treatment for IBS. Most of these have studied cognitive behavior therapy (CBT) but show inconsistent results. Although symptom-related fear and avoidance behaviors have been found to play an important role in IBS, no psychological treatment has targeted these factors primarily. The "third wave" of cognitive behavioral therapies promotes acceptance and behavioral flexibility in the presence of aversive experiences, such as IBS symptoms. Exposure treatment is a behavioral intervention aimed at decreasing fear of arbitrary stimuli. Given the high prevalence of IBS, there is need for delivery formats that allow more patients to gain access to treatment. Internet-delivered cognitive behavior therapy with online therapist support has shown effectiveness in treating both psychiatric disorders and disorders within the behavioral medicine field.

Aims: The general aim of the present thesis was to develop and evaluate an effective psychological treatment for IBS that can be made accessible to a large number of IBS patients. We developed an exposure-based CBT treatment that emphasized acceptance and behavioral flexibility in response to IBS-related experiences. Specific aims of this thesis were to: a) evaluate exposure-based CBT as a group treatment for IBS (study I), b) evaluate exposure-based CBT delivered via the internet (ICBT) for IBS (study II), c) evaluate the long-term effectiveness of ICBT for IBS (study III), d) evaluate the effectiveness and clinical utility of ICBT for IBS (study IV), and e) evaluate the specificity of ICBT for IBS (study V).

Methods: Study I included 34 referred female IBS patients who underwent exposure-based CBT in group format. Study II randomized 85 self-referred IBS patients to ICBT or waiting list. Study III was a long-term follow-up of study II, 75 of the original study's 85 participants (88%) participated in the 15- to 18-month follow-up. Study IV randomized 62 consecutively recruited patients at a gastroenterological clinic to ICBT or waiting list. Study V randomized 195 self-referred IBS patients to ICBT or internet-delivered stress management. The stress-management condition was designed to control for effects of treatment credibility, expectancy of improvement, and attention from a caregiver. The treatment conditions in all studies lasted for 10 weeks.

Results: In all studies exposure-based CBT was associated with improvements in IBS symptoms, IBS-related fear, and quality of life. In studies II and IV, ICBT was more effective than a waiting list and in study V, ICBT was more effective

than internet-delivered stress management. Study I also showed that exposure-based CBT leads to improvement in mental health.

Conclusions: Exposure-based CBT is effective both in group format and when delivered via internet. Both self-referred and clinical samples of IBS patients improve from the treatment. The effects of exposure-based CBT cannot be explained by non-specific factors such as treatment credibility, expectancy of improvement, and attention from a caregiver. ICBT is a promising new treatment modality that can be made accessible to a large number of IBS patients.

LIST OF PUBLICATIONS

I.   Ljótsson B, Andréewitch S, Hedman E, Rück C, Andersson G, Lindefors N. Exposure and mindfulness based therapy for irritable bowel syndrome - An open pilot study. J Behav Ther Exp Psychiatry. 2010;41:185-90.

II.   Ljótsson B, Falk L, Wibron Vesterlund A, Hedman E, Lindfors P, Rück C, Hursti T, Andréewitch S, Jansson L, Lindefors N, Andersson G. Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome - a randomized controlled trial. Behav Res Ther. 2010;48: 531-9.

III. Ljótsson B, Hedman E, Lindfors P, Hursti T, Lindefors N, Andersson G, Rück C. Long-term follow up of internet-delivered exposure and mindfulness based treatment for irritable bowel syndrome. Behav Res Ther. 2011;49:58-61.

IV.   Ljótsson B, Andersson G, Hedman E, Lindfors P, Andréewitch S, Rück C, Lindefors N. Delivering internet-based exposure treatment for irritable bowel syndrome in a clinical setting: a randomized controlled trial. Submitted.

V.   Ljótsson B, Hedman E, Andersson E, Hesser H, Lindfors P, Hursti T, Rydh S, Rück C, Lindefors N, Andersson G. Internet-delivered exposure-based treatment vs. stress management for irritable bowel syndrome: a randomized trial. Am J Gastroenterol. E-published ahead of print.

CONTENTS

LIST OF ABBREVIATIONS

ACC   Anterior cingulate cortex

ACT   Acceptance and commitment therapy

CBT   Cognitive behavior therapy

CGI   Clinical global impression scale

CPSR   Relative change score of the GI symptom diary

CSFBD   Cognitive scale for functional bowel disorders

DBT   Dialectic behavior therapy

GI   Gastrointestinal

GSRS-IBS   Gastrointestinal symptom rating scale – IBS version

IBS   Irritable bowel syndrome

IBS-QOL   Irritable bowel syndrome quality of life instrument

ICBT   Internet-delivered cognitive behavior therapy

ISM   Internet-delivered stress management

MADRS-S   Montgomery Åsberg depression rating scale – self report

MINI   Mini-international neuropsychiatric interview

PSS   Perceived stress scale

VSI   Visceral sensitivity index

1. INTRODUCTION

Irritable bowel syndrome (IBS) is a highly prevalent disorder that is associated with individual suffering and societal costs. Many psychological treatments have been developed for IBS and show mixed results. Despite a clear role of symptom-related stress in symptom exacerbation and presence of excessive symptom controlling and avoidance behaviors in IBS, most psychological treatments do not primarily target these factors. There is also a lack of availability of these treatments, meaning that most IBS patients cannot gain access to an effective treatment.

I began my work on this thesis in the summer of 2005. My aim was to participate in the development and evaluation of a new psychological treatment for IBS that could be made available for a large number of IBS patients. I had just finished my studies at the psychology program and my training in cognitive behavior therapy (CBT) had been influenced by acceptance and commitment therapy. The emphasis of my clinical training had been on helping clients to remain in contact with negative experiences while engaging in behaviors that purposefully moved them in their valued life direction. When meeting patients with IBS, I observed that most of them did not want to experience IBS symptoms and the negative emotions that were associated with these symptoms. They therefore engaged in behaviors that served to avoid symptoms and symptom-related experiences. This behavioral pattern did certainly not help them to live a rich and full life.

I wanted see if a treatment based on accepting IBS symptoms and the emotions and thoughts that were associated with IBS could help these patients. I also saw a clear need for these patients to willingly expose themselves to these symptoms, emotions, and thoughts to relieve the fear and anxiety they had come to associate with them. This constituted the foundation for exposure-based CBT with emphasis on acceptance of IBS symptoms and related experiences.

My supervisors and our research group were then, and still are, involved the development of the "Swedish model" of internet-delivered cognitive behavior therapy (ICBT). I had also written my master's thesis about ICBT for bulimia nervosa and binge eating disorder. Delivering the exposure-based CBT for IBS over the internet would mean that a lot more patients could be treated. For this purpose, I programmed a web platform that could be used to deliver ICBT. That platform has since then been used in numerous studies and in the world's first psychiatric ICBT clinic.

This thesis describes my, my colleagues', and my supervisors' work to develop and evaluate a new treatment protocol and new treatment format for IBS.

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Background

1.1 Epidemiology of IBS

1.1.1 Diagnosis

Irritable bowel syndrome is the presence of recurring symptoms in the lower gastrointestinal (GI) tract, primarily abdominal pain or discomfort, constipation, and/or diarrhea, which cannot be explained by any structural lesions (1, 2). There are potential serious illnesses that can present with these symptoms, most commonly inflammatory bowel disease (Crohn's disease and ulcerative colitis) and colorectal cancer (2). Based on this definition, it could be said that IBS is a diagnosis of exclusion, i.e. it can only be made if other explanations for the symptoms have been ruled out. However, using absence of organic illnesses as a primary diagnostic criterion has proven to lead to extensive medical examinations and tests in order to rule them out as causes of the symptoms (1, 3). Most often the findings are negative and the patient ends up with an IBS diagnosis (4, 5). Therefore, several efforts have been made to develop criteria that can be used to establish a positive diagnosis of IBS and avoid unnecessary testing and examinations.

In 1978, Manning et al. published the first set of diagnostic criteria that were based on their ability to distinguish IBS from inflammatory bowel disease (1). The Manning criteria included abdominal pain relieved by defecation, looser and/or more frequent stools with onset of pain, abdominal distension, passage of mucus in stools, and sense of incomplete evacuation. In 1984, Kruis et al. created a set of criteria that also included "alarm symptoms", such as blood in stool and weight loss, that could be indicative of organic illness (6). However, because of a complicated scoring system these criteria were never widely used (7). Besides being an aid in excluding organic illness, objective diagnostic criteria are also important within clinical research. In a review of treatment trials of IBS in 1988, Klein noted that "not a single IBS treatment trial reported to date has used an adequate operational definition of IBS" (8 p. 233). To meet the need for reliable diagnostic criteria that could also be used in research, the Rome committee was established in the late 1980s (9). In the following years several renditions of diagnostic criteria for IBS were published: the Rome I (1992; 10), Rome II (1999; 11), and Rome III (2006; 12). The latest version, the Rome III criteria, are shown in Box 1. The Rome criteria introduced pain or discomfort as mandatory symptoms in IBS together with symptom chronicity and minimal thresholds for symptom frequency. Common symptoms such as bloating and feeling of incomplete evacuation support the diagnosis but are not part of the Rome III criteria. There are also Rome criteria for classifying IBS subgroups according to symptom predominance, namely IBS with constipation, IBS with diarrhea, mixed IBS, and unsubtyped IBS (12).

Box 1. Rome III diagnostic criteria for IBS.

Recurrent abdominal pain or discomfort* at least 3 days per month in the last 3 months associated with 2 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
 	
Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.
 	
*Discomfort means an uncomfortable sensation not described as pain.
 	
Supportive symptoms that are not part of the diagnostic criteria include:
   • Abnormal stool frequency: ≤ 3 bowel movements per week or > 3 bowel movements per day)
   • Abnormal stool form: lumpy/hard stool or loose/watery stool
   • Defecation straining
   • Urgency
   • Feeling of incomplete bowel movement
   • Passing of mucus
   • Bloating

1.1.2 PREVALENCE

The prevalence estimates of IBS vary considerably between epidemiological studies. Using Rome I and II criteria, Bommelaer et al. (13) estimated the prevalence of IBS to be 1-2% while Ólafsdóttir et al. (14) estimated a prevalence of 32% using Manning criteria. This variation is judged to be a reflection of the different definitions of IBS, where Manning criteria are more inclusive than Rome I-III criteria (15). In the Ólafsdóttir study, using Rome II and III criteria on the same population of 799 adult Icelanders, gave estimates of 5% and 13%, respectively (14). Hahn et al. published data from a large US health survey with 42,392 respondents, which showed that about 3.5% of the respondents identified themselves as having IBS. Of these, about 50% fulfilled neither Rome I nor Manning criteria (16). The "true" prevalence of IBS is therefore difficult to determine, but comprehensive reviews have concluded that IBS affects about 10% of the adult population (15, 17). The prevalence of IBS among females compared to males has been found to be about twice as large (18) and IBS seems to be most common in the ages between 20 and 40 (19).

1.1.3 NATURAL COURSE AND QUALITY OF LIFE

IBS is considered to be a chronic disorder (17). In two population studies that investigated the 10-year natural history of IBS, 67% (20) and 43%-61% (14) of patients who had been diagnosed with IBS retained their diagnosis after 10 years. In a Swedish population study, 55% of IBS patients retained their diagnosis after 7 years, but notably only 13% were symptom-free while 21% reported minor GI symptoms and 11% were diagnosed with functional dyspepsia or reflux disease (21). In a 12-year follow-up study, 30% of IBS

patients were symptom-free at follow-up while 25% were diagnosed with another functional GI disorder (22). Although IBS is chronic for a majority of patients it has not been associated with long-term (over 20 years) increased mortality (23) or susceptibility to organic illness (24).

Much research has investigated the impact of IBS on quality of life. Within this context, the specific term is health-related quality of life, which covers the physical, psychological, and social domains of health (25). In a review it was concluded that IBS patients have impaired health-related quality of life in all three domains compared to normal controls and that symptom severity is negatively correlated with health-related quality of life (26).

1.1.4 SOCIETAL COSTS

IBS is also associated with productivity loss and health care expenditure. Compared with normal controls, IBS patients have nearly tripled work or school absenteeism (18). IBS patients also report that 20% of their work time is non-productive while their colleagues without IBS report that 6% of their work time is non-productive (27). In a large survey, Talley et al. used self-report questionnaires based on Manning criteria to diagnose IBS and found that IBS patients utilized health care at almost double the cost compared to persons without IBS (28). In a survey that diagnosed IBS using the less inclusive Rome criteria, Longstreth et al. estimated the increase in health care costs associated with IBS to be 51% (29). The severity of symptoms was also positively correlated with an increase in health care costs. In 2007, the mean annual direct health care costs in the US were estimated at $5,049 per treatment seeking IBS patient (30). Given the high prevalence of IBS, estimated at 10%, this leads to large costs for society. In Finland, IBS has been estimated to account for up to 5% of the national outpatient and pharmacological expenditures (31).

