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IMPROVING ACCESS AND OUTCOMES IN THE TREATMENT OF OBSESSIVE-COMPULSIVE DISORDER

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Improving access and outcomes in the treatment of Obsessive-Compulsive Disorder
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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To my family, for your unwavering support.

POPULAR SCIENCE SUMMARY OF THE THESIS

Obsessive-compulsive disorder (OCD) is a mental disorder characterised by obsessions ("what if my hands are contaminated, I will spread disease to someone and make them sick!") and compulsions (excessive hand-washing). OCD is often time-consuming and leads to difficulties in normal functioning, for example work or studies, relationships, and a lower quality of life. OCD typically develops gradually during adolescence or early adulthood, and without treatment it is often chronic. Effective treatments for OCD include medication with antidepressants and psychological treatment with cognitive behaviour therapy (CBT).

The studies included in this thesis address several current challenges in the treatment of OCD. First, internet-delivered CBT (ICBT) is a promising new treatment for OCD but it has not been directly compared to face-to-face CBT. Second, CBT needs to be adapted for patients that have both OCD and autism spectrum disorder (ASD). Third, time-consuming assessments by clinicians are currently needed to evaluate the effects of treatment, but self-rated questionnaires could be efficient alternatives. And fourth, ICBT treatments are rarely available outside the countries where they were developed.

Study I was a clinical trial where participants were randomly assigned to one of three treatments for OCD: unguided ICBT, therapist-guided ICBT, or face-to-face CBT. There was a total of 120 participants in the study. The main aim of the study was to evaluate if unguided ICBT and therapist-guided ICBT had a similar clinical effectiveness as face-to-face CBT within a certain margin of error, called non-inferiority. Even though symptoms of OCD improved in all three groups after treatment, non-inferiority could not be established for either of the ICBT treatments. Both unguided ICBT and therapist-guided ICBT were found to be a good use of health care resources, and cost saving compared to face-to-face CBT.

Study II evaluated an adapted CBT treatment for OCD in adults with both OCD and ASD. In total, 19 patients received the adapted treatment that included up to 20 face-to-face CBT sessions. Even though the participants had reduced symptoms of OCD after treatment, full recovery from OCD was rare. The results suggest that more research is needed to develop effective treatments for individuals with both OCD and ASD.

Study III used data from three previous clinical trials to evaluate if a self-rated questionnaire of OCD symptoms, the Obsessive-Compulsive Inventory–Revised (OCI-R), could be used to classify treatment response and remission in OCD. Treatment response means that a patient has experienced a meaningful reduction in symptoms, and remission means that symptoms are minimal and not interfering in everyday life. Optimal cut-offs for both treatment response and remission were estimated and the OCI-R can be used as an alternative when assessments by clinicians are not available.

Study IV was an evaluation of the therapist-guided ICBT treatment from study I when it was implemented and used in the United Kingdom. There was a total of 474 adults with OCD in this trial. After treatment, the symptoms of OCD, anxiety and depression had improved. Therapist-guided ICBT is effective when implemented in this context, but some challenges are discussed.

The four studies included in this thesis showed that: (1) ICBT for OCD is an effective treatment when used in Sweden and the United Kingdom; (2) ICBT can lead to cost savings compared to face-to-face CBT; (3) adapted CBT for OCD is a partially effective treatment for adults with OCD and ASD; (4) self-rated questionnaires can be used to evaluate

treatment effects in OCD when assessments by clinicians are not available. Future directions in the diagnosis and treatment of OCD are also discussed.

ABSTRACT

Effective psychological treatments exist for obsessive-compulsive disorder (OCD) in the form of cognitive behaviour therapy (CBT), but access is limited and adaptations are needed for groups of patients, for example individuals with co-occurring autism spectrum disorder (ASD), that do not respond well to the standard treatment. Moreover, treatment evaluation is not straightforward with multiple definitions and approaches. Standardised criteria for treatment response and remission have been proposed, but empirically validated operationalisations on self-rated questionnaires are lacking. The goal of this thesis was therefore to improve access and outcomes in the treatment of OCD in four empirical studies.

In study I, guided and unguided internet-delivered CBT (ICBT) for OCD were compared to face-to-face CBT in a randomised non-inferiority trial. A total of 120 individuals with a primary diagnosis of OCD participated in the trial, and clinical efficacy as well as cost-effectiveness was evaluated. Participants in all three groups improved but the non-inferiority results for both ICBT treatments were inconclusive as the confidence intervals for treatment difference included the pre-specified 3-point margin on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) at primary follow-up. Both therapist-guided and unguided ICBT were cost-effective when compared to face-to-face CBT.

Study II evaluated an adapted CBT treatment for 19 adults with co-occurring OCD and ASD in an open trial. After treatment, there were significant reductions in OCD symptoms on the Y-BOCS, and the gains were sustained at 3-month follow-up. However, few patients were treatment responders and treatment engagement was low as the patients completed few exposures and homework assignments relative to the number of treatment sessions.

Study III analysed the self-rated Obsessive-Compulsive Inventory–Revised (OCI-R) as a tool to evaluate treatment response and remission after CBT for OCD. The OCI-R was compared to expert consensus criteria using the Y-BOCS and Clinical Global Impression Scale using data from 349 participants in three clinical trials. The optimal cut-off for treatment response was a ≥40% reduction on the OCI-R and the optimal cut-off for remission status was an OCI-R total score of ≤8 points. These empirically validated cut-offs are efficient alternatives to clinician-administered assessments which are not always available in regular clinical practice.

Study IV was a pilot trial of the therapist-guided ICBT treatment from study I, implemented in the United Kingdom's *Improving Access to Psychological Therapies* (IAPT) programme. A total of 474 consecutively referred patients across three IAPT services with a primary diagnosis of OCD were included in the study. After treatment, there were large improvements in self-rated OCD symptoms (d = 1.77), anxiety (d = 1.55), and depression (d = 0.8). The results indicated that therapist-guided ICBT for OCD is an effective treatment when implemented in the IAPT system, but challenges in implementation were identified and discussed.

The studies included in this thesis addressed current issues in the treatment of OCD and evaluations of treatment effects. In summary, the studies showed that ICBT for OCD is an effective treatment when delivered in multiple contexts, and is a cost-effective alternative to face-to-face CBT; that an adapted CBT protocol for adults with OCD and co-occurring ASD is promising but that additional innovations are needed to improve outcomes; and that the self-rated OCI-R can be an efficient tool for treatment evaluation when clinician-rated assessments are unavailable. Directions for future research include further implementation of ICBT for OCD and evaluations of its place in a stepped-care health care model,

exploring new intensive treatment options for individuals with OCD and ASD, and externally validating the OCI-R cut-offs in diverse clinical samples.

LIST OF SCIENTIFIC PAPERS

I. Lundström, L.*, **Flygare, O.***, Andersson, E., Enander, J., Bottai, M., Ivanov, V. Z., Boberg, J., Pascal, D., Mataix-Cols, D., & Rück, C. (2022). Effect of Internet-Based vs Face-to-Face Cognitive Behavioral Therapy for Adults With Obsessive-Compulsive Disorder: A Randomized Clinical Trial. *JAMA Network Open*, *5*(3), e221967. https://doi.org/10.1001/jamanetworkopen.2022.1967

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IV. **Flygare, O.**, Lundström, L., Andersson, E., Mataix-Cols, D., & Rück, C. (2022). Implementing therapist-guided internet-delivered cognitive behaviour therapy for obsessive–compulsive disorder in the UK's IAPT programme: A pilot trial. *British Journal of Clinical Psychology*. https://doi.org/10.1111/bjc.12365

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LIST OF ABBREVIATIONS

ASD	Autism spectrum disorder
CBT	Cognitive behaviour therapy
CGI-I	Clinical Global Impression Scale–Improvement
CGI-S	Clinical Global Impression Scale–Severity
CR	Conditioned response
CS	Conditioned stimulus
CSTC	Cortico-striato-thalamo-cortical circuit
DSM	Diagnostic and Statistical Manual of Mental Disorders
ERP	Exposure with response prevention
GWAS	Genome-wide association study
HiTOP	Hierarchical Taxonomy of Psychopathology
IAPT	Improving Access to Psychological Therapies
ICBT	Internet-delivered cognitive behaviour therapy
ICD	International Classification of Diseases
NMDA	N-methyl-D-aspartate
OCD	Obsessive-compulsive disorder
OCI-R	Obsessive-Compulsive Inventory–Revised
OCS	Obsessive-compulsive symptoms
OFC	Orbito-frontal cortex
SNP	Single nucleotide polymorphism
SSRI	Selective serotonin reuptake inhibitor
TAU	Treatment as usual
Y-BOCS	Yale-Brown Obsessive Compulsive Scale

1 INTRODUCTION

> *"Certain notions are forced into their minds, of which they see the folly and incongruity, and complain that they cannot prevent their intrusion."* – John Haslam, 1798. *(1)*

In my work as a clinical psychologist, I have seen first-hand the devastating effects obsessive-compulsive disorder (OCD) can have on affected individuals. Many patients report that every hour of the day is plagued by intrusive and unwanted thoughts, and efforts to suppress or reduce the distress interferes with every aspect of their lives. I was therefore excited to join the research group of Christian Rück and work on projects that attempt to address several current issues in the assessment and treatment of OCD.

