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Internet-delivered Cognitive Behavior Therapy for Adolescents with Obsessive-Compulsive Disorder

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Internet-delivered Cognitive Behavior Therapy for Adolescents with Obsessive-Compulsive Disorder

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Background: About one in 100 adolescents suffers from obsessive-compulsive disorder (OCD). OCD usually causes severe impairment in social, academic, and family functioning. As OCD often has a chronic course and is associated with a high risk for future psychological problems and disability, it is important to detect and treat the symptoms early in time. Cognitive behavior therapy (CBT) is recommended as the first choice treatment. Unfortunately, most sufferers do not have access to CBT, due to different factors such as limited health care resources and geographical distances. Internet-delivered CBT (ICBT) has been proposed as a solution to make effective treatments more available to patients. The feasibility and efficacy of ICBT are well studied for adults with OCD but have not been established for young people with OCD.

Objective: The main objective of the studies included in this thesis was to develop and evaluate an ICBT intervention for adolescents with OCD. Specifically, we aimed to:

1) test the feasibility and preliminary efficacy of ICBT for OCD in an open pilot study,
2) test the efficacy of ICBT for OCD in a randomized controlled trial,
3) study the cost-effectiveness of ICBT for OCD, and
4) evaluate predictors of treatment response to ICBT for OCD from baseline patient characteristics.

Methods: We developed a novel ICBT intervention for adolescents with OCD and their parents – named "BiP OCD" – and conducted an open pilot study with 21 adolescents with OCD (study I). In the second study, we randomized 67 adolescents with OCD to either ICBT or a waitlist of equal duration (study II). To evaluate the cost-effectiveness of ICBT, we collected cost data on health care utilization, medication use, school absence, and productivity loss in the same sample alongside the randomized controlled trial (study III). All patients that had received ICBT in the randomized controlled trial, either immediately or after the waitlist, were then pooled together (N=61) and analyzed regarding baseline predictors of treatment response three months after ICBT (study IV). Predictor analyses were conducted with classical linear regression as well as with machine learning methodology.

Results: Large within-group effects of ICBT were observed in studies I and II. Between-group comparison with the waitlist group in study II revealed moderately sized treatment effects. Overall, patients were highly satisfied with the intervention. The average clinician time was below 20 minutes per patient and week. Study III identified cost-saving effects of ICBT when compared with untreated patients on the waitlist, indicating that it is more costly for society to not treat those patients than to offer ICBT. In study IV, linear regression analyses could not identify any predictors for ICBT treatment response. However, machine learning algorithms predicted treatment response with high accuracy.

Conclusions: The results presented in this thesis provide support for the feasibility, efficacy, and cost-effectiveness of ICBT for adolescent OCD. Machine learning methodology is a

novel, promising statistical approach that could guide us to more accurate predictions of treatment outcome. The results warrant replication in larger clinical samples and in comparison with active control conditions as well as face-to-face CBT.

LIST OF SCIENTIFIC PAPERS

I. Lenhard, F., Vigerland, S., Andersson, E., Rück, C., Mataix-Cols, D., Thulin, U., Ljótsson, B., Serlachius, E. (2014). Internet-delivered cognitive behavior therapy for adolescents with obsessive-compulsive disorder: An open trial. *PLoS ONE*, *9*(6), e100773.

II. Lenhard, F., Andersson, E., Mataix-Cols, D., Rück, C., Vigerland, S., Högström, J., Hillborg, M., Brander, G., Ljungström, M., Ljótsson, B., Serlachius, E. (2017). Therapist-Guided, Internet-Delivered Cognitive-Behavioral Therapy for Adolescents With Obsessive-Compulsive Disorder: A Randomized Controlled Trial. *Journal of the American Academy of Child & Adolescent Psychiatry*, *56*(1), 10–19.e2.

III. Lenhard, F., Ssegonja, R., Andersson, E., Feldman, I., Rück, C., Mataix-Cols, D., Serlachius, E. (submitted manuscript). Cost-effectiveness of therapist-guided Internet-delivered Cognitive Behavior Therapy for pediatric Obsessive-Compulsive Disorder: Results from a Randomized Controlled Trial.

IV. Lenhard, F., Sauer, S., Andersson, E., Rück, C., Mataix-Cols, D., Månsson, K.N.T., Serlachius, E. (manuscript). Predictors of Outcome in Internet-delivered Cognitive Behavior Therapy for pediatric Obsessive-Compulsive Disorder: A Machine Learning Approach.

CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention-Deficit/Hyperactivity Disorder
AUC	Area under the curve
BiP	Barninternetprojektet
CBT	Cognitive Behavior Therapy
CR	Conditioned Reaction
CS	Conditioned Stimulus
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
ERP	Exposure and Response Prevention
ICBT	Internet-delivered Cognitive Behavior Therapy
OCD	Obsessive-Compulsive Disorder
RCT	Randomized Controlled Trial
SRI	Serotonin Reuptake Inhibitor
UCR	Unconditioned Reaction
UCS	Unconditioned Stimulus
QALY	Quality of life Adjusted Life Years

1 INTRODUCTION

Having a background as a clinical psychologist, I have experienced the problems that mental health services struggle with on a day-to-day basis. The high demand for child and adolescent mental health care at our local unit, with many families that were seeking help, had to somehow be balanced with the limited time in the schedules of the available clinicians. Regularly this led to tough decisions about which families could get earlier appointments and which patients had to wait a bit longer. Over the years, this situation got more and more challenging, with more children and adolescents seeking specialized treatment for their difficulties in a problematic combination with limited resources available at the clinic. It appears that the increasing demand for mental health care is not just affecting the health care services in Stockholm, but is an international trend that burdens many countries' health care systems.

Since I have come in contact with e-health and Internet-delivered treatments I firmly believe that one solution to the dilemmas of modern mental health care will come from innovation and development of new technologies. Gladly, the results in the field of Internet-delivered cognitive behavior therapy (ICBT), including the results presented in this thesis, are promising. The available research indicates that these innovative treatments work, and also that they could save precious time, resources, and costs for health care providers and society. Nevertheless, ICBT is not yet available for children and adolescents.

The prerequisites leading up to the current PhD project were a combination of my own personal and professional frustration over an over-burdened child and adolescent mental health care system, an unusual high concentration of ICBT and obsessive-compulsive disorder (OCD) experts in the Stockholm area, and a critical mass of academic and clinical decision makers that were willing to open up a window of opportunity for the development of this new Internet-delivered treatment for pediatric OCD.

Thanks to this fortunate combination of factors, I have been able to study some of the most relevant questions that one might ask about ICBT for adolescents with OCD, namely "Does it work?", "Who does it work for?," and "Could this be a way to use our limited health care resources more efficiently?". The results presented in this thesis are of course limited by design and method, but provide us with preliminary answers to these important questions and also indicate how to continue the scientific evaluation of this novel intervention.

Importantly, there are currently several initiatives, from ongoing international research in the field of ICBT for children and adolescents to the nationwide implementation of an e-health platform in Sweden, which will further increase the probability that the results presented in this thesis will actually be of use in clinical settings and will contribute to increase the availability of effective care for children and adolescents with mental health problems.

2 BACKGROUND

2.1 CHARACTERISTICS OF PEDIATRIC OBSESSIVE-COMPULSIVE DISORDER

2.1.1 Diagnostic features, prevalence, and course of pediatric OCD

Obsessive-compulsive disorder (OCD) is characterized by recurrent, anxiety provoking thoughts or images (obsessions) and compulsive behaviors or rituals (compulsions), often aimed to prevent a dreaded event or feeling of distress [1]. Typical examples of obsessions are fearful thoughts of being contaminated, catching a disease, or causing harm to others. Typical compulsions are ritualistic checking and excessive washing behaviors. OCD affects one to two out of 100 children [2,3], and similar prevalence rates are also found in the adult population [4,5]. Symptom onset occurs most often before the age of 25 and about 30 to 80% of patients are affected in childhood or adolescence [6,7]. Interestingly, there appear to be two peaks of onset, one in childhood, about the age of 11, and one in early adulthood, around the age of 23 [8].

As prevalence rates from childhood to adulthood do not increase very much, some have speculated that the natural course of OCD is not chronic for all youth, as we otherwise should see accumulating prevalence rates across the lifespan [9]. Indeed, long-term follow-up studies show that only some OCD patients experience a chronic course: 40 to 60% have persisting symptoms in the long-term [9,10]. It should be noted that these rates were observed in treated patients, and little is known about the natural course of OCD in untreated individuals. Studies from the adult field indicate that at least 50% of cases face a chronic course if left untreated [11,12].

