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ENHANCING COGNITIVE-BEHAVIOR THERAPY IN THE TREATMENT OF OBSESSIVE-COMPULSIVE DISORDER

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Enhancing cognitive-behavior therapy in the treatment of
obsessive-compulsive disorder

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Filip Magnusson 1983 – 2009

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ABSTRACT

Background: Obsessive-compulsive disorder (OCD) is a prevalent and disabling condition. Although effective treatments such as cognitive-behavior therapy (CBT) exist, accessibility to this treatment is low and many OCD patients do not respond to CBT.

Aims: The general aim of this thesis was to develop and test new treatment strategies for enhancing both the accessibility and the efficacy of CBT in the treatment of OCD. More specifically, the aims were to investigate:

- The efficacy of internet-based CBT (ICBT) for OCD (Studies I, II, and IV).
- The impact of cognitive interventions in ICBT on obsessive beliefs and OCD symptoms (Study III).
- The efficacy of adding an internet-based booster program to ICBT (Study IV).
- The efficacy of adding the medication D-Cycloserine (DCS) to ICBT (Study V).

Methods: To test the efficacy of ICBT, an open pilot study of a newly developed treatment program was conducted (Study I), followed by a randomized controlled trial (RCT; Study II). Long-term follow-up was assessed at 4-, 7-, 12- and 24-months after ICBT (Study IV). To investigate the role of obsessive beliefs, a longitudinal mediation analysis was conducted on patients receiving ICBT with weekly measurements (Study III). Booster efficacy was tested with an RCT design, where half of the patients who had undergone ICBT were randomized to a three-week booster program (Study IV). To test the efficacy of DCS, a double-blinded RCT was conducted, where 128 OCD patients were allocated to either DCS or placebo as adjuncts to ICBT (Study V).

Results: Large effect sizes favoring ICBT were observed (Studies I and II) and these treatment effects were sustained up to two years after completed

treatment (Study IV). The cognitive intervention, unexpectedly, immediately increased obsessive beliefs and this, in turn, predicted better treatment outcome (Study III). The addition of an internet-based booster program reduced relapse (Study IV). Although there were some indications of faster treatment response in the DCS group, no beneficial effects of DCS as adjunct to ICBT were observed either at post-treatment or at follow-up (Study V).

Conclusions: ICBT is an effective method of administering CBT for OCD. Cognitive interventions in ICBT may have an impact on obsessive beliefs, and play a role in later symptom reduction. There may be beneficial effects of adding a booster to ICBT, but there is no evidence of a beneficial effect through adding DCS to this treatment.

ZUSAMMENFASSUNG

Einleitung: Die Zwangsstörung ist eine verbreitete und für die Betroffenen beeinträchtigende Diagnose. Obwohl effektive Behandlungsansätze existieren, wie beispielsweise die Verhaltenstherapie (VT), ist die Zugänglichkeit von Behandlungen gering und für viele Patienten ist die VT nicht effektiv.

Fragestellung: Die Fragestellung dieser Dissertation war, neue Behandlungsansätze für die Zugänglichkeit und Wirksamkeit der VT in Bezug auf die Zwangsstörung zu entwickeln und evaluieren. Folgende Fragestellungen wurden untersucht:

- Die Wirksamkeit von internetbasierter VT (IVT) für die Zwangsstörung (Studien I, II und IV)
- Der Einfluss von verhaltenstherapeutischen Interventionen im Rahmen der IVT auf zwangshafte Überzeugungen und Symptombild (Studie III)
- Die Wirksamkeit von internetbasierten Booster-Sitzungen als Ergänzung zur IVT (Studie IV)
- Die Wirksamkeit von IVT in Kombination mit D-Cycloserin (DCS, Studie V)

Methoden: Um die Wirksamkeit von IVT zu untersuchen wurde ein neuentwickeltes Behandlungsprogramm getestet (Studie I), welches anschließend in einer randomisierten, kontrollierten Studie (RCT) evaluiert wurde (Studie II). Die Langzeitwirkung der IVT nach 4, 7, 12 und 24 Monaten wurde erfasst (Studie IV). Um die Rolle von zwangshaften Überzeugungen zu studieren, wurde eine longitudinale Mediationsanalyse durchgeführt, die auf wöchentlichen Symptombewertungen im Rahmen der IVT basierte (Studie III). Die Wirksamkeit der Booster-Sitzungen wurde mittels eines RCT-Designs ermittelt, in welchem die Hälfte der Patienten im Anschluss an IVT ein dreiwöchiges Boosterprogramm erhielten (Studie IV). Um die Wirksamkeit von DCS zu untersuchen wurde ein doppelblinder RCT

durchgeführt, in welchem 128 Patienten mit Zwangsstörungen entweder DCS oder Placebo in Ergänzung zu IVT erhielten (Studie V).

Resultate: Es wurden starke Effektstärken zugunsten der IVT festgestellt (Studien I und II) und diese Behandlungseffekte waren bis zu zwei Jahre nach der abgeschlossenen Behandlung nachhaltig vorhanden (Studie IV). Die kognitive Intervention verstärkte unmittelbar zwanghafte Überzeugungen, und dies wiederum prädizierte ein besseres Behandlungsergebnis (Studie III). Die Ergänzung von IVT mit einem internetbasierten Boosterprogramm reduzierte die Rückfallquote (Studie IV). Obwohl es einige Hinweise darauf gab, dass DCS zu einer rascheren Behandlungswirkung führt, konnten keine zusätzlichen Effekte von DCS als eine Ergänzung zur IVT unmittelbar nach der Behandlung oder in der Langzeitevaluation festgestellt werden (Studie V).

Diskussion: IVT ist eine effektive Methode der Vermittlung von VT für die Behandlung der Zwangsstörung. Kognitive Interventionen im Rahmen der IVT haben möglicherweise Einfluss auf zwanghafte Überzeugungen und spielen eine entscheidende Rolle für die spätere Symptomreduktion. Boostersitzungen als Ergänzung zur IVT scheinen eine zusätzliche Wirkung zu erzielen. Hingegen gibt es keinen Nachweis, dass DCS die Wirksamkeit von IVT steigert.

LIST OF SCIENTIFIC PAPERS

- I. Andersson E, Ljótsson B, Hedman E, Kaldó V, Paxling B, Andersson G, Lindefors N, Rück C. Internet-based cognitive behavior therapy for obsessive compulsive disorder: a pilot study. *BMC Psychiatry*. 2011;11:125.
- II. Andersson E, Enander J, Andrén P, Hedman E, Ljótsson B, Hursti T, Bergström J, Kaldó V, Lindefors N, Rück C. Internet-based cognitive behaviour therapy for obsessive-compulsive disorder: a randomized controlled trial. *Psychological Medicine*. 2012;42:2193-2203.
- III. Andersson E, Ljótsson B, Hedman E, Hesser H, Enander J, Kaldó V, Andersson G, Lindefors N, Rück C. Testing the mediating effects of change in obsessive beliefs in Internet-based cognitive behavior therapy for obsessive-compulsive disorder: Results from a randomized controlled trial. (submitted manuscript).
- IV. Andersson E, Steneby S, Karlsson K, Ljótsson B, Hedman E, Enander J, Kaldó V, Andersson G, Lindefors N, Rück C. Long-term efficacy of Internet-based cognitive behavior therapy for obsessive-compulsive disorder with or without booster: A randomized controlled trial *Psychological Medicine*. 2014;44:2877-2887.
- V. Andersson E, Hedman E, Enander J, Radú-Djurfeldt D, Ljótsson B, Cervenka S, Isung J, Svanborg C, Mataix-Cols D, Kaldó V, Andersson G, Lindefors N, Rück C. D-Cycloserine as adjunct to Internet-based Cognitive-Behavior Therapy for Obsessive-Compulsive Disorder: A double-blind placebo-controlled trial (submitted manuscript).