1.2 DIETARY AND PHARMACOLOGICAL TREATMENTS

The American College of Gastroenterology published a review of pharmacological and dietary treatments for IBS in 2009 (32). The use of dietary adjustments, dietary fiber, bulking agents, laxatives, antispasmodic agents, antidiarrheals, or probiotics, was considered to have weak scientific support and questionable beneficial effects. $5HT_3$ receptor antagonists (alosetron), $5HT_4$ receptor agonists (tegaserod), selective C-2 chloride channel activators (lubiprostone), and antidepressant (tricyclics and selective serotonin reuptake inhibitors) had moderate to good quality of evidence of beneficial effects. Alosetron targets diarrhea while tegaserod and lubiprostone target constipation, and all three drugs have primarily shown effect on female IBS patients. However, alosetron and tegaserod have been withdrawn from the US market because of adverse side effects. Alosetron has since then been reintroduced in the US under restricted use for females with severe diarrhea. Antidepressants have been shown to relieve global IBS symptoms and abdominal pain. Antibiotics have also

been studied and show global improvement of IBS with moderate quality of evidence (32).

Hence, there are a few pharmacological therapies that have moderate to strong support for a beneficial effect in IBS. However, there seem to be no studies that show long-term beneficial effects after pharmacological treatment. The longest follow up-periods that have been noted in the literature are up to four weeks (33-39). During follow-up periods, the effects of tegaserod (37) and alosetron (33-36) quickly subside while the effects of fluoxetine (38) and lubiprostone (39) seem to be sustained. However, a four-week follow-up period is not enough to draw any conclusions about long-term effects of fluoxetine or lubiprostone. One exception is the antibiotic rifaximin. In one study about 32% of patients in the rifaximin group reported adequate relief of global IBS symptoms compared to about 25% in the placebo group three months after treatment (40). Notably, the proportion of patients in the rifaximin group reporting adequate relief at post-treatment was almost 50%.

In summary, it seems that most pharmacological treatments with adequate scientific evidence for effect in IBS need to be used continuously for effect. With the exception of rifaximin, these treatments have side effects, leading to the withdrawal of tegaserod and alosetron (32). However, rifaximin is not available for prescription for IBS yet and seems to have a declining effect over time (40).

1.3 BIOLOGICAL PROCESSES ASSOCIATED WITH SYMPTOMS

1.3.1 GASTROINTESTINAL MOTILITY

Since IBS patients display altered bowel habits, much research has been devoted to find disturbances in the gut motility. Many findings indicate altered function along the GI tract in IBS patients. In the upper GI tract and small bowel, these include contractions in the esophagus, delayed gastric emptying, longer/shorter migrating motor complex intervals in the small bowel in constipation/diarrhea predominant patients, and delayed/accelerated small bowel transit in constipation/diarrhea predominant patients (41). However, none of these findings have been consistent between IBS patients or studies (41). In the large bowel the most consistent finding is a prolonged and increased motor activity after ingestion of nutrition (41).

The gut motility has also been found to be reactive to change in emotional state. In a series of multiple case studies during the 1940s, Almy et al. used different methods to induce emotional distress in subjects with and without functional bowel disturbances and observed changes in colonic motility. In the first study (42), seven healthy males were subjected to induction of headache by compression of the head. After a while all subjects showed signs of stress, such as pallor, sweating, heightened blood pressure, or by verbal description. These responses were accompanied by heightened colonic motility and engorgement of the mucosa. In the second study (43), several methods of induction of stress

by physical threat were used in healthy subjects, including cold pain (submerging the hand in ice water), headache, and induced hypoglycemia. This study also included verbal induction of stress. Individual life situations that were associated with emotional distress, e.g. one subject's failure to discipline his rebellious son, were discussed with the subjects. One subject was also deceived to believe that signs of cancer had been found during examination of the colon. In almost all cases where the subjects responded with stress reactions to the physical or verbal stimuli, increases in colonic motility were observed. The last two studies included subjects with functional constipation (44) and IBS with diarrhea, constipation, or alternating predominance (45). Again, when stressful stimuli were presented and subjects reacted with stress, increased motility was observed. The researchers noted that the changes in motility related to stress in the subjects with functional constipation were quantitatively similar to the changes previously observed in healthy individuals (44).

Later studies have confirmed the impact of stress on the GI system, including decreased mouth to cecum transit time (46), increased colonic motility (47, 48), delayed gastric emptying (49, 50), and alteration in duodenal motility (49).

1.3.2 HYPERSENSITIVITY

While disturbed motility patterns may explain the altered bowel habits in IBS, they do not explain the pain experienced by IBS patients. Visceral hypersensitivity, i.e. lowered discomfort threshold to visceral stimulation, is currently considered one of the most important factors in IBS and has been extensively studied. Increased sensitivity to stimulation has primarily been observed in the colon but also in the esophagus, stomach, and small intestine (41). Similarly to the findings regarding gut motility, hypersensitivity has been found to increase in response to stress. In one study, stress induced by listening to conflicting types of music (folk music in one ear and rock and roll in the other) produced stronger unpleasantness and subjectively rated intensity of visceral stimulation in IBS patients than in controls (51). In another study, both physical stress (hand in ice water) and psychological stress (conflicting music) produced decreased perceptual and pain thresholds for visceral stimulation in IBS patients but not in controls (52). In several studies, hypersensitivity has also been found to increase after intake of nutrition (41).

Bloating, a symptom experienced by a majority of IBS patients (53), has also been associated with hypersensitivity. Bloating has not been linked to increased volumes of abdominal gas (54) but there is much evidence for a delayed gas transit time associated with bloating (55). However, delayed transit time seems to be more correlated with measurable abdominal distension than with the bloating sensation (56-58). In one study, only 50% of IBS patients who reported bloating showed abdominal distension (59). Patients who experience bloating without distension have been shown to have increased hypersensitivity compared to patients who experience both symptoms (60). Furthermore, in a

study of pharmacological treatment that targeted gas production, decrease in bloating was only seen in patients without hypersensitivity (61).

1.4 THE ROLE OF STRESS

Although several studies suggest an organic dysfunction in IBS, such as delayed transit of nutrition and gas, there is convincing evidence for stress as a cause of IBS symptomatology. Here, stress is defined as "an acute threat to the homeostasis of an organism, real (physical) or perceived (psychological) and posed by events in the outside world or from within, [which] evokes adaptive responses that serve to defend the stability of the internal environment and to ensure the survival of the organism" (62 p. G519). Stress has been shown to affect both motility and hypersensitivity, presumably causing altered bowel habits and sensations of pain and bloating. Indeed, IBS is often referred to as a "stress-related disorder", but from where does this stress emanate? A number of studies (63-67) have investigated the impact of daily stressors on IBS symptoms. While some studies point toward a causative effect of daily stressors on IBS symptoms the most consistent finding is a reciprocal relationship (67). Thus, the primary source of symptom-causing stress is probably related to daily stressors only to a limited extent. Below, the evidence for psychiatric factors and symptom-related fear as potential sources of stress is reviewed.

1.4.1 PSYCHIATRIC FACTORS

Population-based studies have investigated the prevalence of psychiatric disorders in IBS patients compared to normal controls. All studies reviewed here used random sampling except one that compared all IBS patients within a health maintenance organization to matched controls (68). In these studies, the prevalence of the following disorders was larger among IBS patients than normal controls: generalized anxiety disorder (68, 69), depression, (68, 70, 71), panic disorder (19), panic attacks (68), somatization disorder (68, 71), obsessive compulsive disorder (71), stress reaction (68), impaired mental health (72), life time anxiety or mood disorders (73), and any psychiatric disorder (74). The highest population prevalences of psychiatric disorders in IBS were found for lifetime anxiety or mood disorders (50%; 73), depression (30%; 68), stress reaction (17%; 68), and generalized anxiety disorder (16%; 69).

The prevalence of IBS has also been investigated among patients diagnosed with a psychiatric disorder. In a recent study including 357 psychiatric patients, higher frequencies than population prevalence of IBS were found in patients with generalized anxiety disorder (26%), panic disorder (22%), and depression (25%) (75). Another study examined the prevalence of IBS in patients diagnosed with obsessive-compulsive disorder and found that 35% of patients fulfilled IBS diagnostic criteria compared to 3% of matched controls (76). A review of studies published before 2003 reported increased prevalence of IBS in patients with depression (27-29%), panic disorder (17%-46%), and generalized anxiety disorder (37%) (76).

IBS patients have also been found to have an increased need for social approval (77), a more submissive interpersonal style (78), and feelings of interpersonal inferiority (79) compared to healthy controls. In IBS patients a cognitive style of negative thinking predicts more suffering related to IBS symptoms (80) and general worry and anxiety is positively correlated with pain severity (81). High levels of neuroticism have also been found to be predictive of an IBS diagnosis (82).

1.4.2 SYMPTOM-RELATED FEAR AND AVOIDANCE BEHAVIORS

Pertaining to the previous definition of stress, symptom-related fear is the process where a symptom or symptom-related stimuli is perceived as an acute threat to the homeostasis. In 2001, Mayer et al. suggested that conditioned fear of symptom-related stimuli could be an important characteristic of IBS (83). It was hypothesized that most IBS patients have had negative experiences of symptoms, such as intense abdominal pain or nearly losing control of their bowel, that have been preceded by neutral stimuli. These neutral stimuli could be visceral sensations, e.g. fullness or urgency, and contexts in which these sensations could occur, e.g. time of day or after food intake (83).

An association between symptom-related stimuli and fear in IBS has interesting implications, since both unconditioned (84) and conditioned (85) fearful stimuli draw our attention. Conditioned fear of symptom-related stimuli should therefore increase IBS patients' focus on these stimuli. Several studies have confirmed this. IBS patients show increased attention to pain words compared to normal controls and level of attention is positively correlated with somatic complaints (86). Moreover, IBS patients remember (87) and recognize (88) words describing GI sensations better than controls, and they are more attentive to subliminally presented words that describe GI sensations (89). IBS patients also report that they are more vigilant towards bodily symptoms than controls (90). Catastrophic thinking about pain is also linked to more severe pain in IBS patients (91, 92).

Mayer et al. further suggested that the hypersensitivity towards visceral sensations, such as pain and bloating, may be a function of this conditioned fear (83). The close association between hypersensitivity and fear of IBS sensations has been confirmed in brain imaging studies. During painful rectal stimulation, IBS patients show increased activity in, among other regions, the anterior cingulate cortex (ACC; 93, 94). The ACC has been suggested to play a part in the affective dimension, e.g. fear, of pain (95). In two studies, decrease in pain has also been associated with decrease in ACC activity. Naliboff et al. used repeated exposure to decrease rectal sensitivity in IBS patients and observed lower activity in the ACC while activity in the brain regions that process visceral input did not change (96). Lackner et al. reported that, following cognitive therapy, IBS patients showed decreased global pain and decreased activity in the ACC, among other regions (97). The elevation of hypersensitivity during stress confirms the

association with symptom-related fear, since stress has been found to increase the orientation towards threat stimuli (98). Together, these observations suggest that hypersensitivity is closely linked to, and may even be a function of, a negative emotional valence of visceral sensations.

This constitutes a solid foundation for positive feedback loops between stress and IBS symptoms. The association between fear and GI sensations leads to a decreased threshold for detecting these sensations. Detection of GI sensations will in turn induce stress, because of the same fear association, which will lead to further vigilance towards sensations, such as pain and bloating, and also alter motility, causing constipation or diarrhea. These symptoms further increase the stress and consequently also the IBS symptoms. Situations that are symptom-related will also be sources of stress, such as eating or being far away from a restroom. The increased motility and hypersensitivity induced by intake of nutrition and the general experience of IBS patients that symptoms get worse after eating (99) may even be a stress response to a conditioned fear of food.

A natural response to stimuli that evoke fear is to avoid them. However, long-term avoidance of the multitude of stimuli that could potentially be related to GI symptoms may actually be a key maintaining factor in IBS. By avoiding these stimuli, IBS patients cannot gain new experiences that reduce the fear of the symptoms and associated stimuli, e.g. being able to function despite having symptoms, maintaining control over bowels despite urgency, or experiencing milder symptoms than expected after ingestion of certain foods. Furthermore, avoiding social or work-related situations when experiencing symptoms can cause social isolation and disability. This increases general stress and reduces quality of life, thereby strengthening the negative valence of symptoms.