The presence of comorbid psychiatric diagnoses is the rule rather than the exception, and more than half of children and adolescents with OCD have also other mental health conditions [13]. Increased rates of major depression, anxiety disorders, tic disorders, disruptive behavior, attention-deficit/hyperactivity disorder (ADHD), and mania have been reported [13]. Moreover, OCD in childhood increases the risk of mental health problems in adulthood [14] and is as well associated with higher risk of suicide, compared to individuals without OCD [15].

2.1.2 Impairment and societal impact of OCD

Pediatric OCD is commonly associated with severe impairments in academic, social, and family functioning, with 90% of children and adolescents experiencing OCD-related dysfunction in everyday life [16]. OCD often has negative effects on family life and the parents' everyday functioning, with about half of mothers and one-third of fathers reporting daily occupational impairment due to the child's symptoms [17]. In adulthood, individuals with OCD are more likely to be unemployed, have lower socioeconomic status and income, are less likely to be married and report in general poorer social and occupational functioning than non-affected controls and individuals with anxiety or mood disorders [18].

On a societal level, OCD has been found to generate large direct costs due to health care utilization, but even larger indirect costs due to loss of income, sick leave, and unemployment

[19]. In a study from the U.S., the total cost of OCD was estimated to be $8.4 billion in 1990, 5.7% of the costs of all mental illness, and 18% of the costs of all anxiety disorders [20]. Data from Medicaid-insured patients in the U.S. suggest that the health care costs of OCD are comparable to those found in depression [21]. These numbers indicate that OCD is associated with a significant burden for health care and national budgets, even though more updated cost estimates are needed as well as estimates for European and Scandinavian settings.

2.1.3 Etiology and maintenance of pediatric OCD

Despite extensive research efforts, the exact causes of OCD are relatively unclear. The etiology of OCD is currently understood as a multifaceted interplay between environmental, genetic, and neurofunctional factors (see **Figure 1**). About half of the variance of OCD symptoms is under genetic influence, half under influence of unique environmental factors [22,23]. OCD has a tendency to cluster in families, primarily due to the genetic heritability of the condition, with first-degree relatives having a 5-fold risk of developing OCD [23,24]. Genetic studies indicate a multifactorial interplay between the serotonergic, dopaminergic, and glutamatergic neurotransmitter systems [24].

Environmental risk factors are still poorly understood but are likely to play a role. There is some evidence that perinatal complications [25], stressful life events, and factors related to the reproductive cycle could affect the risk for OCD [26]. Moreover, environmental factors may also play a role in epigenetic mechanisms that turn relevant genes on or off [24].

Some consensus exists about the conceptualization of OCD as a neuropsychological condition, with a neurofunctional circuit that involves cortical, striatal, and thalamic regions – also known as the cortico–striato–thalamo–cortical model of OCD [24].

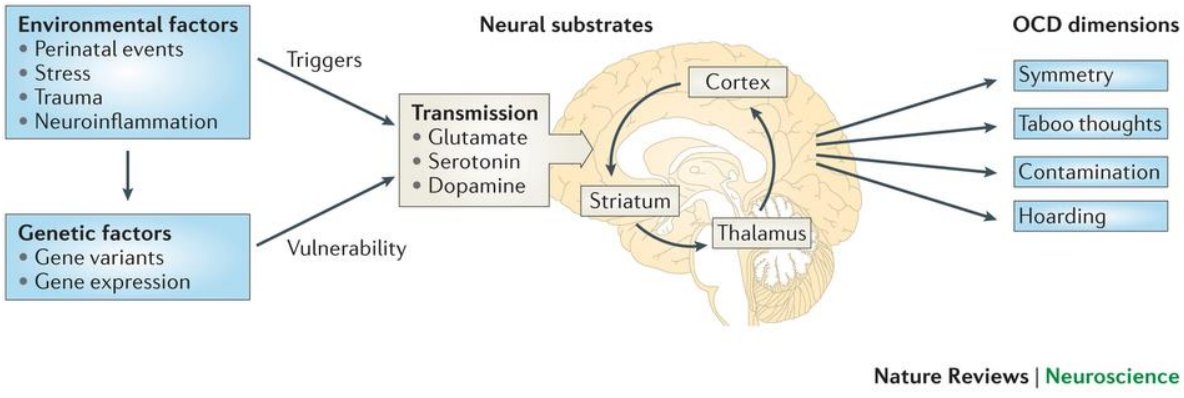

Figure 1: An integrative model of genetics, environment, and neurobiology for the expression of OCD
(reprint from Pauls DL, Abramovitch A, Rauch SL, *et al.* Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective. *Nat Rev Neurosci* 2014;**15**:410–24. doi:10.1038/nrn3746 with permission from the Nature Publishing Group)

Psychological models have aimed to explain the self-maintaining nature of OCD, and have later on contributed to the development of effective psychological treatments. Initially, psychological theories of learning had difficulties in defining the mechanisms of anxiety and

OCD symptoms. The classical pavlovian (learning of behavior through the association of two stimuli) and skinnerian (learning of behavior as a consequence of reinforcement) models predict that a behavior would vanish if not further maintained by association or reinforcement – when, in fact, a typical OCD ritual is maintained and frequently repeated without additional pairing with the original stimulus or any further reinforcement in the skinnerian sense.

The two stage theory of Mowrer [27] expanded the previous learning theories in order to explain fear acquisition and maintenance more accurately (see **Figure 2**). The theory proposed, and demonstrated in animal models, that fear (distress/anxiety) can be acquired in a first step just as Pavlov would have expected it: a previously neutral stimulus (conditioned stimulus, CS = a bell) can acquire fearful properties when associated repeatedly with a fear-eliciting stimulus (unconditioned stimulus, USC = electric shock). In the second step of his theory, Mowrer demonstrated that a learned avoidance behavior (such as a ritual) reduces the distressing emotion and therefore the avoidance behavior is reinforced through the mechanism that we call negative reinforcement. The distress reducing nature of compulsions was later confirmed in a series of lab experiments in humans with OCD [28,29]. In other words, rituals and compulsive behaviors are maintained as they indeed reduce anxiety and distress in the short term.

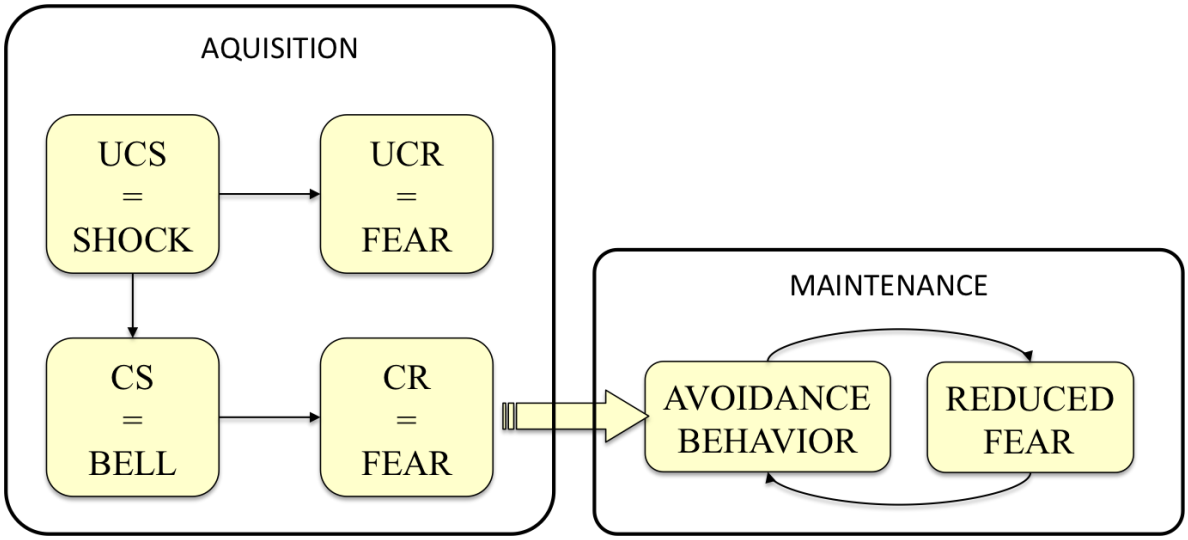

Figure 2: Mowrer's two factor theory
(*Abbreviations*: UCS = unconditioned stimulus; CS = conditioned stimulus; UCR = unconditioned response; CR = conditioned response)

In the 1980's, the behavioristic understanding of OCD was further expanded with a cognitive perspective, underlining that individuals with OCD show typical, erroneous cognitions about the harmfulness of negative outcomes, as well as exaggerated feelings of responsibility for one's thoughts and actions in order to prevent oneself or others from harm [30,31]. It has been demonstrated that unwanted intrusive thoughts or images, as typically found in OCD, are very common in the general population [32]. This emphasizes the notion that intrusive thoughts

are a common phenomenon, and unproblematic for most of us. It is therefore not the occurrence of intrusive thoughts per se, but rather the appraisal of those thoughts as important, unacceptable, immoral, or threatening that creates problematic consequences and symptoms [33].