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LIST OF ABBREVIATIONS

AE	Adverse event
CBT	Cognitive-behavior therapy
DCS	D-Cycloserine
DSM	Diagnostic manual of mental disorders
ERP	Exposure with response prevention
ICBT	Internet-based cognitive-behavior therapy
MEMS	Medication event monitoring system
NMDA	N-methyl-D-aspartate
OBQ-44	Obsessive beliefs questionnaire 44-items
OCD	Obsessive-compulsive disorder
OCI-R	Obsessive-compulsive inventory – revised
RCT	Randomized controlled trial
SRI	Serotonin reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
Y-BOCS	Yale-Brown obsessive-compulsive scale

1 INTRODUCTION

Obsessions and compulsions have accompanied human existence for centuries. In his sermon “religious melancholy” from 1691, the Bishop John Moore of Norwich described the symptoms relating to obsessive-compulsive disorder (OCD) as:

...naughty and Blasphemous Thoughts... starts in their Minds, while they are exercised in the Worship of god...(despite) all their endeavours to stifle and suppress them... the more they struggle with them, the more they increase... ¹ (p.163)

Since then, there has been an impressive amount of research in the field of OCD, and this disorder can now be effectively treated with both medication and cognitive-behavior therapy (CBT).² However, despite the efficacy of CBT in clinical trials for more than 40 years,³ many OCD patients do not receive this treatment,^{4,5} and research is still lacking on possible ways to improve treatment outcome. Furthermore, to enhance the effects of CBT, the active mechanisms in this treatment need further exploration.

I began to plan the work on this thesis together with my main supervisor on a tennis court in August 2009. My aim was to develop and test new treatments that enhance the accessibility and efficacy of CBT in the treatment of OCD. The first aim was to develop and test a new treatment format, internet-based CBT for OCD (ICBT). The second aim was to look more closely at the role of obsessive beliefs during this treatment and correlate this with treatment outcome. The third aim was to try to enhance the long-term effects of ICBT by adding an internet-based booster program six months after treatment completion. A final step was to test whether ICBT could be further enhanced by the medication D-Cycloserine (DCS). I hope the scientific results from this thesis contribute and enhance cognitive-behavior therapy in the treatment of OCD.

Stockholm, Paris, Hemsön; May-July 2014.

2 BACKGROUND

2.1 DIAGNOSTIC FEATURES

In the fifth version of the diagnostic manual of mental disorders (DSM-5), obsessive-compulsive disorder (OCD) refers to the presence of obsessions and/or compulsions.⁶ Obsessions are defined as recurrent intrusive thoughts, images, or urges that cause distress, which the individual tries to suppress or ignore.⁶ Compulsions are described as repetitive (overt or covert) behaviors the individual displays in response to either an obsession or according to rigidly applied rules.⁶ The primary function with compulsions is to reduce distress, or to prevent a feared event or situation.⁶

The revision from DSM-IV to DSM-5 did not have any major effect on the specific OCD diagnostic criteria,^{6,7} but in the fifth version, OCD was moved from the anxiety disorders to a new chapter called “obsessive-compulsive and related disorders” together with body dysmorphic disorder, trichotillomania, skin picking disorder, and hoarding disorder.⁶

Although the DSM-5 description of OCD suggests a functional relationship between obsessions and compulsions (i.e. obsessions evoke distress, compulsions relieve distress), it is technically possible to have obsessions without having compulsions (also known as “pure obsessions”),^{6,8} similarly, it is possible to have compulsions without having obsessions.⁶ The “pure obsessions” diagnostic subtype has been questioned, implying that what appear as “pure obsessions” are in fact covert compulsions.^{9,10}

2.2 CLINICAL CHARACTERISTICS

2.2.1 OCD subtypes

OCD consists of several different phenotypes. The usual way of investigating the different OCD phenotypic subtypes is through a factor analysis with the Yale-Brown obsessive-compulsive scale checklist (Y-BOCS-CL),¹¹ which measures over fifty different types of obsessions and compulsions. The first

study to use a factor analytic approach in this fashion was in the early/mid 1990s by Baer,⁸ who found three different OCD subtypes; (a) hoarding symptoms, (b) contamination/checking symptoms, and (c) pure obsessions. Later, Leckman et al.¹² suggested a four factor model consisting of (a) obsessions and checking, (b) symmetry and ordering, (c) cleanliness and washing, and (d) hoarding. Subsequent factor analyses^{13,14} suggested that the four-factor solution, as stipulated by Leckman et al.,¹² is a reliable symptom model of OCD.

Studies favoring the four factor model use predefined symptom categories i.e. the symptom categories stipulated in the Y-BOCS-CL.¹⁵ One problem with this way of analyzing data is that it misses possible item correlations between the categories on the Y-BOCS-CL.¹⁵ Consequently, it is possible factor analyses have missed other important phenotypes that might group together in ways not previously hypothesized. An example of this is a paper by Pinto et al.,¹⁶ who argue the Y-BOCS-CL category of “aggressive obsessions” in reality consists of two different patient categories; aggressive obsessions (e.g. “I have violent pictures in my mind about stabbing someone to death!”) and obsessions about unintentional harm (e.g. “What if I hurt someone by accidentally forgetting to turn off the stove!”). Instead, studies that use an item-based factor analysis, (i.e. no pre-defined categories) have found a five-factor solution that includes aggressive/taboo obsessions as a separate entity.^{15,17}

Thus, even though OCD consists of several different phenotypes, the shape and form of these phenotypes may differ depending on how the data is analyzed.

2.2.2 Prevalence, comorbidity, and natural course

OCD is a prevalent disorder. The first prevalence study on OCD in 1942 found a prevalence of only 0.3%.¹⁸ Later studies that use more reliable assessment tools have found an average lifetime prevalence of 1-2.5% and an estimated twelve-month prevalence of 1-1.3%.¹⁹

Common comorbid conditions found with OCD are depression,²⁰ social anxiety disorder,²¹ eating disorders,²² schizophrenia,²³ and tic-related disorders.²⁴ Elevated ADHD symptoms are observed in children with OCD,²⁵ but findings are mixed in adult samples.²⁶ There is also a proposed link between autistic traits and OCD,²⁷ and in one study²⁸ about a quarter of patients with autism also fulfilled the diagnostic criteria of OCD.

The longest prospective longitudinal study on OCD, conducted by Skoog & Skoog²⁹ in Sweden from 1947 to 1993, found that, although a majority of patients improved, almost half the sample still had clinically relevant OCD symptoms for more than 30 years. Different symptom dimensions also affect the course of OCD. In a naturalistic two year follow-up study, Mataix-Cols et al.³⁰ found that patients who clustered in the hoarding and sexual/religious obsessions domain did not improve as much as with other OCD subtypes. Similar results were found in another study,³¹ with additional findings that patients with obsessions relating to over responsibility for causing harm had better improvement rates. Furthermore, one study³² indicated that symmetry OCD may have an earlier age of onset than other OCD subtypes and patients with taboo thoughts often have a more fluctuating course in contrast to symmetry OCD.