Several studies have confirmed the importance of symptom-related fear and associated behaviors in IBS. In a university sample, fear of IBS symptoms and fear-related behaviors have been found to be significantly more associated with IBS diagnosis than general worry, anxiety sensitivity, or neuroticism (100). An IBS diagnosis has also been associated with a desire to avoid bodily sensations (90). The level of symptom avoidance and symptom controlling behaviors is also related to severity of IBS symptoms and negative evaluation of IBS symptoms (101). Impaired physical functioning and dysfunctional eating together with number of days in bed and phone calls to the physician because of GI symptoms also predict IBS symptom severity (102). Labus et al. developed the visceral sensitivity index (VSI), aimed at measuring "gastrointestinal symptom-specific anxiety" (103). GI symptom-specific anxiety is a concept that involves the cognitive, affective, attentional, and behavioral dimensions relating to fear of IBS symptom and associated situations. In a validation study of the VSI in an undergraduate sample it was found to discriminate between students without IBS (lowest score), students with IBS who had not sought health care for their symptoms (intermediate score), and students with IBS symptoms who had

sought help for their symptoms (highest score). The VSI was also the only measure that predicted presence of an IBS diagnosis compared to measures of anxiety sensitivity, anxiety, depression, and neuroticism (104). In a sample of IBS patients, the VSI was found to be the strongest predictor of GI symptom severity, compared to presence of other functional GI disorders, anxiety, depression, and gender and was also negatively correlated with quality of life (105).

1.5 PSYCHOLOGICAL TREATMENTS

Several psychological treatments targeting different sources of stress in IBS have been developed and evaluated. Below, studies investigating the effects of the major approaches are summarized. These approaches include psychodynamic therapy, hypnotherapy, cognitive behavioral therapies, and minimal contact cognitive behavioral therapies.

1.5.1 PSYCHODYNAMIC THERAPY

The first randomized controlled trial of a psychological treatment for IBS, published in 1983, was conducted in Sweden and evaluated the effects of short-term (10 sessions) psychodynamic therapy for IBS (106). The treatment focused on coping with stress and emotional problems. In accordance with a psychodynamic theory of psychosomatic disorders (107), the therapy was mainly supportive and was not focused on unconscious processes or other psychoanalytical concepts. A psychodynamically informed therapy has subsequently been evaluated in two additional studies (108, 109). These treatments were focused on emotional problems of the study participants, primarily relationship problems.

The outcomes in these three studies of psychodynamic therapy were positive with improvements both on both psychological measures and in IBS symptoms, with the exception of the last study that did not show long-term effects on pain compared to routine care (109).

1.5.2 HYPNOTHERAPY

Hypnotherapy for IBS is aimed at gaining increased control over the gut and also includes ego-strengthening and confidence-building interventions (110). Several studies have evaluated hypnotherapy for IBS and in a recent review it was concluded that 60%-70% of IBS patients gain substantial symptom improvement from hypnotherapy (111). After hypnotherapy, IBS patients have shown reductions in negative thoughts about their gut function (112) and a reduced sensory and motor response after intake of nutrition (113). These results point towards a reduction of fear of GI symptoms as a result of hypnotherapy.

1.5.3 COGNITIVE BEHAVIORAL THERAPIES

Within the cognitive behavioral field there have been many different approaches to treating IBS. In 1987, Blanchard's group published their first studies

investigating the effects of a multicomponent treatment, including relaxation training, thermal biofeedback, and training in stress-coping strategies on IBS (114, 115). In these studies about 60% of the patients showed clinically significant improvement and these improvements were maintained over a 2- and 4-year period (116, 117). The same group also performed a small study with only 5 IBS patients, investigating bowel sound biofeedback with a 60% response rate (118). Later studies showed beneficial effects of relaxation training (119) and relaxation meditation (120) on IBS with 50%-60% response rates. However, in 1992 the Blanchard group published a study comparing the multicomponent treatment with an attention control condition and did not find any significant differences in treatment effect (121).

In 1994, the Blanchard group published a study that only included cognitive interventions and the treatment was labeled cognitive therapy (122). The rationale for focusing on distorted and maladaptive cognitions was the large prevalence of anxiety and mood disorders in IBS. These psychological problems, primarily anxiety, were hypothesized to underlie the IBS symptoms. A treatment that successfully targeted these psychological problems should therefore also relieve the IBS symptoms (122). The treatment was evaluated in two further studies and showed superiority to an attention control condition (123) and similarity in effectiveness whether administered individually or in group (124). In these studies, 55%-80% of the patients showed a clinically significant improvement after cognitive therapy. However, the studies were small, including only 10-11 patients in the treatment conditions. In 2007, the largest trial by the Blanchard group was published, including 210 IBS patients (125). The study compared group cognitive therapy (n=120) with attention control (n=46) and symptom monitoring (n=44), with discouraging results. The group cognitive therapy was not superior to the attention control in terms of symptom reduction and treatment effects were considerably lower than in the previous studies.

Toner et al. published a study of group CBT for IBS in 1998 (126). The authors argued that previous studies of cognitive behavioral therapies for IBS had not been based on models specific for IBS but rather on general models of psychopathology relating mainly to anxiety and depression. In contrast, their treatment was based on a model developed by Sharpe et al. (127), which stresses the way the IBS patients think about their symptoms. Patients who are convinced that their symptoms are signs of serious illness become more aware of their symptoms, entering into a vicious circle. These thoughts cause dysfunctional behaviors such as excessive treatment seeking or avoidance of symptom provoking activities. These behaviors make it harder for the patient to identify what situations actually contribute to the stress that creates the symptoms. Besides targeting these mechanisms, the treatment also included pain management techniques like distraction and relaxation. Other themes, deemed to be important in IBS (128), included lack of assertiveness, need for

social approval, shame over symptoms, perfectionism, and lack of self-efficacy. Although this treatment was designed specifically for IBS, it failed to show superiority to an attention control condition (126). In 2003, Drossman et al. published a large-scale study that compared the same treatment in individual format (*n*=144) with education (*n*=71) (129). This study also failed to show that the treatment was more effective than an attention control in reducing IBS symptoms.

Boyce et al. published a pilot study of a CBT including relaxation training, breathing training, cognitive restructuring, assertiveness training, and problem solving (130). This seems to be the first study that also explicitly stated that exposure exercises were used. These were aimed at reducing negative thoughts and fear associated with IBS symptoms, by graded exposure to feared situations and behavioral testing of negative predictions about the impact of IBS symptoms. A dysfunctional cognitive style was hypothesized to underlie this catastrophic interpretation of IBS symptoms and the comorbid psychiatric disorders. The pilot trial produced promising results. However, a later study from 2003 comparing the treatment (*n*=35) with relaxation training (*n*=35) and routine care (*n*=33) did not show any differential effects (131). The authors concluded that the effect of any psychological treatment was most likely the result of common factors such a trusting relationship and hope of improvement. The fact that the study had been underpowered was discarded by the authors using post-hoc reasoning.

Above, cognitive behavioral therapies that have been evaluated in at least two studies have been reviewed. There have been additional solitary studies investigating multicomponent CBT protocols, including e.g. relaxation training, cognitive restructuring, and problem solving (but not biofeedback). There are mixed results from these studies. Five studies have shown marked effects on IBS symptom (132-136), while two have failed to show substantial effects on symptoms compared to controls (137, 138) and in one patients experienced symptom relapse during study follow-up (139).

In a meta-analysis from 2004 on psychodynamic and cognitive behavioral therapies for IBS, Lackner et al. concluded that the pooled number needed to treat to gain one clinically significant improvement was 2 (140). However, the meta-analysis did not include the three studies that had failed to show superiority of cognitive therapy or multicomponent CBT to attention control (125, 129, 131). Ford et al. published a more recent meta-analysis and included the Boyce et al. (131) and Drossman et al. (129) studies. They found that the number needed to treat with CBT was 3 (141). But it was also concluded that if the three early studies of cognitive therapy that had been performed by the Blanchard group (122-124) were removed from the analysis, the beneficial effect of CBT on IBS symptoms disappeared. Notably, the study by Blanchard et

al. (125), which showed poor effect of the cognitive intervention, was not included in this meta-analysis either.

1.5.4 MINIMAL CONTACT CBT TREATMENTS

Despite the promising results in many trials during 30 years of research, psychological treatments have not become widely available for IBS patients (142). Efforts to develop more accessible treatments have been made, where the therapist time is minimized and patients are given self-help material that covers the content of treatment. Heitkemper et al. combined a multicomponent self-help book with one session led by a nurse but demonstrated small effects on symptoms (136). Robinson et al. used an informational self-help book and a series of focus group meetings, with little effect on IBS symptoms (143). Sanders et al. used a multicomponent self-help book, but did not include any therapeutic support and the study showed small effects on IBS symptoms (144).

Lackner et al. published a study in 2008 comparing two ways to administer CBT, which included cognitive restructuring and relaxation (145). Patients were randomized to a self-help treatment combined with 4 sessions of therapist contact, to a complete 10-session therapist administered treatment, or to a waiting list control. The study found similar and large improvements in IBS symptoms and quality of life in both treatment conditions compared to the waiting list. The authors concluded that although the idea of low intensity psychological treatments for IBS is appealing, a certain amount of qualified therapist contact is probably needed to achieve satisfactory treatment effects. Subsequently, two studies that used telephone contact to support the patients in working with self-help material were published. Jarret et al. compared usual care with two versions of a 9-session multicomponent treatment, one with 9 face-to-face sessions and one with 3 face-to-face sessions plus 6 telephone sessions (146). Patients in both treatment groups received the self-help book that had been used in the previous study by Heitkemper et al. (136). Both the face-to-face and telephone support groups showed similar and marked improvements in IBS symptoms compared to the usual care group. Moss-Morris et al. randomized IBS patients to a 7-week treatment consisting of a multicomponent self-help book and one face-to-face session plus two telephone sessions or a treatment as usual group (147). Six months after treatment, the treatment group showed large improvements in IBS symptoms compared to the treatment as usual group.

1.5.5 SUMMARY OF PSYCHOLOGICAL TREATMENTS

Several studies have evaluated the effects of different psychological approaches in treating IBS. The support for psychodynamic therapy and cognitive behavioral approaches is mixed, with some studies demonstrating small treatment effects on IBS symptoms. Hypnotherapy seems to be the treatment that most consistently produces positive results. However, although a pilot study suggests that hypnotherapy can be administered at home using pre-recorded CDs (148),

current protocols demand weekly sessions with a trained hypnotherapist. This highlights the large gap between supply and demand when it comes to psychological treatments for IBS. With a 10% prevalence of IBS, all patients in need cannot expect to be treated by professional therapists, regardless of treatment approach. Reducing the amount of therapist time to almost null to fix the treatment gap has not been a successful strategy. Replacing face-to-face sessions with telephone contact and/or reducing the number of face-to-face sessions has been successful. Still, face-to-face sessions require travel on part of the patient during office hours and telephone sessions require scheduling of contact, also during office hours.

Symptom-related fear and accompanying avoidance behaviors has been shown to be the most important predictor of IBS diagnostic status, compared to general psychological distress. Yet, none of the psychological approaches described above have made symptom-related fear and avoidance behaviors the primary target of treatment. In some treatments the role of these factors in IBS have been acknowledged, but other sources of stress such as interpersonal relationships and maladaptive cognitions about the self and the world seem to have been given equal or more weight as maintaining factors. The common inclusion of relaxation techniques in cognitive behavioral therapies could indicate that the primary source of symptom-inducing stress has not been identified in those treatments. If this primary source has been identified and is targeted by treatment, relaxation might not be necessary to control the stress emanating from this source. Perhaps the inconsistencies in effects between trials of cognitive behavioral therapies are an indication that they have partly failed to identify the primary source of symptom-inducing stress.

1.6 OUTLINING A NEW TREATMENT APPROACH

During recent years a new development within the cognitive behavioral tradition has gained interest. This "third wave" of cognitive and behavioral therapies is aimed at reducing emotional avoidance and increasing behavioral flexibility to promote mental and physical health. A new format of treatment-delivery has also emerged during the last decade. Using the internet to provide evidence-based treatments has shown efficacy in decreasing symptom levels in a number of disorders. Exposure is considered by some to be a key intervention in standard CBT but has not been an integral part of CBT-treatments for IBS. Below, the principles of these new developments and how they, together with exposure, can be applied to IBS is discussed.

1.6.1 EXPERIENTIAL AVOIDANCE

The process through which IBS symptoms become associated with stress and avoidance behaviors, leading to even more symptoms, bears much resemblance to the concept of experiential avoidance. According to Hayes et al. (149), experiential avoidance is an unwillingness to experience aversive private events such as bodily sensations, emotions, and thoughts. This unwillingness is

manifested as behaviors that serve to control or escape both the events and the contexts that occasion them. This maps well onto IBS, where symptoms and several symptom-related situations have become aversive. IBS patients try to alter their symptoms, using e.g. symptom-controlling drugs, distraction, or relaxation, or to avoid situations that are likely to cause symptoms, e.g. eating certain foods or stressful situations. Furthermore, they avoid situations that would be threatening if symptoms were present, e.g. social events or being far from a restroom (101).