The current psychological model of OCD integrates cognitive and behavioral mechanisms and can be described as a self-maintaining sequence of events (see **Figure 3)**: Normal cognitive content (e.g. "Have I turned off the stove?") is misinterpreted as threatening ("The house will burn down!"), amplified by maladaptive core beliefs ("I have 100% responsibility to always protect others from harm."). This triggers anxiety and the urge to counteract the obsessive cognitions and feared consequences of one's actions. In the short term, anxiety is reduced by rituals (e.g. repeatedly checking the stove), but in the long term, the cognitive and behavioral drivers of obsessions and compulsions are maintained in a circular manner [33].

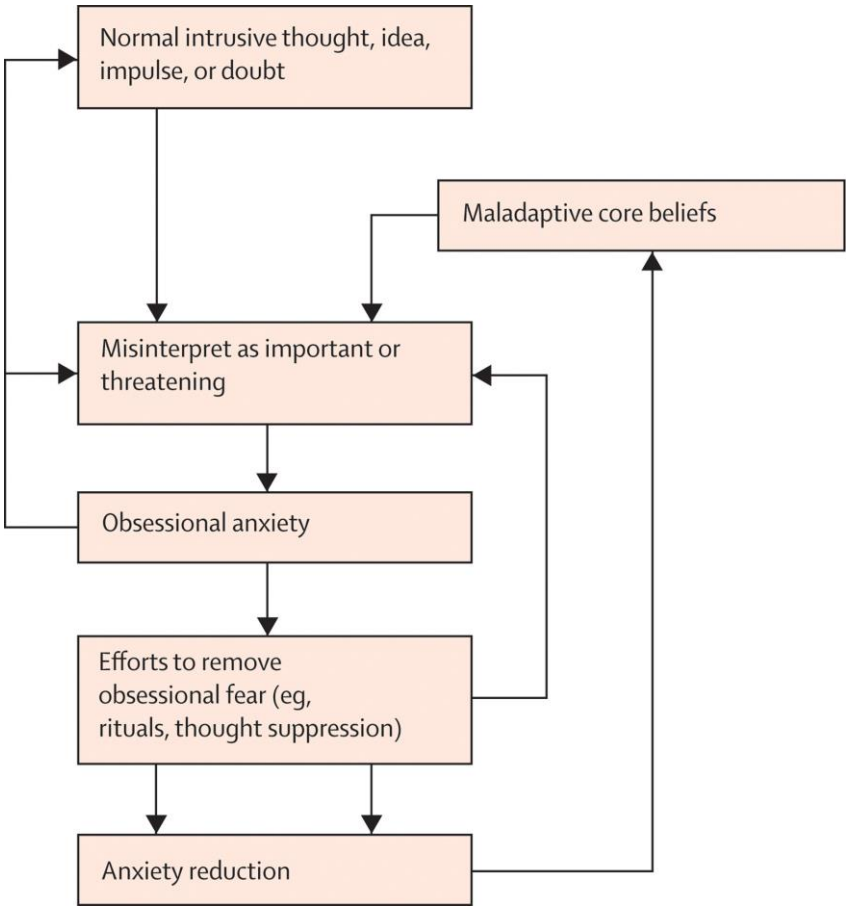

Figure 3: Cognitive behavioral model of OCD

(reprint of Abramowitz JS, Taylor S, McKay D. Obsessive-compulsive disorder. *Lancet* 2009;**374**:491–9. doi:10.1016/S0140-6736(09)60240-3 with permission from Elsevier)

2.2 EVIDENCE-BASED TREATMENTS FOR PEDIATRIC OCD

2.2.1 Cognitive behavior therapy

In the past, OCD was considered an untreatable condition. As late as in the early 1980's, it was stated that *"OCD is notoriously difficult to treat. The abundance of therapeutic approaches available indicates that none is clearly effective in the majority of cases"* (Jenike, 1983, p. 105) [34]. However, the first report of successful OCD treatment can be dated back to 1966. In a case study by Mayer, a new therapeutic approach involving "modification of expectations" and "reality testing" was presented [35]. Even if it should take more than two decades to make Mayer's method known to a broader audience, the method described in his early report became later the gold standard of psychological treatment for OCD and is today known under the term exposure and response prevention (ERP).

In short, ERP consists of 1) exposure to the obsession-eliciting stimulus (e.g. touching a doorknob, and by that triggering intrusive thoughts about germs) combined with 2) the prevention of compulsions or rituals (e.g. not washing the hands despite intrusive thoughts about disease and strong discomfort). ERP is typically done in a gradual, systematic manner over the course of 12 to 14 weeks, and is the main ingredient of the recommended cognitive behavior therapy (CBT) regimen according to clinical expert guidelines [36–38]. Apart from ERP, CBT protocols usually also include psychoeducation, cognitive strategies, and relapse prevention [39]. Little is known about the specific effect of each of those treatment components, though there is a broad consensus that ERP is a necessary ingredient in good-quality CBT for OCD [40,41].

Some controversy exists about what underlying mechanisms in ERP cause the decrease in symptoms that we observe as a result of ERP-based CBT. The most prominent and accepted theory is Foa and Kozak's emotional processing theory [42]. It poses that ERP yields a "corrective learning" process through the initial activation of fear through the feared stimulus and gradual habituation in prolonged presence of the stimulus. Through repetitive exposure to the feared stimulus, as well as subsequent habituation, new, non-fear based information is integrated and replaces the previous fear-based associations. However, it should be mentioned that there have been some criticisms of the emotional processing theory lately and inhibitory learning approaches have been suggested instead. The inhibitory learning model states that fear associations, once learned, do not vanish as a result of exposure, but rather coexist with the new non-fear associations [43]. The model implies a different set of therapeutic strategies, such as creating a maximal discrepancy between and the patient's expectations and the outcome of an ERP exercise, and not necessarily increasing the difficulty of ERP exercises gradually but instead focusing on variability between ERP tasks, which perhaps has beneficial effects for the long-term treatment outcomes [44].

Overall, there is a broad evidence base for the treatment of OCD with CBT, with currently 37 randomized controlled trials (RCTs) in the adult field [45] and 25 in the child and adolescent field [46]. CBT is effective for the majority of children and adolescents with OCD, with about

70% responding to treatment (for comparison, only 9% respond to non-active comparison conditions and 23% to other non-CBT active comparison conditions) [47].

2.2.2 Prediction of CBT treatment outcome in pediatric OCD

Regarding recommendations of which children and adolescents with OCD should be offered CBT, there have been numerous attempts to find reliable predictors of treatment outcome. Prediction studies aim to identify patient characteristics that either increase or decrease the probability of a treatment to be effective, which is important knowledge in order to not offer patients treatment alternatives that are likely to be ineffective. For example, a hypothesis could be that patients with more severe OCD symptoms and several comorbid diagnoses would benefit less from CBT than patients with mild symptoms and no comorbidity.

A summary of previous pediatric OCD prediction studies of CBT outcome from 1995 to 2014 [10,37,48–59] shows that a wide variety of potential predictors of CBT outcome has been studied (see **Table 1**).

Table 1: Summary of significant and non-significant results of previous prediction studies

		Frequency of significant results	Frequency of non-significant results
Demographic variables	Sex	*	xxxxxx
	Age	*	xxxxxx
	Household income/SES		xx
OCD related variables	OCD severity	****	xxxx
	OCD functional impairment	***	xx
	Social adjustment		x
	Onset of OCD		xxx
	Duration of OCD	**	xx
	Insight	*	
	OCD dimensions		x
Comorbidity	Externalizing comorbidity	*	xxx
	Comorbid anxiety		xxxxxx
	Comorbid depression		xxxxx
	Comorbid tics	*	xxx
Family variables	Family accommodation	**	x
	Family dysfunction	**	x
	Family history of OCD		xxx
	Parental psychopathology		xxx
Other	Medication		xxx
	Therapist experience		x
	Therapy adherence	*	x

Note: SES = socioeconomic status;

* = variable has been studied and found a significant predictor of CBT treatment outcome;

x = variable has been studied and was not found a significant predictor of CBT treatment outcome

As can be seen in **Table 1**, the results within the prediction field are largely inconclusive and, currently, there are no reliable clinical or demographic variables that consistently predict outcome across different studies [60]. There could be methodological reasons for this, such as suboptimal predictor selection and measurement, choice and power of the chosen statistical

method, and choice and operationalization of outcome variables [60,61]. To overcome those methodological limitations, it has been suggested to introduce novel machine learning methods when studying predictors [62]. Machine learning is a family of statistical methods with the potential to model complex linear and non-linear data. Machine learning has, for example, been widely explored within the field of cancer prognosis, with over 1.000 published articles on the topic [63]. Currently, machine learning has only been very sparsely applied to the prediction of OCD treatment outcome, with the exception of one study in which remission could be successfully predicted with an accuracy of 75% in a large sample of adults with OCD [64]. Clearly, there is a need for the development of reliable methods to inform clinicians and researchers about which patients have the best chances to benefit from CBT.