One issue is the low availability of effective treatments. Despite decades of research that demonstrate the efficacy of exposure with response prevention (ERP), few patients receive this treatment and often live with OCD for years before getting adequate treatment. Another issue is that the standard structure of treatment may not be feasible for patients that have co-occurring autism spectrum disorder (ASD). A separate issue is that efficient methods to evaluate treatment in clinical practice are lacking.

The goals of my PhD studies were: First, to compare a promising new treatment, ICBT for OCD, to the best current treatment available, face-to-face CBT. Second, to evaluate whether an adapted treatment for individuals with OCD and co-occurring ASD was effective. Third, to see whether a self-report questionnaire on OCD symptoms could be used in treatment evaluation. And fourth, to implement ICBT for OCD and evaluate its efficacy internationally. I hope that the results from this thesis contribute to improving access and outcomes in the treatment of OCD.

Stockholm, Lago di Como; March-May 2022

2 BACKGROUND

2.1 CHARACTERISTICS OF OCD

OCD is characterised by unwanted and intrusive thoughts, images or impulses (obsessions), and repetitive behaviours in response to obsessional distress (compulsions) (2). Obsessions in OCD cause marked anxiety or distress, and the individual tries to ignore, suppress or neutralise them. Compulsions can be both overt behaviour (e.g., hand washing, ordering, checking) or mental acts (e.g., counting, repeating words silently, praying), and are excessive or not realistically connected with what they are designed to neutralise or prevent. Further, to meet diagnostic criteria for OCD the obsessions or compulsions should be time consuming, cause clinically significant distress, or lead to impairment in important areas of functioning (2).

OCD has a lifetime prevalence of 1.3%, and is more common in women (1.5%) than men (1%) (3). Most patients develop OCD during adolescence or early adulthood, and the disorder remains chronic if left untreated (4–6). Development of clinically significant distress and impairment is typically gradual, and individuals who report obsessions or compulsions during childhood are more likely to meet diagnostic criteria for OCD as adults (7). Without treatment, spontaneous recovery is rare (8). The gradual development may delay treatment seeking, and delays of 10-15 years from onset until individuals receive treatment are common (6,9).

As it is often chronic and time-consuming, OCD negatively affects several important areas of life. For example, individuals with OCD have lower educational attainment compared to individuals without the disorder (10) and labor market marginalisation is common (11). Quality of life is impaired and individuals with OCD report a loss of functioning in important areas of life (12). Further, individuals with OCD have twice the risk of premature death compared with the general population (13), likely explained in part by an increased risk of metabolic and cardiovascular complications (14,15). In addition, patients with OCD are at an increased risk of dying by suicide, and the risk remains substantial after adjusting for psychiatric comorbidities (16). Thus, the burden of OCD manifests in both direct and indirect ways, and the disorder results in substantial negative consequences for affected individuals.

Obsessions and compulsions of a certain kind tend to occur together, creating symptom dimensions of OCD. The most empirically validated dimensions are: (a) obsessions about causing harm or making mistakes and checking compulsions; (b) contamination obsessions and washing or cleaning compulsions; (c) unacceptable thoughts about sexuality, religion, or violence and mental compulsions to neutralise those thoughts; and (d) obsessions about order or symmetry and ordering or arranging compulsions (17–19). A patient may experience obsessions and compulsions in multiple dimensions at any given time, and symptoms typically wax and wane over time (20). A majority of patients with OCD also fulfil diagnostic criteria for another psychiatric disorder (21). Depression and anxiety disorders are the most common, with lifetime estimates ranging from 37-74% for major depressive disorder and 38-52% for anxiety disorders (6,22). Co-morbid eating disorders and autism spectrum disorder are also common (6,23).

Distinguishing the symptoms of OCD from those of co-occurring disorders can be a challenge in clinical practice. For example, the symptoms of OCD and eating disorders are similar in that an intensive preoccupation is linked to compensatory/repetitive behaviour (24), however the symptoms tend to cluster distinctly for each disorder and symptom overlap is low (25). Differential diagnosis between OCD and generalised anxiety disorder can be challenging since both obsessions and excessive worrying are repetitive negative

thought patterns. However, obsessions are often experienced as intrusive and inconsistent with one's belief system (ego-dystonic), features that are not seen in worrying and ruminative thoughts (26). Compulsions, on the other hand, can sometimes be similar to the repetitive and restricted behaviours seen in autism spectrum disorder. However, the repetitive behaviours serve different functions: compulsions in OCD are used in order to reduce obsessional anxiety, while repetitive behaviours in autism spectrum disorder are due to restricted interests or insistence on sameness (27).

2.2 ASSESSMENT OF OCD

A diagnosis of OCD is typically made using a semi-structured diagnostic interview, in which a clinician inquires about diagnostic criteria, for example whether the obsessional thoughts are experienced as intrusive and ego-dystonic (2). Diagnostic interviews are often accompanied by the clinician-rated Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (28), which addresses the frequency, distress, and interference from obsessions and compulsions, and the individual's ability to control them. The Y-BOCS has excellent interrater reliability ($r = 0.98$) and internal consistency (Cronbach's $\alpha = 0.89$) (28,29), and is the gold-standard assessment of OCD symptom severity (9).

In an effort to improve the reporting of treatment outcomes in OCD, expert consensus definitions for treatment response and remission have recently been established (30). Treatment response has been defined as a ≥35% reduction on the Y-BOCS compared to baseline, and a Clinical Global Impression Scale–Improvement score of 1 ("very much improved") or 2 ("much improved"). Remission has been defined as a Y-BOCS score ≤12 as well as a Clinical Global Impression Scale-Severity rating of 1 ("not at all ill") or 2 ("borderline mentally ill") (30). Using consistent operationalisations of treatment response and remission facilitates comparison between studies and improves the communication of results between researchers and to the general public.

However, comprehensive assessments by clinicians are not always feasible in clinical practice. Self-reported assessments of OCD severity have therefore been developed as efficient alternatives, and among the most commonly used is the Obsessive-Compulsive Inventory–Revised (OCI-R) (31). The OCI-R has excellent psychometric properties with an internal consistency α for the total score of 0.83, and sub-scale alphas ranging from 0.83 to 0.92 (32). It is sensitive to change in symptoms after CBT (33). In addition, cut-off scores for mild, moderate and severe symptoms are available (34). However, empirically validated cut-offs for treatment response and remission on the OCI-R, which would make it possible to evaluate treatment outcomes in regular clinical practice where resources are limited, are currently not available.

2.3 ETIOLOGY AND MAINTENANCE

Why does an individual develop OCD, and what maintains the disorder once in place? These fundamental questions do not have straightforward answers, but research across multiple levels of investigation has begun to address them. Genetic, neurobiological, environmental and psychological aspects are reviewed below. Although presented separately, a comprehensive theory of the development and maintenance of OCD will have to account for the complex interplay between neural, cognitive, and behavioural aspects (35).

2.3.1 Genetics

There is now robust evidence from twin studies that the risk for OCD is partly due to genetic factors, and the estimated heritability is 45-58% (36,37). Further, population-based

studies have found that the increased risk seen in relatives of patients with OCD is proportional to their genetic relatedness, with the remaining risk being attributed to unique or non-shared environment (38). Thus, OCD tends to cluster in families due to genetic rather than shared environment factors.

The genetic underpinnings of OCD and other psychiatric disorders are not fully known, and much research is underway (39). However, it is likely that common and small genetic variations (with minor allele frequencies of 1-5% in the population) play a key role, with rare and larger variations contributing to OCD risk in a subset of cases (40–42). These genetic variations occur in a single nucleotide pair and are often referred to as Single Nucleotide Polymorphisms (SNPs). The estimated SNP-based heritability of OCD ranges from 0.25 to 0.43 (43,44), but because of the many thousands of statistical tests performed, genome-wide association studies (GWAS) to date have likely been underpowered to detect significant effects of single genetic variations. Large data collections are ongoing that will likely provide well-powered meta-analyses in the future (45,46). In addition to GWAS studies on individuals diagnosed with OCD, one may also investigate the genetics of obsessive-compulsive symptoms (OCS) in the broader population. Multiple GWAS-studies have shown that OCS have an estimated heritability of 42% and genetic risk scores for OCD can predict OCS in the general population (47,48). In summary, the genetic risk for OCD can be attributed to the combination of many small and common variations, each with a small effect. It is also likely that OCS is a continuous trait in the general population with OCD being on the severe end (49).