Experiential avoidance is proposed to be a core component of psychopathology when it is used as a strategy to control private events that are not controllable by will, or when the process of avoidance increases the strength of the undesired experience, or when the means of avoidance create additional suffering (149). Again, IBS fits well with this process. The biological mechanisms that underlie IBS symptoms (e.g. motility and pain processing) cannot be controlled directly and as GI symptoms are part of normal gut functioning they cannot be avoided entirely. Nor is conditioned fear of IBS symptoms and related situations under willful control. The avoidance of IBS symptoms or symptom-related situations has also been associated with increased symptom intensity and functional impairment (101) (i.e. the avoidance increases the strength of the undesired experience and additional suffering).

The role of avoidance of negative emotions and thoughts is also emphasized in contemporary models of many of the psychological disorders that show high comorbidity with IBS, e.g. panic disorder (150), generalized anxiety disorder (151), and depression (152). In addition, IBS patients show increased prevalence of chronic pain (153), which is also heavily influenced by symptom-related fear and avoidance behaviors (154). Rather than being separate disorders within one patient, IBS and these accompanying psychological and physical disorders could therefore be regarded as a behavioral pattern of experiential avoidance.

Experiential avoidance is a key concept within the "third wave" of cognitive and behavioral therapies, which includes therapeutic approaches such as acceptance and commitment therapy (ACT), dialectic behavior therapy (DBT), and mindfulness-based cognitive therapy (155). In ACT and DBT, principal aims of the treatment are to increase acceptance instead of avoidance of negative experiences, by promoting behavioral flexibility in the presence of aversive stimuli instead of exercising control over these stimuli (155, 156). Integral in both treatments is the use of acceptance and mindfulness techniques to achieve these goals.

1.6.2 MINDFULNESS AND ACCEPTANCE

Mindfulness is a practice that originates from Buddhist tradition and has been used within that tradition to decrease the mental suffering that is regarded ubiquitous in human existence (157). The mindfulness-based stress reduction

program, published in 1982, introduced mindfulness as a clinical intervention for chronic pain (158). Since then mindfulness has been evaluated as a clinical intervention for a variety of disorders. In a recent meta-analysis, Hofmann et al. included studies that used mindfulness as a stand-alone treatment for anxiety disorders, depression, pain disorders, medical problems, attention deficit hyperactivity disorder, and eating disorders (159). Overall, mindfulness was moderately effective in improving anxiety and mood symptoms. However, in patients suffering from mood or anxiety disorders mindfulness interventions were associated with large improvements.

Although mindfulness is gaining popularity there are many different clinical applications of mindfulness with significant differences in underlying theory, training, aim, and hypothesized mechanisms (160). Notably, in ACT and DBT, mindfulness is not a stand-alone component but is used as a strategy within the overall agenda of increasing acceptance and behavioral flexibility (160). Within DBT, mindfulness is hypothesized to improve emotional regulation and attentional control while also functioning as exposure to aversive experiences and teaching new behavioral responses, i.e. acceptance instead of attempts to avoid or alter these experiences (156). In ACT, mindfulness and acceptance are closely linked concepts, focused on experiencing internal events without judging them or trying to alter them (160). Mindfulness has been suggested to consist of several behavioral dimensions. *Observing* is the process of observing internal and external experiences, *describing* refers to labeling of internal experiences, *acting with awareness* is an ongoing attention to one's activities, *nonjudging* and *nonreactivity of inner experiences* are two processes that refer to taking a nonevaluative stance towards thoughts and feelings and not reacting to these experiences, i.e. letting them come and go without getting caught up in them (161).

Thus, mindfulness is a behavior that is opposite to distraction from or suppression of aversive inner stimuli such as thoughts or emotions. This is an important aspect of mindfulness, as attempts to control thoughts and emotions often have the paradoxical effect of increasing the strength of the target thoughts or emotions (162). In laboratory studies, mindfulness through focused breathing has led to better improvement in dysphoric mood than rumination and distraction (163) and less reactivity to negative images than worry and free mind-wandering (164). Encouraging acceptance instead of control of negative experiences has been shown to decrease the fear response and avoidance impulses after inhalation of carbon dioxide enriched air (inducing panic-like symptoms), when compared to emotional suppression (165) and diaphragmatic breathing (166). Interestingly, outside mindfulness research the behavior of labeling or describing aversive stimuli has been found to modulate the response to these stimuli. Sensory monitoring, i.e. describing the physical characteristics of a sensation, has been shown to decrease the unpleasantness of painful stimuli (167). Matching an angry or scared face to a label describing the emotion leads

to larger down-regulation in amygdala activity, a brain region involved in the expression of fear (168), than matching with another angry/scared face (169) or the gender of the face (170). Furthermore, the effect of repeated exposure seems to be facilitated when aversive stimuli are paired with labels describing the stimuli (171).

1.6.3 EXPOSURE TREATMENT

Exposure treatment is probably among the most powerful interventions to reduce fear or anxiety associated with a stimulus (172). The main principle of exposure, to repeatedly expose oneself to a feared stimulus in order to reduce the fear of that stimulus, became widely recognized after Wolpe had developed systematic desensitization to treat specific phobias (173). The desensitization procedure included presenting the phobic stimuli to the patient while the patient was in a relaxed state. It was theorized that the relaxed state would "countercondition" and ultimately eliminate the fear elicited by the stimulus (172). However, systematic desensitization had only limited value in treating clinical fears and the relaxed state did not prove to be necessary in exposure treatments (172, 173). In more recent models of exposure, it is emphasized that exposure should target experiential avoidance by eliciting a fear response and facilitate acting in a manner that is not in accord with the fear response, e.g. approaching instead of avoiding (172, 173). Within ACT, the purpose of exposure is not to reduce the fear response but to increase behavioral flexibility in the presence of stimuli that have previously narrowed the behavior repertoire, while being aware of and accepting the feelings elicited by the stimuli (155, 174).

Craske et al. recently summarized experimental studies of the mechanisms of exposure treatment (175). They concluded that effective exposure does not depend on fear reduction during exposure but rather on development of fear tolerance. Exposure exercises should be focused on violating the expectancies of the patient, both on automatic and propositional levels. That is, the exposure should provide new information both regarding what stimuli that follow previously conditioned stimuli and verbal predictions about what will happen during the exposure. Furthermore, the use of safety behaviors may interfere with the exposure since the expectancy violation might be attributed to the safety behavior and therefore not result in new learning. Finally, exposure exercises should be spaced over time and take place in varying context that have close resemblance to the real-life contexts that evoke fear.

1.6.4 INTERNET-DELIVERED COGNITIVE BEHAVIOR THERAPY

In 2009, Hunt et al. published the first study evaluating ICBT for IBS, consisting of relaxation training, cognitive restructuring, exposure exercises, and behavioral experiments (176). This study used e-mail to provide therapist contact and the results were promising with large improvements in IBS

symptoms compared to a waiting list. However, the study had large attrition rates and had not employed any diagnostic procedure.

There are many different approaches that use the internet to deliver psychological treatments. The ICBT employed by Hunt et al. has many similarities to face-to-face CBT. In ICBT the patients learn about the treatment interventions by reading self-help texts that contain both educational material and instructions on how to perform the exercises that constitute the treatment. The general principle is that the treatment should reflect face-to-face therapy in terms of content, but instead of including face-to-face time with a therapist an online therapist guides the patient through the course of the treatment. The therapist contact is most often asynchronous, i.e. the communication does not take place trough real-time chats or video conferencing. Instead, the patient and therapist send messages to each other when it suits them, using e-mail or websites with integrated messaging systems. Usually, there is agreement upon how often the patient should check in with the therapist, e.g. once a week, and how fast the patient should expect to get answers from their therapist, e.g. within 24-48 hours during weekdays.

The therapist gives feedback on homework exercises completed by the patient, answers questions, and provides general support in the patient's work with the treatment. An important therapist task is to grant the patient gradual access to the treatment material. Often, the treatment material is not presented all at once but is divided into chapters, or modules, similar to how manualized CBT is scripted session-by-session. To get access to the next module, or "session", the patient has to complete the homework of the current module and report it to the therapist. In ICBT, therapist time is dramatically reduced compared to face-to-face CBT. Therapists usually spend about 10 minutes per week and patient (177). However, the outcome in ICBT seems to be dependent on a certain amount of therapist contact. Studies including very little or no therapist contact have lower treatment effects than studies including regular contact with a therapist (178, 179).

ICBT carries many advantages compared to traditional face-to-face CBT. These include larger patient volumes per therapist, no need for patients to take time off work to travel to the therapist's office, and patients living in rural and urban areas have equal access to treatment. ICBT also comes with disadvantages. The format makes it harder, but not impossible, to tailor the treatment after individual needs and idiosyncrasies in behavioral patterns. This makes it essential that the manuals are comprehensive and cover the majority of behavioral patterns that patients present with. The target disorder must therefore be well characterized and the diagnostic procedure must select the patients who fit the profile that is assumed in the manual. The treatment also demands much from the patients' ability to plan their treatment, to read the self-

help material and fit instructions and examples to their own behavioral patterns, and to use the internet to communicate with their therapist.

During the last decade, several trials have evaluated ICBT for various psychiatric disorders and health problems. One of the first studies employing the ICBT model described here targeted chronic headache (180). Later studies within the behavioral medicine field have been conducted on e.g. tinnitus, chronic pain, and insomnia with effect sizes similar to face-to-face treatment (181). Within the field of psychiatric disorders, ICBT has shown effectiveness for panic disorder, social phobia, post-traumatic stress disorder, depression, and bulimia nervosa/binge eating disorder (182). Recent studies from our research group have indicated that ICBT is effective for hypochondriasis (183) and may be as effective as cognitive behavioral group therapy in the treatment of panic disorder (184) and social anxiety disorder (185).

1.6.5 Synthesis

IBS is a prevalent, costly, and debilitating disorder. Many patients with IBS also present with psychiatric and psychological problems. Pharmacological treatments come with side effects and require continuous use to be effective. Stress has been implicated as a cause of the major symptoms in IBS. Symptom-related fear and avoidance behaviors seem to be the most distinguishing factors in IBS and are related to illness severity. Although several psychological treatment approaches exist, none of them have symptom-related fear and avoidance behaviors as their primary target. Psychological treatments are not accessible for the majority of IBS patients.

There is an obvious application for exposure in the treatment of IBS. By exposing themselves to IBS symptoms and avoided situations, IBS patients should experience reductions in fear of IBS symptoms. However, these patients often show a wide repertoire of avoidance behaviors, as mirrored by the psychiatric and psychological comorbidities they present with. Within the third wave of CBT there is an emphasis on acceptance of inescapable negative experiences and behavioral flexibility in the presence of these experiences. Presenting exposure exercises in a context of acceptance and behavioral flexibility and using mindfulness to potentiate the exposure may both be specifically targeting IBS and broadly targeting an avoidant behavioral pattern. Using the internet to provide the treatment allows for large-scale implementations, which is necessary given the large prevalence of IBS.

2. Aims of the thesis

The overarching aim of this thesis was to develop and evaluate an effective psychological treatment for IBS that can be made accessible to a large number of IBS patients. The means to achieve this aim were to develop an exposure-based CBT treatment that emphasized acceptance and behavioral flexibility in response to IBS-related experiences and deliver this treatment via the internet. Five studies were conducted to evaluate the effectiveness of these means in achieving the aim.

2.1 Study I

The aim of this study was to evaluate exposure-based group CBT in the treatment of IBS. Participants were recruited through referral from gastroenterological clinics. We hypothesized that engaging in exposure exercises aided by mindful awareness would improve IBS-symptoms, quality of life, GI symptom-specific anxiety, and global functioning. We also hypothesized that the treatment would increase the willingness to be in contact with negative experiences. This would lead to a general improvement in mental health as expressed by psychiatric diagnoses. We also hypothesized that these improvements would be maintained 6 months after treatment.

2.2 Study II

The aim of this study was to evaluate exposure-based ICBT in the treatment of IBS. Participants were recruited through self-referral. We hypothesized that, compared to a waiting list control group, the treatment group would improve IBS-symptoms, quality of life, GI symptom-specific anxiety, depressive symptoms, and global functioning. We also hypothesized that these improvements would be maintained 3 months after treatment.

2.3 Study III

The aim of this study was to evaluate the long-term effects of exposure-based ICBT for IBS. The participants from study II were included in this study. We hypothesized that improvements in IBS symptoms, quality of life, and GI symptom-specific anxiety that had been achieved in treatment would be maintained 15-18 months after treatment.

2.4 Study IV

The aim of this study was to investigate the effectiveness and clinical utility of exposure-based ICBT within regular clinical practice. Participants were consecutively recruited from a gastroenterological clinic. We hypothesized that, compared to a waiting list control group, the treatment group would improve IBS-symptoms, quality of life, GI symptom-specific anxiety, depressive symptoms, and global functioning. We also hypothesized that these improvements would be maintained 12 months after treatment.

