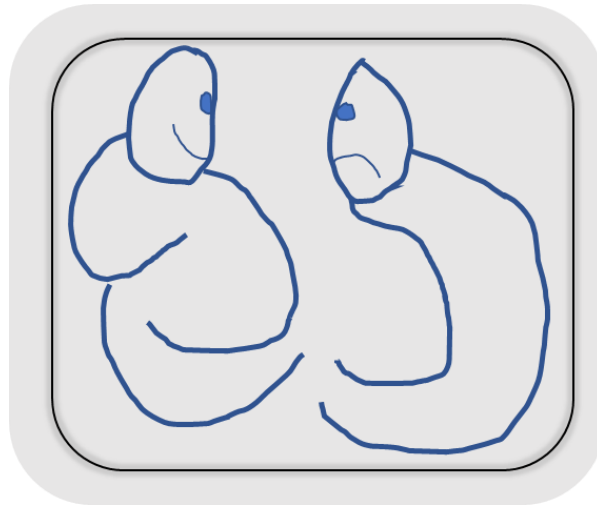


From Department of Clinical Neuroscience
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THE EFFECTIVENESS AND COST-EFFECTIVENESS OF
COGNITIVE BEHAVIORAL THERAPY ADMINISTERED
IN GROUP OR VIA THE INTERNET FOR PATIENTS
WITH IRRITABLE BOWEL SYNDROME

Hugo Wallén



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The effectiveness and cost-effectiveness of cognitive behavioral therapy administered in group or via the internet for patients with irritable bowel syndrome

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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Once you have found the causes of behavior, there is less you need to attribute to an internal act of will, and eventually, I think we need to attribute nothing to it.

B.F Skinner

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA AV AVHANDLINGENS INNEHÅLL

I genomsnitt lider var tionde person i världen av IBS. Sjukdomen är lite vanligare i västländer och i synnerhet hos kvinnor. Diagnosen fastställs av en läkare som först måste göra undersökningar för att utesluta andra tillstånd med liknande symtom. Kännetecknande för IBS är buksmärtor och förstoppning eller diarréer och i många fall upplever också den drabbade att magen blir uppblåst och gasig och att behov av toalettbesök kan komma plötsligt och ofta. Det finns många orsaker till varför man drabbas och det är svårt att veta exakt vad som är genetik och vad som beror på miljö i det enskilda fallet.

Sjukdomen är inte farlig i sig men kan vara hemskt besvärlig. Många drabbade får försämrad livskvalitet och i vissa fall kan den bli så hindrande att man inte klarar av att arbeta eller gå i skola.

Behandling ges vanligen i olika steg. Det första steget är information om sjukdomen och rådgivning om livsstil och kost. Nästa steg kan vara att lägga upp en särskild diet. Om detta inte hjälper kan det bli aktuellt med medicinering. Det finns idag ingen medicin som botar själva sjukdomen utan i stället kan olika symtom lindras med smärtstillande, laxerande eller stoppande läkemedel. Som ett sista steg om inget annat hjälper rekommenderas psykologisk behandling.

Det har gjorts försök med olika sorters psykologisk behandling men i nuläget är antingen hypnoterapi eller kognitiv beteendeterapi det som rekommenderas. Kognitiv beteendeterapi är den terapiform som man forskat mest på och möjligen också den terapiform som det finns bäst tillgång till.

I min avhandling har jag undersökt effekterna av en särskild sorts kognitiv beteendeterapi för IBS som är baserad på att patienten får exponera sig för både mat man tidigare undvikit och situationer i vilka man antingen brukar uppleva symtom eller där man är särskilt rädd för att symtom ska uppstå.

Syftet med exponering är att dels minska rädslor som patienterna lider av och som många gånger blivit förstärkta genom åren till dess att de helt tagit över patientens liv, dels vänja patienten vid att hantera sjukdomssymtomen så att man kan leva ett mer normalt liv trots dem. Paradoxalt nog verkar det som att när man utsätter sig för olika saker som man föreställt sig kommer att förvärra sjukdomen så minskar i stället symtomen vilket skapar en positiv spiral. Ju bättre effekt man får av behandlingen desto mer vågar man prova nya saker och desto mindre lider man av sin sjukdom.

Vi har låtit 750 patienter gå igenom en behandling som skapats av Brjánn Ljótsson vid Karolinska Institutet och funnit att den är mycket effektiv, även i sedvanlig rutinsjukvård. Vi har provat att ge behandlingen ansikte-mot-ansikte i grupper om 4-6 patienter, men också via internet som en guidad självhjälp. I båda fallen minskar symtomen med i genomsnitt mer än 30% vilket är en så kallad kliniskt signifikant förbättring.

Behandlingen tar ca 10 veckor att gå igenom och en majoritet av patienterna upplever att deras livskvalitet förbättrats avsevärt efteråt. Vi har också sett att denna behandling är lönsam

ur ett samhällsperspektiv eftersom patienter som får behandlingen minskar sitt behov av läkemedel, sjukvårdsbesök och dessutom kan återgå i arbete i många fall.

POPULAR SCIENCE SUMMARY OF THE THESIS

Irritable Bowel Syndrome (IBS) is a common disorder that affects approximately one out of ten individuals worldwide. The symptoms and the severity of symptoms vary between individuals but for the diagnosis to be made, the patient must experience abdominal pain at least once a week for the last three months and the pain should be associated with defecation and or a change in frequency or form of stool. Other common symptoms include bloating, flatulence, sense of urgency and abdominal cramps. Because there are no structural abnormalities to be found in IBS, the diagnosis is based on international symptom criteria's (the Rome IV criteria). There are several other disorders that can be associated with one or more of these symptoms and complementary investigations are, if needed made in the individual case. IBS is not dangerous, but it can be very bothersome, and it is not unusual that the condition leads to sick leave from work and low quality of life.

Many IBS patients benefit from changed food and eating habits and a consultation with a dietitian is therefore recommended in the start of a treatment. If the symptoms remain, it may be necessary to see a physician and to get a prescription of medication. The medications used vary depending on the patients' symptoms and may include laxatives, analgesics and antidepressants. For some patients, the symptoms persist despite change of diet and medications. In these cases, it may be useful to try a psychological treatment. The most researched psychological treatment for IBS is cognitive behavior therapy (CBT) but hypnotherapy is also used quite frequently and has performed well in clinical trials.

Professor Brjánn Ljótsson at Karolinska Institutet has developed a specific form of CBT for IBS in which exposure is a key component. The treatment has five steps, and it starts with general information and education about the disorder and how behaviors may maintain focus on and vigilance towards symptoms. The treatment continues with values-based behavior change with the purpose of establishing a lifestyle in which meaningful activities replace focus on symptoms and behaviors intended to minimize symptoms. An essential step in the treatment is that patients are encouraged to expose themselves to situations evoking symptoms or situations in which they fear symptoms and to reduce safety and control behaviors (i.e., repeated toilet visits, taking unprescribed medications and eating certain foods). The last step in the treatment is a relapse prevention program with exercises to maintain a widened behavior repertoire and a summary of what has been learned.

It takes approximately 10 weeks to go through the treatment which can be delivered face-to-face, individually or in groups or over the internet. In the present doctoral thesis, three clinical studies on the effectiveness and cost-effectiveness of this treatment are presented. In those three studies more than 750 patients have received the treatment and together with earlier studies almost 1000 patients have been included in clinical trials forming a relatively stable foundation for evidence of the treatment effectivity.

We have compared CBT including exposure with CBT without exposure to see if the exposure component makes the treatment more costly and if that cost pays back in saved expenses along the road. We found that the exposure component made the treatment approximately 20% more expensive due to more time spent by psychologist and patient. But on the other hand, costs for medication, sick leave and further visits to health care were reduced significantly more in the group that received CBT with exposure than in the other group, making the treatment profitable for society with the exposure component returning almost 6 times the investment 6 six months after treatment.

In two different studies we examined the effectiveness of the treatment by comparing patients' symptom levels before and after treatment and at six months after treatment. In the first of these studies patients received treatment at a gastroenterological clinic in Stockholm and the treatment was given in groups of 4-6 patients. On average, symptoms were reduced from pre-treatment to six months after treatment with 34% and the effect size was calculated to Cohens $d=0.95$ which is considered a large treatment effect. The other study was conducted at the Internet Psychiatry Unit in Stockholm where patients can receive the same treatment but delivered via the internet. 309 consecutively recruited patients underwent treatment for 12 weeks and as an average their symptoms were reduced by 31% and the effects size was Cohens $d=1.30$ which is considered a very large effect. These studies both show that the exposure-based CBT can be very useful in clinical routine care and the second study also showed that in average only two and a half hours of psychologist time is needed per patient when the treatment is delivered over the internet.

The thesis also aims to add some knowledge regarding potential working mechanisms of this treatment. The exposure component makes the treatment more effective, but through which means? It has been argued by different researchers that anxiety related to specific IBS-symptoms play a crucial role in retaining and potentially exacerbating the IBS-symptoms. Gastro-intestinal specific anxiety makes the patient hypervigilant towards bodily cues such as early signs of pain, swollen abdomen or bowel movement and it motivates the patient to try to find ways to avoid possibly painful or embarrassing situations by establishing avoidance or safety behaviors as mentioned above.

Exposure therapy is often used in behavioral treatment to reduce such behaviors and to create relearning when someone has developed extensive fear of specific stimuli such as spiders, large open areas or elevators. One hypothesis is therefore that the exposure component in the IBS-treatment would lead to changes in the behavioral pattern and thereby reducing hypervigilance and perception of symptoms.

We have found that behavior change predicts symptom relief during treatment confirming earlier studies and pointing to behavior change as a central process in the treatment. This is an important step in the understanding of how psychological treatment works but still the exact nature of working mechanisms in psychological treatment is to be further explored and uncovered.

ABSTRACT

Background

Irritable Bowel Syndrome (IBS) is a benign but debilitating disorder. It is the most commonly diagnosed gastrointestinal condition and affects between 7-21% of the world's population. It is characterized by abdominal pain and altered bowel habits. Patients with refractory IBS tend to develop behavioral avoidance that may severely affect life quality and lead to aggravated symptoms. Psychological treatment has emerged as a potent way of treating patients with IBS. Professor Brjánn Ljótsson at Karolinska Institutet has developed a cognitive behavioral treatment protocol specific for IBS. One of the core components in the treatment is exposure to feared stimuli such as specific foods or situations. Four different RCTs have proven the efficacy of the treatment. In randomized controlled trials the goal is to find a potential treatment effect and the setting is normally adjusted to eliminate confounding factors (i.e., by careful selection of patients and by utilizing specially trained staff that is supervised during the treatment phase and by providing many examinations or questionnaires to patients). Clinical routine care may often differ from the context of a randomized controlled trial, and it is therefore important to examine the effectiveness of a potentially effective treatment under real world circumstances. When a new and potentially more effective treatment is developed health care managers must decide whether it should be implemented in routine care or not, and one of the important questions concerns the costs for the new treatment in comparison to already implemented methods. Knowledge regarding cost-effectiveness is therefore needed.

Aims

The general aim of the present thesis is to examine the real-world effectiveness of the exposure-based cognitive behavioral treatment (ECBT) our research group has developed and to evaluate its cost-effectiveness to provide managers in health care with a better foundation for good decisions.

Specific aims of this theses were to: a) evaluate the cost-effectiveness from a societal perspective of the exposure component in the ECBT when delivered over the internet (study I), b) evaluate the real-world treatment effectiveness of the ECBT when delivered face-to-face in a group format and to investigate possible predictors of treatment outcome (study II), and to evaluate the real-world effectiveness of the ECBT when delivered over the internet and to replicate an earlier finding that behavioral change predicts symptom-reduction and thus a potential working mechanism of the treatment (study III).