Thus, OCD is a prevalent condition and it appears that different phenotypes have different courses in the development and maintenance of OCD.

2.3 ETIOLOGY AND MAINTAINCE OF OCD SYMPTOMS

2.3.1 Genetic contribution

OCD is a heritable disorder. A meta-analysis from 2011³³ found heritability rates of about 35-46% and another large Swedish study,³⁴ which used both population based data and twin registers, found a genetic heritability estimate of 50%. Although both OCD, body dysmorphic disorder, and hoarding disorder share a major part of the genetic variance, skin picking disorder and trichotillomania do not appear to fit genetically with the rest of

the disorders in the “obsessive-compulsive and related disorders” chapter in the DSM-5.³⁵

Although genetic factors explain a large proportion of the variance behind OCD, research has failed to identify any specific genes as underlying causal factors. A comprehensive meta-analysis³⁶ of gene candidates only found small effect sizes (Cohen’s $d = 0.001-0.259$) of each candidate gene. The genes with most stable findings were mainly related to serotonin and catecholamine modulation, but there were some indications that dopamine- and glutamate related genes might be involved. Recent genome wide association studies^{37,38} have found some promising preliminary results, but sample sizes have been small.

Thus, although genetic factors are important, the specific genes underlying OCD remain unknown.

2.3.2 Neurobiology

Certain areas in the brain correlate with OCD symptoms. Perhaps the best empirically supported neuroanatomical framework of OCD is the “cortico-striato-thalamo-cortical” model, which involves dysfunction in multiple brain areas, such as the orbitofrontal cortex, striatum, anterior cingulate cortex, dorsal lateral prefrontal cortex, and thalamus.³⁹⁻⁴¹ Furthermore, activity in specific brain areas correlates with specific OCD symptom dimensions^{42,43} and some abnormal structural activity is heritable, suggesting there are specific underlying biomarkers in the development of OCD.^{44,45} However, an important limitation with most neuroimaging studies is that they are correlational by nature i.e. it is not possible to make inference on causality.⁴⁶

Thus, although neuroscience has contributed important findings to this field, further experimental studies, designed to elucidate the causal biological mechanisms underlying the development and/or the maintenance of OCD, are needed.

2.3.3 Psychological explanations

The two-factor theory, stipulated by Mowrer in the early and mid 20th century,⁴⁷ is probably one of the most influential psychological models of OCD.⁴⁸ According to the Mowrerian theoretical framework, an obsession is a conditioned stimulus (CS) that evokes a fear/anxiety response (conditioned response; CR). This CR, in turn, functions as a discriminative stimulus for a compulsion (operant behavior).⁴⁸ Thus, the function of the compulsion is to temporarily relieve the fear/anxiety stemming from the obsession (negative reinforcement), but this also means the CS-CR relation is maintained and increases the probability of future compulsions.⁴⁸ Although data regarding the specific fear acquisition process of OCD (i.e. the original causal factor) is still lacking,^{48,49} studies from the 1970s⁵⁰⁻⁵³ provide evidence that obsessions evoke anxiety and compulsions relieve anxiety. Furthermore, studies also show that the strength of the CS-CR relationship is maintained by compulsions^{54,55} and compulsions can also causally induce OCD-related cognitions.⁵⁶⁻⁵⁸

Another psychological model that has received much attention is the cognitive theory of OCD, which was mainly developed by Salkovskis⁵⁹ and Rachman^{60,61} during the 1980s and 1990s. The background to this theory were studies^{62,63} presenting a high prevalence of intrusive thoughts (85%) in the normal population (e.g. stabbing someone to death, becoming a pedophile etc.) i.e. the thought content did not differ between the normal population and OCD patients. In light of these and other findings, the cognitive theory of OCD stipulates the difference between OCD and normal people is not the thought content, but instead the obsessive beliefs i.e. how the individual interprets the meaning of the obsession.^{59,60,61} For example, if a person thinks it is deeply immoral and dangerous to have sexual thoughts about his/her mother, this subject will probably have a higher probability of generating a higher negative appraisal of these thoughts than to someone who does not think it is dangerous *per se* to have these kind of thoughts. The negative appraisal, in turn, increases the probability of relying on compulsions. The cognitive model of OCD has garnered extensive support in basic experiments,⁶⁴⁻⁶⁹ but a limitation with many of these studies is that

they have mainly used samples from the normal population and not from clinical patients.⁷⁰

The combination of classic conditioning (obsessions is associated with a fear response), operant conditioning (compulsions), and cognitive factors (obsessive beliefs) forms the cognitive-behavioral model of OCD (Figure 1).⁷¹ One important aspect is there are no major theoretical conflicts within the CBT model of OCD. The concept of obsessive beliefs fits well in the two-factor model as “establishing operations” i.e. other factors that increase or decrease the power of the reinforcer.^{72,73}

Thus, although the cognitive-behavioral model does not provide adequate explanation of the specific cause of OCD, it does provide a feasible and empirically grounded explanation of why and how OCD is maintained.

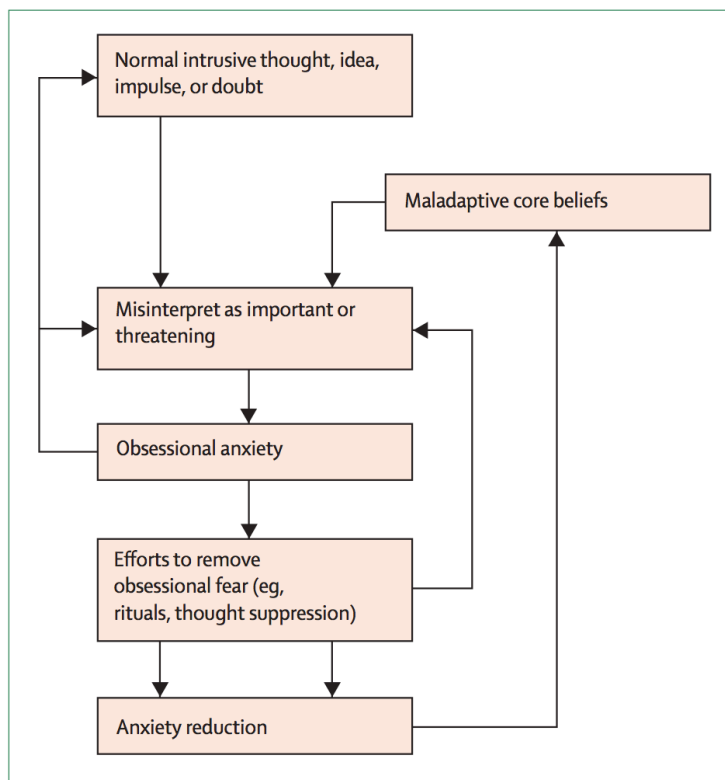


Figure 1: The CBT model of OCD⁷¹ (p. 494)

2.4 TREATMENT OF OCD

2.4.1 Pharmacological treatments

Pharmacotherapy is an effective treatment for OCD. Clomipramine is a serotonin reuptake inhibitor (SRI) and was the first substance to receive experimental support in clinical trials.^{74,75} Subsequent trials found selective SRI (SSRI) had the same effects as Clomipramine, but with fewer side effects.^{76,77} There is a dose-response relationship with SRI i.e. a higher dosage correlates with better treatment response.⁷⁸ Neuroleptics have also been tested as an adjunct to SRI in the treatment of OCD, but the results are mixed.^{79,80}

2.4.2 Psychological treatments

Cognitive-behavior therapy (CBT) is an effective treatment for OCD. In the psychological model of OCD, the patient exposes him/herself to the CS (i.e. the obsession) and refrains from rituals and other compensatory behaviors.⁴⁸ This is known as “exposure with response prevention” (ERP).⁴⁸ Through repeated ERP, the fear/anxiety response is hypothesized to be gradually extinguished.^{81,82} Recent research has also suggested that ERP does not only result in fear extinction, but the patient also develops better anxiety toleration and an increased sense of self-efficacy.^{82,83} In addition to ERP, cognitive interventions change the establishing operations i.e. reduce negative appraisals and reinforce the patient in refraining from rituals.