2.5 Study V

The aim of this study was to investigate the specificity of exposure-based ICBT for IBS. We therefore compared it with a credible internet-delivered control treatment based on stress management principles. Participants were self-referred. We hypothesized that the treatments would be perceived as equally credible by the participants but that exposure-based ICBT would be superior to internet-delivered stress management in reducing IBS-symptoms. We also hypothesized that this difference would be maintained 6 months after treatment.

3. THE EMPIRICAL STUDIES

First the common elements of the studies are presented. Then each study is presented with details on participant recruitment, design, analysis, results, and methodological discussions. Finally, the results on IBS-specific outcomes shared between the studies are summarized. Table 1 provides an overview of the studies' characteristics with regards to aims, design, assessment points, and participant demographics.

3.1 MEASURES

Table 2 provides an overview of the outcome measures used in each study. In studies II-V all self-assessments except the GI symptom diary were administered online. Online assessment has been shown to be reliable and produces results very similar to traditional paper-and-pencil administration (186).

3.1.1 MEASURES OF IBS SYMPTOMS

In studies I and II the GI symptom diary (187) was used. It is a measure of primary IBS symptoms (abdominal pain and tenderness, diarrhea, constipation, and bloating) and additional common GI symptoms (flatulence, belching and nausea). Based on the primary symptoms, a relative change score between -1 and 1 can be calculated (CPSR; 125). A CPSR score of ≥ 0.5, which means at least 50 % reduction in primary symptoms, is considered a clinically significant improvement (188). Studies II-V used the gastrointestinal symptom rating scale – IBS version (GSRS-IBS; 189), which measures the severity of GI symptoms experienced in the last week. Since IBS-symptoms have been shown to be intermittently clustered and occurring about once a week (190), three to four weeks of symptom monitoring with the GI symptom diary and GSRS-IBS was used to establish a reliable assessment of symptom severity in all studies.

In studies III and V we used another measure of clinically significant improvement. Adequate relief of IBS symptoms was assessed by asking the participants: "In the past week, have you had adequate relief from IBS pain or discomfort?"(191).

3.1.2 MEASURES OF IBS-RELATED IMPAIRMENT

The irritable bowel syndrome quality of life instrument (IBS-QOL; 192) includes IBS-related domains such as dysphoric thoughts, symptoms interference with activity, food avoidance, and impact on relationships. The level of GI symptom-specific anxiety, i.e. the cognitive, affective, and behavioral responses to GI symptoms and related contexts, was measured using the visceral sensitivity index (VSI; 103). The IBS-QOL and VSI were used in all studies. In study V we also included the cognitive scale for functional bowel disorders (CSFBD; 193), which measures negative thoughts about bowel function and personality characteristics thought to be linked to IBS, e.g. perfection and need for social approval.

Table 1. Characteristics of the studies in the thesis.

	Study I	Study II	Study III	Study IV	Study V
Study aim	Evaluation of efficacy of exposure-based cognitive behavior group therapy for IBS	Evaluation of efficacy of internet-delivered exposure-based cognitive behavior therapy for IBS	Long-term follow-up of study II	Evaluation of effectiveness of internet-delivered exposure-based cognitive behavior therapy for IBS in a clinical setting	Comparison of internet-delivered exposure-based cognitive behavior therapy with internet-delivered stress management for IBS
Sample	Patients referred from gastroenterological clinics	Self-referred patients diagnosed with IBS	Participants in study II	Consecutive patients at one gastroenterological clinic	Self-referred patients diagnosed with IBS
Design	Open study	RCT, waiting list-controlled	Follow-up	RCT, waiting list-controlled	RCT, two treatment conditions
Assessment points	Pre-treatment, post-treatment, 6-month follow-up	Pre-treatment, post-treatment, 3-month follow-up (treatment group only)	15-18-month follow-up after treatment	Pre-treatment, post-treatment, 12-month follow-up (treatment group only)	Pre-treatment, post-treatment, 6-month follow-up
Sample size	34	85	75	62	195
Participant characteristics					
Female	100%	85%	86%	74%	79%
Age (*sd*)	34.6 (11.0)	34.6 (9.6)	35.9 (8.9)	34.7 (11.2)	38.9 (11.1)
Years with IBS (*sd*)	11.2 (7.8)	14.0 (11.4)	15.5 (11.0)	11.5 (11.7)	14.9 (11.2)
Some college or more		64%		64%	77%

Table 2. Outcome measures used in the studies.

Measure	Study I	Study II	Study III	Study IV	Study V
GI symptom diary	Pre Post 6 mo f-u	Pre Post			
GSRS-IBS		Pre Post 3 mo f-u	15-18 mo f-u	Pre Post 12 mo f-u	Pre Post 6 mo f-u
Adequate relief			15-18 mo f-u		Post 6 mo f-u
IBS-QOL	Pre Post 6 mo f-u	Pre Post 3 mo f-u	15-18 mo f-u	Pre Post 12 mo f-u	Pre Post 6 mo f-u
VSI	Pre Post 6 mo f-u	Pre Post 3 mo f-u	15-18 mo f-u	Pre Post 12 mo f-u	Pre Post 6 mo f-u
CSFBD					Pre Post 6 mo f-u
MADRS-S	Pre Post 6 mo f-u	Pre Post		Pre Post 12 mo f-u	
Sheehan disability scales	Pre Post 6 mo f-u	Pre Post		Pre Post 12 mo f-u	
HADS					Pre Post 6 mo f-u
PSS					Pre Post 6 mo f-u
MINI & CGI	Pre Post 6 mo f-u				
Treatment credibility scale		During treatment			During treatment
Working alliance inventory					During treatment

For each study and outcome measure the assessment points are given. *Pre*: pre-treatment assessment; *Post*: post-treatment assessment, *X mo f-u*: Follow-up assessment X months after treatment.

3.1.3 MEASURES OF GENERAL DISTRESS

The Montgomery Åsberg depression rating scale – self report (MADRS-S; 194) is a measure of depressive symptoms. The Sheehan disability scales (195) assess symptom-induced disability in three domains, social, work, and family. The MADRS-S and Sheehan disability scales were used in studies I, II, and IV.

In Study V the 10-item version of the perceived stress scale (PSS; 196) was used to measure the degree to which daily situations were perceived as stressful by the participants. In the same study we used the hospital anxiety and depression

scale (HADS; 197), which measures the levels of anxiety and depression on two separate subscales.

In study I psychiatric interviews were conducted by the study psychiatrist and included the mini-international neuropsychiatric interview (MINI; 198) and the clinical global impression scale (CGI; 199).

3.1.4 MEASURES OF TREATMENT PROCESS VARIABLES

In studies II and V we used the treatment credibility scale (200) to measure how participants perceived the treatments, namely how credible the treatment seemed and how successful participants predicted that the treatment would be in alleviating their problems. In study V we also included the working alliance inventory (201) to measure how participants rated the quality of the contact with their online therapist.

3.2 EXPOSURE-BASED COGNITIVE BEHAVIOR THERAPY

Some adjustments in how the treatment was presented were made between each study based on how it was received by the participants. However, the main interventions and theoretical framing of the treatment were the same throughout all the studies. Below, the treatment is described more extensively than in the papers describing the studies.

Two features of this treatment separate it from other CBT protocols for IBS. First, it is rooted in a behavioral and functional perspective in that it views human behavior as an adaptation to environmental contingencies (172). Thus, the behavioral, cognitive, and emotional dimensions of experiential avoidance in IBS are seen as learned responses to IBS-related stimuli. Although they are maintaining factors in IBS they are themselves not caused by negative thinking patterns or some other behavioral predisposition. Instead, they are caused by historical associations between IBS symptoms and negative experiences and historical reinforcement of behaviors that have served to avoid and control these experiences. These reinforcers have typically been temporary relief of symptoms or anxiety. Second, this behavioral pattern is countered through acceptance of IBS symptoms and related cognitions and feelings through exposure exercises combined with mindful awareness. Mindful exposure changes the association between symptom-related stimuli and fear but also introduces new consequences that can influence future behavior. These consequences are typically reinforcers that have come to occur less frequently or not at all because of the avoidant behavioral pattern. These may be reinforcers that are dependent on engaging in e.g. social events, spontaneous behavior, physical activity, or difficult tasks at work.

The exposure-based treatment consists of three main themes. The first theme is education about a psychological model of IBS, explaining the relationship between behaviors that serve to control or avoid symptoms, stress, symptom awareness, and symptom severity. The patients' own experiences of the

historical short-term reinforcement of avoidance and control behaviors and ongoing detrimental effects of these behaviors on quality of life are discussed from this perspective.

The second theme is mindfulness and acceptance; patients are taught a 15 minute mindfulness exercise to be practiced daily and a brief exercise aimed at bringing the patient into immediate awareness of current GI symptoms, thoughts, feelings, and behavioral impulses. Negative thoughts in the presence of aversive stimuli are explained to be a natural consequence of the negative valence of these stimuli and are part of the avoidant behavioral pattern. Patients are encouraged to take an accepting stance towards these thoughts instead of trying to alter or suppress them. Changing the avoidant behavior will eventually attenuate dominating and disturbing negative thinking.

The third theme is exposure, chiefly divided into three categories. 1) Exercises that provoke symptoms, such as certain foods, physical activity, and stressful situations. 2) Abolishment of behaviors that serve to control symptoms, such as distraction, excessive toilet visits, eating certain foods, resting, and taking over-the-counter medications. 3) Exposure to real life contexts where symptoms are unwanted, such as attending a meeting when experiencing abdominal pain, riding the bus with fear of losing control of the bowels, or attending a party while feeling bloated and unattractive. These three categories of exposure exercises are often combined, e.g. eating symptom-provoking food before a meeting while wearing uncomfortably tight clothes, and not visiting the toilet before the meeting. The problem with safety behaviors, i.e. behaviors that are believed to lower the risks associated with an exposure exercise, is explained and they are weaned.

The exposure exercises are presented to serve two purposes. Engaging in exposure exercises will probably result in long-term extinction of the fear response to the aversive stimuli, leading to reduction in symptoms. But exposure also serves to broaden the behavior repertoire in the presence of aversive stimuli. Using exposure exercises with the sole purpose to reduce IBS symptoms could prove to be insufficient. IBS symptoms are not under willful control and are part of the normal variations in gut functioning – thus even successfully treated patients will experience GI symptoms (but probably identify them as IBS symptoms) during the rest of their life. Fear-responses to symptoms and associated situations may also linger even after successful exposure exercises. Thus, future variations in symptoms may trigger the fear response, leading to more symptoms and associated negative thoughts and emotions. This underlines the importance of using exposure exercises to practice reacting to aversive stimuli with behaviors that allow access to important reinforcers, rather than with avoidance or control behaviors that preclude the access to these reinforcers. This practice ensures that these reinforcers will be accessible even in future presence of these aversive experiences.

Patients are also instructed on how to use mindfulness during exposure. By observing and labeling their environment, i.e., aversive, neutral, and positive internal and external stimuli, they will counter distraction from and suppression of thoughts and emotions. By attending to any impulses to flee the situation or decrease the intensity of symptoms they will also be less inclined to act on these impulses. Patients are also instructed to predict how they think the exposure will play out before the exposure exercises. After completing the exercises they compare their experience with their prediction.

Throughout treatment, acceptance of aversive experiences that cannot be controlled without causing secondary suffering is emphasized. Exposure to these experiences is conceptualized as acceptance of them and willingness to be in contact with them. At the end of treatment the risk of relapse into strategies of symptom control and avoidance is discussed.

3.3 INTERNET-DELIVERED CBT

Studies I, II, IV, and V employed ICBT as it is presented in the Background. The treatment was based on the exposure-based CBT protocol. The treatment material was presented on printer-friendly web pages and divided into several successive steps. All participants had an assigned online therapist. To progress through treatment, participants had to report that they had worked through a treatment step to get access to the next. During treatment, participants also had access to an online closed discussion forum where they could discuss their treatment with each other.

3.4 STUDY I

Table 3 displays relevant effect sizes and proportions of clinically significant improvements together with results from associated statistical tests in all studies. All studies were approved by the regional ethics committee.

3.4.1 PARTICIPANTS

Female participants, between the age of 18 and 65, were included in the study if they had been diagnosed with IBS at a gastroenterological outpatient clinic. Patients were excluded if any somatic or psychiatric disorder deemed to interfere with treatment was present. Information about the study was spread to gastroenterological clinics in Stockholm, Sweden, and patients were referred to the study psychiatrist. Most participants were referred to the study from their gastroenterologist. A total of 34 participants were included.