2.2.3 Pharmacological treatment

Serotonin reuptake inhibitors (SRIs) are recommended as a secondary treatment alternative for pediatric OCD, either as monotherapy or in conjunction with CBT as a combined treatment [36–38]. SRIs are effective for a substantial proportion of patients, with 50% treatment responders (versus 25% treatment responders in placebo conditions) [47].

A common recommendation is that severe cases of OCD should receive combination treatment of CBT and SRIs [37]. However, that recommendation appears to be based on one single trial [65], and it has in fact not been demonstrated in the results of the study that combination treatment is superior in severe OCD cases. Recent meta-analyses have concluded that there is no empirical evidence that the combination of CBT and SRIs would be more effective than CBT monotherapy [46,66]. SRIs are however an important treatment alternative when CBT is not available, or as part of a clinical strategy in personalized multimodal treatment.

2.3 THE DILEMMA OF ACCESSIBILITY

Considering that about 20% of children and adolescents suffer from a mental disorder [67] and that half of all adult mental disorders have an onset before the age of 15 [68], the early detection and treatment of childhood psychological disorders is an important public health question. Evidence-based psychological interventions for the treatment of pediatric mental disorders exist. However, many sufferers do not receive those treatments, presumably as a consequence of limited therapeutic resources and access to them [67,69].

In the case of OCD, there are large geographic inequalities regarding the availability of proper assessment and treatment [69,70], and a majority of cases are not detected by the health care system [71]. In addition, diagnosed OCD cases are seldom treated with effective psychological interventions [72]. As a result, many patients' suffering is prolonged. For instance, one study in adults with OCD found that the delay from OCD symptom onset (12 years of age) to receiving effective treatment was on average 17 years [73]. A study in children indicated that the delay from OCD onset to receiving treatment was about 3.5 years [10].

Little is known about the treatment barriers that keep children and adolescents with OCD from receiving effective treatment. Studies from the adult field have identified several treatment barriers, including treatment costs [74], lack of insurance coverage [74], doubt about treatment being beneficial [74,75], belonging to an ethnic minority [75,76], as well as shame and stigma [74,77]. An obvious but understudied barrier is whether families live geographically close to those mental health services that provide adequate treatment [78].

Moreover, the implementation of evidence-based practices within health care has been lagging behind due to organizational challenges [79]. Studies indicate that when implemented in regular health care, CBT often is delivered with suboptimal quality [80]. In fact, one study showed that, of the clinicians that offer CBT for pediatric OCD, only one third would provide effective ERP-based treatment [72]. Another study found that 95.5% of youth with OCD had received inadequate CBT in primary psychiatric care prior to referral to a specialized clinic [81].

2.4 INTERNET-DELIVERED COGNITIVE BEHAVIOR THERAPY

Given the challenges of implementation of evidence-based care and the low accessibility of good quality CBT, the development of e-health and Internet-delivered mental health interventions has been proposed [82]. Internet-delivered Cognitive Behavior Therapy (ICBT) has emerged as a cross-disciplinary development of psychological intervention research and modern information technology. The content and treatment components of ICBT are not different from regular CBT, the only difference being that ICBT is presented to the patient via the Internet [83]. The ICBT format is very similar to that of an Internet e-learning course, with educative texts, visual material such as images and videos, exercises to work with and, if therapist support is included, e-mail functionality.

Internet-delivered interventions have the potential to make evidence-based treatments more accessible to patients, as those interventions are less bound to temporal and geographical barriers. The main additional advantage of ICBT over other innovative formats such as treatments given via the telephone [84] or web-camera [85] is that therapist times can be markedly reduced to on average 10 to 20 minutes per patient/week [86]. Some studies have tested a self-guided ICBT model without therapist support, which of course, even more, minimizes the resources required from health care. However, meta-analytic results from the adult OCD field indicate that interventions with therapist contact yield larger effect sizes and lower dropout rates than pure self-guided interventions [87]. Yet, there is little available evidence regarding this question from the child and adolescent ICBT field [88].

Overall, there is a substantial body of evidence for ICBT in adult patient populations with several systematic reviews and over 100 RCTs indicating effectiveness for various psychiatric conditions [89–91]. Studies have consistently demonstrated positive results of Internet-based treatments' efficacy compared to non-active controls, but have also been able to show results comparable to standard face-to-face CBT [92]. In addition, there have been rare but highly successful examples of implementation of ICBT in regular mental health care for adults in Sweden, Australia, and the Netherlands [93–95].

In the OCD field there have been several ICBT studies on adult patients that have repeatedly shown effects comparable to face-to-face CBT with large effect sizes and about 50 to 60% treatment responders [86,96–99], and sustained long-term effects up to two years after treatment [100]. Previous to the trials presented in this thesis, no study had demonstrated the efficacy of ICBT for children or adolescents with OCD.

2.4.1 ICBT for children and adolescents

Despite the fact that children and adolescents are the most active age group on the Internet, with a usage of over 90% [101], research on ICBT for pediatric patient populations has been significantly lagging behind.

A comprehensive systematic review and meta-analysis from 2016 included both randomized and non-randomized ICBT studies from the child and adolescent field and identified twenty-five studies [88]. About half of the studies concerned somatic conditions, targeting, for example, overweight and pain disorders. The other half of the studies corresponded to the psychiatric field, with anxiety disorders being the most frequently studied diagnostic area.

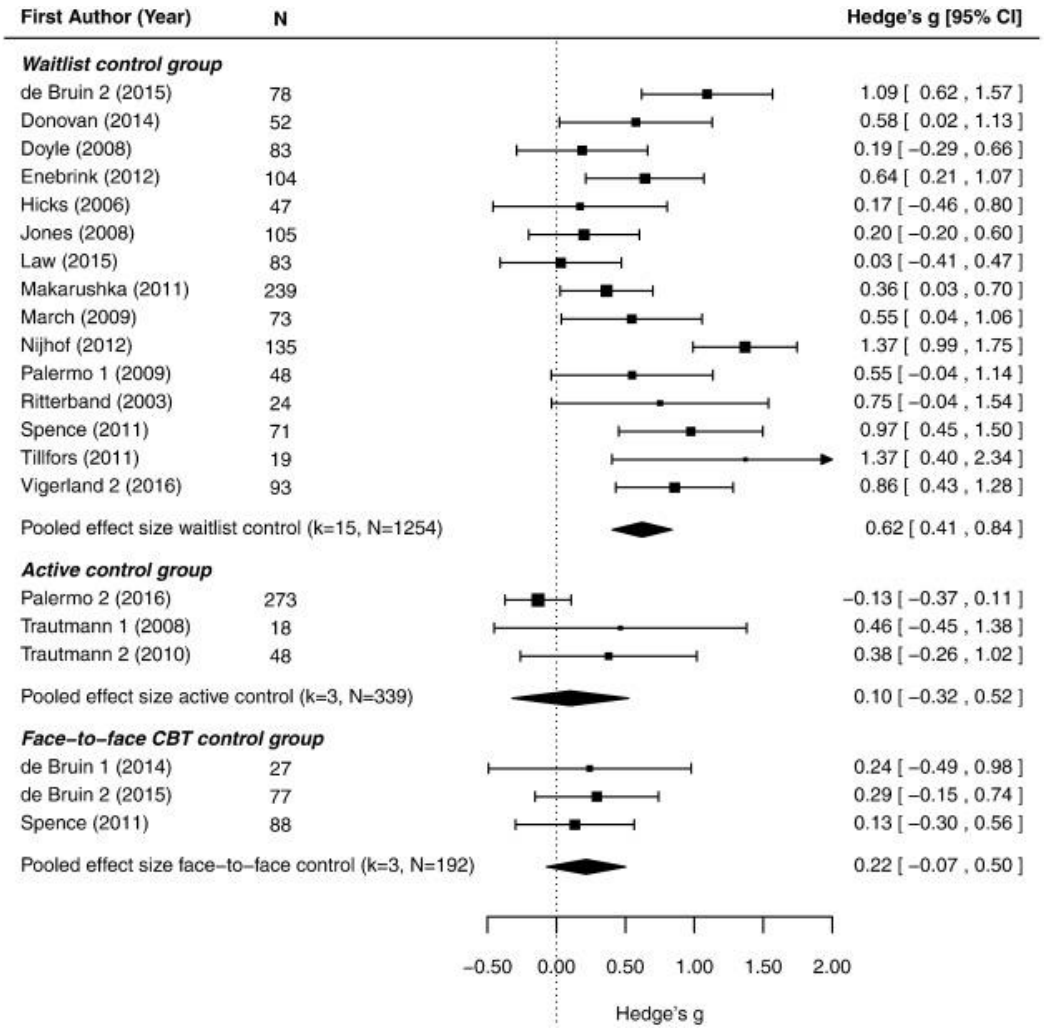

Figure 4: Between-group effect sizes of ICBT in children and adolescents compared to waitlist, active control and face-to-face CBT