Meyer⁸⁴ was the first to test ERP for OCD in the 1960s, and the first randomized trial was published a few years later.^{3,85,86} Subsequent, numerous trials testing CBT for OCD have found large effect sizes² that appear to be equal, irrespective of whether the treatment content is focused on cognitive or behavioral factors.²

2.4.3 Combination treatments

There is little evidence CBT can be enhanced by adding SRI. A recent meta-analysis⁸⁷ found that, although CBT can be an effective adjunct to SRI, the reverse is not true, i.e. SRI do not give any incremental response to CBT.

One drug that has shown promise is D-Cycloserine (DCS). DCS was originally developed as a treatment for tuberculosis, but it is also an effective adjunct to CBT for anxiety disorders.^{88,89} DCS binds to the glycine recognition site at the N-methyl-D-aspartate (NMDA) receptor, and this process increases the probability of glutamate release and enhances NMDA receptor activation.⁹⁰⁻⁹² This is an important process for fear memory and learning via synaptic plasticity and long-term potentiation.⁹⁰⁻⁹² Studies from the early 1990s found NMDA antagonists can block fear extinction in rats and that NMDA agonists, such as DCS, have the opposite effects i.e. they enhance fear extinction.^{88,89} ERP in CBT is based on fear extinction⁷¹, therefore, a logical step would be to use DCS as an adjunct to this treatment. Several double blinded RCTs indicate that DCS can be beneficial for patients with anxiety disorders,⁹³ and three double-blinded RCTs have been conducted with DCS for adult OCD. Storch et al.⁹⁴ found no beneficial effects of DCS with a 250 mg dose (n=24). Kushner et al.⁹⁵ used a 125 mg dose (n=32) and found differences between group effect sizes on session 4, with lower OCD symptoms in the DCS group. The number of dropouts in the DCS group was substantially lower (6%) than the placebo group (35%). In another study by Wilhelm et al.⁹⁶, the participants (n=23) received 10 CBT sessions with 100 mg DCS and placebo. After half the treatment, differences between group effects of OCD symptoms were observed but, although the DCS group had substantially lower symptoms, both at post-treatment ($d=0.64$, 95% CI; -1.48-0.22) and at follow-up ($d=0.68$, 95% CI; -1.52-0.18), these effects failed to reach statistical significance. The findings are also mixed in pediatric OCD.^{97,98}

Thus, although studies find DCS enhances more rapid treatment effects in OCD, these effects level out at post-treatment. However, none of these previous studies has sufficient statistical power to detect significance

between group effect sizes in the medium range at post-treatment or at follow-up.

2.5 CURRENT ISSUES IN THE TREATMENT OF OCD

A selection of some of the current issues in the treatment of OCD that would benefit from further attention and exploration are presented below.

2.5.1 Treatment accessibility is low

Despite CBT being investigated for more than 40 years in clinical trials with large effect sizes,^{2,3} treatment accessibility is still low. In the UK, only 5% of adults with OCD actually receive CBT⁴, similarly in the USA, only 7.5% of OCD patients have received CBT.⁵ A proposed reason for these low numbers is the current lack of properly trained CBT therapist within the health care system.⁹⁹⁻¹⁰¹ Moreover, geographical distances and embarrassment due to symptoms can be possible explanations.^{102,103} Thus, despite strong evidence in terms of efficacy, it appears difficult to make CBT accessible to those in need.

2.5.2 Do we need the therapist?

As treatment availability is low, an alternative strategy could be to provide the patient a self-help manual that he/she can work with on his/her own without meeting a therapist. This could overcome many barriers and health care would be able to offer a cheap, accessible treatment. In addition, some research has suggested that OCD patients can actually achieve better treatment effects when ERP is conducted in their natural environment, and by themselves, i.e. without a therapist being present.^{52,59,104} If ERP is more effective when conducted in the patient's natural environment, then self-

help treatment should work optimally, as this treatment format is carried out by the patient themselves in their home environment.

The effectiveness of self-help treatments for treating OCD has been evaluated, and a number of different self-help treatments with no, or low degree of, therapist input have been empirically tested for OCD. However, effect sizes have been shown to be inferior compared to face-to-face CBT.¹⁰⁵⁻¹¹³ Hence, therapist input in CBT for OCD appears important, but the question remains as to what role the therapist has. From my clinical experience working with OCD, I've observed that many patients have difficulties in both understanding the psychological model of OCD (i.e. generalizing the overall learning principles and making them applicable to their own situation) and also initiating ERP on their own between sessions. In line with this observation, there are also empirical findings indicating OCD patients have impaired cognitive flexibility^{114,115} and are more dependent on external stimuli/proxies in their information processing.^{116,117} One possible interpretation of the therapist's role could therefore be to regard the therapist simply as a factor that (a) interacts and provides additional information in order to make the CBT model relevant and applicable to the individual, and (b) provides high frequency positive reinforcements (i.e. external stimuli/proxy) that helps the patient initiate and increase the frequency of ERP behaviors.

If (a) and (b) are correct, then the treatment of OCD does not necessarily need to be in the form of face-to-face sessions, but could be a remote treatment given that it fulfills both these criteria. One treatment format that could be a viable way of fulfilling these criteria is internet-based CBT with therapist support (ICBT). As it has been developed in Sweden, ICBT can be described as therapy that in its content mirrors face-to-face treatment, is time limited, has consecutive access to each treatment modules (chapters), and is guided by an online therapist.¹¹⁸ The patient works with online self-help text, and does homework assignments that are examined by a therapist in order to proceed to the next module.¹¹⁸ One critical component in this Swedish approach to ICBT is that the treatment is supported by an online therapist that can help the patient to adapt the overall treatment principles

to his/her situation.¹¹⁸ ICBT is effective for numerous conditions¹¹⁹ and the treatment is more effective when supported by a therapist.^{120,121} The advantages of ICBT are that it can overcome geographical and practical barriers for the patient and one therapist can treat about four to five times more patients than with conventional CBT.¹¹⁸ The combination of a self-help treatment with high accessibility and a high degree of therapist input may be an optimal solution to the problems of making CBT available and effective in treating OCD.