3.4.2 INTERVENTION

The group treatment consisted of 10 weekly 2-hour group sessions lead by two psychologists, with 4-6 participants in each group. The first four sessions were focused on teaching the participants the psychological model underlying the treatment and mindfulness exercises. In the remaining six sessions the focus was on planning and evaluating between-sessions exposure exercises. Throughout the treatment all sessions were therapist-lead. Although participants in the

group interacted during sessions and coffee breaks, sharing of personal information or peer-support was not considered part of the therapeutic process and was not encouraged (nor discouraged) by the therapists.

3.4.3 ASSESSMENTS

The study included a psychiatric assessment including the MINI and CGI. The self-assessments included the GI symptom diary, IBS-QOL, VSI, MADRS-S, and Sheehan disability scales. All assessments were conducted at pre-treatment, post-treatment, and at 6-month follow-up.

Table 3. Reported within- and between-groups effect sizes and proportion of clinically significant improvements for all studies, together with results from associated significance tests.

	Study I	Study II	Study III		Study IV	Study V	
Measure			ICBT	WL		Post	F-U
The GI symptom diary							
Primary symptoms	0.83*	0.83*					
Pain	0.64*	0.64*					
Constipation	0.35*	0.76					
Diarrhea	0.43	0.32*					
Bloating	1.02*	0.94*					
% CPSR ≥ 0.5 or % Adequate relief	50%	ICBT: 40% WL: 2%*	52%	65%		ICBT: 69% ISM: 58%	ICBT: 65% ISM: 44%*
GSRS-IBS		1.21*	1.11*	0.94*	0.75*	0.38*	0.44*
IBS-QOL	1.30*	0.93*	0.91*	0.94*	0.82*	0.51*	0.31*
VSI	1.40*	0.64*	0.79*	0.79*	0.74*	0.33*	0.37*
CSFBD						0.52*	0.36*
MADRS-S	0.59	0.43*			0.61		
Sheehan disability scales	1.21*	0.47*			0.21*		
HADS anxiety						0.04	0.14
HADS depression						0.01	0.08
PSS						-0.02	0.06

All effect sizes are Cohen's *d* and * marks *p*<.05 for associated statistical tests.
Study I: Within-group effect sizes for improvements from pre-treatment to post-treatment assessment. *Significant dependent t-test. **Study II**: Between-groups effect sizes comparing treatment group and waiting list at post-treatment. *Significant interaction effects of 2x2 repeated measures ANOVA or Chi-2 for difference in CPSR proportions. **Study III**: Within-group effect sizes for improvements from pre-treatment to 15-18-month follow-up with missing values replaced by pre-treatment scores based on all participants in study II and separately reported for Study II's original treatment group (ICBT) and waiting list after being crossed over to treatment (WL). *Significant dependent t-test. **Study IV**: Between-groups effect sizes comparing treatment group and waiting list at post-treatment. *Significant interaction effects of mixed models analysis. **Study V**: Between-groups effect sizes comparing treatment group and waiting list at post-treatment (Post) and 6-month follow-up (F-U). *Significant interaction effects of mixed models analysis or Chi-2 for difference in adequate relief proportions.
ICBT: Internet-delivered exposure based CBT. *ISM*: Internet-delivered stress management.

3.4.4 ANALYSIS

Dependent t-tests were used to examine the treatment group's change from pre-treatment to post-treatment and to test if treatment gains were sustained at follow-up. At post-treatment and follow-up, the proportion of participants who had a CPSR score ≥ 0.5 (50% improvement on primary GI symptoms), the proportion of participants who were recovered from diagnosable pre-treatment psychiatric conditions, and the proportion of participants who were much or very much improved according to the CGI were calculated.

3.4.5 RESULTS

Twenty-nine of the 34 participants (85%) completed the post-treatment assessment and 30 (88%) completed the 6-month follow-up.

Participants showed significant improvement on all symptoms measured by the GI symptom diary at post-treatment, except for diarrhea. The treatment effects on bloating and the composite primary symptom score were large. The effects on the VSI, IBS-QOL, and Sheehan disability scales were large and significant. Effects on MADRS-S were non-significant. All improvements were maintained at the 6-month follow-up.

The proportion of patients with CPSR scores ≥ 0.5 was 50% at post-treatment and 44 % at 6-month follow-up. At pre-treatment, 14 (41 %) of the patients fulfilled at least one DSM-diagnosis (e.g. dysthymia, panic disorder, agoraphobia, and generalized anxiety disorder). Of the 14 patients diagnosed with a disorder at pre-treatment, 6 (42%) and 9 (64%) no longer fulfilled diagnostic criteria at post-treatment and follow-up, respectively. As judged by the CGI, 22 (65%) and 21 (62%) were considered much or very much improved at post-treatment and follow-up, respectively.

3.4.6 METHODOLOGICAL CONSIDERATIONS

This study did not include a control group, which limits the validity of the trial. However, in a review of CBT for IBS, Blanchard found that in 15 of 16 trials CBT was superior to a waiting list or treatment as usual control group (202). This indicates that active treatments have effects beyond those of time. Our recruitment method also limits the generalizability of the results. Participants were referred by gastroenterologists who may have selected patients on basis of perceived suitability for a psychological treatment. Thus, the study did probably not include a representative sample of IBS patients. The psychiatrist who assessed the patients is part of the research team and may have been biased towards detecting improvement after treatment. An independent assessor would have been preferable.

3.5 Study II

3.5.1 Participants

Participants were eligible for the study if they declared to have had a previous diagnosis of IBS established by a physician and if they presently fulfilled Rome III criteria for IBS (12). The study did not include a gastroenterological examination and we therefore used telephone interviews to confirm diagnostic criteria and exclude patients with symptoms that in a live care setting would have rendered a somatic investigation to rule out organic disease. Patients with suicide ideation or severe depressive symptoms, substance dependence, or psychiatric disorders were also excluded. Participants were recruited through self-referral. Information about the studies was spread to websites and newspapers. Gastroenterological clinics located in Stockholm were also informed about the studies. The study included 85 participants.

3.5.2 Interventions

Participants were randomized to 10 weeks of ICBT (n=42) or a waiting list (n=43). The online therapists were 2 graduate psychology students in the last term of the five-year psychology program. They had completed clinical training including supervised psychological treatment and clinical placement. They spent a mean of 16.5 minutes (sd=8.5) per week and participant during the treatment.

We had the ambition to exert some control over the effects of attention and weekly activity in the study. Participants randomized to the waiting list were therefore given access to an online discussion forum (separate from the one used by the treatment intervention) where suggestions about general discussions regarding IBS were given. Participants were also allowed to initiate contact with an online therapist if they wished to receive general support, but were offered no CBT-based advice on how to handle IBS symptoms or psychological distress. Besides sending an introductory message, the therapist did not initiate contact with participants on the waiting list. However, the activity of the waiting list participants in the discussion forums and utilization of therapist contact was almost negligible.

3.5.3 Assessments

The assessments included the GI symptom diary, GSRS-IBS, IBS-QOL, VSI, MADRS-S, and the Sheehan disability scales. These were administered at pre-treatment and post-treatment for both groups. At 3-month follow-up the treatment group also completed the GSRS-IBS, IBS-QOL, and VSI. After two weeks of treatment, the treatment group completed the treatment credibility scale.

3.5.4 Analysis

We used 2x2 repeated measures ANOVA and calculated the interaction effects between group and time to test for improvements in the treatment group

compared to the waiting list. The proportion of participants who had a CPSR score ≥ 0.5 post-treatment was calculated. We also examined the relationship between completing the treatment and the rated treatment credibility. Dependent t-tests were used to examine if treatment gains were maintained from post-treatment to 3-month follow-up for the treatment condition.

3.5.5 RESULTS

Thirty-eight of 42 (90%) in the treatment group completed the post-treatment and 3-month follow-up assessments and all 43 (100%) in the waiting list completed the post-treatment assessment.

Except for constipation, all interaction effects were significant. Large between-groups effects were observed on primary symptoms, bloating, GSRS-IBS, and IBS-QOL. Moderate effects were observed on pain and the VSI. The between-groups effects on the MADRS-S and Sheehan disability scales were low. Using a CPSR score ≥ 0.5 as measure of clinically significant symptom reduction, 17 of 42 (40%) in the treatment condition and 1 of 43 (2 %) in the waiting list were improved, a significant difference. All improvements in the treatment group were maintained at the 3-month follow-up.

When comparing the treatment credibility scores of the 29 participants who completed the treatment and the 11 who did not complete the treatment, a significant difference was revealed, with a large between-groups effect size (Cohen's $d = 0.92$).

3.5.6 METHODOLOGICAL CONSIDERATIONS

In this study, we did not include a proper diagnostic procedure but relied on a previous diagnosis that was confirmed in a telephone interview. Therefore, we cannot be sure that all participants actually fulfilled Rome III criteria for IBS. The use of self-referral also limits the generalizability of the study. We included limited therapist contact and an online discussion forum in the waiting list condition to exert some control over the effects of attention. But the activity in the waiting list was negligible. An active control group that included credible treatment interventions would have been preferable to control for the non-specific effects of a psychological treatment.

3.6 STUDY III

3.6.1 PARTICIPANTS

In study III all participants from study II were contacted for follow-up assessments. Within study II they had been randomized to either ICBT or waiting list. After the conclusion of study II the waiting list was crossed over to treatment. Thus, at the time of follow-up, all participants in study II had been offered ICBT. Seventy-five of the original study's 85 (88%) participants agreed to participate in the follow-up. The original treatment group was followed up 18

months after treatment and the waiting list was followed up at 15 months after completing the treatment (mean 16.4 months).

3.6.2 Assessments
The assessments included the GSRS-IBS, IBS-QOL, VSI, and the adequate relief question.

3.6.3 Analysis
Within-group effect sizes were calculated for the improvement from pre-treatment to follow-up. We used dependent t-tests to assess whether these improvements were significant and to test if treatment gains were sustained from post-treatment to the follow-up. The proportion of participants reporting adequate relief was calculated. Missing follow-up values were replaced with pre-treatment values, meaning that the calculations also included the 10 participants from Study II who did not participate in Study III. These calculations were made separately for the original study's treatment group and waiting list, which had been crossed over to treatment. We also examined if participants who had completed the whole treatment had better long-term outcomes than participants who had not completed the treatment.

3.6.4 Results
There were significant improvements from pre-treatment to follow-up on all measures, the GSRS-IBS, IBS-QOL, and VSI, and improvements were maintained from post-treatment to follow-up. The within-group effect sizes from pre-treatment to follow-up were large on the GSRS-IBS and IBS-QOL and near-large on the VSI. At follow-up, 52% of participants in the original study's treatment group and 65% of the waiting list participants reported adequate relief (59% of the total sample).

When participants who had completed the treatment (n=62) were compared to the participants who had not completed the treatment (n=13), there were significant differences on the IBS-QOL (between-groups d=0.84) and VSI (d=0.72). The difference between the groups on the GSRS-IBS was borderline significant (p<.06 and d=0.68). Furthermore, a significantly larger proportion of completers reported adequate relief, 74% compared with 33%.

3.6.5 Methodological considerations
Since the waiting list in study II had been offered treatment we could not compare the long-term effects with a control group. Crossing over patients from waiting list to treatment also introduces some methodological problems because of possible interaction effects between being on a waiting list and then participating in treatment. However, there did not seem to be any major differences between the original study's treatment group and waiting list at the follow-up. This indicates small, if any, interaction effects in the waiting list.

3.7 STUDY IV

3.7.1 PARTICIPANTS

The participants in study V were recruited consecutively at a gastroenterological clinic in Stockholm. Participants were eligible for the study if they fulfilled the Rome III criteria for IBS (12), were between 18 and 65 years old, had no presence of current or previous inflammatory bowel disease, did not suffer from such severe diarrhea that symptom-modifying antidepressants were judged to be the treatment of first choice, and if they were willing to participate in the study.

As our aim was to recruit patients who attended a regular gastroenterological clinic and minimize selection bias, no information about the study was spread through advertisements or to other caregivers in Stockholm. All included participants were given standardized information about IBS and basic dietary and lifestyle advice on how to manage their IBS (i.e., treatment as usual). If appropriate they were also given information about over-the-counter drugs and/or prescribed medication. Of 117 patients who were eligible and considered for the study, 11 were prescribed antidepressants, 12 declined participation, 12 were excluded for other reasons, 5 patients could not be reached within the recruitment period, 15 patients were included but dropped out before randomization, and 62 were randomized.

3.7.2 INTERVENTIONS

The 62 participants were randomized to 10 weeks of ICBT (*n*=30) or a waiting list (*n*=32). Two clinical psychologists managed the online therapeutic contact. The therapists spent a mean of 7.3 minutes (*sd*=5.2) per patient in the ICBT condition and week. Similarly to study II, the waiting list included a limited supportive therapist contact and an online discussion forum. Also similarly to study II, the activity in the waiting list was almost negligible.