To understand whether the co-occurrence of OCD and other disorders can be explained by shared genetic vulnerability, researchers have begun to compare the shared common genetic risk between disorders. To date, the strongest overlap has been observed between OCD and anorexia nervosa, as well as OCD and Tourette syndrome (50–52). There is also genetic overlap between OCD and bipolar disorder and schizophrenia, however to a lesser extent (51). Interestingly, although OCD and autism spectrum disorder share some characteristics (e.g., repetitive behaviours), they are not genetically correlated (51).

2.3.2 Neurobiology

Moving up several levels from genetic expression, via molecular and cell-level analysis, to brain circuitry: how are the results from genetic studies on OCD expressed in the brain? Findings to date point to abnormalities in the system that regulates the neurotransmitter glutamate (53). Converging evidence from neuro-imaging, neuropsychological and pharmacological research also points to the cortico-striato-thalamo-cortical (CSTC) circuit as key to understanding the neurobiological footprint of OCD (54,55). The CSTC model of OCD stipulates that reduced inhibition from cortical regions via the striatum leads to hyperactivity in the thalamus and orbito-frontal cortex (OFC) (56). Hyperactivity in the OFC has been linked to obsessions, and the repetitive and ritualistic nature of compulsions is driven by activity in the striatum (57). When compared to individuals without the disorder, patients with OCD have larger volumes of hyperactive regions (e.g., the pallidum), and smaller volumes in inhibitory regions (e.g., inferior parietal cortex) (58).

2.3.3 Environmental risk factors

In addition to uncovering the genetic and—in extension—neurobiological expression, to understand why an individual develops OCD we must also investigate the factors that represent environmental risk for OCD. Historically, studies on potential environmental risk factors for OCD have been lacking prospectively collected data with twin-design to control for genetic or unmeasured environmental factors, increasing the risk for recall bias and potential confounding (59). A compounding issue is that the studies often involve small

samples at specialist OCD clinics, meaning that the patients studied are likely among the most severe with high levels of co-morbidity and a long illness duration (59). For example, stressful life events (e.g., illness, unemployment, harassment and abuse, marital and familial problems) may play a role in the development of OCD and its course, however results to date are inconsistent (60). Other potential environmental risk factors are birth complications, pregnancy and the postpartum period, and infection, as shown in large population-based studies (59,61–63). Some indicators of socioeconomic stress, for example one or both parents outside the labour market or living with only one parent, have been associated with a higher risk of OCD in a large national cohort (64). Studies on potential environmental risk factors have been plagued by potential familial confounding and spurious findings in small samples, but large rigorous studies are available for a subset of proposed risk factors.

2.3.4 Psychological models

2.3.4.1 The cognitive behavioural model of OCD

A foundation for the cognitive behavioural model of OCD comes from the two-factor theory developed in the 1950's and 1960's that combines classical and operant learning principles to explain the relationship between obsessions and compulsions (65). Obsessions can be viewed as conditioned stimuli (CS) that elicit anxiety, a conditioned response (CR). The CR then acts as a discriminative stimulus for compulsions, which are negatively reinforced through anxiety reduction and temporary removal of the obsession. However, by performing compulsions to reduce anxiety, one also reinforces the association between obsessions and anxiety, thus maintaining OCD over time (65).

Complementing the learning theory model of OCD, cognitive theory stipulates that obsessions and intrusive thoughts are part of normal experience and common, but that the *interpretations* of those obsessions is what is associated with OCD (26,66,67). In other words, the way someone interprets their intrusive thoughts will affect how they feel and behave in response to them. A common negative interpretation of thoughts associated with OCD is an inflated sense of responsibility for harm, for example that failing to prevent harm is equal to having caused the harm in the first place. Another is believing that having a thought about an action is like performing the action, thereby also interpreting the intrusive thought in a catastrophic way. Such negative and catastrophic interpretations of the intrusive thoughts lead to negative emotions and prompts the use of compulsions to reduce obsessional distress (68).

The cognitive behavioural model of OCD combines classic conditioning (obsessions elicit anxiety), operant conditioning (compulsions are negatively reinforced through anxiety reduction), and cognitive theory (dysfunctional beliefs increase the anxiety from obsessions) into a psychological model of the maintenance of OCD, shown in figure 1 (69).

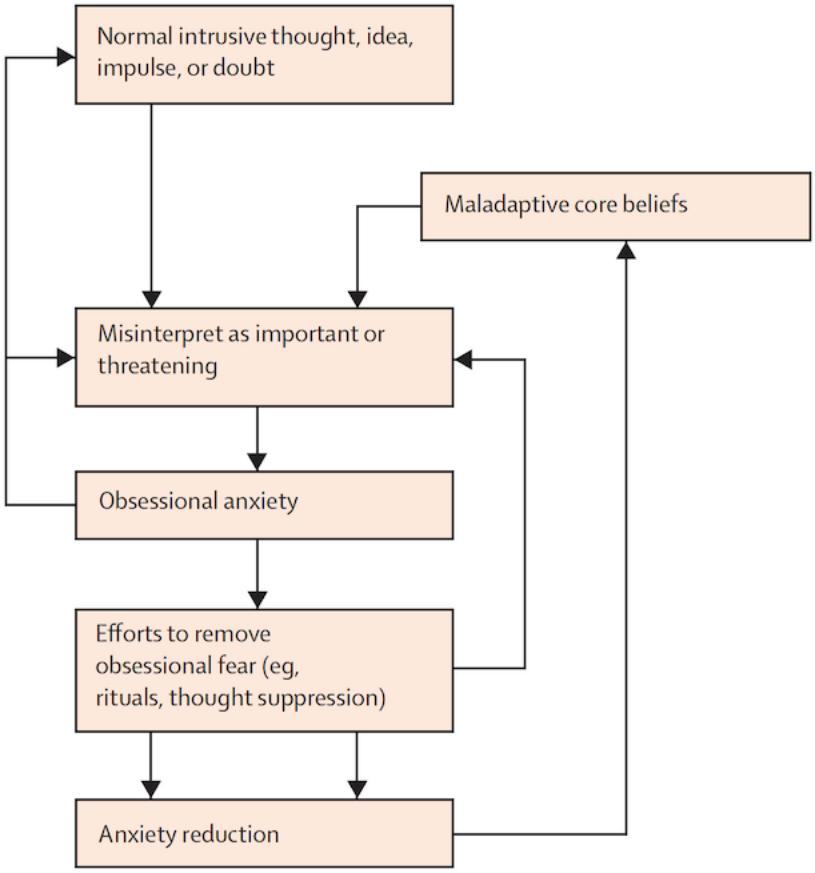

Figure 1. The Cognitive behavioural model of OCD. Figure from Abramowitz et al., 2009. Reprinted with permission from Elsevier.

2.3.4.2 OCD as excessive habit formation

The traditional cognitive-behavioural account of OCD stipulates that obsessional distress prompts the individual to perform compulsions, and—importantly—that compulsions are voluntary behaviours negatively reinforced by the reduction of anxiety. However, some researchers argue that compulsions should not be understood as goal-directed behaviours in response to obsessions, but rather as behaviours resulting from excessive habit formation (70).

One common dichotomy in cognitive neuroscience is that of goal-directed versus habitual behaviour (71). Both types are needed as they each have their benefits and drawbacks. Habits are fast and efficient but rigid and inflexible, whereas goal-directed behaviour is flexible but takes effort to perform. Habitual and goal-directed behaviour are associated with different brain networks, and OCD has been linked to over-activity in the habitual network (e.g., the caudate nucleus) (72) and under-activity in the goal-directed network (e.g., dorsolateral prefrontal cortex) (73). This imbalance between habitual and goal-directed behaviour leads to a bias towards habits in OCD, shown in multiple experimental tasks (74). For example, patients with OCD are more likely to continue with responses that have previously been rewarded even when the reward is no longer present (72,75). Together with addiction and eating disorders, OCD is thus thought to be a compulsivity disorder characterised by a bias towards learning habits (76). What is the role of obsessions in this model of excessive habit formation in OCD? The proponents suggest that obsessions may be a consequence of the compulsive urge; a product of the cognitive dissonance that occurs when the patients' cognitions and their compulsive behaviour mismatch (77).

Intriguing as these findings are, the habit theory has not yet resulted in novel approaches to the management or treatment of OCD. Beyond the habitual model of OCD outlined above, one possibility is that obsessions and compulsions arise from two distinct and independent processes that benefit from separate interventions. Another possibility is that obsessions and compulsions could both be caused by disruptions in the goal-directed system, leading to automatic thoughts (obsessions) and automatic behaviour (compulsions) (77). Nonetheless, compulsivity and habit formation are widely viewed as important constructs for future research in OCD (78).

2.4 TREATMENT

Evidence-based treatment options for OCD include pharmacological and psychological treatment, either as standalone treatments or in combination (79). Swedish and international treatment guidelines recommend either a course of CBT or medication with selective serotonin reuptake inhibitors (SSRIs) as first-line options (80–83).