Methods

Study I randomized 309 self-referred patients to internet-delivered CBT (ICBT) with or without exposure (WE) and examined the costs of the intervention as well as potential cost reductions for society and related them to treatment effects. **Study II** used data from the electronic medical record at a gastroenterological clinic and compared symptom burden before and after patients went through a group based ECBT face-to-face. The study included 129 patients with refractory IBS. Baseline data was used to try to create a prediction model for treatment outcome. **Study III** included 309 consecutively recruited patients at the Internet Psychiatry Unit who received a 12-week internet-based ECBT for IBS. The effectiveness of the treatment was calculated at the end of treatment and six months after treatment started. In

the study a random intercept cross-lagged panel model was used to investigate the relationship between behavioral change and symptom reduction over time.

Results

In both effectiveness studies (studies II and III) the patients were significantly improved after treatment and the calculated effect sizes indicated that the treatment effect is large. In study II, 52.7% of the patients had a symptomatic reduction measured with GSRS-IBS of 30% or more which is considered a clinically significant improvement. There was not enough support for the construction of a prediction model based on pre-treatment characteristics that would predict symptomatic improvement. The cost-effectiveness study (study I) showed that the exposure component makes the treatment approximately 20% more expensive, but that the money invested in exposure pays back with almost 6 times the investment in saved expenses from a societal perspective during the six months following the treatment. There is an 84% chance that the ECBT will be more cost-effective than ICBT-WE if society is willing to pay no more for the ECBT than for the ECBT-WE. Finally, in study III, we also found support for the hypothesis that the symptom reduction patients experience after ECBT is related to behavior change during the treatment, prior to the outcome.

Conclusion

ECBT is highly effective, also under real world circumstances, both when delivered face-to-face and over the internet. The exposure component in the treatment is related to behavior change that in turn predicts treatment outcome, thus pointing to a possible chain of events partly explaining the working mechanism of the treatment. Lastly, we conclude that it is very cost-effective from a societal perspective to include exposure in the treatment since the extra costs are weighed out many times by saved expenses down the road.

LIST OF SCIENTIFIC PAPERS

- I Wallén, H. Lindfors, P. Andersson, E. Hedman-Lagerlöf, E. Hesser, H. Lindefors, N. Svanborg, C. Ljótsson, B. (2021) "Return on investment of internet delivered exposure therapy for irritable bowel syndrome: a randomized controlled trial." *BMC Gastroenterology* 21:289, <https://doi.org/10.1186/s12876-021-01867-6>
- II Wallén, H. Ljótsson, B. Svanborg, C. Rydh, S. Falk, L. Lindfors, P. (2022) "Exposure based cognitive behavioral group therapy for IBS at a gastroenterological clinic—a clinical effectiveness study." *Scandinavian Journal of Gastroenterology*, 57:8, 904-911, <https://doi.org/10.1080/00365521.2022.2047220>
- III Wallén, H. Ljótsson, B. Lindfors, P. Forsell, E. Lindefors, N. Hesser, H. Svanborg, C. "Effectiveness of internet delivered exposure based cognitive behavior therapy for IBS, and the effect of reduced avoidance on outcome" (Manuscript)

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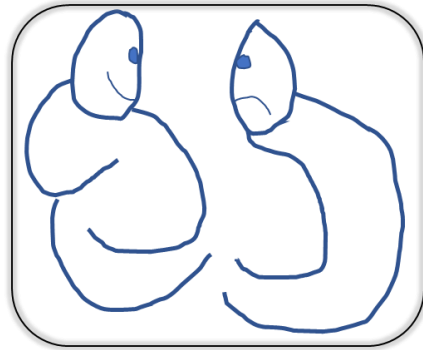
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LIST OF ABBREVIATIONS

6MFU	Six Months Follow-Up
CBT	Cognitive Behavior Therapy
CFI	Comparative Fit Index
CUA	Cost Utility Analysis
DALY	Disability-Adjusted Life Years
DGBI	Disorders of the Gut-Brain Interaction
ECBT	Exposure-based Cognitive Behavior Therapy
EMR	Electronic Medical Record
FDA	Food and Drug Administration
FGI	Functional Gastrointestinal Disorders
FODMAP	Fermentable Oligosaccharides, Disaccharides and Monosaccharides and Polyols
GSA	Gastrointestinal Specific Anxiety
GSRS-IBS	Gastrointestinal Symptom Rating Scale
HCP	Health Care Professional
IBS	Irritable Bowel Syndrome
IBS-BRQ	Irritable Bowel Syndrome – Behavioral Responses Questionnaire
IBS-C	Irritable Bowel Syndrome, Constipation predominant
IBS-D	Irritable Bowel Syndrome, Diarrhea predominant
IBS-M	Irritable Bowel Syndrome, Mixed subtype
IBS-U	Irritable Bowel Syndrome, Unspecified subtype
ICBT	Internet delivered Cognitive Behavior Therapy
ICBT-WE	Internet delivered Cognitive Behavior Therapy Without Exposure
ICER	Incremental Cost-Effectiveness Ratio
HRQOL	Health Related Quality of Life
KI	Karolinska Institutet
LFD	Low FODMAP Diet
MADRS-S	Montgomery-Åsberg depression Rating Scale – Self Assessment
MICE	Multiple Imputation by Chained Equations
NICE	The National Institute for Health and Care Excellence
NNT	Numbers Needed to Treat
OECD	Organization for Economic Co-operation and Development
PPP	Power Purchasing Parity
QUALY	Quality-Adjusted Life Years
QOL-IBS	Quality of Life in Persons with IBS
RCT	Randomized Controlled Trial
RI-CLPM	Random Intercept Cross-lagged Panel Model
ROI	Return on Investment
SEK	Swedish Krona
SF-12	The RAND 12-item Short Form Survey Instrument
SLSO	Health Care Services Stockholm County
SRMR	Standardized Root Mean Square Residual
TAU	Treatment as Usual
TIC-P	Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness
USD	United States Dollar
VSI	Visceral Sensitivity Index
WHO	World Health Organization
WTP	Willingness to Pay

INTRODUCTION

According to Japanese traditions the term “hara no aru hito”, meaning a “*person with belly*”, represents a person in balance and control. And the term “hara no nai hito”, translates to “*a person without belly*” and signifies the opposite – a person easily startled, nervous and lacking calm and stability. The “hara” or center of the body is the place where both physical and mental stability is located. These simple connotations point towards two of the main themes in this thesis, namely the relation between body and soul in general and the importance of the gut in particular.



In western medicine the relation between somatic disorders and psychological functioning has been somewhat problematic. The incongruence stems from many of the bodily functions being fully understood and described in detail but the psychological functioning in humans far from scientifically explained.

The gap in our knowledge is largely due to psychological processes taking place in the brain, an organ still a mystery, and so complex that its operations at best can be described from one perspective at a time (i.e., electric impulses, blood flows, biochemical reactions, biological structures, etc.) and rarely as an understandable whole.

But even though the relation between psyche and soma is not fully understood there are no hesitations as to whether such a relation exists. In the context of gastroenterology, several diagnostically different expressions for this relation traditionally have been labeled “functional disorders”. One of these disorders, namely IBS, can be described as a pandemic since it affects a large proportion of the world’s population which is the Merriam-Webster dictionary definition of the word.

It is with great enthusiasm and curiosity I have thrown myself into the dire task of penetrating the relationship between psyche and soma to the presumptive benefit of mankind by studying the effects of psychological interventions for irritable bowel syndrome.

Since there are really very few original thoughts left to think (most of the work already made by someone else) I have had the fortune to run into very bright and insightful colleagues whose thoughts I have appreciated, learned from, and hopefully elaborated during the work with this thesis.

I hope our collective work will result in a better understanding of, and increased access to, effective treatments for this plague.

Hugo Wallén
Göteborg, September 2022

LITERATURE REVIEW

IBS – characteristics

Irritable bowel syndrome (IBS) is one of the most common chronic diseases in the world. It is known that about one in every 20 patients seen by GPs has a functional bowel disorder with IBS being the most frequent condition they see [1]. Patients tend to see a physician for their symptoms between the ages of 30 and 50 years [2]. It affects one out of ten persons [3] and due to its chronic relapsing course, up to 50% of patients consult a physician for these symptoms [4]. More than a third of the patients referred to a gastroenterology clinic is generally diagnosed with functional gastrointestinal disorders (FGI) [5].

The IBS diagnosis is made based on internationally accepted diagnostic criteria (The Rome IV-criteria) [6]. There are currently no specific biomarkers for IBS that can be used in the diagnostic process [7]. Several other disorders can be associated with one or more of these symptoms and complementary investigations are, if needed, made in the individual case. Patients with IBS also tend to suffer from extraintestinal symptoms such as urinary problems, headaches, lethargy, sleeping disturbances, backache and others [8]. Extraintestinal symptoms in IBS patients are associated with decreased quality of life and increases costs for health care [9].

Diagnostic Criteria*

Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with **two or more** of the following criteria:

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

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Figure 1.
Diagnostic criteria for IBS according to the Rome Foundation. Version IV.

Multiple studies show that IBS negatively impacts quality of life [10-14]. It is also known that patients with IBS visit the doctor more frequently, use more diagnostic tests, consume more medications, miss more workdays, have lower work productivity, are hospitalized more frequently, and are more depressed than controls without gastrointestinal symptoms [15]. From a patient perspective, life with IBS is filled of frustration and a sense of isolation and a search for a niche in the health/sick role continuum [16].

Patients describe that living with IBS is a constant pressure. They normally feel worry, anticipation and anxiety, even when no symptoms are present. [17]. It affects relations (both emotionally and intimately) and makes life feel impaired. Patients with IBS also report that their relations with health care providers are frustrating. In one study by Halpert et al, a

majority of the patients viewed their relationships with health care providers negatively [18]. The negative experiences primarily concerned lack of empathy and not being heard.

Pathophysiology of IBS

IBS has traditionally been labeled a “functional gastrointestinal disorder” (FGID). But the term has been debated among patients, researchers and clinicians. The arguments against it are based in both the fact that recent years’ research has shown that multiple specific pathophysiological processes play a role in FGIDs and in a concern that the term “functional” can promote stigmatization by fostering the inaccurate notion that the syndrome has no real physical causes. In an article from The Lancet in 1983 three researchers concluded that:

“To determine the relative frequency of different diseases and of functional gastrointestinal disorders among patients referred by general practitioners to a gastroenterology clinic, 2000 patients referred over a five-year period were studied. 980 had organic diseases, of which peptic ulcer, oesophagitis, and inflammatory bowel disease accounted for about half. 888 patients had functional disorders of the gastrointestinal tract, without any disease. Among these, various syndromes could be distinguished; abdominal pain with altered bowel habit (irritable bowel syndrome, spastic colon type) accounted for about half of these patients”[19].

We know much more about the pathophysiology today than in 1983 and even if there are still pieces missing in the puzzle there is a growing consensus that there is nothing “functional” about IBS and that there is indeed a disease behind the symptoms. The Rome foundation (theromefoundation.org) is an independent not-for-profit organization that has decided to offer “Disorders of the Gut-Brain Interaction” (DGBIs) as a new umbrella term for functional gastrointestinal disorders [20].

For many years, the underlying structural or biochemical explanation for IBS has been largely unknown, even though several clinicians and researchers have proposed different theories [21]. This has been frustrating since interventions directed towards symptoms rather than causes rarely are sufficiently effective [22]. It has also led to the subtyping of IBS into categories based on the predominant stool pattern (i.e., constipation or diarrhea predominant IBS) mainly because interventions are based on symptoms. Over time, research has shown that the symptoms associated with IBS probably stem from different underlying biological processes and that with evolving knowledge, more adequate and precise examinations could lead to a new subtyping based on disease mechanisms, rather than symptoms [23].

Genetics

Twin studies have found that IBS show higher concordance in monozygotic twins than in dizygotic twins indicating that there might be a genetic factor influencing the prevalence of IBS [24-26]. Adjusting for anxiety and depression however, removed the statistical significance of the genetic effect [25], pointing to a possible shared common causal pathway and thereby strengthening the theory of a biological gut-brain interaction. This conclusion has also been supported by a recent genome-wide analysis of 53,400 IBS-patients where the researchers found that four out of six genetic susceptibility loci for IBS also were significantly associated with anxiety and mood disorders [27]. The correlation between IBS and anxiety persisted also when removing individuals with the two disorders comorbidly indicating that there is a common genetic pathway rather than one disorder leading to the other. Other studies have found that a missense mutation in the SCN5A-encoded voltage gated sodium channel, type V (alpha subunit) can be found in approximately 2% of the IBS population [28].