2.5.3 Do we need cognitive interventions?

The way cognitive interventions achieve their effects in the treatment of OCD is not known. According to the cognitive model of OCD, interventions should be aimed at changing the individual's belief system, which, in turn, reduces the negative appraisals in relation to the obsession, and this, in turn, makes the patient less prone to rely on compulsions.^{60,61} Although the full cognitive therapy packages has shown efficacy in several trials,¹²²⁻¹²⁴ there are few experimental research studies that test the specific mediating effects of cognitive interventions i.e. do these interventions really change obsessive beliefs? And does this change in obsessive beliefs really mediate symptom reduction? As mixed findings are reported on this,¹²⁵⁻¹²⁸ there is a need to investigate the role of cognitive interventions in CBT. Knowledge about the mediating effects of specific interventions in CBT is important because it can provide clues on how to further enhance this treatment.¹²⁹

2.5.4 Can we achieve better treatment effects with boosters?

Whether the long-term effects of CBT for OCD can be improved by adding maintenance treatment is unknown. In 1963, Hans Eysenk¹³⁰ proposed the idea that patients who receive behavior therapy can lessen the probability of relapse

*...by using treatment processes emphasizing partial reinforcement, overlearning, spaced trials and supportive conditioning*¹³⁰ (p. 17)

Although treatment components such as relapse prevention strategies have garnered efficacy in CBT for OCD,^{131,132} there is no experimental evidence supporting the use of so-called “booster programs” i.e. additional treatment some months after the main treatment is finished. This is an important issue, as many clinicians include booster sessions in their protocols, apparently without proper evidence supporting these interventions.^{94,133,134}

2.5.5 Can we achieve better treatment effects with D-Cycloserine?

Whether DCS can enhance the effects of CBT in the treatment of OCD has not been established. Only three published RCTs have tested DCS as an adjunct to CBT for adult OCD.⁹⁴⁻⁹⁶ Two of these trials^{95,96} found significant effects of DCS at mid treatment, but these effects were not sustained at post-treatment. However, none of the studies had sufficient statistical power to detect significance between group effect sizes in the medium range at post-treatment. Consequently, DCS may be an effective drug in treating OCD, but large-scale trials are needed.

3 AIMS OF THE THESIS

The aim of this thesis was to develop and test treatments that could enhance both the accessibility and the efficacy of CBT for OCD. The specific aims of each study are presented below:

3.1 STUDY I

The aim of this study was to test the within-group effects of a new treatment, internet-based CBT (ICBT) for OCD. The hypothesis was ICBT would generate significant within-group improvements from pre- to post-treatment.

3.2 STUDY II

This study tested the efficacy of ICBT for OCD when controlling for both time and basic attention. The hypothesis was ICBT would generate significant between-group effects, compared to an active control condition at post-treatment.

3.3 STUDY III

The aim of study III was to test the impact of the cognitive interventions focused on changing obsessive beliefs within an ICBT treatment. The hypothesis was that randomization to ICBT would generate a lower degree of obsessive beliefs and this reduction would mediate further symptom reduction later in treatment.

3.4 STUDY IV

The aims of this study were to ^{a)} investigate the long-term outcome of ICBT

for OCD and ^{b)} test if the long-term effects could be further improved by adding an internet-based booster program six months after ICBT. The hypothesis was all participants who received ICBT would have sustained effects up to two years after completed treatment. In addition, participants who received the booster program would have lower relapse rates at a slower pace.

3.5 STUDY V

The aim was to test whether DCS could further enhance symptom reduction in ICBT. The hypothesis was DCS would generate better treatment effects at post-treatment and at follow-up than placebo. A secondary aim was to replicate previous findings that DCS generates faster treatment effects.

4 METHODS

4.1 DESIGNS, ASSESSMENTS, AND ANALYSES

Study I was an open pilot study, in which 23 OCD patients received ICBT. The main outcome was the Yale-Brown obsessive-compulsive scale (Y-BOCS),¹¹ which was assessed by psychiatrists at pre- and post-treatment. Within-group effects were tested with paired *t*-tests.

Study II was a randomized controlled trial with 101 OCD patients allocated on an 1:1 ratio to either ICBT or to a control condition, consisting of online support therapy. Blinded assessors administered the Y-BOCS via telephone pre- and post-treatment and at 4-months follow-up. The assessors were all psychology students in their final year of training under supervision. Group- and time effects were analyzed with an analysis of covariance.

Study III used process data from Study II. The independent variable was randomization to the cognitive intervention in the ICBT treatment or to the control condition. The mediator was defined as the change in obsessive beliefs from pre-treatment to immediately after completion of the cognitive intervention task. The outcome was defined as symptom reduction after completion of the cognitive intervention task. Obsessive beliefs were assessed by the obsessive-beliefs questionnaire 44-items (OBQ-44),¹³⁵ which was administered pre-treatment, immediately after completing the cognitive intervention task, and post-treatment. Weekly OCD symptom ratings were assessed by the obsessive-compulsive inventory – revised (OCI-R).¹³⁶ To control for time effects, each participant in the ICBT group had a randomly paired participant in the control condition. Mediation was tested with a joint significance test (i.e. the product of the two paths constituting the mediation path) with bootstrapping. As a secondary analysis, the mediation analysis was repeated but with cross sectional data at post-treatment (i.e. longitudinal data was not used).

Study IV used follow-up data (telephone administered Y-BOCS) for 93 patients who had received ICBT. The assessment points were 4-, 7-, 12- and 24-months (telephone interviews). Half of the sample was randomized to a

three-week internet-based booster program six months after receiving ICBT. Assessors were both experienced clinicians and psychology students and were blinded to treatment allocation. Booster efficacy was tested by regression- and Kaplan-Meyer analyses.

Study V was a double-blinded randomized controlled trial where all patients (n=128) received 12 weeks of ICBT and were allocated to either DCS (50 mg) or placebo. Compliance was monitored with a digital medication event monitoring system (MEMS). Primary outcome was the Y-BOCS, which was administered by a clinician at pre- and post-treatment and at 3-months follow-up. DCS efficacy was tested with a regression framework (intention-to-treat) and process data from all participants and the completer sample were also analyzed as secondary analysis.

4.2 SAMPLE CHARACTERISTICS

To recruit patients into Study I, information about the study was sent to mental health care units in Stockholm County, Sweden. Studies II-V were advertised in national newspapers and the majority of patients in these trials were recruited through this media: of the patients, 58-66% were women, and most had a university degree and worked full time. Furthermore, a majority of patients had tried some medical or psychological treatment before entering the treatment studies. The mean Y-BOCS pre-treatment score in the studies ranged from 20 to 23.

4.3 TREATMENTS

4.3.1 The ICBT treatment

Studies I, II, III, and V used an ICBT treatment developed by the Rücklab research group at Karolinska Institutet. This treatment mainly followed the Swedish approach i.e. the patient worked online with written self-help material (about 100 pages) and homework assignments that were examined by a therapist.¹¹⁸ In addition, the treatment program had some

interactive features, such as the treatment text adjusted itself based on the patient's subtype (i.e. washing, checking, symmetry, violent thoughts).

Previous research and clinical experiences were integrated into the development of this treatment program, i.e. the online self-help manual was combined with therapist input. In this model, the therapist was regarded as a factor that could (a) help the patient to make the CBT model relevant to his/her situation and, (b) reinforce ERP-behaviors in the patient. To maximize this input, a high frequency approach was used with proactive therapists who sent an email in the treatment platform if the patient had not logged in for 3 days. A text message was also sent to the patient's cell phone each time the therapist sent an email. All patients were informed of the high frequency treatment approach before entering the studies.

The ICBT treatment content and procedures were similar in all studies. One difference was the treatment length (15 weeks in Study I, 10 weeks in Study II, and 12 weeks in Study V). Furthermore, students were used as therapists in Study II instead of experienced psychologists, as in Studies I and V. In Study V, 2-3 phone calls were planned with the patient to discuss ERP and medication compliance.