2.4.1 Pharmacological treatment

Medication with SSRIs, a class of medications that limit the reuptake of serotonin from the synaptic cleft into the presynaptic neuron, is the recommended first-line pharmacological treatment for OCD. Several meta-analytic studies have concluded that treatment with SSRIs is more effective than placebo (79,84). The tricyclic antidepressant clomipramine has outperformed SSRIs in some trials (85) but the most recent evidence suggests that the difference is small and not statistically significant (79). For patients who do not respond to SSRI alone, antipsychotic medication can be used as an augmentation strategy (86).

One limitation of SSRIs is that an onset period is needed before reaching an efficacious dose. Therefore, alternative medications such as the N-methyl-D-aspartate (NMDA) glutamate receptor antagonist ketamine have been evaluated. Initial results have been promising, but the field is still developing and the long-term efficacy is unclear (87,88).

2.4.2 Psychological treatment

Exposure with response prevention (ERP) is a type of cognitive behavioural therapy for OCD with more than 40 years of research to support its efficacy (89). ERP involves systematic and gradual exposure to the obsessive thoughts, images, or impulses that cause anxiety, while partially or completely refraining from compulsions (90). ERP can be delivered individually, in group, or via the internet, and treatment typically lasts 10-15 weeks with one session per week (9). The proposed mechanism of action is fear reduction by activation of memory structures that are modified or replaced through systematic exposure (91). According to the emotional processing framework, exposure therapy exerts its effects by activating the fear structure (exposure to an obsession), after which new information—incompatible with the current memory structure—is incorporated (learning that the feared outcome did not occur despite refraining from compulsions) (91). Factors thought to promote emotional processing include long and repeated exposures without distractions (92). A key indicator of successful emotional processing is habituation, i.e. that the emotional response to a feared stimulus decreases over time, both within a single exposure and between exposure sessions (93).

However, the view that within-session habituation is needed for long-term change in emotional responses has been challenged by proponents of an inhibitory learning framework for exposure therapy (94). According to this model, within-session habituation to stimuli is mediated by other mechanisms than long-term outcomes and should not be used as an indicator of successful learning (95). Rather than replacing the fear memory,

according to this theory, exposure therapy works by introducing a new non-threat association for the feared stimulus that competes with the fear memory for retrieval (96). This means that fear tolerance, rather than fear reduction, should be a primary goal of exposure therapy (95). Applied to the treatment of OCD, this theoretical framework leads to exposures that maximise expectancy violation (e.g., "I will not tolerate this level of intense obsessions"), combine multiple fear cues (e.g., incorporate external, cognitive and physiological cues simultaneously), and are conducted in varied contexts to maximise the generalisability of learning (94,97). It remains to be seen, however, whether ERP for OCD conducted in accordance with an inhibitory learning approach leads to better results compared to the traditional emotional processing approach.

Recent developments in CBT—also called third-wave CBT—such as mindfulness-based CBT, are characterised by emphasising the function and meaning rather than the content of thoughts. A recent meta-analysis on 10 studies comparing mindfulness-based interventions to passive or active control conditions found no statistically significant difference on OCD symptoms (98). When ERP only or ERP plus mindfulness were compared directly, there were no differences in effectiveness between the treatments (99). Similar results were found in a randomised controlled trial comparing ERP to ERP plus acceptance and commitment therapy, as there were no between-group differences in OCD symptoms after treatment (100). A third novel treatment approach is metacognitive therapy, which has shown preliminary efficacy as a self-help manual for OCD (101), but metacognitive therapy did not lead to improved outcomes compared to standard ERP in a randomised controlled trial (102). Thus, the evidence to date suggests that novel CBT approaches do not outperform ERP, and adding novel CBT approaches do not provide additional gains compared to ERP alone in the treatment of OCD.

Rather than modifying the content of treatment, some researchers have begun to evaluate treatments that alter the intensity of treatment delivery. For example, An intensive 4-day treatment has shown promising results in a number of effectiveness studies (103,104) with sustained effects long-term (105). Delivered in a group format of 5-6 patients and with one therapist per patient, the treatment is delivered in just 4 consecutive days followed by three weeks of self-guided ERP. Although the treatment uses ERP as the main component of therapy, the intensive format has led to some changes in the approach to exposures. For example, rather than gradual exposures with increasing difficulty, patients are encouraged to select ERP tasks with the largest potential for change, often resulting in challenging ERP exercises or completing multiple steps at once (for example, lighting dozens of candles in all rooms of an apartment, blowing them out "in bulk" and then leaving the apartment without checking). Since the treatment lasts full days, ERP is often conducted outside the clinic and in multiple contexts in order to maximise the generalisability of learning (103). The studies to date report high rates of response and remission and notably few patients drop out of treatment, likely due to the short and intensive treatment format (103–105). These initial results are promising, but direct comparisons to the standard approach with weekly individual sessions are lacking.

Individuals who fulfil diagnostic criteria for autism spectrum disorder (ASD) benefit less from standard CBT treatments when compared to individuals without ASD (106). Difficulties associated with ASD often interfere with therapy processes necessary for successful ERP, for example communicating about emotional states (107,108) and identifying alternative behaviours to compulsions (109). Further compounding the issue is that repetitive thoughts and behaviours seen in ASD and OCD often overlap and can be hard to distinguish (110,111). To address the challenges associated with treating co-occurring OCD and ASD, an adapted treatment protocol has been developed and shown promising results in initial trials (112,113). However, replications in other contexts are

needed as the conditions to offer and deliver a complex adapted treatment may differ between health-care systems and countries.

2.4.3 Combination treatments

A combination of pharmacological and psychological treatment is common in regular clinical practice. In a landmark study, the effect of ERP or Clomipramine alone, or in combination, was compared to pill placebo (114). The results indicated that both ERP and Clomipramine were superior to placebo, but that a combination of Clomipramine and ERP did not yield better results than ERP alone. In OCD patients with moderate symptoms despite medication with SSRIs, ERP was a more effective augmentation treatment compared to risperidone, an atypical antipsychotic that can be used in combination with SSRIs (115). A recent study concluded that patients who benefit from ERP can safely discontinue medication with an SSRI with non-inferior outcomes compared to patients who continue their SSRI (116). In light of these findings, Swedish treatment guidelines recommend ERP as the first priority, followed by pharmacological treatment using SSRIs, SSRIs in combination with antipsychotic medication, and combined psychological and pharmacological treatment (83).

The limited added benefit from combining ERP with SSRIs have led researchers to look elsewhere for possible enhancements of psychotherapy. One promising finding was that the compound D-Cycloserine, a partial NMDA agonist, enhanced fear extinction in animals and also in humans in early trials (117). However, the early enthusiasm has waned: there was no added effect from D-Cycloserine plus ICBT for OCD versus ICBT alone in a double-blind randomised trial (118), and a recent individual patient data meta-analysis concluded that adding D-Cycloserine to psychotherapy for various anxiety disorders and OCD did not produce additional gains (119).

2.4.4 Internet-delivered CBT

The advent of internet-delivered CBT (ICBT) for common mental disorders in the past 15 years has drastically improved access to effective treatment for many mental disorders. A typical ICBT treatment contains psycho-educational texts, worksheets and questionnaires delivered via an online platform (120). Support is often provided via asynchronous messaging, although some treatments are self-guided with no clinician involvement. The key difference to traditional face-to-face lies in the mode of delivery rather than content, and ICBT treatments often have weekly modules that match the course of a face-to-face protocol (121).

The ICBT approach to treatment has multiple strengths. First, treatment access is highly flexible as patients are able to access the treatment at a time and location convenient to them, which removes logistical barriers to attending face-to-face sessions at a clinic. Second, ICBT platforms provide a highly structured environment for treatment delivery, reducing the risk of therapist drift and helping both patients and therapists to focus on important treatment components (e.g., ERP practice in OCD). Third, since all communication is done via a treatment platform, it is possible to monitor and give feedback on therapist behaviour. Findings to date indicate that the rate of undesirable therapist behaviour in ICBT is low, although there is a dearth of research on this topic (122,123). And fourth, the highly standardised structure of ICBT treatments means that less therapist time per treated patient (5-15 minutes weekly) is needed compared to conventional CBT which typically involves one 45–60-minute session per week (124).

There have been hundreds of randomised controlled trials evaluating the efficacy of ICBT treatments for various disorders, but the comparisons have often been to waitlist control.

Directly comparing the efficacy of ICBT and face-to-face CBT is key to understanding the appropriate place for ICBT in health care. Crucially, if ICBT is found to have comparable efficacy to face-to-face CBT, it is possible to increase treatment availability while maintaining clinical outcomes (125). Direct comparisons can also inform treatment selection, as it will be possible to evaluate if ICBT or face-to-face CBT are suitable for certain groups of patients. Therapist-guided ICBT has shown equivalent effects to face-to-face CBT for various conditions in meta-analyses (g = .05 [95% CI, −.09 to .20]) (125,126), but such studies for OCD have been lacking prior to study I in this thesis. Further, ICBT treatments are often highly cost-effective compared to their face-to-face counterparts due to requiring less therapist time (127), but no such direct comparison had been done for OCD prior to study I in this thesis.