But even if evidence support the notion that genetics play a role in the development of IBS the general correlation is weak, and it is not satisfactorily proven that this genetic influence is given from conception. The complete picture may be even more complex since there are findings suggesting an epigenetic mechanism from environmental factors influencing the symptomatic expression of IBS [29]. Epigenetic mechanisms alter gene expression without alterations of underlying DNA sequence [30] and are essential in the forming of phenotypes [31]. Environmentally induced biological changes may include stress, specific nutrients or microbial metabolism [29].

Infections, inflammation and disturbances in the microbiota

It is known that about 10% of patients who contracts a bacterial intestinal infection later develop a post-infectious IBS [32]. This could potentially be explained by postinfectious dysbiosis. Fecal transplantation has been tried with the purpose of reestablishing a more balanced microbiota in the intestinal system in patients with IBS and the results have been mixed [33, 34], indicating that the microbiota is a relevant factor in the development of IBS for some patients but that more knowledge is needed about the optimal way to create a better gastrointestinal ecosystem. It has also been proposed that low-grade mucosal inflammation, particularly mast cell activation, may play a role in the pathogenesis of IBS for some patients even though findings are diverging and the studies methodologically heterogenous making conclusion less certain [35].

Brain alterations

Most functions in the body are coordinated or controlled by the brain. It is therefore not surprising that damages to, or disturbances in, the brain functions may lead to bodily dysfunctions in various ways. An epidemiological study showed that traumatic and adverse childhood experiences are associated with IBS and gastrointestinal symptom severity [36].

Diffusion tensor imaging has been used to locate abnormalities in white matter regions of the brain in some patients with IBS [37, 38] and functional magnetic resonance imaging of the brain has been used to, among other findings, identify dysfunctional endogenous inhibition of pain and concomitant aberrant activation of brain areas involved in pain processing and integration in some IBS-patients [39]. The endocrine system is affected in IBS, particularly from stress, which has been associated with both amplified gut sensations and altered cortisol responses [40].

An important aspect concerns the experience of pain in patients with IBS. Even though there might be a disturbed motility in the colon due to biological alterations or abnormalities in the abdomen, this does not necessarily cause pain. But in most patients with severe IBS the visceral pain sensitivity is also abnormal in the sense that they perceive more pain than healthy controls do when exposed to the same pain inducing stimuli. This has been shown experimentally by inducing pain in the colon with a barostatic pressure [41-44].

The exact cause and mechanisms of visceral hypersensitivity in patients with IBS are not known but experiments with mice have for example shown that it is possible to medically induce a distorted and elevated hypersensitivity from the colon [45]. This relates to receptors in the colon and to pathways between the brain and the colon (i.e., the brain-gut axis). I shall not try to go further into the exact biochemical functioning of the pain-related pathways in the brain (this is already way outside my comfort zone), since it will not be relevant for the thesis, but it is important to understand that the subjectively experienced pain in patients with IBS

has an underlying biological explanation even though it may not fully be explored at this point in time.

The role of anxiety in IBS – Gastrointestinal Specific Anxiety (GSA)

In IBS as well as in most medical conditions, environment and genetics mutually contribute to the onset of symptoms [46]. The IBS symptoms are by nature aversive and may create fear of new or worse symptoms. There are also shared genetic properties in IBS and anxiety [27]. Patients with IBS have significantly higher levels of anxiety and depression than healthy controls [47]. Anxiety and depression symptomatology should be systematically checked and treated in IBS patients, as psychological factors are important moderators of symptom severity, symptom persistence, decisions to seek treatment, and response to treatment [47].

The term anxiety refers to a state in which physiological, emotional and cognitive processes create an urgent sense of danger or catastrophe in the individual [48]. Anxiety and fear share common traits. The reaction may or may not be related to reality or actual danger. In IBS-patients the anxiety is often related to gastrointestinal symptoms [49]. Expressions of anxiety among patients are for example thoughts about potential catastrophes that might occur if no toilet is available or vivid and unpleasant images about the inside of the bowel. The anxious thoughts may be provoked by sensory input from the body but might also arise from other situational stimuli [50]. Respondent or conditioned learning is an important factor in establishing conditioned stimuli for gastrointestinal specific anxiety in IBS [51] and through a process of generalization new stimuli may be conditioned in a chain reaction [52].

A neutral stimulus as an invitation to dinner or the smell of particular foods may become conditioned if it is associated with an unconditioned stimulus provoking pain or embarrassment. Gastrointestinal anxiety is a key element in operant conditioning among IBS patients. Anxiety is a very aversive feeling that can be removed in short term by avoiding situations in which it is triggered and thereby creating behavioral learning in a contingency driven by negative reinforcement. If a stimulus is conditioned to become aversive it becomes discriminative in the operant process, signaling that an avoidance behavior may be followed by the removal of anxiety.

Fear of aversive stimuli tend to drive hypervigilance and avoidance [53, 54]. Avoidance may, at a certain magnitude, become such a hindrance of enjoying life that it results in passivity, rumination and isolation to such a degree that it causes depression. Therefore, both anxiety and depression may follow in the wake of a severe IBS.

GSA is a broader term than only anxiety. It refers to worry, fear, vigilance, sensitivity and avoidance behaviors [55]. It may perhaps best be defined by what is measured with the visceral sensitivity index, a scale developed to measure GSA.

In *Figure 2* I have tried to visually explain the relationship and interaction between the IBS symptoms, anxiety and depression.

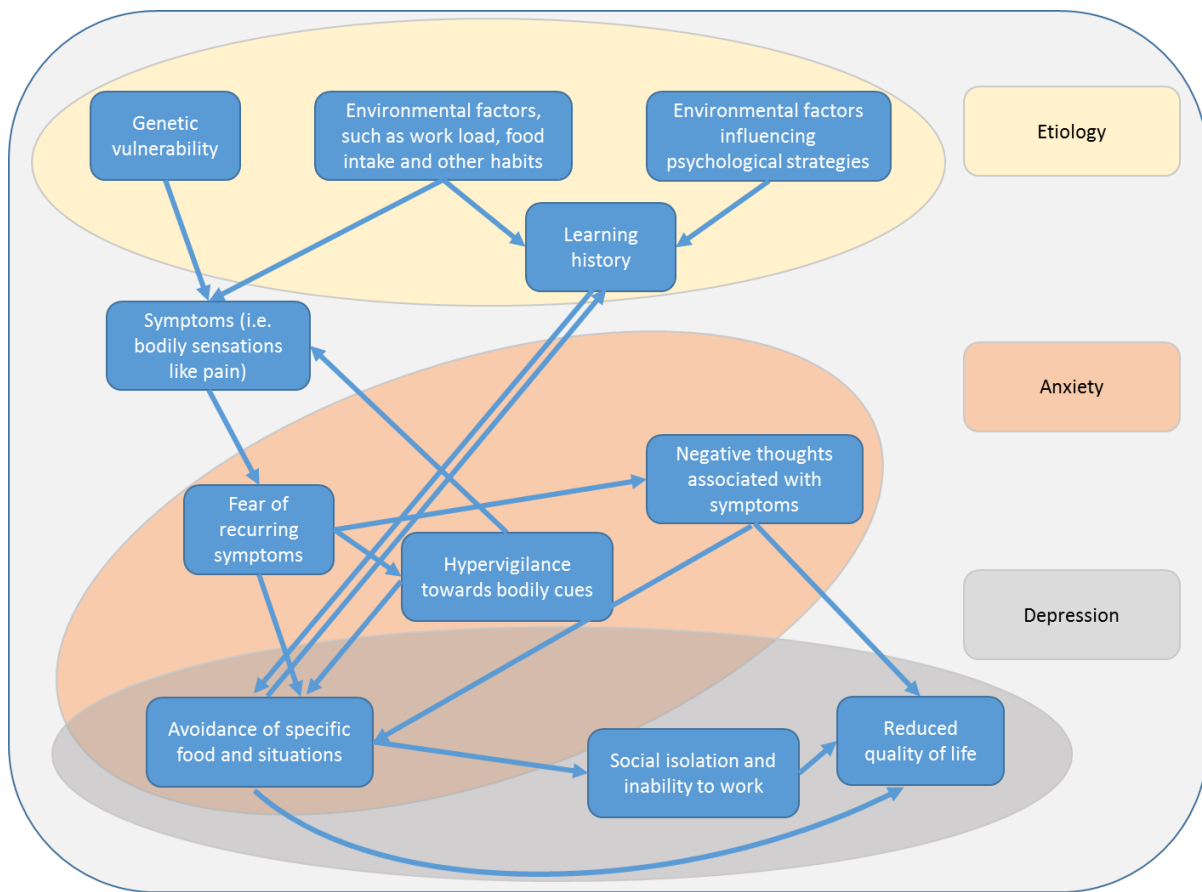


Figure 2. The relation between IBS-symptoms, their etiology and comorbid states of anxiety and/or depression. The figure shows how symptoms may cause fear, hypervigilance and negative or pessimistic thoughts and how they lead to avoidance of situations that may evoke the feared stimuli. The avoidance cause isolation and reduced quality of life.

Burden on society - costs

Several attempts have been made to calculate the costs associated with IBS [56]. A variety of methods have been used with a spectrum of cost variables. Some studies focus on the costs for the individual patients, some on the costs for the health care sector and others have tried to calculate the costs for the society as a whole. The identified areas of costs comprise medications – prescribed and over the counter, health care visits, complimentary therapies such as yoga instructors, zone therapists, healers or support groups, costs for medical examinations, inpatient bed costs, costs for sick leave, unemployment and time spent by nonprofessional care givers such as partners or parents. Attempts have also been made to sum the costs for lost work productivity (both sick leave and presenteeism) and inability to do household work.

The costs of the medical examinations, treatments, drugs and sick leave have been equated with the economic consequences of the flu [57]. A recent meta-analysis of 24 studies showed that the costs for IBS in European countries with universal healthcare coverage averaged almost €3000 annually per patient. Approximately half of the costs were direct while the other half consisted of indirect costs [56]. The study also showed that the costs were slightly higher in countries with insurance-based health systems. Those findings align with studies from the

United States where only the direct costs associated with IBS-D were \$2,268 per patient and year [58]. Given that the relation between direct and indirect costs is the same in the U.S. as in Europe the total cost per patient in the U.S. should be approximately €4000 which is coherent with the tendency towards slightly higher costs in insurance-based health care systems. Europe has approximately 740 million inhabitants and with a prevalence of 10% and a cost of €3000 per patient the total costs for IBS in Europe should be about €222 billion annually. Even if the individual suffering is not considered, the sheer burden of costs on society should be a good reason to try to find better treatment strategies for IBS.

IBS treatment

General recommendations

Good treatment for IBS starts with a mutual and empathic relation between the health care professionals and the patient. It is important that the patients' problems are taken seriously even though the condition might be seen as benign. Effective relationship and shared understanding may lead to improved quality of life and symptoms, reduced health care visits and enhanced adherence to treatments [59]. It is also important that the diagnosis is made with clear, concise and confident language (i.e., "she is diagnosed with.." or "she is suffering from" rather than "working impression is..." or "may be suffering from...") [60].

When diagnosis is made, the first-line treatments include information to the patient about the condition and support for self-management. It is particularly important to identify and address, thoughts, fears and pre-conceptions about the diagnosis that patients may have and to reduce stigma [61]. It may also be a good idea to give advice of regular exercise and dietary counseling such as having regular meals, take time to eat, reduce intake of sorbitol, alcohol or insoluble fiber (wheat bran) and make sure to drink enough and perhaps try oat-based breakfast cereals [62].

As a secondary step, the specialized care may offer consultations with a dietician. One diet that often is recommended is the so called "FODMAP"-diet, which is low in fermentable oligosaccharides, disaccharides and monosaccharides and polyols [62].