(reprint from Vigerland S, Lenhard F, Bonnert M, Lalouni, M *et al*. Internet-delivered cognitive behavior therapy for children and adolescents: A systematic review and meta-analysis. *Clin Psychol Rev* 2016;**50**:1–10. doi:10.1016/j.cpr.2016.09.005, creative commons license)

Figure 4 presents the between-group effect sizes from the meta-analysis, comparing ICBT to waitlist, active control conditions, or face-to-face CBT. The effect size for ICBT when compared to waitlist was moderate. The comparisons with active control conditions and face-to-face CBT were few, with only three studies each, and conclusions from those comparisons were therefore rather limited. Several methodological weaknesses were found in the field, e.g. several trials with unblinded assessors, not reporting intent-to-treat analyses and no monitoring of adverse events. The authors highlighted the need for more rigorously conducted studies and warranted more systematic reporting of core features of ICBT such as therapist times, cost-effectiveness, and geographic reach [88].

To conclude, ICBT appears to be a promising intervention for children and adolescents with various mental health conditions, but it is currently unclear whether ICBT could be effective for pediatric OCD.

2.4.2 Cost-effectiveness of ICBT

A health care intervention is considered cost-effective if it yields better outcomes than another intervention in relation to the costs that each intervention is associated with [102]. In other words, if a new intervention A yields better outcomes than the standard intervention B, and intervention A is cheaper than B, then A is more cost-effective. In situations where a new intervention is more expensive but also more effective than the standard intervention, an evaluation has to be made to decide whether the additional benefits of the new intervention are worth the additional costs. This is determined by the health care system's "willingness to pay" for the additional effect of the more expensive intervention [102]. Costs can be estimated on different levels (e.g. costs for the individual, costs for the health care sector, or costs for society as a whole).

In ICBT, it would be reasonable to assume that cost savings can be made, given the Internet-delivered format which does not require the patients and parents to travel to the clinic and does not interfere with school or working times in the same way than regular CBT. Also, therapist times are usually reduced, compared to face-to-face interventions, indicating cost savings for the health care system [89].

A systematic review of ICBT for adult patient populations concludes that ICBT probably is a cost-effective intervention when compared to no treatment control conditions [89]. In addition, a study in adult social anxiety disorder demonstrated that ICBT was equally effective but more cost-saving than face-to-face CBT [103]. To the best of my knowledge, there are currently no published studies that have presented data on the cost-effectiveness of ICBT in the pediatric anxiety or OCD and related disorders field.

Importantly, it should be mentioned that there is very little knowledge about the cost-effectiveness of gold standard face-to-face CBT or pharmacological treatments for pediatric OCD. A comprehensive systematic review done by the UK National Institute of Health Research in 2016 did not find any empirical cost-effectiveness data on standard face-to-face CBT or SRI treatment for pediatric OCD [104]. This highlights the need to not only evaluate novel interventions, but also the established gold standard treatments from a health economic perspective.

3 RESEARCH QUESTIONS

The objective of this Ph.D. project was to develop and evaluate a novel ICBT treatment for adolescents with OCD. The project aimed to answer the following questions:

1. Is ICBT a feasible and effective treatment for adolescents with OCD?
2. Is ICBT for pediatric OCD associated with health-economic benefits for society and health care providers?
3. Which OCD patients does this treatment work for?

In order to answer these questions, the project was divided into four different studies:

Study I: Development and test of the feasibility of ICBT for pediatric OCD in a pilot study

Study II: Evaluation of the effectiveness of ICBT in a randomized controlled trial

Study III: Analysis of cost-effectiveness of ICBT compared to untreated patients (same study sample as study II)

Study IV: Analysis of predictors of treatment outcome (same sample as study II)

4 THE EMPIRICAL STUDIES

4.1 THE ICBT INTERVENTION

The ICBT platform, called BiP platform (Barninternetprojektet), was initially built in 2010 and specially tailored to accommodate the needs and graphical preferences of children and adolescents. Since then, the BiP platform has been used in several ICBT projects for children with anxiety [105,106] and adolescents with irritable bowel syndrome [107,108], and is currently being used in ongoing trials for children and adolescents with OCD, tics/Tourette's syndrome, social anxiety disorder, excessive worry, functional gastrointestinal disorders, and self-harm. The platform has continuously been optimized regarding graphical appearance and functionality and can be used for the presentation of written text, video and audio material, images, forms to fill in, and functionality for communication with clinicians through e-mails and comments.

The ICBT content of the OCD intervention, "BiP OCD", was developed in 2012. BiP OCD is completely web-based and involves both the adolescent as well as the parents. The 12-week intervention consists of 12 chapters that contain texts to read and films and illustrations to watch, as well as different kinds of exercises for the adolescents to do on their own and together with the parent. The content of BiP OCD is in line with expert recommendations of CBT for pediatric OCD [37,109]. It is divided into three treatment phases (see **Table 2**), starting with psychoeducation regarding OCD and the rationale for cognitive behavioral interventions. The second phase is the main part of the treatment and contains behavioral interventions, mainly ERP, as well as cognitive restructuring. Phase three addresses problem solving, maintenance of treatment gains, and relapse prevention. Through a separate login, parents get access to material that focuses on parent-specific content, such as family accommodation, parental coping strategies, and how to support the adolescent to adhere to the treatment and practice ERP. During the treatment period, participants have regular contact with the therapist through e-mails, standardized forms, and occasional phone calls.

Table 2: An overview of the content of BiP OCD

Treatment phase	Chapter	Parent chapters	Adolescent chapters
Psychoeducation	1	Introduction to ICBT	Introduction to ICBT
	2	About OCD	What is OCD?
	3		We are cracking the code: The OCD circle
	4	Exposure and response prevention	Building a hierarchy
Exposure and response prevention (ERP)	5		Testing exposure
	6	Being an exposure coach	Planning your ERP training
	7		New steps with ERP
	8	When the family has OCD	ERP – frequent problems and solutions
	9		More new steps with ERP
	10		Talking back to OCD - Coping with obsessions
Relapse prevention	11		The final sprint
	12		Your treatment in the rear-view mirror

BiP OCD was initially tested in an open pilot trial, study I [110], and has been further developed between study I and study II [111]. Besides a general update of the material, a smartphone application was added to support the intervention. The smartphone app was designed with functionality to plan and register ERP exercises. **Figure 5** displays screenshots from BiP OCD.

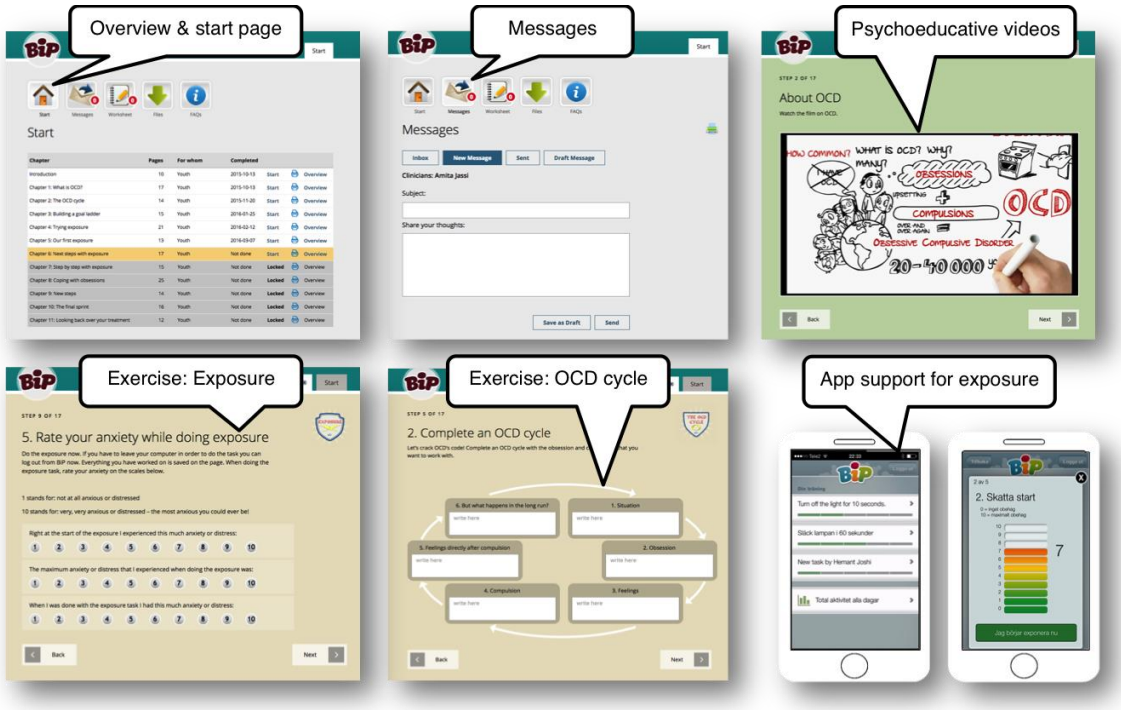

Figure 5: Screenshots from BiP OCD

4.2 STUDY I: FEASIBILITY OF ICBT FOR ADOLESCENTS WITH OCD

Aim

The primary aim was to test the feasibility and within-group efficacy of the ICBT intervention. The study was also a way to collect information about how to further improve the intervention, as well as to guide proper sample size calculations for the subsequent RCT.