4.3.2 The cognitive intervention

The cognitive intervention (Study III) comprised the third module of the ICBT. In this module, the patient first read about obsessive beliefs and the way they can aggravate OCD symptoms through negative appraisals. The patient was instructed to read different examples of obsessive beliefs, such as inflated sense of responsibility, intolerance of uncertainty, and over-importance of thoughts. Secondly, the patient received homework assignments with questions about this topic (e.g. "what is the difference between re-evaluating an obsessive belief and persuade oneself the obsession is not true?"). Then, the patient was instructed to re-evaluate his/her own obsessive beliefs through a worksheet integrated into the treatment platform. The patient used this worksheet to write about a recent obsession that he/she had. The next step was to use the information in

module 3 to categorize which obsessive beliefs were at play relating to this obsession. The patient answered questions about how his/her obsessive beliefs could cause negative appraisals and how this, in turn, could maintain OCD symptoms. Lastly, the patient was instructed to re-evaluate the meaning and significance of the obsession by writing alternative thoughts in the worksheet (e.g. “elaborate whether it is really dangerous to have these thoughts, given that more than 80% of the population has them”). The patient did these exercises daily but for no longer than one week. The average time spent on these exercises was 3-4 days before proceeding to the next module. This module mainly focused on “mind work” i.e. to write down, discuss, and re-evaluate the belief system relating to the obsession. There were no other focused in vivo interventions, such as guided behavior experiments, included in the module. Thus, this was not a full cognitive therapy package, only a specific part of it.

4.3.3 The booster treatment

The internet-based booster treatment followed the same procedure as the ICBT protocol (i.e. written self-help material, consecutive access, integrated online therapist contact), but the treatment content differed. In the ICBT treatment, the therapist was regarded as a factor with the main function of reinforcing ERP-behaviors. The focus in the booster treatment was instead to get the patient to develop factors in his/her natural environment that could reinforce further ERP. Thus, instead of coaching the patient several times per week to do ERP, the therapists coached the patient to have a support person that he/she could have weekly check-ups with and plan the upcoming week. The patient also analyzed the period between the ICBT and the booster treatment and used these data to make a prognosis on how to proceed with ERP and identify potential stressors that could intervene with further improvement. Thus, the focus of this treatment was to develop elements that could maintain treatment progression in the patient’s natural environment.

4.3.4 The DCS treatment

DCS/placebo capsules were given as adjunct to ICBT in five specific ERP exercises. Guided by data from a DCS meta-analysis,⁸⁹ the dose was set to 50 mg, once a week for five weeks, administered just before the ERP exercises (i.e. within 60 minutes prior to ERP). When patients had completed the psychoeducation and ERP hierarchy, they engaged in daily exposure exercises, as implemented in the standard ICBT protocol. Once a week, DCS/placebo was taken within one hour before a planned ERP exercise. Therapists and patients had telephone contact before the first capsule and cooperatively decided on suitable ERP exercises to combine with the capsule intake. All patients were informed that it was vital to carry out the ERP exercises as planned after taking DCS/placebo. The patients registered each capsule intake and the following exposure exercise online. Medication compliance was verified with a medication event monitoring system (MEMS), which is a microelectronic chip inside each medication bottle that registers date and time of each bottle opening, thus, providing a detailed picture of adherence.¹³⁷

4.4 SAFETY PARAMETERS

The ICBT treatment was provided on an encrypted web page with an 128-bit SSL certificate. No one except the researchers involved had access to the treatment platform. All activity in the server was logged and monitored and therapists used a double authentication procedure to access the treatment platform.

Adverse Event (AE) data were collected in Studies II, IV, and V. Study II included AE questions in the post-treatment interviews. Study IV used self-rated online assessments of AE at 12- and 24-months, with detailed follow-up questions on the possible event. If the event was assessed as important, a clinician immediately phoned the patient to obtain more information. Study V used clinician assessments at mid-treatment, post-treatment and at 3-month follow-up. The patient also completed weekly online AE self-rated assessments, which were followed-up by a clinician.

4.5 ETHICAL CONSIDERATIONS

All studies were approved by the regional ethics committee in Stockholm, Sweden. The Swedish medical product agency approved Study V, which was monitored by an independent party to ensure compliance to the Helsinki declaration.

5 RESULTS

5.1 STUDY I

Internet-based cognitive-behavior therapy for obsessive-compulsive disorder: a pilot study

All participants completed the primary outcome. A large within-group effect size was observed ($d = 1.56$; 95% CI 0.89–2.22) with 61% responders and 41% in remission at post-treatment. The total therapist time per patient was 92 minutes.

5.2 STUDY II

Internet-based cognitive-behavior therapy for obsessive-compulsive disorder: a randomized controlled trial

Attrition rate was low (1%) on the primary outcome. There was a significant interaction effect with a large between-group effect size ($d=1.12$; 95% CI 0.69–1.53) favoring ICBT. The effects were sustained at follow-up. The total therapist time per patient was 129 minutes.

5.3 STUDY III

Testing the mediating effects of change in obsessive beliefs in Internet-based cognitive-behavior therapy for obsessive-compulsive disorder: Results from a randomized controlled trial

The cross-sectional analysis, i.e. post-treatment between-group analysis, confirmed the hypothesis that obsessive beliefs were reduced and that this, in turn, mediated improvement at post-treatment. However, the longitudinal (main) analysis revealed opposite results i.e. the patients

actually increased their obsessive beliefs immediately after receiving the cognitive intervention. Furthermore, with the joint interaction term, this increase mediated later symptom improvement.

5.4 STUDY IV

Long-term efficacy of internet-based cognitive-behavior therapy for obsessive-compulsive disorder with or without booster: A randomized controlled trial

The effects from ICBT were sustained at follow-up for the entire sample (within group effect size from pre-treatment to follow-up; $d = 1.58-2.09$): 32 out of 47 participated in the booster treatment. There was an interaction effect favoring the booster group at 7-months, but not at 12- or 24-months. There was also an interaction effect favoring the booster group at 7-, 12- and 24-months, with fewer relapses. Furthermore, the Kaplan–Meier analysis indicated a slower relapse rate in the booster group. The total therapist time per patient (including reading all previous communication in the ICBT treatment) was 72 minutes.

5.5 STUDY V

D-Cycloserine as adjunct to internet-based cognitive-behavior therapy for obsessive-compulsive disorder: A double-blind placebo-controlled trial

Both groups made large improvements with 61-69% responders, but there were no significant interaction effects of group and time. Completer analysis indicated slightly faster response for the DCS at week 9, but these effects were non-significant at post-treatment and at follow-up. The total therapist time was 79 minutes.

6 DISCUSSION

6.1 IS ICBT AN EFFECTIVE TREATMENT FOR OCD?

ICBT is an effective treatment for OCD (Studies I and II), with effect sizes in the same range as face-to-face treatments of OCD.² Furthermore, the effects are sustained up to two years after treatment is completed (Study IV).

Although Study V was not designed to test ICBT specifically, the results indicated ICBT produces large effect sizes, irrespective of DCS or placebo allocation.