Pharmacological treatment may be necessary in the IBS-treatment and should be based on the nature and severity of symptoms. Medication may include, antispasmodics, laxatives, antidiarrheals, tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs) [62].

Patients that do not respond or respond poorly to the above interventions after 12 months and who develop a continuing symptom profile are considered refractory [62]. Psychological treatment is in this case a recommended strategy. Several psychotherapies have shown efficacy in the treatment of IBS. The British and the American societies of gastroenterology recommend the use of cognitive behavior therapy or gut-directed hypnotherapy [59, 60].

Psychological treatment for IBS

Psychotherapy for patients with IBS can be very efficacious and without distinguishing between specific therapies the NNT¹ has been calculated to 4 [95% CI, 3.5 – 5.5] [63]. There are many forms of psychotherapy, and the taxonomy is sometimes confusing. Since no international consensus exists regarding the definitions of psychotherapeutic interventions, classifications are often based on the title of, or self-definition in, each study [64]. This can lead to reviews separating the effect of CBT from the effect of stress management, mindfulness or psychoeducative therapy when the latter three in reality are, or may be, subcomponents in the former [65].

Even though there are a few published RCTs on psychodynamic therapy for IBS [66-68] the main research body concerns either CBT (including variants such as mindfulness, stress management, relaxation, contingency management or psychoeducation) or gut-directed hypnotherapy.

Gut-directed hypnotherapy (GDH) involves an introduction where suggestions for imaginative experiences are presented. This is followed by hypnotic induction in which the patient is guided into a trance state which is a form of deep relaxation with altered consciousness [69]. The therapist then uses the suggestions for alterations of perception, sensation, emotion or thought, focusing on control and normalization of gastrointestinal function.

The therapy involves several sessions in which trance and suggestions are used and the patient is given exercises between sessions. In clinical trials, 7-12 sessions are most frequent [69]. Evidence indicates that high volume GDH is significantly more effective than low volume GDH in reducing IBS symptoms [70]. GDH is a well-established treatment for refractory IBS and it has the potential to save costs from a societal perspective [71], but the availability is scarce [69].

Cognitive behavioral therapy is the most studied form of psychotherapy for IBS [72] and most of the studied psychological treatments for IBS are based on CBT [73]. There is solid evidence that this form of therapy is effective in the treatment of IBS and that the effects are sustained at both short-term and long-term follow-up [74]. As mentioned above it may be challenging to create a taxonomy over therapies since there is a lack of official definitions and interventions sometimes overlap between psychological traditions.

CBT is an umbrella term for multiple specific therapies that share common traits [75]. These therapies are built on a common theoretical framework where behaviorism [76] and information processing theory [77] constitute the foundation. Empirical preclinical and clinical research has led to development of interventions focusing on behavior, thinking and emotions. Generally, these interventions involve efforts to change or create new behavioral or thinking patterns. The goal is to help patients learn new ways of coping with the various aspects of life [78]. Interventions that often are used in CBT are psychoeducation, cognitive restructuring, relaxation, mindfulness exercises, exposure, goal setting and functional analysis among others.

¹ The number of patients needed to treat (NNT) signifies how many patients in average must be offered a certain intervention in order to get at least one patient that responds to the intervention. NNT 4 therefore indicates a 25% efficiency of the treatment.

Over 30 randomized controlled trials have been conducted on CBT for IBS [79]. Those treatments are all based on a common theoretical and practical framework, but they are not identical. Of particular interest in this thesis is a form of CBT that involves exposure to feared stimuli (ECBT). Professor Brjánn Ljótsson at Karolinska Institutet has developed a specific ECBT-protocol and four different RCTs based on this protocol have been conducted [80-83]. The results show that this form of treatment is highly efficacious in the treatment of IBS.

Avoidance behaviors or exposure in the treatment of IBS?

It seems like a paradox that both the avoidance of food and exposure to food may relieve patients of IBS symptoms. It has been argued that the reason could be that there are many subgroups of patients in the IBS-population since the pathophysiology is very complex and possibly different for individuals with the same symptomatic expression [84]. It should however be noted that interventions made with the best intent from health care providers can sometimes aggravate problems for patients. Diets, medications and frequent visits to health care may function as a behavioral avoidance that maintain, rather than improve the condition. It follows therefore that a thorough assessment of the patient's habits, behaviors, fears and values should be made before introducing diets [84-86].

It is however common that various diets are suggested in treatment recommendations for IBS [59, 60, 62]. Recommendations regarding diets concern both inclusion and exclusion of specific foods or food contents [87]. A large proportion of IBS patients complain about subjective intolerance to various foods such as beans, chocolate, eggs, dairy products, leafy vegetables, nuts, onions and spicy food [88-90]. Even though some IBS patients may suffer from food allergies there is no evidence that the prevalence of such allergies is higher in IBS-patients than in the rest of the population [91].

Two common exclusion diets regard either dietary reduction of gluten or of fermentable oligosaccharides, disaccharides and monosaccharides and polyols (FODMAP). There is evidence that a low FODMAP diet (LFD) may reduce IBS-severity to a certain extent [92] and also improve quality-of-life in patients with IBS, even though it is questionable if the change is so large that it is clinically meaningful [93]. Concerns have been raised regarding the long term nutritional adequacy of LFD [94, 95] and the overall effect on the gut microbiota [96]. There is little evidence of reduction in IBS symptoms from diets excluding gluten [97, 98].

Even if a LFD may be beneficial from a symptom perspective in short term, the idea is not to continue with this diet for the rest of the patient's life [86]. But when normal eating is supposed to be reintroduced again patients may encounter difficulties. Avoidance of specific food may create a fear of the physical reactions to those foods and it has experimentally been shown that fear may increase when avoidance is not possible [99]. This was also confirmed in a case series study from 2020. Patients in the study struggled with reintroduction of avoided foods and compliance was low [100]. There is also a risk that fear is generalized from one food source to another by classic learning principles. Studies have confirmed that a subset of patients with IBS run the risk of developing avoidant food intake disorder [85]. There is thus a risk for a circular process in which avoidance leads to fear, and fear leads to further avoidance. And this vicious circle is difficult for patients to break on their own.

One common component in CBT is exposure. Exposure treatment is often used to help break the pattern of avoidance and fear [101]. In this form of treatment, behavioral psychologists

create a safe and controlled environment in which to “expose” individuals to the things they fear and avoid. The exposure in a safe environment helps reduce fear and decrease avoidance [102]. There are at least four different types of exposure [103]; 1) in vivo exposure, in which the patient actually faces the feared stimuli in real life, 2) imaginal exposure, in which the psychologist guides the patient through vivid images of the feared stimuli, but only in the patient's imagination, 3) virtual reality exposure, in which advanced techniques are used to create an environment of images, sounds and perhaps even smells to expose the patient to a feared stimulus, 4) interoceptive exposure, in which various methods are used to bring about physical sensations that are feared, for example breathing through a straw to create the sensation of suffocation.

For IBS patients the feared stimuli tend to be related to either pain or embarrassment [55]. As mentioned above, it is common that patients start avoiding specific foods, sometimes in adherence to advice from dietitians or others [104]. The fear-avoidance contingency is often related to pain. But the symptoms do not only include pain, but also flatulence and acute need to empty the bowel. Due to those symptoms, patients may find themselves in embarrassing situations or dread ending up in such. Avoiding elevators, buses, gatherings or being far from a toilet are therefore common behaviors among severely affected IBS patients [105].

Avoidance tends to generalize from one stimulus to another until there are a vast number of stimuli that are avoided [52]. The in-vivo exposure for IBS patients includes finding out which food or situations are feared and by controlled experiments help the patients expose her or himself to those stimuli. The effect of successful exposure is that patients discover that they have been avoiding situations or food that do not provoke symptoms and/or that they can handle the symptoms even when they occur, but at the same time enjoy situations in life they have missed out on. These discoveries usually lead to increased quality of life and lessened symptom burden. In *Figure 3* I have tried to visualize how the exposure treatment may create new learning and alter the vicious circle of hypervigilance, fear and pain.

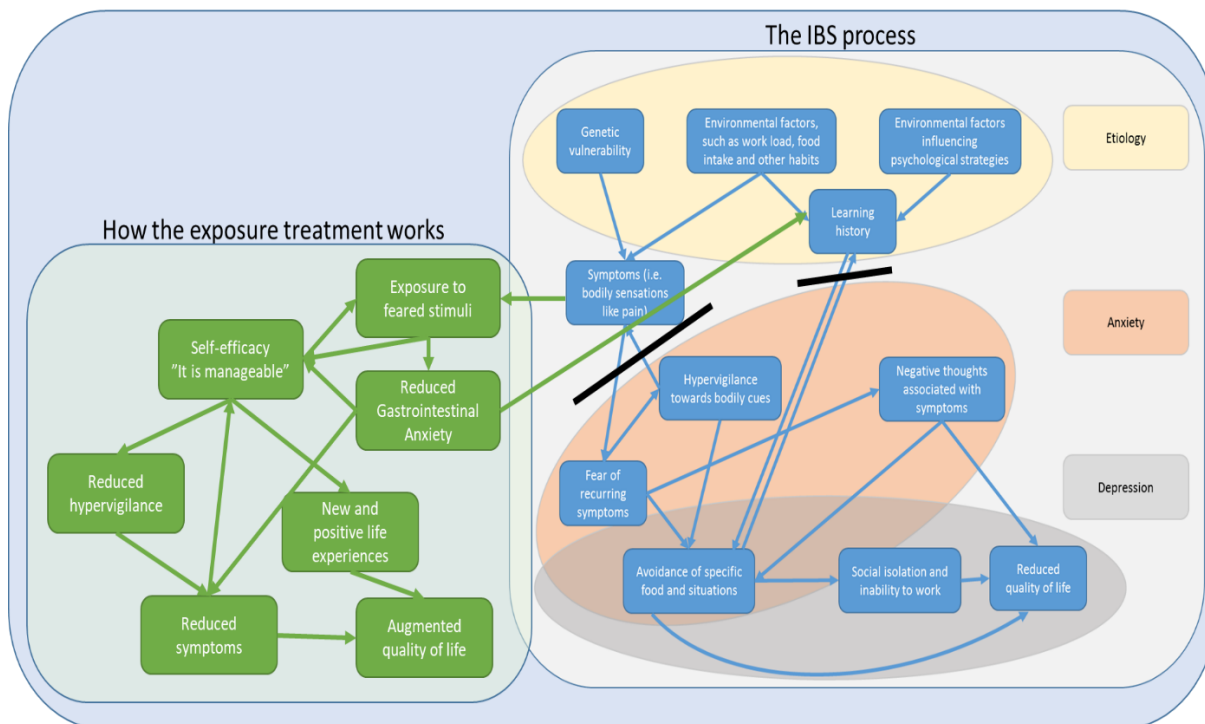


Figure 3. How exposure treatment may reduce anxiety and depression among IBS patients and lead to better quality of life.

The figure shows how exposure may create new learning for patients with IBS and lead to reduced GSA and a feeling of self-efficacy that encourages them to engage in activities they have been avoiding. When false catastrophic fears are unveiled, hypervigilance lessens, and new stimuli can be explored. This positive spiral leads to improved quality of life and reduced IBS symptom burden.

Working mechanisms in CBT

We know that exposure based CBT for IBS is efficacious [79]. But there is still uncertainty as to exactly *how* it works. The idea behind the exposure is to reduce fear and avoidance behaviors. And we know that fear and avoidance are the key components in GSA which has been well documented as an important factor for severity of GI-symptoms and quality of life in IBS [50]. It is therefore a good idea to test if exposure may change GSA and if change in GSA in turn may lead to change in symptom severity. This was made in a mediation study by our research group, and the authors found that GSA mediates the effect of exposure therapy for IBS [106]. This study was followed up by another study comparing different potential mediators of treatment outcome against each other [107]. The main finding was that behaviors directly related to the specific symptoms of IBS (endogenous to the condition, i.e., avoidance of foods or situations related to the symptoms) were more important to target than general anxiety or behaviors that were unrelated to the condition (exogenous factors) and that behaviors rather than thoughts mediated the outcome.