2.4.4.1 Internet-delivered CBT for OCD

The first trial on ICBT for OCD was published in 2011 (128) and since then several programmes have been developed (129–132) and evaluated in clinical practice (133–135). The programmes share an emphasis on ERP, with multiple treatment modules dedicated to introduce and practice the techniques involved. ICBT for OCD is a cost-effective treatment compared to face-to-face CBT (shown in study I), waitlist (136) and treatment as usual (132).

One such ICBT treatment for OCD has been developed in Sweden and is used in studies I and IV in this thesis (137,138). The treatment consists of ten modules that emphasise the use of ERP and treatment lasts 10-14 weeks. It has demonstrated efficacy in several randomised controlled trials (118,139), and results are maintained up to two years after treatment (140). The treatment modules included are shown in table 1.

Table 1. Modules included in ICBT for OCD

Treatment module	**Content**
1. Introduction to the treatment	Introduction to CBT Information about OCD
2. A CBT model of OCD	Psychological model of OCD with patient examples
3. Thinking mistakes in OCD	Common cognitive biases and unhelpful interpretations of thoughts in OCD
4. Introduction to ERP	Goal setting Planning ERP exercises
5. More about ERP	Best practices in ERP
6. Imaginal exposure	Instructions to get started with imaginal exposures
7. Re-exposure	Undoing habitual compulsions
8. Difficulties during treatment	Common problems in ERP Motivation traps
9. Long-term goals and values	Increasing valued behaviours Aligning ERP exercises with long term values
10. Summary and wrap up	Maintaining progress Relapse prevention

2.4.5 Improving treatment access at scale: the IAPT approach

The low availability of evidence-based psychological treatments for mental disorders is a global issue (141,142). Put simply, two options to increase availability are to increase the number of therapists or use treatments that require less therapist time per treated patient

(141). The *Improving Access to Psychological Therapies* (IAPT) programme in the United Kingdom has successfully trained a new cadre of therapists but has not yet used ICBT treatments to their full potential.

The IAPT programme launched in 2008 with the goal of providing evidence-based CBT treatment for common mental disorders to at least 25% of the population in need (143). To meet the goal, over 10 000 new therapists have been trained in delivering CBT for anxiety and depression, and the IAPT programme now provides over 600 000 courses of treatment in a given year (144). There is also an emphasis on outcome monitoring with pre- and post-treatment data available for 98% of patients seen (145). However, despite the successful launch and progress of IAPT, there is still an unmet need as only 16% of individuals with mental disorders in the UK community receive treatment in IAPT (143). The benefit of training new therapists can potentially be magnified by using ICBT treatments that enable those therapists to treat more patients (146). However, IAPT does not currently offer ICBT for OCD to more than a small fraction of all patients (144). By implementing ICBT for OCD into an already well-established system for psychological treatment, it would be possible to rapidly expand access to effective treatment for OCD in the United Kingdom.

2.5 SUMMARY

OCD is a severe and clinically heterogeneous psychiatric disorder with a negative impact on quality of life and functioning. Effective psychological treatment is available in the form of exposure with response prevention, but not everyone benefits from the standard treatment and availability is limited. Several questions regarding treatment and treatment evaluation in OCD remain. First, while ICBT for OCD has shown promising results, it has not been directly compared to face-to-face CBT in terms of clinical efficacy and cost-effectiveness. Second, individuals with co-occurring OCD and ASD benefit less from standard CBT protocols. An adapted treatment protocol has been developed, but has not yet been evaluated in Sweden. Third, definitions of treatment response and remission in OCD rely on resource-intensive assessments administered by clinicians, and efficient alternatives using self-rated questionnaires are lacking. And fourth, although the United Kingdom has expanded access to evidence-based CBT treatment through its IAPT programme, internet-delivered treatment options for OCD are lacking.

3 RESEARCH AIMS

The overall aim of this thesis was to address current research gaps in the psychological treatment of OCD and evaluation of treatment effects. The specific aims of each study are listed below.

3.1 STUDY I: EFFECT OF ICBT VERSUS FACE-TO-FACE CBT FOR ADULTS WITH OCD

The aims of this study were to (a) investigate whether therapist-guided and unguided ICBT are non-inferior to face-to-face CBT, (b) evaluate the cost-effectiveness of both ICBT treatments in relation to face-to-face CBT, and (c) to determine whether source of referral (referral by a clinician or self-referral) moderated the treatment effects.

3.2 STUDY II: EFFECTIVENESS OF ADAPTED CBT FOR OCD WITH CO-OCCURRING ASD

The aim of this study was to evaluate the clinical effectiveness of an adapted CBT protocol in adults with OCD and co-occurring ASD treated at a specialist OCD unit.

3.3 STUDY III: TREATMENT RESPONSE AND REMISSION IN OCD USING THE OCI-R

The aim of this study was to establish empirically derived cut-offs for treatment response and remission using a self-rated questionnaire for OCD.

3.4 STUDY IV: IMPLEMENTATION OF ICBT FOR OCD IN THE UNITED KINGDOM

The aim of this study was to evaluate the effectiveness of ICBT for OCD when implemented at three IAPT services in the United Kingdom.

4 THE EMPIRICAL STUDIES

4.1 STUDY I

4.1.1 Methods

Study I was a randomised controlled trial comparing therapist-guided ICBT, unguided ICBT, and face-to-face CBT for adults with OCD. A total of 120 participants were included in the study and assessments were conducted from baseline up to 12 months after treatment. The ICBT treatment consisted of 10 modules delivered via a secure online platform, with or without therapist support (139). The face-to-face CBT protocol consisted of 16 sessions delivered over 14 weeks (twice weekly for the first two weeks and one session per week during subsequent weeks) (90). The primary end-point was at three months follow-up. The primary outcome measure was the clinician-rated Yale-Brown Obsessive Compulsive Scale (Y-BOCS), rated by assessors blind to treatment allocation. The study evaluated a non-inferiority hypothesis for both guided and unguided ICBT, i.e. that the upper 90% confidence interval of the mean Y-BOCS difference compared to face-to-face CBT would not exceed 3 points. The primary end-point was at 3-months follow-up. Secondary outcomes included a full health economical evaluation of cost-effectiveness and moderator analyses of source of referral (self-referral versus clinical referral).

4.1.2 Main results

At the primary 3-month follow-up, patients in all three treatment groups had improved, however the confidence intervals for both therapist-guided ICBT (Y-BOCS difference = 2.10 [90% CI -0.41 to 4.61]) and unguided ICBT (Y-BOCS difference = 5.35 [90% CI 2.76 to 7.94]) included the 3-point margin and the non-inferiority results were inconclusive (see figure 2). The estimated treatment costs were $6795 (SE = $237) for face-to-face CBT, $603 ($176) for therapist-guided ICBT and $249 ($168) for unguided ICBT. Both ICBT treatments were associated with substantial cost savings compared to face-to-face CBT when costs were analysed from a societal perspective: therapist-guided ICBT = $6153 (95% CI $4536 to $7563), unguided ICBT = $5761 (95% CI $4145 to $7298). Source of referral did not moderate overall Y-BOCS change over time (time-by-source of referral interaction effect, $Z = 0.03$ [95% CI, −0.06 to 0.13]; SE = 0.05; $P = .53$) or change over time across groups (therapist-guided ICBT, $Z = −0.13$ [95% CI, −0.35 to 0.09], SE = 0.11, $p = .26$; unguided ICBT, $Z = 0.04$ [95% CI, −0.19 to 0.27], SE = 0.12, $p = .74$).