3.7.3 ASSESSMENTS

The assessments included the GSRS-IBS, IBS-QOL, VSI, MADRS-S, and the Sheehan disability scales. These were administered at pre-treatment and post-treatment for both groups and at 12-month follow-up for the treatment group.

3.7.4 ANALYSIS

Main outcome variables were analyzed using a linear mixed effects model fitted with full information maximum likelihood estimation (203). The superior qualities regarding missing data as well as increased power compared to the traditional repeated measures ANOVA make mixed models the preferred choice for longitudinal data analysis (204). We used the fixed effects interaction between group and time to examine the difference in rates of change between the treatment condition and waiting list from pre- to post-treatment.

3.7.5 RESULTS

Twenty-three of 30 (77%) in the treatment group completed the post-treatment and 20 of 30 (67%) completed the 12-month follow-up. Twenty-eight of 32 (88%) of the participants in the waiting list completed the post-treatment assessment.

Significant interaction effects from the mixed models analyses were obtained on the GSRS-IBS, IBS-QOL, VSI, and Sheehan disability scales but not on the MADRS-S. On the GSRS-IBS, IBS-QOL, and VSI the between-groups effects at post-treatment were about large and on the Sheehan disability scales the effect was small. All improvements in the treatment group were maintained at 12-month follow-up.

3.7.6 METHODOLOGICAL CONSIDERATIONS

This study addressed the limitations regarding recruitment in studies I and II by consecutively recruiting a clinical sample. However, although we had the ambition of conducting a study in clinical setting, many properties of the study are not part of a clinical setting. The use of a waiting list and extensive assessments may very well have made some patients less inclined to volunteer for the study or drop out after inclusion. Furthermore, a sample of patients at a gastroenterological clinic may not be generalizable to the whole IBS population. Similarly to study II, we had almost no activity in the waiting list, meaning that it did not provide any control over the non-specific effects of a psychological treatment.

3.8 STUDY V

3.8.1 PARTICIPANTS

The recruitment procedure in study V was almost identical to study II. We spread information about the study on the internet and to gastroenterological clinics in Stockholm. Participants had to declare that they had been diagnosed with IBS when applying for the study. Rome III criteria were confirmed in a telephone interview and participants with alarm symptoms, suicide ideation, or severe depressive symptom or substance dependence were excluded. The study included 195 participants.

3.8.2 INTERVENTIONS

Participants were randomized to ICBT (n=98) or internet-delivered stress management (ISM; n=97). Both treatments lasted for 10 weeks.

The stress management protocol was developed specifically for study V to ensure that relevant criteria for a credible control condition were met. The aim was to include elements that are common to all psychological interventions, e.g. a rationale for the interventions, acquisition and practice of new behaviors, expectancy of improvement, and therapeutic alliance (205). Participants in the study were informed that they would be randomized to one of two different

psychological treatments that were known to be effective in treating IBS, but they were not aware of the differences between the treatments.

Stress management is based on the common notion that IBS symptoms are exacerbated by daily stressors (65) and that better coping with these stressors should alleviate the burden of symptoms. The treatment interventions were: 1) Progressive applied relaxation, used to put the body in a state of immediate relaxation in response to IBS symptoms and psychological distress. 2) Dietary strategies, such as eating small but regular meals, taking enough time to eat, and becoming more aware of associations between certain foods and IBS symptoms. 3) Problem solving strategies used to divide daily hassles into smaller and solvable problems. 4) Advice on how to increase the quality of sleep using common sleep hygiene strategies. The stress management did not include any elements that encouraged the participants to engage in activities despite having symptoms (e.g., exposure) or to reduce their symptom controlling activities.

We used 6 therapists in the study, 4 graduate psychology students and two clinical psychologists. The therapists were randomly assigned participants from both conditions in equal numbers to control for any therapist-specific effects. In the ICBT group the therapists spent a mean of 10.1 minutes (sd=7.5) per participant and week writing messages to the participants and in the ISM group they spent 7.8 minutes (sd=6.2) per week and participant.

3.8.3 ASSESSMENTS
The assessments included the GSRS-IBS, IBS-QOL, VSI, CSFBD, HADS, and PSS at pre-treatment, post-treatment and 6-month follow-up for both groups. The adequate relief question was asked at post-treatment and 6-month follow-up. During treatment, the treatment credibility scale was administered after 2 and 5 weeks and the working alliance inventory as administered after 4 weeks.

3.8.4 ANALYSIS
We used the same analytic strategy as in study IV, a linear mixed effects model fitted with full information maximum likelihood estimation. We used the fixed effects interaction between group and time to examine the difference in rates of change between the ICBT and ISM from pre-treatment, via post-treatment, to 6-month follow-up.

In study V we also examined if the two treatments, ICBT and ISM, differed in terms of credibility and induction of expectation of improvement (as measured by the treatment credibility scale), therapeutic alliance with the online therapist (as measured by the working alliance inventory), or the amount of attention the participants received (as measured by the number of messages the online therapists sent). The proportions of participants reporting adequate relief in the two treatments at post-treatment and 6-month follow-up were also calculated and compared.

3.8.5 RESULTS

Ninety-seven of 98 (99%) ICBT participants and 94 of 97 (97%) ISM participants completed the post-treatment assessment and 87 (89%) of the ICBT participants and 82 (85%) of the ISM participants completed the 6-month follow-up.

There was a significant effect of group and time over the post-treatment and follow-up periods in the mixed models analyses on all IBS-specific outcome measures (GSRS-IBS, IBS-QOL, VSI, and CSFBD) but not on the general distress measures (HADS anxiety and depression and PSS). The between-groups effect sizes were in the small to moderate range at post-treatment and follow-up. Significantly more participants in the ICBT group than in the ISM group reported adequate relief at follow-up, 65% vs. 44%.

There were no differences on the process measures (the treatment credibility scale and working alliance inventory) or in the number of messages received from the online therapist between the groups.

3.8.6 METHODOLOGICAL CONSIDERATIONS

The study did not employ a proper gastroenterological examination and included self-referred participants. Therefore, the limitations regarding diagnostic procedure and generalizability in study II also pertain to this study. The research group is also biased towards favoring the ICBT treatment over the ISM treatment. This may have affected the therapists in their contact with the patients but also the interpretation and presentation of the data. However, we believe that the primary goal of the study, to control for the non-specific effects of a psychological treatment, was met despite this bias.

3.9 SUMMARY OF THE STUDIES

In the studies different data reporting and analysis strategies and different comparison groups were used. This makes it difficult to compare the results between the different conditions and get an overall impression of the effectiveness of exposure-based CBT. To allow for such comparison and evaluation the pre- and post-treatment scores for the IBS-specific measures shared between two or more of the studies (the GI symptom diary, GSRS-IBS, IBS-QOL, and VSI) were extracted from studies I, II, IV, and V. Within-group effect sizes, comparing post-treatment and pre-treatment, were calculated using three different strategies to handle missing data. 1) Using all available data, meaning that participants who dropped out of the studies before post-treatment still contributed to the pre-treatment values. 2) Using only data from participants who completed both the pre- and post-treatment assessments. 3) Replacing missing post-treatment values with pre-treatment values (last observation carried forward). Dependent t-tests were performed to test the significance of these pre- to post-treatment improvements.

Table 4 displays observed pre- and post-treatment scores for the GI symptom diary, GSRS-IBS, IBS-QOL, and VSI for all conditions in the treatment studies.

Looking at the results of exposure-based CBT the effect sizes on all measures are centered on 0.9-1.0 in all studies. The large dropout in study IV makes it an exception with lower conservative estimates of effect sizes on GSRS-IBS and IBS-QOL. Study I, which evaluated group treatment, has markedly higher effects on the IBS-QOL and VSI than the internet-delivered treatments.

In study V it was concluded that the internet-delivered CBT was superior to internet-delivered stress management, which is also clear in this presentation. The within-group effect sizes are about 0.5 on all measures for that treatment.

Participants on waiting lists (studies II and IV) did not improve on any outcomes during their stay on the waiting list. The only change that was observed was a significant deterioration on the IBS-QOL in the study IV waiting list.

Table 4. Observed pre- and post-treatment scores in Studies I, II, IV, and V with within-group effect sizes.

Measure	Pre-treatment			Post-treatment				Within-group effect size		
Study - condition	*n*	*m*	*sd*	*n*	*m*	*sd*	Missing	Obs	Comp	LOCF
GI symptom diary♩										
Study I - GCBT	34	5.1	2.7	33	2.9	2.8	3%	0.83*	0.79*	0.71*
Study II - ICBT	42	5.7	2.8	34	3.1	2.8	19%	0.95*	0.81*	0.61*
Study II - WL	43	5.2	2.5	43	5.2	2.6	0%	-0.04	-0.04	-0.04
GSRS-IBS										
Study II - ICBT	42	36.1	9.4	41	21.4	13.6	2%	1.27*	1.30*	1.28*
Study IV - ICBT	30	31.6	11.1	22	18.8	9.6	27%	1.24*	1.09*	0.61*
Study V - ICBT	98	34.5	10.5	96	23.3	12.7	2%	0.97*	0.98*	0.97*
Study V - ISM	97	34.3	9.4	90	28.1	12.4	7%	0.57*	0.56*	0.54*
Study II - WL	43	36.6	11.8	43	34.3	12.6	0%	0.19	0.19	0.19
Study IV - WL	32	26.7	11.8	28	27.5	14.4	13%	-0.06	-0.02	-0.02
IBS-QOL										
Study I - GCBT	34	51.9	20.2	33	77.5	19.1	3%	1.30*	1.28*	1.11*
Study II - ICBT	42	51.8	19.1	38	71.8	19.9	10%	1.02*	0.98*	0.89*
Study IV - ICBT	30	67.4	20.9	23	82.6	13.4	23%	0.89*	0.69*	0.39*
Study V - ICBT	98	57.1	19.1	97	75.7	17.7	1%	1.01*	1.01*	1.00*
Study V - ISM	97	55.5	18.9	94	65.7	21.1	3%	0.51*	0.53*	0.51*
Study II - WL	43	53.8	18.9	43	53.0	21.3	0%	-0.04	-0.04	-0.04
Study IV - WL	32	75.5	18.8	28	67.0	22.8	13%	-0.41*	-0.33*	-0.30*
VSI										
Study I - GCBT	34	47.7	18.3	33	24.0	15.6	3%	1.40*	1.36*	1.24*
Study II - ICBT	42	44.1	15.1	38	30.2	17.8	10%	0.84*	0.87*	0.81*
Study IV - ICBT	30	32.5	18.0	22	14.8	15.1	27%	1.07*	1.05*	0.70*
Study V - ICBT	98	38.5	16.8	96	24.9	16.9	2%	0.80*	0.79*	0.78*
Study V - ISM	97	38.6	16.4	91	30.5	16.8	6%	0.48*	0.52*	0.49*
Study II - WL	43	43.3	17.5	43	41.9	18.7	0%	0.07	0.07	0.07
Study IV - WL	32	27.3	16.1	28	26.3	17.5	13%	0.06	0.19	0.17

*$p<.05$ for dependent t-test. ♩Composite score of primary GI symptoms. *Obs*: Effect sizes calculated on all available data. *Comp*: Effect sizes calculated only on participants completing both pre- and post-treatment assessment. *LOCF*: Effect sizes with missing post-treatment scores replaced with pre-treatment scores. *GCBT*: Exposure-based group CBT. *ICBT*: Internet-delivered exposure-based CBT. *ISM*: Internet-delivered stress management. *WL*: Waiting list.
GCBT and ICBT effects sizes are framed.

4. GENERAL DISCUSSION

4.1 INTERPRETATION OF RESULTS

The aim of this thesis was to develop and evaluate an effective psychological treatment for IBS that can be made accessible to a large number of IBS patients. The means to achieve this aim were to develop an exposure-based CBT treatment that emphasized acceptance and behavioral flexibility in response to IBS-related experiences and deliver this treatment via the internet. Five studies were conducted to evaluate the effectiveness of these means in achieving the aim. In the first pilot study, the treatment was delivered in group format and in the following three treatment studies, it was delivered via internet. We hypothesized that the treatment would lead to improvements in IBS symptoms, quality of life, and GI symptom-specific anxiety.

In all four treatment studies these hypotheses were corroborated. In terms of effect sizes, the exposure-based CBT generally produced large within-group effects and large between-groups effects when waiting list was used as comparison condition. We used different definitions of treatment response between the studies. A 50% reduction of symptoms was used in studies I and II and gave a response rate of 40% and 50%, respectively. Subjectively rated adequate relief was used in studies III and V and gave a response rate between 52% and 69%. In study IV we did not report a dichotomous response rate. It is difficult to judge which measure gives the "true" rate of treatment responders. However, it seems reasonable to conclude that at least 50% of the patients who were included in these studies experienced a subjectively rated long-term adequate relief of IBS-related pain and discomfort.