A year later, a study was published by Windgassen et al (2019), in which the authors found no evidence that reduction in avoidance behaviors mediates symptom reduction but rather that a reduction in safety behaviors, IBS-related cognitions and general anxiety would predict a better outcome [108]. There are some methodological limitations in that study making the results less certain. In the study the authors measured the mediators after treatment, several

weeks apart and the outcomes were not assessed until 9 months after the last mediator assessment, implicating that the analyses could not be used to show whether the outcomes changed before, after or simultaneously with the mediators [109].

A meta-analysis from 2017 included nine different studies and the results supported the notion that reduction in avoidance behaviors indeed is a mediator of outcome in ECT for IBS [110] and this aligns with a basic assumption in behaviorism, that change in behavior may forego change in perception [76, 111-113].

There are several psychological treatments for IBS that have been tested in randomized controlled trials and it is possible that their effects are mediated by different mechanisms, but it may also be true that all those mechanisms are parts of the same chain of events. If a change in behavior may predict a change in symptoms and that a reduction in symptoms produce a sense of self-efficacy it may be unnecessary or even counter-productive to try to target the self-efficacy directly. In general, I think it makes sense to try to influence the chain of events as much “upstream” as possible.

Internet delivered psychological treatment

When the internet became commonly accessible by the mid-1990's, psychologists started developing, evaluating and providing treatment over distance using digital communication [114]. Some experiments had been conducted earlier, but the technology had not allowed for more than very simple means of communication.

Over the years, digital technique has been used in various forms together with or without psychologists to provide psychotherapy for many different conditions [115]. There is great variation in how much time and support the psychologist spends communicating with the patient. In some of the trials, the therapy consists of direct communication via e-mail, text messages, chats or real time video and the psychologist spends at least as much time as the patient does with the therapy. Others are more like computer games or self-help manuals, structured in a way that make the patients' answers or questions guide the path without any psychologist intervention at all [115].

Our research group has mainly focused on a format often called therapist guided, internet delivered, cognitive behavior therapy. This form of therapy is commonly used in Sweden and consists of a combination of self-help material and e-mail-like support. The treatment is normally accessible through an online platform and requires that the patients identify themselves with a secure log in. The platform contains modules with information in different formats and combinations. Usually texts, videos and audio files combined with screening forms and exercises [116]. The results from the forms and reports and the questions patients ask are available to the therapist at any time. The therapist answers questions and gives feedback and support on a regular basis but normally spends less than 100 minutes guiding a patient through a ten week program [117]. Using the internet to deliver psychological treatment carries several important advantages compared to traditional face-to-face treatment (e.g. patients can choose where and when they access their treatment, clinicians need to spend less time per patient enabling them to focus their time on treating more patients or on patients that require extra attention [118] and the format allows for better follow-up and research on treatment [119]).

Over the last 20 years, more than 300 controlled trials of internet delivered psychotherapy have been conducted for different disorders and target populations [117]. Most of the research on psychological treatment over the internet concerns cognitive behavior therapy even though there are a few studies on other therapies as well (i.e., interpersonal therapy or psychodynamic therapy). The evidence so far indicates that therapist-guided ICBT is as efficacious as face-to-face CBT [117]. An observation is that patients on average complete 80% of the treatment both in ICBT and face-to-face CBT, but fewer patients in ICBT relative to face-to-face CBT complete the full treatment [117]. Several studies have been conducted on internet delivered cognitive behavior therapy for IBS and the results show large reductions in symptom severity and disability, few adverse events, high rates of patient rated therapeutic alliance and low societal costs relative to face-to-face treatment [81, 83, 120, 121].

Effectiveness vs efficacy

Research studies may be designed in a variety of ways. The gold standard when it comes to evaluating treatment effects is a randomized controlled trial (RCT), but sometimes other designs better serve the purpose of the study. A case-control study may for example be the best alternative when the researcher wants to find a predictor of an outcome that is relatively rare in a population. But even if the aim of the study is to evaluate a treatment effect and an RCT design is chosen, there may still be other factors influencing the design.

When new treatments are tested for the first time it is important that the eventual effects of the treatments are discovered. The researcher must therefore be careful to avoid risks for confounding factors. In order to do so, the standardization of the experiment becomes crucial. Every aspect of the procedure should be rigorously checked for confounders, resulting in a strict treatment regimen, clear exclusion and inclusion criteria for participants, mandatory training for staff, supervision of every moment of the trial and careful monitoring of treatment progress. But all these ambitious research processes may in themselves cause problems with the external validity of the study. Perhaps the effects of the treatment would be much smaller or possibly vanish completely if the research team was not involved so actively in the treatment process? Or if the staff had more “ordinary” training or the patients weren’t selected so carefully? This type of trial, designed to find possible treatment effects under perfect scientific conditions is called *efficacy study*. But a treatment that has good results under rigorously controlled study conditions may sometimes be less effective in a clinically naturalistic environment [122].

To ensure that the effects from the efficacy study hold in a more naturalistic environment a clinical *effectiveness study* is needed. This type of study is designed without constant monitoring and presence of the research team and with few or no exclusion criteria among patients and with use of regular staff etc. Gartlehner and colleagues (2006) point out that clinical effectiveness studies should focus on patients in primary care if possible and that the eligibility criteria should allow the study population to reflect the heterogeneity of the full population with comorbidity, variable compliance rates and use of other medications for example [123]. They also argue that effectiveness studies should focus on health outcomes rather than symptom scales only and that the study time must be comparable to routine care treatment time and that intention-to-treat analyses are recommended since “factors such as compliance, adverse events, drug regimens, comorbidities, concomitant treatments, or costs can alter efficacy. A “completers only” analysis would not take these factors adequately into account”[123].

Cost-effectiveness in treatment

Research and development within health care has led to numerous advancements in treatment over the years. Medications with more precise and more curing effects are developed. But all the research and the work in laboratories cost a lot of money and the medicals produced are sometimes very expensive. It is debated whether the advancements in efficiency are proportional to the costs for the new treatments [124]. The development of a new pharmacotreatment often involves preclinical trials that start in a chemistry laboratory and continue with animal trials. After the initial pre-clinical research and development, the new drug may be tested in different types of trials involving humans.

In the field of psychological treatment there is rarely any need for advanced chemistry. The principles of behavior therapy have however been established in animal-based studies in laboratories [125, 126] but most of the development is carried out with humans as study population. This is possible since there seem to be comparatively few, and small risks with psychological treatment [127, 128]. Maybe also because psychotherapy with mice tend to be of minimal value in the development of new treatments. The costs for the development of new psychotherapies are mainly related to the number of psychologists and patients involved in the trials.

When it comes to calculation the cost-effectiveness of a treatment WHO offers the following definition:

Cost-effectiveness Analysis quantifies the gains, or setbacks, in population health as a result of a particular policy or intervention. The gains are typically measured in disability-adjusted life years (DALYs), representing a weighted combination of mortality and morbidity effects of an intervention. (Other possible denominators could include cost per life saved or cost per life year saved, but these fail to capture the morbidity element.) CEA furthermore provides for the quantification of the net costs of the intervention (promotional, preventative, curative, or rehabilitation), and an assessment of those costs per disability-adjusted life year that is saved. [129]

There are however other definitions of cost-effectiveness to be found in research articles. Some authorities claim that cost-effectiveness is the appropriate term when the study is based on relevant patient data other than quality of life or QALYs/DALYs for example symptoms scales, and that the term cost utility analysis (CUA) should be used when the outcome data is based on health related quality of life (HRQOL) [130].

Psychological treatments (particularly cognitive behavior therapy; CBT) is cost-efficient for multiple medical conditions [131-134] and our research group has found indication that this is the case also for IBS [135]. Some of the studies are based on HRQOL as a measure of outcome and sometimes on other patient relevant outcome measures (i.e., symptom rating scales).

Even if research is made on cost-effectiveness in psychological treatment, much knowledge is still missing. Cognitive behavioral treatment is an umbrella term for numerous specific therapies based on the same principles. But the specific therapies differ significantly from each other in their composition. Common components are agenda, goal setting, functional analysis, behavior experiments, home assignments, exposure, relaxation, vocational and skills training, cognitive restructuring etc. The “dosage” and relative importance these components are given in each therapy is still not based on solid scientific ground. It would be useful to

know how effective each of them is and what the costs related to each component is. In that way cost-effectivity could be made part of the equation when a specific treatment is designed.

RESEARCH AIMS

The general aim of this thesis was to provide decision makers with facts that will make it easier to know whether it will be meaningful to implement ECBT in daily routine care. The research questions posed were therefore related to treatment effectiveness and costs as I believe those two areas are the most important in such decisions.

More specifically, the aims were:

1. To investigate how effective exposure-based cognitive behavioral therapy is in routine care under real-world conditions if it is
 - a) administered face-to-face in group. (Study II)
 - b) administered via the internet. (Study III)
2. To investigate if patient characteristics are associated with treatment outcome in a group-based CBT for IBS. (Study II)
3. To investigate the *cost difference* between CBT with or without exposure when delivered over the internet. (Study I)
4. To investigate the relative *cost-effectiveness*, from a societal perspective, of ICBT with exposure and ICBT without exposure. (Study I)
5. To investigate the relationship between change in behavior and change in symptom levels. (Study III)

MATERIALS AND METHODS

First, common elements of the studies are presented. Then the design of each study is described, followed by the results in study order.

Intervention

Even though the three papers in this thesis differ from each other in significant ways, they share a few common traits. One of them is that the same intervention (treatment) is used in all studies. It was developed by Brjánn Ljótsson at Karolinska Institutet and is described in a treatment manual that details what psychologists should do, say and focus on during each session and step of the treatment². It has also been described in Brjánn Ljótsson's doctoral thesis and in several published studies, perhaps best in Ljótsson et. al (2014) (or in the attached papers) [83].

In summary, it is based on behavior therapy and acceptance and commitment therapy, both therapy forms belong to the CBT tradition. The treatment is divided into five different steps and the patient must complete one step before taking the next (In *Figure 4* I have made an illustration of the treatment process). In a face-to-face situation a session normally lasts 45-60 minutes, but if the setting is a group therapy additional time is needed and therefore the sessions last approximately 90 minutes.

When the treatment is delivered over the internet, the steps are renamed to modules and there are no specific sessions, since the patient can access the treatment at any time. The patient must unlock each module by completing the previous one in order to get access to the material in it. In the internet version, the psychologist follows the patient's progress by logging in to the treatment platform where all patient interaction is logged and registered and through an e-mail like communication system.

² The manual can be accessed by writing to brjann.ljotsson@ki.se (but it has not yet been translated from Swedish).