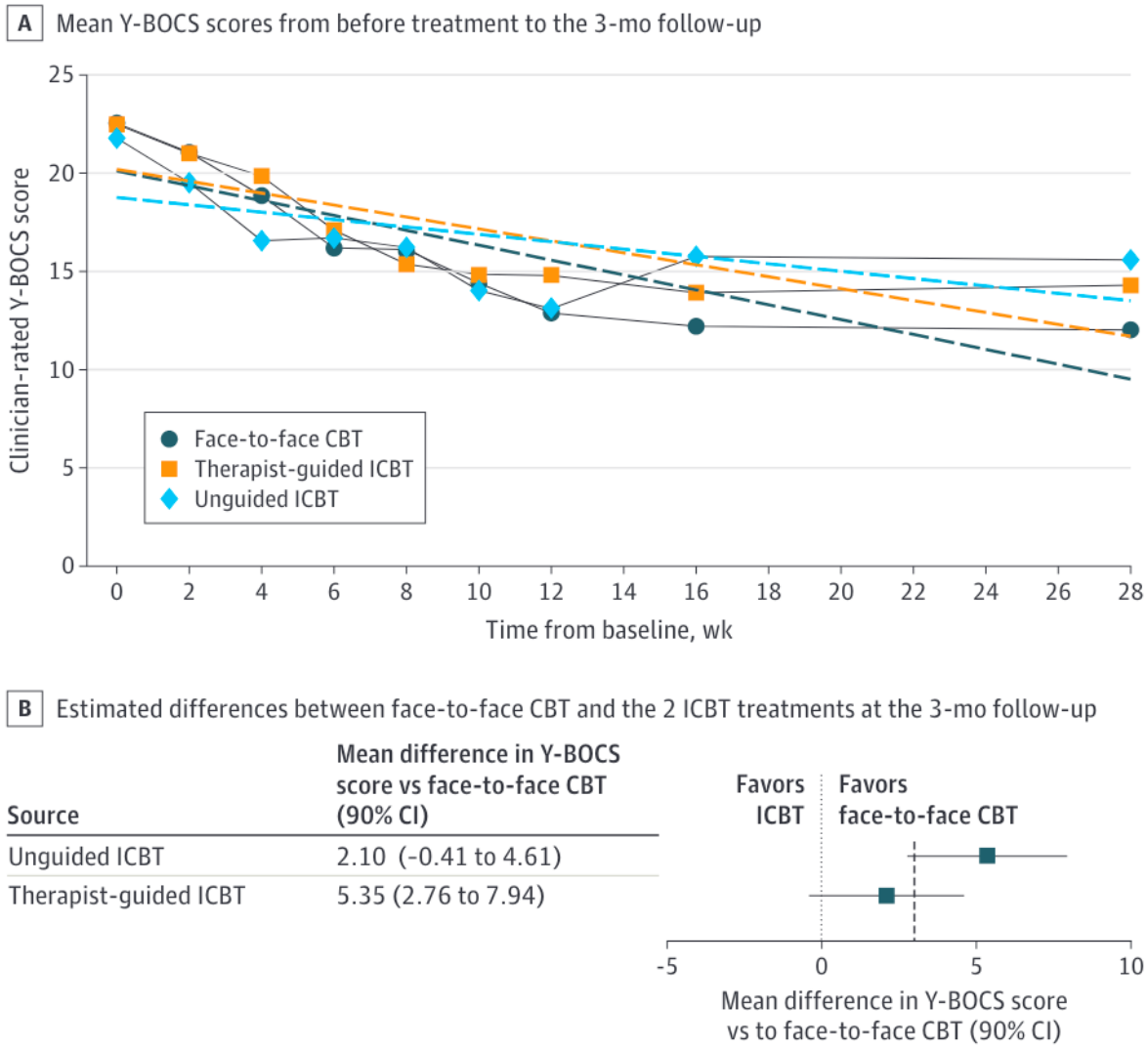

Figure 2. Y-BOCS scores over time and non-inferiority hypothesis. Reused from Lundström et al., 2022 under a CC-BY license. Panel A shows clinician-rated observed (solid lines) and estimated (dashed lines) Y-BOCS scores from before treatment to the 3-month follow-up. Panel B shows estimated differences between face-to-face cognitive behavioral therapy (CBT) and the 2 internet-based cognitive behavioral therapy (ICBT) treatments at the 3-month follow-up. The dotted line indicates the prespecified noninferiority margin of 3 points on the Y-BOCS.

4.2 STUDY II

4.2.1 Methods

Study II was an open, uncontrolled trial that included 19 adults with co-occurring OCD and ASD seen at a specialist OCD unit. The treatment consisted of an adapted CBT protocol with up to 20 sessions delivered face-to-face at the clinic or in the participant's home. The primary outcome was the clinician-rated Y-BOCS. Secondary outcomes included treatment response and remission according to international consensus definitions. Assessments were conducted at pre-treatment, mid-treatment, post-treatment and 3-month follow-up.

4.2.2 Main results

The treatment was associated with statistically significant improvements from pre- to post-treatment (Y-BOCS change = -7.72 points, d = -1.48 [95% CI -2.30 to -0.64]) and to

follow-up (Y-BOCS change = -6.25 points, *d* = -1.2 [95% CI -2.05 to -0.33]). Three participants (16%) were classified as treatment responders at both post-treatment and follow-up. Four participants (21%) were in remission at post-treatment, and one (5%) remained in remission at follow-up.

4.3 STUDY III

4.3.1 Methods

Data from three clinical trials on CBT for OCD, delivered via the internet or face-to-face, were combined for study III with a total sample size of 349 participants. Cut-offs on the Obsessive-Compulsive Inventory–Revised (OCI-R) were created at every 5% interval of improvement and at every score at post-treatment to evaluate treatment response and remission, respectively, compared to expert consensus criteria for treatment response (Y-BOCS reduction ≥35% and CGI-I 1 or 2) and remission (Y-BOCS score ≤12 and CGI-S 1 or 2). The cut-offs were evaluated using receiver operating characteristics analysis and Cohen's kappa, which measures agreement while controlling measurement error, was used to select optimal cut-offs.

4.3.2 Main results

A ≥40% reduction on the OCI-R from pre- to post-treatment was the optimal cut-off to classify treatment, with a sensitivity of 0.72, a specificity of 0.79, and overall accuracy of 75%. For remission status, the optimal cut-off was ≤8, which resulted in a sensitivity of 0.57, a specificity of 0.83, and overall accuracy of 74%.

4.4 STUDY IV

4.4.1 Methods

Study IV was an open trial evaluating the effectiveness of therapist-guided ICBT for OCD when implemented at three IAPT services in the United Kingdom. Consecutively seen patients with a primary diagnosis of OCD were offered the treatment (n = 474). Therapists at multiple levels of seniority received training in using the treatment platform. The primary outcome was self-rated symptoms of OCD on the OCI-R. Secondary outcomes included symptoms of depression, anxiety, level of functioning, and patient satisfaction with the treatment.

4.4.2 Main results

At post-treatment, there were large improvements in OCD symptoms (*d* = 1.77 [1.58 to 1.97]), depression (*d* = 1.04 [0.85 to 1.23]), and anxiety (*d* = 1.55 [1.36 to 1.73]). Level of functioning was improved across domains, with medium effect sizes (*d* = 0.51 to 0.72). A majority of patients were completely or mostly satisfied with the treatment, found the online materials to be helpful, experienced the treatment platform as easy to use, and found it easy to communicate with their therapist on the platform. Post-hoc analyses showed that level of seniority, but not increasing experience in working with the treatment specifically, moderated treatment outcomes.

4.5 ETHICAL CONSIDERATIONS

All studies included in this thesis were conducted with ethical approval, and followed the principles of Good Clinical Practice (147) when applicable and declaration of Helsinki (148). Further, all participants in the studies provided written informed consent prior to

being included. Specific ethical considerations at different stages of the studies are reviewed below.

First, several ethical considerations should be considered during study planning. For study I, a power calculation was performed to ensure that the results would be informative. Further, the full trial protocol was pre-registered online at clinicaltrials.gov (NCT02541968) and published before analyses began (149). As a waitlist comparator is not always a defensible choice when there are effective treatment options available, all participants in study I received an active treatment in the form of ICBT or face-to-face CBT. In addition, since the effects of ICBT are not as well established as face-to-face CBT, those who did not respond to ICBT at the 3-month follow-up received extra face-to-face CBT.

To ensure participant wellbeing during treatment, symptoms were continuously monitored weekly or biweekly in studies I and IV, or mid-treatment in study II. Participants rated depressive symptoms and frequency of suicidal thoughts on a weekly or bi-weekly basis, and there were local routines in place to conduct structured suicide risk assessments and provide additional care if needed. Adverse events were assessed and reported in a transparent manner in studies I, II and IV. The procedures in study I were monitored by an external party, Karolinska Trial Alliance, which ensured that the study was conducted in accordance with Good Clinical Practice principles (147).

As all studies included in this thesis involved the management of sensitive information, several measures were in place to ensure the integrity of all participants. First, the online treatment platform used in studies I and IV had a number of security features such as two-factor authentication and using secure servers to store information, and data could only be accessed by authorised study personnel. Data collected during visits at the clinic in studies I and II were stored in locked archive rooms. Second, whenever results were presented and communicated, they were anonymised and analysed at the group level to prevent the identification of individual participants.

The studies were, to the extent possible within the ethical permits, conducted according to open science principles in order to maximise the value generated by the research (150). For example, the statistical analyses used to generate results and figures for all studies were carefully documented and uploaded to online repositories to improve transparency. Further, the results are available to the public through open access publications (studies I, IV) or as open access pre-print versions (studies II, III). The analytic strategy for study I was outlined in the study protocol (149) which was published before data collection was complete and before any analyses on the data started. This commitment to report the results as described in the study protocol limited the influence of what has been called *researcher degrees of freedom*, undisclosed decisions in the reporting of results (151).