Methods

We conducted an open trial with twenty-one adolescents with OCD aged 12 to 17. All patients received ICBT. The primary outcome was the clinician-rated Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) [112] administered before, after, and three and six months after treatment. Secondary outcomes were self- and parent-rated measures of OCD, comorbid symptoms, and impairment.

Main results

ICBT yielded significant symptom severity reductions on the CY-BOCS with large within-group effect sizes from pre- to post-treatment (*d*=2.29 [95% *CI* 1.5–3.07]) and 57% treatment responders. Additional symptom reductions were observed at the 3-month follow-up, where 71% of patients reached responder status. Significant reductions were also found on patient- and parent-rated measures of OCD severity and impairment, as well as on measures of comorbid anxiety, depression, and family accommodation. The average therapist time spent per patient and week was 19.5 minutes. The ICBT intervention received good to very good satisfaction ratings from the patients.

4.3 STUDY II: EFFICACY OF ICBT FOR ADOLESCENTS WITH OCD

Aim

This study aimed to test the efficacy of ICBT for adolescent OCD in a randomized controlled study design. In addition, adverse events, clinician times, and geographic reach were measured.

Methods

Sixty-seven adolescents with OCD aged 12 to 17 years were randomly assigned to either ICBT or a waitlist for a period of 12 weeks each. Patients on the waitlist crossed over to ICBT after the initial 12 weeks. Measures were taken at pre-, post-, and three months after treatment. The primary outcome measure was the clinician-rated CY-BOCS [112], administered by blinded raters. Secondary outcomes were self- and parent-rated measures of OCD, comorbid symptoms, and impairment.

Main results

ICBT was superior over the waitlist in reducing OCD symptom severity with a moderate between-group effect size (*d*=0.69 [95% *CI* 0.19–1.18]) and 27% treatment responders, compared to 0% in the waitlist. Patients continued to improve on the CY-BOCS from post-treatment to the 3-month follow-up, with 32% responders at that time point. Patients on the waitlist that crossed over to ICBT demonstrated a similar reduction of symptoms after treatment and at 3-month follow-up. There were no severe adverse events. The average therapist time per patient and week was 17.5 minutes. Most patients in the sample lived within a 20 km range from the clinic; however, some patients lived more than 400 km away.

4.4 STUDY III: COST-EFFECTIVENESS OF THE ICBT INTERVENTION

Aim

The aim of the study was to explore the cost-effectiveness of ICBT in pediatric OCD patients compared to untreated patients on a waitlist.

Methods

Sixty-seven adolescents with OCD aged 12 to 17 years participated in a single-blind RCT comparing ICBT to a waitlist control for a period of 12 weeks (study II). Clinical effectiveness outcomes were defined as treatment responder rates and change in Quality Adjusted Life Years (QALYs) from pre- to post-treatment. Cost data on health care use, informal resource use, prescription drugs, prescription-free drugs, school absence, and productivity loss, as well as the cost of ICBT was collected.

Main results

There was a significant difference in the percentage of treatment responders in ICBT compared to the waitlist group (27% versus 0%, respectively). No effect on QALYs was observed. Compared to the waitlist group, ICBT generated substantial cost savings, averaging -144.98USD (95% *CI* [-159.79, -130.16]) per patient. The cost savings were mainly driven by reduced health care use in the ICBT group relative to the waitlist. From a health care provider perspective (i.e. considering general health care costs, medicine costs, and the cost of ICBT), the additional cost of ICBT was about 20US$ per patient or 2.3US$ per additional responder.

4.5 STUDY IV: PREDICTION OF ICBT TREATMENT OUTCOME

Aim

As the literature on prediction of treatment outcomes in OCD is inconclusive, possibly due to suboptimal statistical methods, we aimed to test a novel machine learning approach for the prediction of ICBT outcome for pediatric OCD.

Methods

All sixty-one adolescents with OCD that had received 12 weeks of ICBT in a previous RCT (study II) were analyzed. Available demographic and clinical baseline variables were used to predict treatment outcome. Outcome (treatment response) was assessed three months after ICBT. Four machine learning algorithms were implemented (one linear and three flexible models), as well as, for comparison, a classical logistic regression analysis.

Main results

Multivariate logistic regression could not detect any significant predictors. In contrast, all four machine learning algorithms performed well in the prediction of treatment response, with 75 to 83% accuracy. Amongst the variables with the highest importance for predictive accuracy were OCD onset, duration of OCD, self- and clinician-rated symptom severity, functional impairment, avoidance, and depressive symptoms.

4.6 ETHICAL CONSIDERATIONS

All studies were approved by the Regional Ethical Review Board in Stockholm. The general risk of participating in this research was evaluated as low, as no serious side effects of CBT or ICBT are known. All patients and primary caregivers were informed verbally and in writing about the prerequisites for participation. Prior to inclusion of the first patients, we identified three important aspects to ensure optimal safety and integrity of the participating families: a) clear and age-appropriate informed consent for participation in the studies, b) data security of the ICBT platform and online self-ratings via encrypted servers and double authentication, c) and implementation of clinical routines concerning severe events or worsening of symptoms during ICBT or follow-up. Regarding the latter, our research unit was integrated into the regular child and adolescent mental health service in Stockholm when study II was conducted and could therefore refer to outpatient and inpatient, as well as specialized services, including a specialized OCD unit where patients could receive follow-up treatment if needed after participation in the ICBT study.

As the tolerability of the novel ICBT intervention was not known prior to studies I and II, patients were a) informed that they could opt-out of participation anytime during the studies, and b) monitored by experienced clinicians as well as through weekly self-ratings to detect any signs of deterioration. Adverse events and patient satisfaction ratings were collected systematically at post-treatment.

Finally, one could wonder if participation in an experimental treatment study involves a risk of not seeking other, more effective help, or, if ICBT would fail in being effective, a risk of giving patients the impression that CBT in general is ineffective. This potential risk was addressed by clear information to the patients that our ICBT intervention was a novel treatment format and currently in a developmental phase, and that regular face-to-face CBT would be the first alternative in case ICBT would not produce beneficial results. My personal clinical impression is that the participation in our trials did not keep patients from seeking help but, in contrast, was in many cases the first contact with psychological assessment and treatment, which later on facilitated identification of other comorbidity, such as autistic traits or anxiety disorders, and might therefore have been a “door opener” for some families for additional indicated psychiatric care.

5 DISCUSSION

5.1 IS ICBT FEASIBLE FOR ADOLESCENT OCD?

Study I aimed to inform us about the feasibility of BiP OCD in a sample of adolescents with OCD. As this was the first time that ICBT was tested for pediatric OCD, this was an important step and one that would impact the planning and design of studies II to IV. We found that all patients and parents in study I participated in the intervention. The adolescents completed on average eight of the twelve chapters while almost all parents completed all five parental chapters. BiP OCD received overall high satisfaction ratings from the patients. Clinically and technically our impression was that BiP OCD performed according to our expectations. Patients and parents communicated with the online therapists via exercises and messages through the platform, with occasional telephone calls if needed. The general structure and rationale of the treatment content appeared to be age-appropriate and comprehensible for the patients. Only very few patients expressed a preference for face-to-face CBT when asked at post-treatment.

The initial construction and design of BiP OCD was based on previous experiences with ICBT and treatment of OCD from within our group. Important conceptual cornerstones of the intervention were the three distinct phases of treatment (psychoeducation, ERP and relapse prevention) presented successively over 12 chapters within 12 weeks, the limitation of written text to a minimum and instead an emphasis on visual material, and the inclusion of parents as a supportive part of the intervention. These conceptual features were chosen out of practical considerations and previous experiences and were evaluated in an admittedly rather unstructured manner. According to qualitative patient interviews [113] and discussions within our group, our conclusion was that a) the general structure of the intervention was functional and intuitive for patients and clinicians, b) that the patients appreciated the flexible and accessible treatment format, and c) that adolescents manage to partly take responsibility for their ICBT treatment, but also need to be supported by their parents and an online therapist.