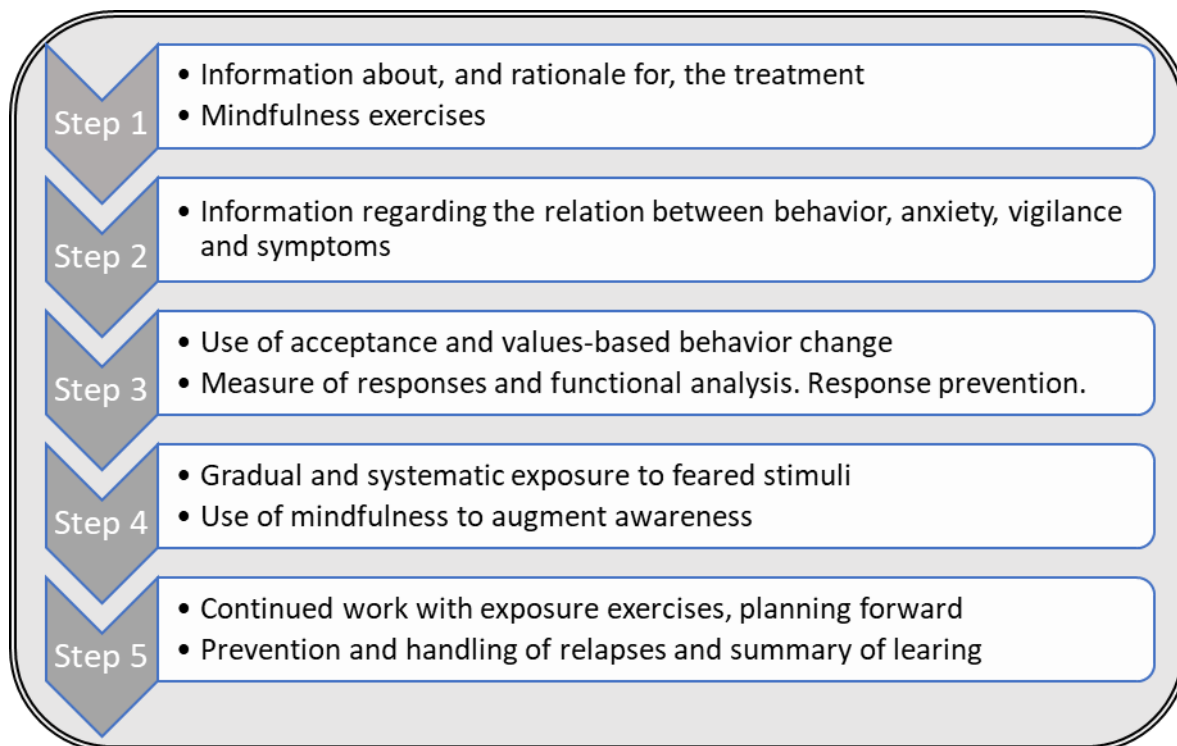


Figure 4. Schematics of the design of the exposure-based treatment for IBS.

The treatment is given in five steps (but in **study II** the fourth step was divided into two, for practical reasons). The first three usually take three sessions and the last two can continue for 7-9 sessions since they contain a lot of exercises and planning of new routines. Sessions are usually given weekly, making the treatment 10-12 weeks long. The same pace is applied on the internet delivered version of the treatment.

Primary outcome measure

Another shared property of the studies is that the same primary outcome measure was used in all three of them. The Gastrointestinal Symptom Rating Scale – IBS version [136] is a self-rating questionnaire with 13 questions that the patients were asked to complete before and after treatment. In **study I** and **study III** the patients also completed the questionnaire at follow-up six months later.

The scale measures the severity of gastro-intestinal symptoms with questions such as: “*Have you been bothered by ABDOMINAL PAIN during the past week*” or “*Have you been bothered by an URGENT NEED TO HAVE A BOWEL MOVEMENT (need to go to the toilet urgently to empty the bowel) during the past week?*”. The patients choose from one of seven given options with ascending severity. The first is “*No discomfort at all*” and the last is “*Very severe discomfort*”. The answers are then scored from 1-7 and the complete scale therefore yields a result between 13 and 91. The psychometric properties of the scale when used in the general population are excellent [137] and it has some advantages over other scales measuring IBS symptoms, for example the Irritable Bowel Syndrome Severity Scoring System (IBS-SSS) [138]. One of them being that it is easier to interpret a full scale result and that the relation between disability and the subscales of pain versus diarrhea/constipation seem to be more accurate in GSRS-IBS [137].

Study designs and data analysis

Study I was a randomized controlled trial, including 309 patients with IBS who received an internet delivered CBT. The participants were recruited through self-referral. Eighty percent were female, and the mean age was 42 years. In average the participants were diagnosed with IBS 8 years before the study.

The study was divided in two arms which both contained the same treatment. But in one arm the participants received the full treatment including exposure (ICBT), and in the other arm patients received a reduced version of the treatment, without exposure (ICBT-WE). Cost data were collected with the Trimbos/iMTA questionnaire for Costs associated with Psychiatric illness (TIC-P; [139]). Clinical outcome and costs were assessed at three time points, pre-treatment, post-treatment and at follow-up six months after treatment.

We calculated the incremental cost-effectiveness ratio based on changes in symptom severity and costs in the two groups and repeated the analyses in 5000 bootstrap replications to obtain a confidence interval. We also calculated the return on investment based on the extra cost for the exposure intervention related to the gains in terms of reduced societal costs after treatment in the two groups.

Study II was a pragmatic effectiveness study in the form of a case series evaluation at a gastroenterological clinic in Stockholm. We included 129 patients with diagnosed, refractory IBS in the study. The mean age was 36 years and 83% were female. The intervention consisted of ten sessions group based ECBT over a period of ten weeks. The Quality of life in persons with IBS (QOL-IBS) [140] inventory was used as secondary outcome measure together with The Visceral Severity Index (VSI) [55] and The Montgomery Åsberg depression rating scale – self report (MADRS-S) [141].

Within-group mean differences were evaluated based on data from the electronic medical record and effect sizes were calculated as Cohen's *d* by dividing the pre- to post-treatment average difference with the baseline standard deviation. We also calculated the proportion of responders to treatment defined as an individual reduction on the primary outcome measure of 30% or more. This is a definition recommended by the U.S. Food and Drug administration when evaluating pharmacological treatment effectiveness in IBS [142].

Patient characteristics pre-treatment were used in a multiple regression analysis with the GSRS-IBS score post-treatment as the dependent variable with the intention to discover possible predictors of treatment outcome.

Study III was a clinical effectiveness study at the Internet Psychiatry Clinic in Stockholm. The clinic has been using our treatment protocol since 2015 and all patients who underwent the internet delivered ECBT at the clinic from April 2015 until October 2020 were included in the study, thus encompassing 309 patients with IBS of different subtypes.

The mean age among the patients was 34 years, there were 65% females and the patients had in average suffered from IBS for 11 years. About a half of the patients had somatic comorbidity and one out of ten patients was on full or partial sick leave when treatment started.

We collected data on IBS-symptom severity (GSRS-IBS), IBS-related avoidance (Irritable Bowel Syndrome – behavior rating questionnaire (IBS-BRQ) [143]), Gastrointestinal specific anxiety (Visceral Sensitivity Index (VSI) [55]) and quality of life (RAND 12-item short form survey instrument (SF-12) version 1 [144, 145]). Data was collected pre-treatment, post-treatment and at follow-up six months after treatment start. Data on symptom severity and behavioral avoidance was also collected weekly during treatment. Multiple imputation based on chained equations (MICE) was used to handle missing data [146].

Symptom severity mean differences were compared with paired samples t-tests and effect sizes were calculated as Cohen's *d* at post-treatment and at follow-up. A random intercept cross-lagged time panel model was used to examine the time-related correlation between avoidance behaviors and IBS-symptoms based on the weekly measures.

Ethical considerations

Exposure may be an unpleasant experience

All studies in this thesis have been evaluated by the Swedish authority of ethical considerations (or its predecessors) and we have been granted permission to conduct them. That does however not mean that there are no risks or ethical difficulties associated with the studies.

Exposure to feared stimuli might feel counterintuitive for most people. The immediate and first reaction to fear is to avoid the source of it. And when the realization comes that you are about to actively seek out feared situations and to challenge yourself in them, the feeling you get can be far from pleasant. Anxiety, remorse and maybe anger may arise even though the situation is carefully planned, and someone is standing beside you (literally or figuratively). Many psychologists are reluctant to use exposure with their patients due to its aversive nature and fear that the patients may be exposed to iatrogenic harm.

I do believe that the long-term benefits from exposure in IBS treatment outweighs the unpleasant experiences in short term and I have in this thesis described the theoretical and empirical support for this belief. This does not mean that exposure treatment is a possibility for everyone or that patients should be persuaded to take this treatment. It is very important that they are informed about the treatment and its rationale before the exposure starts, and that they always are given the choice to terminate or change treatment if they wish to do so. We are glad though, to see that most patients tend to continue the treatment until it is completed.

Not everyone improves

To my knowledge there is no treatment that is effective for all patients. The ECBT used in our studies is no exception. Not all the patients in our studies were helped by the treatment and some patients even deteriorated from pre-treatment to post-treatment. The first study was a randomized controlled trial and would therefore allow to draw conclusions regarding both positive and negative effects of treatment. That was also made in the original efficacy study by Ljótsson et al (2014) and the conclusion was that there were no significant differences between groups. (It may however be noted that both arms contained active treatment). The aim of study I in this thesis was to analyze societal costs and gains as a complement to the other findings already made. Study II and III however, were not RCTs and thus much more difficult to use to make inferences regarding harm as a consequence of the treatment. We

could not know what would have happened to the patients in case they wouldn't have received the treatment. During the treatment any identified deterioration could be addressed by the psychologist, but after treatment the patient had to seek health care again.

In research on harmful psychological treatments it has been pointed out that harm may be both direct (i.e. the treatment causes deterioration) and indirect (the treatment prevents patients from improving in a way they otherwise would have done) [147]. Since both study II and III were based on data from routine care there was no data available regarding adverse events.

I have become increasingly interested in harm from psychological treatment and I will try to capture this phenomenon better in coming studies as I believe that knowledge of harms is equally important as of benefits.

When discussing ethical aspects of the present thesis I think it is important to point out that both study II and III were based on data from regular care and that no changes were made to the patients' care as a consequence of the research. There are therefore fewer ethical considerations to be made as a result of the research than what would have been the case if the studies were the main purpose of the interventions.

Integrity

Integrity may be a challenge in the digital age. It is important that data is kept safe and that the right person gets access to information. We have tried to make sure that no information is lost, manipulated or ends up in the wrong place. In study I and III both the patients and the health care provider logged in to the treatment platform with two-factor authentication and the data was encrypted and stored on secure servers within the Stockholm Region. Data was managed in such a way that it was impossible to connect results with identified patients.

RESULTS

In **study I**, we found that the average treatment cost in the ICBT arm was 1277.9 USD compared to 1064.4 USD in the ICBT-WE arm.

Calculation of the incremental cost-effectiveness ratio (ICER) yielded an estimate of -301.69, indicating that reducing GSRS-IBS with one point in the ICBT group compared to the ICBT-WE group incurred a societal gain of 302 USD. At a willingness-to-pay of 0 there would be an 84% chance that ICBT is more cost-effective than ICBT-WE, but if society would be willing to spend up to 800 USD for one point of improvement on the GSRS-IBS the probability of higher cost-effectiveness in the ICBT group vs ICBT-WE would increase to 99%.

We also performed a *return-on-investment analysis showing that for every extra USD spent on ICBT relative to ICBT-WE society will gain 5.64 USD in saved costs, six months after treatment.*

The percentage of participants that demonstrated clinically significant improvement (30% reduction or more on the GSRS-IBS) was 52% in the ICBT-WE group and 66% in the ICBT-group, yielding a number needed to treat (NNT) of 7.14. When calculating the ICER based on clinically significant improved patients the result was -8651.94 indicating that if 7.14 patients were treated with ICBT rather than with ICBT-WE, there would be one more clinically significant improved patient at a cost that was 8651.94 USD lower in total, from a societal perspective, after 6 months.

The results from **study II** are presented in *Table 1*. The primary outcome measure (GSRS-IBS) as a mean went from 49.24 (SD = 11.54) pre-treatment to 37.03 (SD = 10.03) post-treatment. This was a reduction of 34% in average. The difference was statistically significant ($p = >.001$), and the effect size calculated as Cohen's d by dividing the pre-, to post-treatment average difference with the baseline standard deviation was 1.06 [CI 0.86 – 1.28] which is considered a large effect size.

The results were similar for the secondary outcome measures. The patient's quality of life when measured with the IBS-QOL was improved with 68.2% and went from 42.29 (SD = 15.71) pre-treatment to 71.12 (SD = 16.38) post-treatment and gastrointestinal specific anxiety measured with VSI was reduced from 50.29 (SD = 12.64) pre-treatment to 28.21 (SD = 14.23) post-treatment which represents a 43.9% improvement. Both changes were statistically significant ($p >.001$) and corresponded to effect sizes of Cohen's $d = 1.84$ [CI 1.56 – 2.12] for IBS-QOL and Cohen's $d = 1.75$ [CI 1.47 – 2.03] for VSI, both considered large effect sizes

The third secondary outcome was depression measured with MADRS-S and it showed the same trend with a reduction from 16.87 (SD = 6.86) pre-treatment to 10.35 (SD = 6.23) post-treatment ($p >.001$). The effect size was calculated to Cohen's $d = 0.95$ [CI = 0.76 – 1.15], which is also considered a large effect size.