5 DISCUSSION

5.1 IS ICBT FOR OCD A NON-INFERIOR AND COST-EFFECTIVE ALTERNATIVE TO FACE-TO-FACE CBT?

The aim of study I was to evaluate the non-inferiority and cost-effectiveness of therapist-guided ICBT and unguided ICBT, compared to face-to-face CBT in a randomised clinical trial. After 14 weeks of treatment, patients in all three groups showed improvements in OCD symptoms, however the non-inferiority results were inconclusive for both ICBT treatments as the confidence intervals crossed the pre-specified margin of 3 points on the Y-BOCS. Both therapist-guided and unguided ICBT were associated with large cost reductions compared to face-to-face CBT, and cost savings remained at the 12-month follow-up after non-responders in both ICBT groups had received additional face-to-face CBT.

The findings from study I extend the literature on digital treatments for OCD by directly comparing the efficacy and cost-effectiveness of guided and unguided ICBT to face-to-face CBT. The results for the therapist-guided treatment are in line with previous studies (118,139), and the efficacy of the unguided ICBT treatment is similar to other minimal contact treatments for OCD (152,153). The non-inferiority margin chosen, 3 points on the Y-BOCS, was more conservative than previous non-inferiority studies in children (154), adolescents (155) and adults with OCD (156), which have chosen margins of 4 or 5 points on the Y-BOCS. Had the non-inferiority margin in study I been set to 5 points, for example, therapist-guided ICBT (but not unguided ICBT) would have been non-inferior to face-to-face CBT.

The choice of a non-inferiority design has implications for how the results should be interpreted. One issue is that the choice of non-inferiority margin can be highly subjective and no strict guidelines exist, but a common recommendation is that the margin should be no more than 50% of the treatment effect of the standard treatment compared to placebo (157). A recent meta-analysis that included six studies comparing CBT to placebo found that the mean difference was 10 points on the Y-BOCS (9), indicating that a non-inferiority margin of up to 5 points is acceptable. A second issue relates to the reporting of results. In superiority trials, intention-to-treat analyses yield conservative estimates of treatment effects because all participants assigned to treatment are included, regardless of adherence. However, in a non-inferiority trial this conservative estimate of treatment effects can increase the probability of a non-inferiority result, and per protocol analysis (including only participants who adhered to the treatment) is recommended as a complement (157). The per protocol analysis in study I (reported in the online supplement) did not alter the conclusions of the non-inferiority evaluation.

Study I incorporated several design choices and procedures to increase the credibility of the results. For example, the same therapists provided treatment in both the therapist-guided ICBT and face-to-face CBT treatments to reduce the influence of individual therapist factors, masking integrity checks indicated that assessors at post-treatment and follow-up were blind to group allocation, and an independent unit monitored that the trial was conducted according to good clinical practice principles. Some limitations should nonetheless be mentioned. First, even though the unguided ICBT treatment did not involve any therapist support, the participants underwent regular assessments before, during, and after treatment, which may have served as reminders to engage with the treatment materials. Second, the exclusion criteria used limit the generalisability to other populations, for example individuals with co-occurring OCD and ASD. Third, the trial was powered to detect group differences on the Y-BOCS which had additional measurement points

compared to secondary outcomes, and findings on secondary outcomes should therefore be considered exploratory.

5.2 IS ADAPTED CBT AN EFFECTIVE TREATMENT FOR ADULTS WITH OCD AND CO-OCCURRING ASD?

After receiving treatment with an adapted CBT protocol, patients showed statistically significant reductions in OCD symptoms with large effect sizes at post-treatment and 3-month follow-up. However, relatively few patients were classified as responders (16%) and being in remission (21%).

The results from study II are in line with two previously published evaluations of the same protocol. In a first pilot study including 24 individuals with OCD and ASD, the authors found that adapted CBT led to larger reductions in OCD symptoms compared to treatment as usual (TAU), with a within-group effect size of $d = 1.01$ (112). In a subsequent study, 46 patients were randomised to either adapted CBT or anxiety management and results were similar with a within-group effect size of $d = 1$ in the adapted CBT group (113).

Despite these promising results, it is clear that further treatment development is needed to improve the modest results seen in study II and previous evaluations of the same protocol. First, homework compliance was relatively low with less than half of the homework assignments completed according to plan. Second, patients did not always attend regular weekly sessions, as the average number of sessions was 16 but the average treatment length was 33 weeks. And third, patients completed 7.9 ERP exercises on average, which is less than what would be expected from an adapted and extended treatment protocol. These limitations indicate that patients in study II may not have gotten an adequate 'dose' of CBT, and specifically ERP—seen as the core component in CBT for OCD—was lacking.

5.3 CAN THE SELF-RATED OCI-R BE USED AS A TOOL FOR TREATMENT EVALUATION?

The objective of study III was to establish empirically derived cut-offs for treatment response and remission on the self-rated OCI-R. The optimal cut-off for treatment response was ≥40% (overall accuracy 75%), and the optimal cut-off for remission status was a total score of ≤8 (overall accuracy 74%).

There are no previous studies that evaluate the psychometric properties of the OCI-R as an indicator of treatment response and remission. The child version of the OCI-R has empirically derived cut-offs for treatment response (≥20-25% reduction) and remission (total score ≤6-8) that are similar to those found in study III (158), but differences between the adult- and child-versions of the OCI make direct comparisons difficult. Previous evaluations of the OCI-R include severity benchmarks (34), sensitivity to change after treatment (33) and cut-offs for clinically significant improvement (159). The results from study III add to the growing literature of pragmatic uses of self-rated measures like the OCI-R when comprehensive clinician-rated assessments are not available.

Multiple limitations in study III deserve mention. First, hoarding symptoms are included as a sub-scale in the OCI-R but hoarding is classified as a separate disorder in the DSM-5 (2). As patients with primarily hoarding symptoms were not included in the studies from which data is taken, this likely has a negative impact on the accuracy of the OCI-R. Second, the participants in the studies were mostly self-referred and thus highly motivated to undergo treatment, which may not be generalisable to patients in regular psychiatric clinics. It is important that the cut-offs found in study III are externally validated in representative samples of OCD patients in clinical practice.

5.4 IS ICBT FOR OCD AN EFFECTIVE TREATMENT WHEN IMPLEMENTED IN THE UNITED KINGDOM?

After treatment with therapist-guided ICBT at three IAPT units in the United Kingdom, there were improvements in self-rated symptoms of OCD, anxiety and depression with large effect sizes. Level of functioning improved in all domains with medium effect sizes, and a majority of participants were completely or mostly satisfied with the treatment.

The gains observed after treatment with OCD-NET are comparable to or larger than reference IAPT data, which includes outcomes for patients that received face-to-face CBT. Initial studies on the therapist-guided ICBT protocol in Sweden and New York, USA, yielded improvements on the OCI-R that are similar to those observed in this trial (118,139,160). Compared to implementations of other digital treatments for OCD in the United Kingdom and Australia, the treatment used in study IV was associated with larger improvements (133–135). However, as the studies were conducted in different contexts with other measures of OCD symptoms, direct comparisons are difficult.

Some limitations should be considered when interpreting the results from study IV. First, since there was no control group it is possible that the observed changes were due to other factors than the treatment itself, for example the passage of time or caregiver attention not specific to the treatment itself. Second, treatment activity was relatively low and promoting engagement remains a challenge in remote treatments. It is likely that some patients did not receive the full 'dose' of treatment as they never reached modules 4 and onward where ERP is introduced. Third, the outcome measurements were made through self-report and evaluations using gold-standard assessments such as the Y-BOCS are needed.

5.5 FUTURE DIRECTIONS

What does the future hold for the psychological treatment of OCD? Any such predictions are likely to have low accuracy, but some interesting new developments regarding the classification of mental disorders, modes of treatment delivery, and targets for treatment are discussed below.

5.5.1 Classifying and understanding mental disorders

Before developing strategies to treat mental disorders, we must understand what kinds of things they are; how we conceptualise mental disorders influences the way we treat them. The dominant model used for classifying mental disorders is represented by the DSM and International Classification of Diseases (ICD) (2,161). In these classification systems, mental disorders are conceptualised as distinct diagnostic categories, where the symptoms seen in mental disorders are caused by an underlying entity (the disorder), but debate about how mental disorders should be classified and understood is not new (162,163). The DSM-III, introduced in 1980, improved upon the previous state of affairs by establishing a lingua franca for classifying mental disorders that could be applied regardless of the theoretical orientation of the clinician (164). The use of structured diagnostic criteria has since then enabled research into the biological, behavioural and cognitive aspects of clearly defined disorders to progress, and treatments have been developed to treat specific disorders. However, issues with the current system includes rampant comorbidity with few distinct markers for individual disorders and large within-disorder variation in symptom profiles (165). Two developments that describe alternative theoretical frameworks, the Hierarchical Taxonomy of Psychopathology (HiTOP) and the network theory of psychopathology, have recently gained traction.