Summarizing the accumulated knowledge from studies I and II, an improvement of BiP OCD would be to facilitate ERP further by clearer examples and routines as well as instructional video examples of how to conduct effective ERP exercises. Also, as adherence with the intervention is one of the key factors, we believe that the parental chapters could provide more detailed information about ERP, and how to support the adolescent in the best possible way to facilitate the treatment process. Reward systems, encouragement, and prompting are examples of tools that parents could make use of to a greater extent to support their adolescent.

Between studies I and II we developed a mobile phone app which aimed to support ERP exercise training and registration. Guided by user data and clinical impression, we were surprised that the app appeared to add only limited functionality to the treatment, and was used frequently only by a minority of the patients. This led us to the conclusion that the next

version of BiP OCD, which currently is in the making, will not include the mobile phone application.

Limitations

The feasibility aspects were evaluated in a qualitative manner with a pragmatic approach, rather than guided by an underlying theoretical framework. The disadvantage of a pragmatic approach is that some lessons learned tend to become implicit knowledge, available to those who have been directly involved in the process of the studies, but not apparent to others and difficult to pinpoint from an evidence-based research perspective. A more systematic way to approach the feasibility question would be to structure the data collection and analysis according to a theoretical framework. For example, Ritterband presents a theoretical model of various aspects of internet interventions, including technical, intervention, behavior change and symptom improvement aspects [114]. Such models could help the field of ICBT to approach feasibility and design questions more methodical, with better operationalizations of key aspects and better possibilities to exchange important knowledge when constructing new or updating existing ICBT interventions.

5.2 IS ICBT EFFECTIVE FOR ADOLESCENT OCD?

Our initial pilot study and the subsequent RCT demonstrated that ICBT was effective for adolescents with OCD. ICBT yielded significant symptom reductions over the course of the 12 weeks of treatment and, somewhat unexpected, additional improvements during follow-up. The symptom severity levels three months after ICBT were on average in the subclinical range, about 10 points on the CY-BOCS in the pilot study and about 14 points in the RCT, which is well in the range of the effects usually seen in face-to-face CBT [47]. Seventy percent of patients in the pilot study and one-third of patients in the RCT responded to the intervention. The difference in responder rates between the pilot and the RCT was rather surprising, and it appears that patients in the pilot study on average improved more than in the RCT. Apart from a true difference in effect, there are several methodological differences between the two studies that could explain the discrepancy: different study designs, unblinded vs. blinded assessors, a more strict definition of response and remission in the RCT, differences in the patient samples, and changes in the ICBT intervention.

The delayed treatment effect from post-treatment to 3-months follow-up was not predicted by us, as this is not typical in face-to-face CBT for pediatric OCD, where the immediate symptom reductions normally occur at post-treatment and then are sustained during follow-up [84]. As we have observed additional improvements during follow-up in two different studies (study I and study II), as well as in a previous ICBT study on childhood anxiety [115], this could indicate a different pattern of improvement in ICBT. This, in turn, would mean that the true effect of ICBT is underestimated after 12 weeks of treatment. The primary endpoint in future trials should therefore be set at the 3- or 6-months follow-up time point.

By and large, the ICBT treatment effects that were found in studies I and II are in line with the pooled effects of ICBT for children and adolescents presented in a recent meta-analysis

that found moderate between-group effect sizes of ICBT compared to waitlist, and large within-group effects from pre- to post-treatment [88]. As stated by Vigerland et al., ICBT for children and adolescents is still in a developmental phase, and there are several unknown variables that need to be explored in order to potentially increase the efficacy of ICBT, such as the involvement of the parents, the presentation of ICBT content, and the amount of therapist contact [88]. An ongoing Australian study of ICBT in pediatric OCD currently evaluates a completely unguided intervention, and the results from that trial will bring more knowledge about the advantages of self-guided ICBT and whether any reduction in efficacy can be detected when excluding therapist support [116].

Limitations

Several limitations apply to the presented efficacy results. First, the patient samples in studies I and II consisted predominantly of self-referrals and individuals volunteering for study participation. This might have introduced a selection bias in the data, as volunteers might be more motivated than clinician-referred patients, or could differ in other relevant characteristics from regular patients. In addition, the high proportion of highly educated parents indicates a possibly selected sample. This is likely a result of the recruitment process and advertisement for the studies in local newspapers. Yet, the samples had critical clinical characteristics such as moderate to severe OCD symptom presentation and clinical valid rates of comorbidity. About half of the patients had previously been in contact with the child and adolescent mental health services, indicating a subsample with clinical relevance. Still, effectiveness studies in clinical settings are needed to further validate the results.

In addition, the design of studies I and II limit the generalizability of the efficacy results, with study I being an open trial without control condition and study II a single-blinded RCT with a waitlist control. The waitlist enabled us to control for the passage of time and thus rule out spontaneous remissions and the effect of repeated clinical assessments. Indeed, no patient on the waitlist achieved responder status, confirming that spontaneous remissions are unlikely to occur in OCD patients. An active comparator, however, would have enabled us to control for unspecific therapeutic factors, such as therapist contact and expectancy effects. When planning for the RCT, the choice of comparison condition was not straightforward. The comparison with a psychological placebo condition was not found intuitive at the time as ICBT is not a new treatment per se, but rather a new treatment *format* of CBT, and a logical comparator would therefore have been another treatment format of CBT. A comparison with face-to-face CBT would have been most informative, but was found premature at that early stage.

5.3 IS ICBT A COST-EFFECTIVE INTERVENTION?

Study III indicated that treating pediatric OCD with ICBT was associated with substantial cost-savings for society compared to leaving patients untreated on a waitlist. The cost-saving effect was observed already after 12 weeks of treatment and the main driver was the continued health care consumption in the waitlist group. This suggests that untreated OCD is associated with general health care utilization to a markedly larger extent than in treated

cases, and together with other service utilization, medication costs, school absence, and reduced productivity, the cost of not treating OCD could be higher than the cost of treating OCD with ICBT. From a health care provider perspective, the study indicated minimal additional costs for offering families the ICBT service, 20US$ per patient, or 2.3US$ per additional responder. The minimal additional health care cost was mainly due to two factors, the low cost of ICBT, and the continued utilization of health care in the waitlist group.

Overall, as there are very few cost-effectiveness evaluations within ICBT for children and adolescents as well as within pediatric OCD, these results are an important first step towards a health economic evaluation of both fields.

Limitations
The cost-effectiveness results are limited to a 12-week perspective as patients on the waitlist directly were crossed over to ICBT, and further long-term cost comparisons could therefore not be made. As there seem to be additional clinical effects of ICBT during follow-up, we could hypothesize that these are accompanied by additional cost reductions. Critically, future studies should be designed with a longer controlled follow-up period to capture the cost-effectiveness trajectory in the long run.

Moreover, included in the cost estimates of ICBT were the maintenance costs of technical platform support and therapist costs. Not included, and more difficult to estimate, were the ICBT development costs. A service provider that would be interested in developing a new program and Internet platform would have to consider technical and content development costs as a one-off investment on top of the estimates presented in study III.

As stated before, the results are also limited by a possibly selected study sample. In addition, the sample was not optimally powered for cost-effectiveness analyses, which is reflected in the confidence intervals of the cost estimates. The results should therefore be seen as preliminary. Furthermore, the cost data was mainly based on parent reports and could be flawed by recall bias or measurement error. Another way to collect more objective and reliable cost data would be to use medical records and registries, which would also be a more refined way to collect data over a longer time perspective.

5.4 WHICH PEDIATRIC OCD PATIENTS DOES ICBT WORK FOR?

Study IV aimed to identify relevant patient characteristics for the prediction of treatment response three months after ICBT. Despite classical regression analysis failing to identify significant predictors, machine learning demonstrated that treatment response of ICBT could be predicted with good accuracy, even with a moderately sized sample. The machine learning algorithms could predict treatment outcome at three months follow-up with 75 to 83% accuracy, which is comparable to the accuracy estimates found in previous machine learning prediction studies of remission in adult OCD [64] and methylphenidate response in children with ADHD [117]. In our study, there was a slight advantage of the linear machine learning model over the non-linear models. However, as confidence intervals were overlapping and the sample size was modest, this difference should be interpreted cautiously.

The limitations of classical linear regression were also exemplified in the study, as predictor candidates were identified in the univariate analyses, but none reached significance in the multivariate analysis. This was probably due to collinearity of the two remaining variables in the model, age of OCD onset and duration of OCD. As this is a methodological limitation of our results, this problem would be expected to occur when multivariate linear regression is used in the kind of clinical data that is available in pediatric OCD studies. As the machine learning approach does not aim to identify single significant predictors in the same manner than linear regression, but rather patterns of predictors, issues like collinearity and non-linearity are less problematic.