The attempt to predict treatment outcome based on available pre-treatment patient characteristics yielded no support for the prediction hypothesis, since none of the used variables produced a statistically significant result in the regression analysis.

Table 1 Results on outcome measures before and after treatment including effects sizes.

	N	Mean	SD	Improvement	Cohen's d	95 % CI	t-test p -value
GSRS-IBS pre-treatment	129	49.24	11.54				
GSRS-IBS post-treatment	129	37.03	10.03	34.0%	1.06	[0.86, 1.28]	<.001
QOL-IBS pre-treatment	128	42.29	15.71				
QOL-IBS post-treatment	128	71.12	16.38	68.2%	1.84	[1.56, 2.12]	<.001
VSI pre-treatment	126	50.29	12.64				
VSI post-treatment	126	28.21	14.23	43.9%	1.75	[1.47, 2.03]	<.001
MADRS-S pre-treatment	127	16.87	6.86				
MADRS-S post-treatment	127	10.35	6.23	38.6%	0.95	[0.76, 1.15]	<.001

Abbreviations: CI: Confidence Interval. GSRS-IBS: The Gastrointestinal Symptom Rating Scale for IBS. QOL-IBS: The Quality of Life in persons with Irritable Bowel Syndrome. VSI: The Visceral Sensitivity Index. MADRS-S: The Montgomery-Åsberg Depression Rating Scale.

The data from **study III** showed that the patients improved significantly on all outcome measures from pre-treatment to post-treatment and that the effect was even larger at follow-up. *The primary outcome measure (GSRS-IBS) was improved from pre-treatment to follow-up at six months after starting treatment from 48.06 (SD = 11.26) to 33.06 (SD = 10.81) which is a reduction of 31.2%. The result was statistically significant ($p > .001$), and the effect size was large - Cohens $d = 1.30$ [CI 1.08 – 1.51].* The results on all outcome measures are presented in Table 2.

The estimates generated with the random intercept cross-lagged panel model indicated that *there was a time related predictive effect from IBS-BRQ to GSRS-IBS but that the reverse association had limited evidence.* The first relation was supported by statistical significance testing which yielded $p > .001$ for all examined time points while the reverse case only had one statistically significant effect between week 8 and 9 of the treatment.

The time that the psychologists spent on each patient during treatment was measured and as an average each treatment in the study used 2 hours and 45 minutes. Omitting patients who did not complete the full treatment, the time spent by psychologists increased to 3 hours and 13 minutes per patient.

Table 2. Patient rated outcome measures at treatment start, directly after treatment and six months after treatment started with effects sizes based on comparisons with pre-treatment observations. Uncertainty of results based on imputed data is reported with fraction of missing information (fmi).

		Observed data			Results based on imputed data (n=309)					
		N	Mean	SD	Mean	SD	t(df)	p-value	Cohens d [95% CI]	fmi
GSRS-IBS	PRE	309	48.06	11.26	48.06	11.26				
	POST	254	36.66	13.29	37.51	13.57	t(255.2) = 14.23	<.001	0.94 [0.80-1.08]	.14
	FU6	127	33.06	10.81	33.45	11.40	t(104.2) = 13.61	<.001	1.30 [1.08-1.51]	.53
IBS-BRQ	PRE	309	104.71	24.75	104.71	24.75				
	POST	251	67.95	28.58	70.22	29.01	t(269.2) = 22.28	<.001	1.39 [1.24-1.55]	.10
	FU6	127	60.69	24.54	62.14	24.32	t(90.2) = 17.41	<.001	1.72 [1.48-1.96]	.59
VSI	PRE	309	49.75	14.76	49.75	14.76				
	POST	251	30.12	17.58	31.45	17.70	t(229.1) = 19.81	<.001	1.24 [1.09-1.39]	.19
	FU6	126	23.83	17.18	25.48	16.97	t(69.7) = 14.10	<.001	1.64 [1.38-1.91]	.78
SF-12 Phy	PRE	308	45.91	7.81	45.90	7.81				
	POST	251	49.51	7.65	49.74	7.77	t(222.0) = -6.24	<.001	0.40 [0.27-0.53]	.21
	FU6	124	51.07	7.19	42.93	11.16	t(71.6) = -4.73	<.001	0.49 [0.28-0.70]	.22
SF-12 Men	PRE	308	38.00	11.10	49.04	7.77				
	POST	251	43.73	11.03	38.00	11.09	t(215.5) = -7.18	<.001	0.45 [0.32-0.57]	.67
	FU6	124	45.41	10.79	44.89	11.30	t(77.9) = -6.43	<.001	0.62 [0.42-0.82]	.64

Pre, post and FU6 refer to assessment points pre-treatment (at the same day treatment started), post-treatment (at the same day treatment ended) and at follow-up, 6 months after treatment started. GSRS-IBS: The Gastrointestinal Symptom Rating Scale for IBS, IBS-BRQ: The Irritable bowel Syndrome – Behavioral Responses Questionnaire, VSI: Visceral Sensitivity Index, SF-12 phy and men: RAND 12-Item Short Form Survey Instrument, physical and mental functions respectively, fmi: fraction of missing information in multiple imputations. Differences, changes and effect sizes are based on comparisons with baseline values. Degrees of freedom for t-tests are adjusted using the small-sample approximation [148].

DISCUSSION

As a research field, psychology spans from philosophy to a natural science. The medical domain of psychology in which psychotherapy or psychological treatment is a part, is relatively young. The first person identified as a psychologist was Wilhelm Maximilian Wundt, who died only a hundred years ago (1832 – 1920). The first psychotherapies were developed in the latter half of the 19th century [149]. Modern behavioral psychotherapeutic approaches trace their roots to the works of B.F. Skinner in the mid-1950s.

The psychotherapeutic development over the last 30 years has been extremely rapid and clinical psychology has gradually approached clinical medicine. Up until the beginning of the 20th century, every physician could prescribe their own recipes and there was no standardization and very limited regulation around prescriptions. The development within psychological treatment resembles the development in pharmaco-treatment in several ways. It is gradually taking steps away from psychologists prescribing their own mixtures to a standardization of carefully evaluated treatment packages with a specific content.

Psychological treatment is “packaged” in a protocol or manual. It contains different components that may or may not be “active”. Psychotherapy is given in “doses” according to treatment regimens. There are different delivery methods of psychotherapy. As with all effective treatment, it is also well documented that erroneously prescribed or mixed psychotherapy may create hazards to the patient [150].

I believe that psychological treatment within health care should be analyzed in much the same way as pharmacological treatments. They should be standardized, broken down into components, analyzed in efficacy as well as effectiveness studies and their benefits as well as their risks should be evaluated. The research aim should be to find optimal mixes and doses to provide maximal treatment effect to minimal cost and risk for the patient and society.

The general aim of this thesis is to provide some facts that may help managers in health care to take informed decisions regarding the use of ECBT in clinical routine care. I will in the following section discuss the methods in, and results from, the three studies in the light of this aim.

Is ECBT for IBS effective in clinical routine care?

It may be argued that a control condition is needed for a statement to be made about treatment effectivity. We have in earlier studies compared our treatment protocol with control conditions such as waitlist [81], placebo treatment [120] or active control [82, 83] and found that there are treatment effects over and above mere attention or expectancy from patients. The question next to be answered is whether the treatment effect will be found also in a clinical context where few exclusion criteria are used and when no researchers are present.

The observed differences from pre-treatment to post-treatment and at follow-up in the studies presented in this thesis are larger than in the earlier RCTs probably signifying that the treatment effect seen in RCTs also is to be expected in clinical routine care and that a certain amount of placebo effect is added to the true treatment effect.

In study II and III the results were similar, with reductions in IBS symptoms averaging 34% and 31% respectively. The effect sizes were large (Cohens d 1.06 and 1.30 respectively). It is impossible to discern the proportions of placebo from real effects and from my perspective there is no real need for doing that. Placebo effects are as real as other effects and what matters is that patients' quality of life is better after than before treatment and that the effect is sustained over time.

We measured quality of life with IBS-QOL and SF-12 in study II and III, respectively, and observed large or moderate effect sizes post-treatment (Cohens d 1.84 and 0.40, respectively). The difference in effect sizes between studies is probably due to the different outcome measures used. IBS-QOL is focused on IBS-related quality of life and therefore very sensitive to change in symptoms whereas SF-12 is a more generic measure of quality of life and will be more affected by aspects in life other than IBS- symptoms. Study II did not contain any follow-up data as most clinics do not follow-up on their patients after discharge, but in study III results from post-treatment were sustained at follow-up. There are also earlier results from studies indicating that treatment results are sustained at 3-, 6-, 12-, 15- and 18-months [80-82, 151].

With that said though, it is a limitation that study II did not include follow-up data. And in study III, the patients were supposed to answer questionnaires at follow-up, but many patients choose not to do so. We therefore had a large proportion of missing data at follow-up. We tried to compensate for this using multiple imputation (MI). Even though this method has proven to be accurate in many studies [152], there is always a chance that the imputed data is biased.

We have accounted for the uncertainty of data by providing information of the fraction of missing data (fmi). In the model we included all variables that we had access to and that we believed could possibly be related to missingness. We therefore made the MI under the assumption of missing at random. But there may still be relevant factors related to missingness of which we are unaware. Patients with a certain result may have been more or less willing to provide information at follow-up.

The data at post treatment in study II is not imputed and in study III there was significantly less missing at post-treatment than at follow-up. The results from study II and III are similar and fit the hypothesis. I therefore believe that even if the true values differ from the ones we found, they will not point in a completely different direction.

The form of ECBT we have used in our studies is developed in Sweden and not so widely adopted in other countries yet. Especially not the form we used in study I and study III in which patients receive treatment via internet but still have a psychologist guiding them through the process. For the question to be answered with certainty this treatment must be spread and adopted in more countries and other research groups must evaluate the effectiveness. But the two effectiveness studies in this thesis encompass 435 patients receiving treatment in routine care. No exclusion criteria were used other than what would be normal in any such setting. The results clearly point to the effectivity of the treatment. Even though a large treatment effect may not be fully proved yet, since data from other countries and research groups still are missing, I feel confident to say that the current studies give enough support for the method to be further implemented in Sweden as well as in other countries with respect to its effectiveness.

Can the results be generalized to other settings?

Results from one site may or may not be possible to obtain at other sites depending on several factors. Are the results true or do they depend on confounding factors? Do patients or participants differ between sites? Are there cultural aspects or other site dependent parameters such as access to materials or trained staff to account for results? Can cultural differences influence processes or outcome?

The gastroenterological clinic that provided data for study II does probably not differ much from settings in other comparable clinics around the western world in other aspects than the presence of employed psychologists. The training and experience among physicians and nurses, and the materials and investigation methods used, resemble what is normal in western hospitals. It might however be possible that doctors and nurses at the study clinic were more used to, and positive towards psychologists and psychological treatment methods than what normally is the case since this particular clinic had psychologists in the staff.

The patient characteristics in study II and III resemble those seen in other studies of refractory IBS. There are no evident biases in the studies as far as patient selection is concerned. In both study II and III all patients treated at the clinics were included in the study and in study III that meant all patients that ever were accepted for treatment. The lack of randomization might be seen as a weakness in the studies, but it may also be a strength in the sense that it gives a high ecological validity to the study design. No changes were made to routine procedures at the clinics due to study purposes.

In Sweden, the digital infrastructure is well developed. More than 95% of the population has access to internet in their homes [153] and 98.7% of all Swedes 18-67 years old can identify themselves digitally [154]. A well-developed digital infrastructure is needed for the implementation of the internet-delivered form of our ECBT for IBS. But for the group therapy version, no digital infrastructure at all is needed.