5.5.1.1 Dimensions over categories

Whether mental disorders should be understood as discrete categories or continuous dimensions is a long-standing issue in psychiatry. A summary of the literature found that most latent variables of interest for clinicians are dimensional rather than categorical (166). This view is well in line with research on genetic and environmental risk factors, which often indicate dimensionality (for example the shared genetic risk for obsessive-compulsive symptoms and OCD) (49). Proponents of the dimensional view of psychopathology have also suggested that the dimensions can be organised in a hierarchy. Within this taxonomy, OCD is currently clustered among fear-based disorders (e.g., anxiety disorders such as panic disorder and social anxiety disorder), which are in turn within the internalising cluster (167). This is in contrast with the category "disorders of compulsivity" suggested by the habit formation theory of OCD, where OCD is clustered with eating disorders and addiction (76). However, proponents of the HiTOP classification recognise that the structure of clusters may change over time (168). Interestingly, looming above the current highest level of defined clusters (e.g., internalising disorders and thought disorders) is an additional level of "higher-order dimensions". As some researchers have argued, perhaps there is a common underlying construct, often named the *p-factor*, that represents a general underlying susceptibility for all mental disorders (169,170).

Translated to clinical practice, a dimensional and hierarchical model of psychopathology could result in a stepwise approach to assessment. For example, a clinician may first establish which higher-order cluster best captures the symptoms described by a patient (e.g., internalising or thought cluster) and then move further down the hierarchy (e.g., panic or social anxiety), with increasing specificity at each step of assessment (171). A dimensional approach also suggests the use of trans-diagnostic treatment approaches, for example the Unified Protocol approach which has been found to be effective in treating a range of anxiety disorders by targeting shared mechanisms (e.g., emotion dysregulation) (172). One advantage of a trans-diagnostic approach is that less training is needed for therapists; rather than administering separate interventions for each disorder, therapists would receive training in fewer approaches applicable to multiple disorders. Streamlining therapist training is particularly useful in large-scale implementations such as IAPT where study IV was conducted.

5.5.1.2 Symptoms as networks

The network theory of psychopathology refutes the notion of reductionism beyond symptoms altogether (173). Rather than shifting the emphasis from underlying discrete disorders to continuous dimensions, in this theory symptoms are not seen as passive "output" from an underlying cause, but as active components in a causal network (174,175). For example, certain symptoms may have many links to other symptoms, and if those links are strong those symptoms are central in the network. When two disorders have shared symptoms, the symptoms that link the two disorder networks together are called bridge symptoms (176). An episode of a mental disorder can in this framework be understood as the activation of a network of causally linked symptoms. Once activated, the network of symptoms can then be self-reinforcing and maintain the disorder. Recovery occurs when symptoms deactivate or the links between symptoms weaken (177).

The network theory of psychopathology has been used to understand the comorbidity profiles of OCD and related disorders, but studies investigating mechanisms of treatment are lacking. As mentioned in the introduction, one study found that the symptom clusters associated with OCD and eating disorders were largely distinct from one another with few potential bridge symptoms (25). On the other hand, distress from obsessions is a potential bridge symptom between OCD and depression in patients with both disorders (178).

Participants in study II in this thesis fulfilled diagnostic criteria of both OCD and ASD, and understanding the network structure for patients with this common comorbidity could shed light on potential bridge symptoms or central symptoms that would be prioritised treatment targets. However, there are no such studies to date.

A second application of network analysis is to model symptom networks over time, for example to investigate how they change during the course of treatment. A pioneering study found that, for patients with both depression and insomnia, treatment effects on depressive symptoms are likely indirect through improvements in sleep (179). A recent study compared the effects of CBT and supportive psychotherapy in the treatment of body dysmorphic disorder, and found that both treatments were effective but through distinct mechanisms (180). Network analysis is thus a promising approach to evaluate proposed theoretical mechanisms of treatments. However, the field is still developing and important methodological challenges, for example how to aggregate and compare findings across studies, remain (181).

5.5.2 The opportunities and risks of digital treatments

As the use of smartphones, wearable devices, and computers becomes nearly ubiquitous, there is an opportunity for researchers to analyse the digital traces left on these devices (182). Often combined with machine learning to detect meaningful patterns in the large data sets generated, sensory data and other digital traces include rich information about behaviour and possibly also mental states. For example, it is possible to detect sleep disturbances by analysing patterns of smartphone use (183), predict future depressive episodes by behaviour on social media platforms (184), and accurately monitor symptoms of Parkinson disease using smartphone sensors (185). An advantage of these new sources of data is that they require no additional effort from patients. Interventions based on digital traces could be tailored to the patient's current mood and delivered in a timely fashion, for example suggesting behavioural activation strategies when a depressed individual sleeps more than usual and is not leaving their home (186). Research on such timely and tailored interventions is still in its infancy and, to my knowledge, there are no interventions designed for OCD based on data from smartphone use and sensors.

An alternative approach is adapting existing treatments for delivery via a smartphone. Studies evaluating the use of smartphones to deliver CBT for OCD have shown mixed results (187,188) and there are no randomised controlled trials. A meta-analysis that included 66 randomised trials of app-based interventions for other disorders found small to medium effect sizes compared to control groups (e.g., depressive symptoms $g = 0.28$ [95% CI 0.21 to 0.36]) (189). There are several outstanding issues that need to be addressed before smartphone-based treatments can be recommended as treatment options. First, there is a paucity of high-quality, direct evidence for most apps (190,191). Second, improved data safety is needed to ensure that the sensitive data collected is used with the interests of patients in mind (192,193). Third, user engagement is low with few patients using treatment apps to their full potential (188). To address these challenges, multiple initiatives are now underway, for example websites that provide information about treatment apps (194), establishing standards for smartphone apps and digital mental health (195), and involving patients directly in the design and testing of treatment apps (196).

5.5.3 Broader treatment targets

A third aspect worth considering when reflecting on future directions of the field is which types of outcomes should be assessed. The dominance of symptom reduction as a primary outcome in psychiatry research has led to treatments for mental disorders that are, with a few exceptions, effective in reducing the symptoms associated with the disorders (197).

However, other outcomes are often overlooked and it is unclear to which extent there are spillover effects from CBT for OCD on these distal outcomes (198).

Quality of life and level of functioning outcomes are often measured but are rarely the target of interventions. For example, the treatment studies in this thesis (studies I, II and IV) included measures of quality of life and functional impairment, and while these outcomes improved after treatment, the effects were attenuated compared to the symptom reduction outcomes. Study II in particular demonstrated that reducing symptoms alone may not be sufficient to improve quality of life and general functioning in adults with OCD and ASD. There is some evidence that return-to-work interventions can reduce the number of sickness absence days when added to CBT for depression (199), but such studies in OCD are lacking. In addition to alleviating economic stress for the individual, interventions that improve the ability of individuals with OCD to actively participate on the labour market can have a positive impact on society at large by reducing the burden of disease (200,201).

A second overlooked area is the role of physical exercise in the treatment of OCD. There is now robust evidence to show that OCD is associated with a higher risk of cardiovascular and metabolic complications such as obesity, type 2 diabetes mellitus, and various diseases in the circulatory system (14). Physical exercise can improve symptoms of depression and anxiety (202,203), but high-quality trials in OCD are lacking. Wider health parameters are notably absent from treatment planning and outcome monitoring, and barriers to implementation include insufficient knowledge and training among clinicians (204) and low motivation among patients (205). Seeing as clinician- and patient-related factors may vary between health care contexts and disorders, research into the optimal prescription and delivery of physical exercise interventions in OCD is needed. Viewed more broadly, a widespread integration of physical exercise into mental health care can have a positive impact on mental health (206), cardiovascular and metabolic complications (207), and age-related disease (208).

It should be noted that despite being discussed separately, the outcomes are likely intertwined. For example, gainful employment may result as a consequence of successful treatment of symptoms. However, a work-related context also likely includes corrective information that changes dysfunctional beliefs and disrupts excessive habitual behaviour, thus serving as a catalyst for change in symptoms. Indeed, there is much to learn about the role, timing, and format of add-on interventions that look beyond symptom reduction in the treatment of OCD.

6 CONCLUSIONS

The aim of this thesis was to improve access and outcomes in the treatment of OCD by evaluating an internet-delivered CBT treatment, an adapted CBT treatment for individuals with co-occurring ASD, and evaluate the use of a self-rated questionnaire in measuring treatment outcomes. In short, the four included studies demonstrated that:

- Therapist-guided ICBT, compared to face-to-face CBT, is a cost-effective treatment for adults with OCD. However, the non-inferiority of therapist-guided ICBT could not be conclusively demonstrated.
- Unguided ICBT is probably less efficacious than face-to-face CBT for adults with OCD, but is a cost-effective alternative that requires no therapist input.
- Adapted CBT for adults with OCD and co-occurring ASD is partially effective but further innovations are needed to improve treatment for this group of patients.
- When clinician-administered assessments are not available or are unfeasible, the self-rated OCI-R can be used to evaluate treatment outcomes in OCD.
- Therapist-guided ICBT for OCD is an effective treatment when implemented in IAPT services in the United Kingdom.

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