ICBT has the potential to improve the treatment of OCD in different ways. First, the effect sizes were in the same range as face-to-face CBT,² but the therapist time was only 79-129 minutes for a whole treatment (Studies I, II, IV, and V). Thus, this is probably a highly cost-effective treatment with the possibility of treating a larger amount of patients with fewer resources. Secondly, ICBT is an accessible treatment for the patient. The most common reasons for participation in the studies were either practical (e.g. it was not possible for the patient to visit a therapist during office hours) or because of geographical distance (e.g. the patient lived too far away from a psychiatric unit). The combination of high accessibility and being able to work with the treatment at home, while still having a high frequency of therapist support, is a major strength with this treatment format. Thirdly, although ICBT is a flexible treatment format for overcoming practical and geographical barriers, it is also a highly structured treatment in terms of content and context of delivery, and this minimized the risk of therapist drift.¹³⁸ A fourth strength with ICBT is that it could serve as a platform for training therapists, for example in Study II, psychology students in their final year of training were used as therapists. The experience from this trial indicated ICBT provided a good basis for junior therapists to learn the CBT treatment components for OCD and it was easy for the supervisor to monitor the therapist and give feedback. This supports evidence that inexperienced therapists at Master's level can have the same capability as experienced

therapists if proper supervision is provided.¹³⁹ Thus, ICBT has the potential to serve as a secure and accessible education tool.

Are the effects of ICBT meaningful compared to other self-help treatments? The answer is yes. As seen in Figure 1, computer based CBT (BT-STEPS)¹¹² and bibliotherapy with¹⁴⁰ or without¹⁰⁷ minimal therapist support does not seem to produce as large within-group effect sizes as study I, II, IV and V did (pooled means). The only treatment with similar effect sizes as the studies in this thesis is an Australian ICBT protocol^{141,142} with similar design and procedures (i.e. high frequency therapist input). Thus, the therapist does seem to matter when delivering remote CBT for OCD patients.

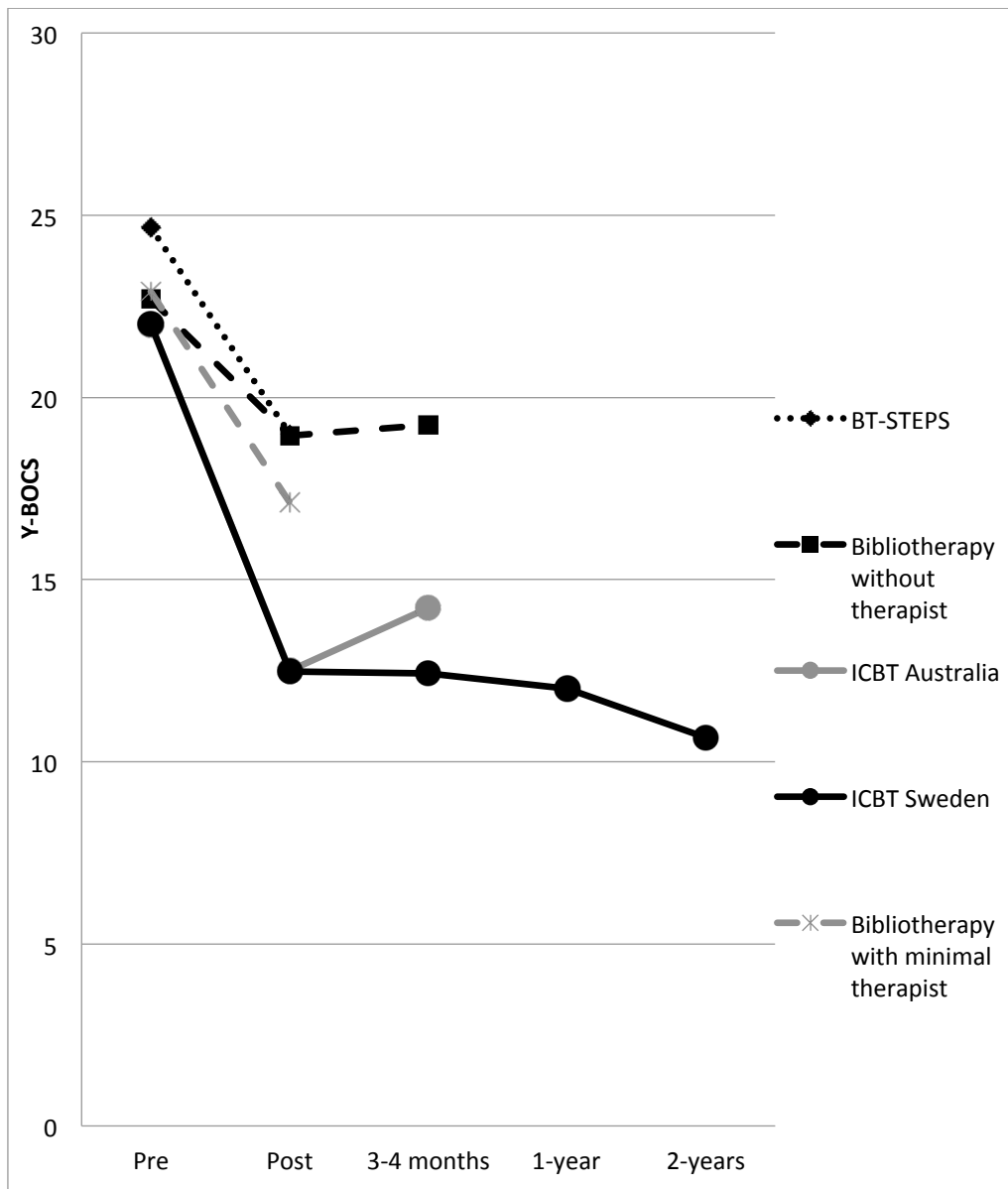


Figure 2: The ICBT protocol compared with other published self-help treatments.

Is ICBT only for the light OCD patients i.e. those with high education level and low symptom burden? One major limitation with the studies included in this thesis, is that most patients had a high educational degree. Thus, the

results from these studies may not be generalizable to the whole OCD population. On the other hand, just because many patients had high educational degree does not, by logic, follow that ICBT does not work for patients with other baseline characteristics as well. In fact, a prediction analysis of study II (not included in this thesis)¹⁴³ could not find any predictive effects of education. In addition, the educational degree in the present trials do not differ that much from other trials testing face-to-face CBT for OCD.^{124,144} Thus, this selection bias is not a problem exclusively related to ICBT but to CBT in general. Furthermore, the prediction paper of study II showed that, although high baseline OCD severity predicted less chance of remission, high baseline OCD severity also predicted higher degree of symptom reduction i.e. the effect sizes were not driven by patients with light symptoms but instead by the patients with medium-to-severe symptoms. It may be that the patients seeking ICBT are different compared to the patients that clinicians meet at a psychiatric ward, but we do not yet have proper evidence to say for whom this treatment work for. Thus, ICBT is probably not only for “light patients”, but this question needs further research in order to be answered correctly.

Should we implement ICBT for OCD within regular health care? The answer to this question may depend on the way ICBT is implemented. If we think of ICBT as a replacement to face-to-face therapy within regular psychiatry, we definitely need to test it in a non-inferiority trial for regular psychiatric patients. Thus, the studies presented in this thesis do not give us enough reason to replace face-to-face therapy with ICBT, because they do not meet the criteria of non-inferiority trials, and recruitment was conducted through advertisements. On the other hand, if we regard ICBT as a complement for people who would not otherwise seek or be offered treatment (e.g. due to stigma, practical circumstances etc.)^{103,145}, then testing ICBT vs. face-to-face would make less sense, as this would obviously not be the treatment of choice for this patient group. Future research should look more into this issue in order to give a more detailed picture of the patients who seek ICBT treatments. It is still reasonable to assume that ICBT might replace face-to-face therapy in some settings for some patients, and a recommendation is therefore to test this treatment in a non-inferiority trial. Furthermore, an

important issue in all clinical research is to test if a treatment also works in a regular clinical setting and not only in randomized clinical trials.¹⁴⁶ Although ICBT works within regular health care for other conditions such as panic disorder,¹⁴⁷ and depression,¹⁴⁸ it needs to be tested also for OCD.