The two clinics in the effectiveness studies in the thesis are quite different from each other. One is a traditional gastroenterological clinic with face-to-face meetings as a standard. Most of the care is given by physicians or nurses and the clinic has a wide spectrum of gastrointestinal disorders among the patients. The other clinic is specialized on internet-delivered psychological treatment and most of the care is given by psychologists. There are no face-to-face treatments and the only gastrointestinal disorder treated at the clinic is IBS.

However different the two clinics are, the treatment results are similar, pointing to a robustness in the treatment as long as its content is provided in the way it was intended. The differences in treatment environment in the studies alongside similarities in results should therefore be indicating that there is a good chance for transference of effects when implemented in a new location elsewhere.

It has however been argued that psychological treatments that are developed in a culturally specific context may be limited in their universal applicability [155]. Cultural adaptations of psychological treatments for depression have made the treatments significantly more effective [156]. It is therefore possible that the treatment we used in our studies may be less efficient in a culturally different context.

Given therefore that a clinic is located in a country with similar cultural context as Sweden and that the clinic can employ a CBT-trained psychologist who is willing to work in a gastroenterological setting, I believe it is a good chance that implementing the ECBT used in our studies should yield similar outcome.

In study I, costs and savings related to ECBT were analyzed and they will be further discussed in next paragraph, but it should be mentioned here that costs may vary a good deal between countries. Especially costs related cost of health care interventions and to income. It is therefore more difficult to draw conclusions about generalizability of cost than treatment effects.

What are the costs and revenues of ECBT?

The cost of treatment can be calculated differently depending on the perspective used. It is possible to apply a patient perspective, a care giver perspective or a societal perspective to mention a few. In study I, we applied a societal perspective meaning that we tried to analyze the costs and benefits associated with treatment from a broad perspective. But we still had to make decisions regarding definitions. The costs associated with a treatment were in our study defined as the time spent by psychologist and patient multiplied with basic income assumptions. We did not calculate costs for any hard- or software used or for the treatment platform or the development or hosting of it. On the other hand, this was a randomized controlled trial and most of those costs would be the same in both groups and therefore equalized between conditions. The development of the internet version of the treatment is a onetime cost and should be divided between all patients that are ever treated.

In study I the psychologists spent 1.68 hours per patient in the arm that included exposure. This can be compared to the 2.75 hours spent per patient in study III. The treatment continued for 10 weeks in study I and for 12 weeks in study III which means that psychologists spent approximately 10 and 13 minutes respectively per patient and week. The patients however, spent considerably more time on the treatment than the psychologists. In study I the patients in the exposure arm spent 36.11 hours in treatment as an average (for study III we do not have data on time spent by patients). The main body of the treatment cost therefore stem from patient time in treatment, while the direct costs for the clinic of providing internet delivered ECBT to patients will correspond to the psychologist time only.

It may be that the first patients will take more time from the psychologist than the one hundred and first as a function of practice. It may also be somewhat more time consuming to have only one patient to treat via internet than if the psychologist has several patients and divide the total time with the number of patients. The results from our studies suggest that 2-3 hours per patient is a good estimate for experienced psychologists. In Sweden this would, as of Sep 2022, correspond to a total cost of 107.25 USD/patient (based on a salary for a psychologist of 45000 SEK/month and employer taxes and fees of 43%). This can be compared with the mean annual direct health care cost per IBS-patient reported by Goodoory, V., Black, C. & Ford, A. (2022) in United Kingdom which was £556.65 (equal to 601.52 USD on the 26th of September 2022) [157]. They also found that higher levels of psychological comorbidity, depression and gastrointestinal anxiety as well as lower quality of life were associated with significantly higher costs. The treatment used in our studies is designed to specifically target GSA and the results from our studies indicate large effects on

quality of life. We can therefore assume that there is a good chance of cost-efficiency for internet-delivered ECBT also from a health care perspective, even though that hypothesis needs more studying.

From a societal perspective the costs of IBS are much higher than from the health care providers' perspective. This is mainly due to costs associated with patients' inability to work, study or to maintain the household. We have in study I showed that the exposure based ICBT is cost-effective from a societal perspective compared to ICBT without exposure. We calculated the incremental cost-effectiveness ratio and found that the relative cost-difference for reduction of one point on the GSRS-IBS was -302 USD. This means that society will save 320 USD by using the ICBT rather than the ICBT-WE. Both treatments significantly reduced societal costs from pre-treatment to 6MFU. The total intervention cost rose with approximately 20% from 1064 USD to 1278 USD when the exposure component was added but the lowered societal costs as a result of that investment was calculated to 5.64 times as much.

What did we learn regarding the working mechanisms of ECBT?

Since study III of the present thesis was not a randomized controlled trial, we could not perform a true mediation analysis, but we could still use our weekly collected data on avoidance behaviors and symptomatic improvement with a modified cross-lagged panel model to evaluate if change in avoidance would predict change in symptoms. In this way we hoped to replicate the findings from the earlier study.

The result indicated that reduction in avoidance behaviors indeed predicted reduction in symptoms and that the reverse scenario was not the case. This is an important finding, strengthening the argument for targeting behavioral change in IBS-treatment

The outcome measure of behavioral avoidance used in the study was The Irritable Bowel Syndrome - Behavioural Responses Questionnaire (IBS-BRQ) [143]. But in a study by Windgassen et. al. [108], where the same outcome measure was used, the authors divided the scale into subscales based on whether the items were focused on avoidance of, or control over, stimuli. The subscales were labeled safety-behaviors and avoidance behaviors. This may seem like semantics, but I do believe that there is a relevant distinction. It would be interesting to use the data we have collected to do that.

The present study does however confirm findings from both our and other research groups and I think it is safe to say that the treatment exerts its influence over symptoms through change in behavior.

Another interesting aspect of working mechanisms concerns changes on a biological level. CBT targets behaviors, cognitions, emotions and perception. All of those may be considered psychological components, but essentially, they all stem from biochemical processes in the brain and the body. It would therefore be of interest to find the biological correlates to the changes produced by CBT. This was made in a recent study by Jacobs et al (2021) in which fecal analyses of gut microbiome and MRI-imaging of brain functioning was compared between responders and non-responders to CBT for IBS [158]. The results showed that CBT modulates gut microbiome as well as changes in the connectivity between multiple cortical networks. The study did also give indications that it may be possible to predict treatment

outcome of CBT based on pre-treatment levels of specific relations between *Clostridialis* and *Bacteroidales* in the gut microbiota.

I find it very plausible that there are biological correlates to psychological traits and that psychological treatment may advance its effectivity, specificity and credibility by reliably demonstrate changes on a biological level from psychological treatment.

In study II, patients' baseline characteristics were used in a regression model with the purpose of finding factors that would predict treatment outcome. The model failed to find statistically significant correlations and we could therefore not conclude that treatment outcome could be predicted by the characteristics we used in the model.

But in light of the mentioned study by Jacobs et. al., it would be interesting in the future to get access to biological data such as gut microbiota and FMRI of the brain and possibly hormone levels to see if it is possible to discern a more biochemic pathway of change mechanisms and possible treatment outcome predictors in CBT.

Internet vs face-to-face?

The ECBT for IBS that has been developed by our research group has been tested both face-to-face and via the internet. We have established evidence of its efficacy and its effectiveness in both delivery formats. We have not yet conducted an RCT in which we compare the two delivery formats against each other and to my knowledge no one else has done that either. It is therefore not possible to say which method is most effective.

But there are other things we know, pointing to a significant advantage for the internet-delivered version over face-to-face treatment; Firstly, there is a huge difference in costs for the two methods, an individual face-to-face therapy will cost at least five times as much as an internet-delivered therapy due to more time spent by the therapist. A group therapy of 5 patients may be only 50% more time consuming, but there are challenges in creating functional groups to consider and some more time is needed around the therapy (i.e., welcome and goodbye, questions after session, handling of no-shows etc.). Secondly the internet-delivered treatment is not affected by distance and can be tailored to fit the patients work or other habits in the sense that it is accessible at all hours of the day and week. Thirdly, the internet delivered format can allow the psychologists to handle more patients per day since there will be no time lost to no show or to waiting for, or escorting, patients in and out of the therapy room and to small talk.

There are also other benefits to internet delivered CBT such as minimizing the risk for therapist drift [159] and to be a good training ground for newly examined psychologists or psychologists that are new to the gastroenterological field. This comes with the format of the treatment being very rigid and instructive to both patient and health care provider. Internet delivered psychotherapy also offers considerable advantages for patient care, in particular for monitoring safety, progress and outcome [159].

I do therefore believe that the use of internet delivered formats of CBT have come to stay. It is part of the digital revolution within health care, and it may compensate for the scarcity of trained professionals.

CONCLUSIONS

In my thesis, I have presented three different studies encompassing 747 patients that have received exposure-based cognitive behavioral therapy for IBS. I wanted to investigate aspects that are relevant for further implementation of this method in health care.

I conclude that this form of treatment is very efficacious. A large proportion of the patients get a clinically relevant symptom improvement, and their quality of life is significantly augmented. These effects are also found in regular health care conditions such as they are in a gastroenterological clinic where no routine adjustments are made due to research purposes.

The treatment can be offered both face-to-face and via the internet. If it is offered face-to-face in groups of 4-6 patients the treatment demands less psychologist time than in individual therapy but produces a good result. And if it is offered via internet, this treatment has the potential to save a lot of money from a societal perspective.

The treatment's effect is mediated by change in avoidance behavior, and it is sustained for at least six months after treatment.

I believe that the treatment protocol developed by Brjánn Ljótsson and colleagues should be spread and implemented as much as possible for the good of patients with IBS.

POINTS OF PERSPECTIVES

Clinical implications

There are a few obvious implications of the research in this thesis. The first is that the ECBT is an effective treatment also in routine care with refractory IBS-patients. This means that physicians should consider this treatment when patients do not improve in their condition. Another is that the treatment is highly cost-effective, particularly when given over the internet pointing to the importance of creating an infrastructure for such treatment.

Another, less obvious, aspect concerns the behavior pattern among IBS-patients in which avoidance behaviors tend to generalize and to further establish the condition. Health care seeking, diets and the use of various medications may all be part of this pattern. The constant ambition to control symptoms may result in augmented hypervigilance and to worsened quality of life and inversely letting go of control behaviors may provide patients with more opportunities to enjoy life which in turn will result in a feeling of control of, or at least a better coping with, the disorder.

It is therefore important for health care providers to be aware of their role in the symptomatology of the disorder so that they do not contribute to it by providing opportunities for avoidance when exposure would have been a more fruitful way of tackling the situation.

It is well established in almost all health care context over the world by now that scarcity of staff already is or will be a major obstacle for the future. Finding solutions to this problem is one of the greatest challenges we face. I believe that technology may be one of the most important pieces in solving the puzzle. Internet delivered psychotherapy will provide health care with an opportunity to treat more patients with the same number of staff, but it also demands an infrastructure with internet access, treatment platforms and easily available software. There is already an industry for manufacturing, distributing and selling medications, but within the field of psychological treatment much of this is still not in place.

I believe that there is now a good opportunity for regulatory as well as commercial institutions to take steps forward in order to advance access to digitally enhanced psychological treatments.

Future research

Many questions remain unanswered and there is need for more research in the area of IBS and psychology. I would like to see more research on biological markers for treatment. Clearly psychological treatment does something with the organism and it would be of great interest if it was possible to discern treatment effects on a more objective level than what questionnaires can provide.

It would also be of interest to pin different psychological treatments against each other to see which ones are most effective. As an example, it seems reasonable to compare gut-directed hypnotherapy with exposure-based CBT in a randomized controlled trial. If different psychological treatments exert their effect through different means it could also be possible to find additive effects of multiple psychological treatments.

More research is needed in the field of cost-effectiveness. How little treatment is needed for a reasonably good treatment effect? Can we shorten the treatment time? Would it be possible to

use AI instead of a psychologist? Could we save society costs by offering psychological treatment at an earlier phase of the disorder?

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