We also hypothesized that the treatment would lead to reductions in comorbid psychiatric problems, since it emphasized behavioral flexibility in the presence of aversive stimuli. This hypothesis was confirmed in study I, where 64% of the participants who had fulfilled criteria for a DSM-diagnosis before treatment no longer did so at 6-month follow-up. In studies II, IV, and V this hypothesis was not explicit. However, significant reductions in depressive symptoms were noted in studies II and IV but with small effect sizes. In study V there was no difference between the two active treatment groups on the depression and anxiety scales, which could be interpreted as a contradiction of the hypothesis that the nature of the exposure-based intervention leads to broad effects on mental health. However, since depression is not present in all IBS patients, calculating an overall reduction score introduces ceiling effects in attainable effects sizes. Proper investigation of this hypothesis in studies II, IV, and V would therefore require better analysis of the data. The effects on global functioning are similarly modest, with between-groups effects of 0.21 and 0.47 compared to the waiting lists in studies II and IV, respectively. Again, this is probably due to a large spread in disability with many participants presenting with very little disability.

The studies used 3-, 6-, 12-, 15-, and 18-month follow-up periods and clearly show that treatment gains were maintained over time. This is in sharp contrast to pharmacological studies where the general rule is that discontinuation of the treatment leads to symptom relapse. With response rates over 50% that are sustained over time, these studies show a definite advantage of exposure-based CBT over pharmacological treatments. In study III, the long-term effects of actually engaging in the treatment become clear when comparing the follow-up scores for completers and non-completers. On all outcome measures, including adequate relief, there were meaningful differences between the two groups.

In light of the high societal costs of IBS we have made cost-effectiveness analyses on data collected in studies II and III, which have been published separately (206). The analyses showed that compared to the waiting list the ICBT leads to cost reductions of $16,806 per successfully treated patient and year. These cost reductions were mainly driven by reduced work loss and were maintained at 15-18-month follow-up.

Study IV was designed to investigate the effectiveness and clinical utility of the treatment. We consecutively recruited patients from one gastroenterological clinic. In the discussion of the paper describing study IV we argue that the study shows that the exposure-based CBT may be effective for a larger proportion of IBS patients than studies I and II indicated. This discussion is based on the fact that the participants included in the study had less impairment as measured by the VSI and IBS-QOL than the participants in the previous studies. Since participants in those studies were referred and self-referred it could be concluded that referring gastroenterologists and patients have higher cut-offs regarding impairment than is necessary to achieve large improvements from treatment. However, I now believe that there are other explanations for this difference in impairment that do not support this conclusion. It could be that patients with more impairment are underrepresented in a consecutive sample of patients making their first visit at a gastroenterological. However, these patients would not be underrepresented in studies I and II, thus increasing the average impairment in those studies.

I think that it is more interesting to use study IV to make inferences about the acceptability of the treatment in a clinical setting. Based on available data in paper IV, acceptability could be defined as the proportion of eligible patients who ended up completing the post-treatment assessment. Of 117 patients who fulfilled eligibility criteria and were considered for the study, 62 were eventually randomized and of the 30 who were randomized to treatment, 23 (77%) participated in the post-treatment assessment. Extrapolating the dropout-rate in the treatment group to the whole randomized sample, 48 (77% of 62) patients could be considered as treatment completers. The acceptance rate of ICBT in a clinical setting could thereby by approximated to 41%, as 48 of 117 eligible patients would have started treatment and participated in the post-treatment

assessment. Compared to the other studies, this study had much larger rates of dropout after inclusion and randomization. Given that the previous studies had samples selected by referral or self-referral, this difference is not surprising. The consecutive recruitment probably resulted in a sample that was less motivated to engage in treatment within a clinical trial. In light of this, a 41% completion rate could be viewed as the minimum acceptance rate of ICBT in a clinical setting. If all study-related activities, such as extensive assessments and randomization, were removed the acceptance rate would probably have been higher. Also, because of the study design, patients who were prescribed antidepressants were excluded. In a clinical setting they would probably have been offered ICBT if symptoms still remained after the pharmacological treatment. Based on this, it is reasonable to believe that at least 50% of outpatients at a gastroenterological clinic would complete exposure-based ICBT with effects similar to the self-selected samples.

Study V evaluated the specificity of the exposure-based protocol by pitting it against a stress management protocol. In light of the previous studies (125, 129, 131) that had failed to show superiority of CBT compared to a credible control, we judged it necessary to put our treatment to the same test. We made sure to power the study so that meaningful between-groups effects could be detected. Although the between-groups effects on IBS-specific measures were rather small, between 0.33 and 0.52 at post-treatment, these results are still of great importance. They clearly show that the effects of exposure-based ICBT are not due to attention from a caregiver, credibility of a treatment, or expectancy of improvement. The differences in outcome between the treatments are the result of the specific ingredients in the ICBT condition and not non-specific factors. It could be argued that the study also shows that it is better to engage in exposure exercises than in the symptom control strategies that were used in the stress management condition. From a theoretical point of view this is a reasonable assumption as fear of symptoms and related avoidance behaviors seem to be key maintaining factors in IBS, and these factors were not the explicit target in the stress management treatment. However, study V was not primarily designed to compare two distinct treatment strategies. The stress management treatment was not written by experts in that line of IBS treatment while the exposure-based treatment is based on clinical experience in CBT for IBS with emphasis on acceptance and behavioral flexibility. It should also be noted that we have a bias towards favoring ICBT over the stress management treatment. Notwithstanding these limitations, study V indicates that exposure-based CBT is superior to symptom control strategies.

4.2 CONTEXTUALIZING

How does the treatment work? Although we observed improvements in the "GI symptom-specific anxiety"-construct, using the visceral sensitivity index, we have not performed any meditational analyses. Simple correlational analyses showing no associations between changes in symptoms and changes in

symptom-related fear would be an indication that the proposed mechanisms are not correct. However, the visceral sensitivity index might not be sensitive enough to capture change in symptom-related fear and avoidance behaviors and a low correlation may therefore be uninformative. Similarly, significant correlations would not be very informative. Using two assessment points, before and after treatment, is not sufficient to establish a mechanism of action. As proper meditational analysis requires more sophisticated methods, we have focused on presenting relevant outcome data together with the theory underlying the treatments. We have, however, collected weekly measures of the VSI and GSRS-IBS in study V and plan to analyze these data to investigate putative mechanisms of action.

In these studies, we deliberately used a minimal set of interventions. We did not include cognitive restructuring or specifically target other likely sources of stress in IBS, such as anxiety, depression, interpersonal relationships, perfectionistic behavior, or daily stressors at home or at work. We wanted to contrast our treatment with multicomponent treatments and target only one hypothesized mechanism. Many other psychological treatments, maybe with the exception of hypnotherapy, have targeted so many putative mechanisms that it is difficult to determine what mechanisms are at play and which are most important. By targeting one mechanism in a manualized minimal contact treatment, we have obtained a 50% treatment response. In light of this, I believe that our studies make an important theoretical and conceptual contribution to the IBS research. IBS can be conceptualized in several different ways. From a diagnostic perspective, IBS is the presence of altered bowel habits and abdominal pain or discomfort in the absence of structural lesions (1, 2). From a pathophysiological perspective, IBS is a disorder characterized by motor abnormalities, sensory dysfunction, and nervous system dysregulation (207). From a biopsychosocial perspective, IBS is an organic disorder modulated by psychosocial factors, which can predispose, precipitate, and perpetuate the disorder and affect its clinical manifestation and outcome (208). From a cognitive perspective, IBS is a dysfunctional cognitive style that leads to negative interpretations of bodily symptoms, oneself, and the world, causing stress and IBS symptoms (122, 126, 130). I would like to add a functional perspective to these conceptualizations. From this perspective, IBS can be understood as a disorder characterized by GI symptoms and learned behavioral[1], cognitive, and emotional responses to these symptoms and related stimuli. These learned responses, e.g. fear of symptoms, avoidance and control behaviors, and help-seeking behaviors, are self-perpetuating. In other words, IBS is a process of experiential avoidance where the avoided stimuli are related to GI symptoms. Whether this conceptualization of IBS is better than any other conceptualization is an empirical question. According to the "pragmatic truth criterion" (209), a

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[1] Strictly speaking the overt behavioral part of the response should be denoted "motor", since the cognitive and emotional responses are also learned behaviors.

conceptualization that leads to a desired outcome is a correct conceptualization. Following this criterion, there may be some truth to our conceptualization, since a treatment based on it has led many IBS patients to report less suffering (which is our desired outcome).

Still, with a 50% treatment response rate there is need for further research on how the remaining 50% can be helped. Participants in study I (group treatment) showed larger improvements in quality of life and GI symptom-specific anxiety than participants in the other studies did. Maybe some patients need individualized treatments because of unusual behavioral patterns or inability to work independently with the treatment. Continued face-to-face work with IBS patients may also feed clinical experience into the ICBT manuals, making them applicable to more patients. The conceptualization may also have to be broadened and include other sources of stress than experiential avoidance. In the Background, it was stated that there is mixed support for multicomponent CBT. However, the minimal contact multicomponent CBT interventions that were published between 2008 and 2010 (145-147, 176) all show sizeable effects on IBS symptoms. Both Lackner et al. (145) and Moss-Morris et al. (147) emphasized that the CBT protocols in their studies were based on empirical and clinical observations, perhaps explaining their success. If future studies, preferably using credible control conditions, show similar effects it should be investigated which interventions in these protocols are effective. Perhaps adding cognitive restructuring as a therapeutic tool would enhance the effectiveness of our treatment. Indeed, the imaging study by Lackner et al. indicated that cognitive restructuring decreases fear of and vigilance towards IBS symptoms (97). Targeting other sources of stress, such as depression, anxiety, daily stressors, or interpersonal relationships could also be a valuable addition.

What should the treatment be called? It is important to point out it is not acceptance and commitment therapy or mindfulness-based cognitive therapy, or any other defined treatment within the third wave of CBT. Compared to our treatment, ACT is much less focused on symptom relief (209) and mindfulness-based cognitive therapy and the mindfulness-based stress reduction program contain at least 4-5 times more training in mindfulness (160). In the papers, the treatment has been called "exposure and mindfulness-based therapy", "CBT based on exposure and mindfulness", "exposure treatment", and "exposure-based CBT". Clearly, we have found it difficult to find one name for the treatment. In this thesis, it has been referred to as "exposure-based CBT". I, now, believe that this is the best title. Traditional CBT includes homework, discussions about cognitions, treatment goals, behavior change, structuring of the treatment, focus on the current life situation, explicit advice and guidance, and a treatment rationale (210). All these elements are present in our treatment. However, the treatment does not contain cognitive restructuring but is focused on exposure exercises, separating it from many other CBT protocols. This deserves to be stated in the name. But having "mindfulness" in the title placed

the treatment under the "mindfulness meditation" heading in a recent review of psychological treatments for IBS (208). In the end, the best description of a treatment is not given by its name but by explaining the theoretical basis for it and the actual interventions that are used. I believe this is provided in this thesis.

4.3 LIMITATIONS

Important methodological limitations of the individual studies are highlighted in the previous section. However, some issues regarding generalizability remain. First, as seen in Table 1, 64%-74% of the ICBT patients had studied at university. In the Swedish population, 32% between the age of 25 and 64 have a university degree (211). As discussed in the background of the thesis, ICBT requires the patient to be able to work independently and apply the treatment model to his or her behavioral pattern. Suitability for ICBT and level of education may therefore be correlated. Second, most IBS patients are diagnosed and treated in primary care (212). As we have not had primary care as recruitment base we do not know if our results can be generalized to the larger IBS population. Finally, diagnostic criteria have been developed to aid in positive diagnosis and research, but do not define IBS. IBS is the presence of symptoms in the lower gastrointestinal tract, primarily abdominal pain or discomfort, constipation, and/or diarrhea, which cannot be explained by any structural lesions (1, 2). Many patients who identify themselves as having IBS do not fulfill diagnostic criteria (16), the agreement between a clinical diagnosis and a criteria-based diagnosis of IBS is low (213), and clinical guidelines have stated that the Rome criteria are too narrow for primary care (214). All these limitations point in one direction. Exposure-based ICBT should be evaluated for patients with representative educational levels that have been diagnosed in primary care.

5. CONCLUSIONS

An aim of the thesis was to investigate the overall effectiveness and usefulness of exposure-based CBT for IBS. The studies included in the thesis show that the treatment is effective in group and delivered via the internet. It targets symptoms, fear of symptoms, and related avoidance behaviors, quality of life, and also comorbid psychiatric problems. It has specific short- and long-term effects and is useful for referred, self-selected, and tertiary care IBS patients. Further analyses have also shown that it is associated with societal cost reductions.

My hope is that this thesis will contribute to the understanding and future treatment of irritable bowel syndrome.

6. ACKNOWLEDGEMENTS

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