6.2 DO WE NEED COGNITIVE INTERVENTIONS?

The cognitive framework of OCD, which was stipulated by Salkovskis in 1985,⁵⁹ makes much sense, but the empirical literature is limited. The aim with study III was therefore to test whether obsessive beliefs was a relevant and workable construct that could improve treatment outcome.

The results from study III did not come out as expected. Although the secondary cross-sectional analysis in study III were in accordance with the stipulated hypotheses (ICBT decreased obsessive beliefs, which, in turn, mediated better treatment outcome), the main analysis actually showed opposite results (ICBT increased the degree of obsessive beliefs and this increase predicted better treatment outcome).

Thus, the results from this study were mixed, but indicated obsessive beliefs might play a role in ICBT outcome. In a larger context, the results were similar to the conflicting results between the longitudinal and cross-sectional analyses in two previous studies investigating the mediating effects of obsessive beliefs in CBT.^{127,128} This emphasizes the importance of caution when interpreting mediation data.¹⁴⁹

The results from Study III are interesting. One explanation of the mixed findings could be that the cognitive intervention simply provided the patients with better insight that meant the patient understood the questions better at the OBQ-44 and was motivated to change his/her behaviors. The results also highlighted that different conclusions can be drawn depending on the design and assessment points. Thus, longitudinal designs are essential for investigating treatment mediators. Future research should

include a dismantling study that compares treatments with and without cognitive interventions. This is an important issue as pure behavior therapy can reduce obsessive beliefs as much as cognitive therapy.^{125,128} However, close assessments are needed, not just symptoms and obsessive beliefs, but also detailed measurements of ERP compliance, habituation, as these factors may function as moderated mediators or mediated moderators. This may in turn elucidate the role of obsessive beliefs in CBT, and provide us an answer to whether the cognitive paradigm is relevant for the treatment of OCD.

6.3 CAN WE ACHIEVE BETTER TREATMENT EFFECTS WITH BOOSTERS?

There were some beneficial effects of adding a booster as an adjunct to ICBT (Study IV), indicating internet-based booster programs could be included in the treatment of OCD. However, both groups improved and the incremental effects of the booster treatment were small. On the other hand, the resource use of adding the booster treatment was also small (in total 72 minutes per patient). As this was one of the first studies to study the beneficial effects of adding a booster as an adjunct to ICBT, replication studies are needed before firm conclusions about the real effects of internet-based booster programs can be drawn.

The treatment content (Study IV) was developed by the Rücklab research lab at Karolinska Institutet and has not been previously evaluated in the treatment of OCD. A major limitation in this study was that we did not measure the behaviors we aimed to change. The focus of the booster treatment was that the patient should establish reinforcers in their natural environment that could increase the probability of continuing ERP (e.g. weekly meetings with a support person). However, these behaviors were not measured directly. As these behaviors are considered to mediate symptom reduction, they should also have been measured. Thus, the mechanisms of change in this treatment are unknown. As the control group did not receive any additional treatment besides ICBT (they were unaware of the booster treatment), the effects in the booster group might have been

driven by basic therapist attention, and not the treatment content. Future research should focus on measuring the stipulated treatment mechanisms and not just the outcome.

6.4 CAN WE ACHIEVE BETTER TREATMENT EFFECTS WITH D-CYCLOSERINE?

DCS produced a slightly faster treatment response but the end-point effects were non-significant (Study V). Both treatment conditions had large within-group effects and most patients were classified as treatment responders, both at post-treatment and at follow-up.

An important factor in this study is that the patient completed the treatment at home; therefore, capsule intake was not controlled by a clinician. Thus, there is a risk the patient simply did not take the capsule or, alternatively, the patient took the capsule but did not swallow it. MEMS was used to reduce this risk and all units, except two bottles, were retrieved and verified against the self-assessment data that the capsule intake data was reliable and consistent with the bottle opening times. Thus, there is reliable data on each bottle opening. There is always a theoretical risk that the patient simply threw the capsule in the toilet instead of swallowing it, but this risk should be considered as small for two reasons. First, the patients who participated in this study were all positive to the medication and did not have any problems with the study agenda. Secondly, at each follow-up assessment it was double-checked with each patient that he/she actually took the capsule at the time of the bottle opening. All patients verified the information was correct; therefore, the data from Study V should be considered reliable.

Although study V had negative findings, it provided important experiences. One lesson learned is that it was relatively easy to recruit patients and to administer the treatment. Study V was completed within a three-year period – including all preparation, manufacturing of DCS, applications and follow-up assessments – and the recruitment period was short (all patients were included within a year). Even though double-blinded pharmacotrials

are not easy or cheap to undertake, this was facilitated by the ICBT treatment administration platform. Despite being one of the largest DCS study for OCD and in a country with a relative small population of nine million people, this trial was completed relatively fast. Other similar large-scale pharmacotrials often have longer recruitment periods, even up to 10 years.^{81,150} Thus ICBT could be a promising research tool for studies demanding large sample sizes.

Is DCS still relevant for future clinical research? The answer is yes. Although study V was adequately powered, it is still possible that there are important moderating or mediating effects of DCS. For instance, in both animal and human studies, DCS produces better between session habituation when patients have greater within session habituation,¹⁵¹⁻¹⁵³ and it is reasonable to assume this might also be the case with ICBT, even though the data from each specific DCS ERP-exercise (including within and between session habituation data) have not yet been analyzed in the current data set. In addition, neither CBT nor DCS may work entirely on fear extinction processes, as DCS improves also other information processes, such as reward based decision-making⁹⁰ and auditory long-term memory.¹⁵⁴ Aside from extinguishing fear, some research suggest that ERP improves self-efficacy and/or fear toleration⁷⁵ and may also have different effects on different emotions. For example, in the prediction analysis from data in Study II,¹⁴³ self-reported disgust predicted worse treatment response to ICBT compared to patients with fear/anxiety reactions. It has been suggested in the literature that disgust extinction does not depend on fear habituation¹⁵⁵⁻¹⁵⁹ and it could also be that the degree and/or type of emotional response moderates DCS response in ICBT. Thus, although DCS did not have an overall effect in the OCD sample, DCS may work for some patients under some circumstances. Therefore, there is a need to analyze the data more closely and focus on specific phenotypes (e.g. obsessional content, emotional response, obsessive beliefs) and treatment processes (e.g. within- and between session habituation, self-efficacy) that may play a role in outcome.

7 CONCLUSIONS

- ICBT is an effective treatment for OCD.
- It is still unclear whether cognitive interventions are needed, but the findings indicate there may be a relation between obsessive beliefs and treatment outcome.
- It is possible to achieve some improved long-term effects through a booster as adjunct to ICBT, but replication trials are needed before any further conclusions can be made.
- Treatment effects do not appear to be enhanced through DCS as adjunct to ICBT.

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