The results of study IV provide therefore first exploratory evidence that machine learning could be a promising new statistical approach for the prediction of pediatric OCD treatment and ICBT outcome.

Limitations

The prediction results from study IV are limited by a possible sample selection bias, as described earlier for study II, and should be replicated in a bigger sample of patients from a clinical context. This is important, as we would want to make predictions of ICBT treatment outcome within regular care and on patients that present at the regional mental health care services.

Amongst the most important variables in the algorithms that predicted response to ICBT we identified OCD onset, duration of OCD, self- and clinician-rated symptom severity, functional impairment, avoidance, and depressive symptoms. This could indicate that patients that were detected and treated earlier and had a less severe clinical presentation were the ones that benefited the most from ICBT. At the same time, machine learning algorithms cannot be interpreted in the same intuitive way as linear regression results, and especially results from non-linear algorithms can be rather intricate [118]. The machine learning results should be understood as an interactive pattern of all included variables, and while some variables were identified as more important than others, their individual contribution should not be taken out of the context of all the available data. One weakness of machine learning is therefore the loss of interpretability, in the sense that it might not allow us to state that patients that had high scores on a particular variable did have worse outcomes. Simply put, machine learning might be most useful in situations where the aim is to predict, but not to make inferences about individual predictors.

All prediction analyses in this thesis were conducted on demographic variables and, predominantly, total scores from the clinical rating scales. Machine learning, in contrast to classical regression, is able to handle information on single item level. The reason we chose to use total scores instead of single items is that we aimed to compare machine learning with a classical linear regression and base the analyses on the same information. Future studies should however make use of machine learning algorithms' full potential and provide single item information alongside with total scores.

5.5 FUTURE DIRECTIONS

Further improvement of ICBT

As ICBT for children and adolescents still is a field in its early stages, there are many open questions about how to design and present an ICBT intervention in the best possible way to yield optimal clinical results. The studies presented in this thesis are designed to answer the question "Does it work?", but leave the actual intervention as a black box with unknown mechanics on the inside, and thus tell us little about "Why does it work?". Various central aspects of ICBT, such as length of intervention, graphical presentation, text and image content, degree of parental involvement and therapist support, are currently poorly understood. As mentioned before, a theoretical framework could guide researchers to systematically accumulate valuable knowledge about the most important ingredients of a successful ICBT intervention for children and adolescents. Some intervention characteristics could be experimentally randomized or studied by means of mediation analysis, e.g. length and intensity of the intervention or degree of parental support, whereas other aspects might require qualitative patient interviews and focus groups, e.g. readability of written material and appearance of visual material.

Continued evaluation of the clinical efficacy of ICBT

The next logical step regarding clinical efficacy of ICBT for pediatric OCD would be to compare BiP OCD with an active control, such as treatment as usual, or standard face-to-face CBT. The majority of patients in studies I and II that previously had been in contact with the child and adolescent mental health services had received general counseling. It might therefore be the case that many patients currently are offered unspecific, supportive psychological treatment, perhaps due to the absence of CBT-trained clinicians. Therefore, an unspecific supportive intervention would be a credible comparison condition to ICBT.

Naturally, a head-to-head comparison of ICBT with gold standard face-to-face CBT would be very interesting and important. The responder rates and average symptom reductions in study II are suggesting that ICBT might be less effective than face-to-face CBT, at least at post-treatment. A direct non-inferiority comparison would inform us if that indeed is true, and, in that case, how much of a discrepancy there is between the effect of CBT and ICBT. It has been proposed earlier that ICBT could be the first step in a stepped-care care model of OCD treatment, with face-to-face CBT and multimodal treatment reserved for more complex and severe cases [119]. Even if ICBT would be less effective than face-to-face CBT, it is intuitive that such a stepped-care model could save limited resources and might be attractive for different kinds of patients, and their different needs and preferences.

Further evaluation of the cost-effectiveness of ICBT

Related to the previous section and the further evaluation of the clinical efficacy of ICBT, the next step for the evaluation of the cost-effectiveness of ICBT should involve comparisons with other active treatments. Regarding the comparison with treatment as usual and unspecific supportive therapy, such treatments are expected to yield suboptimal effects but still involve clinician time and booked appointments, which in turn is associated with costs

for health care providers and society. It would therefore be interesting to compare the involved costs in relation to the effects that are yielded by unspecific interventions, such as general counseling or supportive therapy, compared to ICBT.

ICBT should also be compared directly with gold standard face-to-face CBT, and even if face-to-face treatment might be expected to be more effective than ICBT, ICBT could still be cost-effective, due to reduced clinician times (about 17 to 20 minutes per patient and week, compared to about 45 to 60 minutes in face-to-face CBT).

Critically, as OCD is associated with profound impairments in family, educational, and occupational everyday life [16], a long-term follow-up of ICBT-treated patients would be very interesting regarding societal functioning and productivity indicators. Such an evaluation could preferably be done within the Swedish registries, which contain rich longitudinal information on psychiatric and somatic diagnoses, health service utilization, sick leave, and employment status. A more refined long-term data collection of treatment effects and societal costs would therefore provide us with important insights on ICBT and whether it has potential to prevent functional and productivity impairments that often are associated with OCD.

Optimized prediction of ICBT outcome

As study IV suggested feasibility and accuracy of machine learning in the prediction of ICBT treatment response, a next important step would be to replicate these preliminary results in a larger clinical sample. Preferably, this would be done with separated recruitments of patients to first train the algorithms in one sample and then test the algorithms in a new sample, which would greatly expand the validity of results and would establish generalizability of the algorithm.

Another interesting study would be to replicate Kim et al.'s methylphenidate study [117] in an OCD sample and include genetic, imaging, environmental, neuropsychological, and psychometric data in the prediction of OCD treatment response. This combination of different sources of predictors has in fact been a successful strategy within cancer research, where many studies combine a multivariate set of genomic, clinical, histological, imaging, demographic, epidemiological, and protein data [63]. A comparable approach has been applied from within the field of therapygenetics, which is a development from within the genetics field and aims to predict psychotherapy outcome based on genes. E.g., in one study of CBT for child anxiety, a combination of genetic, demographic and clinical variables could successfully predict CBT outcome (area under the curve, AUC =.62–.69), using linear regression with cross-validation [120].

Such multidimensional prediction approaches appear promising, as they more closely reflect how we theoretically understand the causes and mechanisms of psychopathology, namely as a dynamic interplay of genetic, environmental, neurofunctional, and psychological mechanisms [24]. A problem in the previous OCD literature has been a large proportion of underpowered studies with not large enough samples to detect multiple predictors [60]. As

ICBT studies traditionally have been successful in recruiting large patient samples relatively quick, with inclusion processes usually completed within one year, combining large-scale ICBT trials with a multidimensional data collection from various sources, using machine learning as a tool to analyze the complex data, would be an interesting new development within the prediction field.

Dissemination of ICBT and evaluation of increased availability

The overarching aim of the line of research presented in this thesis is to increase the availability of effective psychological treatment for pediatric OCD. If ICBT after rigorous scientific evaluation proves to be an effective, cost- and resource-efficient intervention with the potential to bridge existing treatment barriers, the next necessary step would be implementation on a broader scale. Implementation studies could inform health care providers and decision makers of important issues to consider before integration of ICBT within a local service or the national health care system. An example of a regional implementation trial is a currently ongoing evaluation of ICBT for pediatric anxiety and OCD through a collaboration of our research group with the child and adolescent mental health care service in Östersund, a Swedish rural region where one clinic covers a large, sparsely populated area.

Apart from practical issues, there are specific questions that are associated with the implementation of ICBT that should be addressed within implementation trials, such as technical and clinical safety, reimbursement, maintenance and updates of the technology, the ongoing evaluation of ICBT effectiveness within clinical practice and legal questions about ownership and responsibilities.

As increased availability of psychological treatment is the goal, it would be important if the availability of treatment could be measured locally and nationally. Swedish registries cover various aspects of health care on a national level, but not yet the availability of psychological treatments. There are current initiatives to implement national quality registries of both psychological treatments within child and adolescent mental health care, as well as ICBT registries. An installation of those registries could give us highly relevant data about the geographic distribution of services and could inform us about under-supplied regions and guide the allocation of resources more equitable as we believe it currently to be the case.

6 CONCLUSIONS

The aim of this thesis was to develop and evaluate ICBT for adolescent OCD. Four studies were conducted to evaluate the feasibility, efficacy, cost-effectiveness, and prediction of treatment outcomes using ICBT. In summary, the research project demonstrated that:

- ICBT is a feasible intervention for adolescents aged 12 to 17 years with OCD
- ICBT is a clinically effective intervention for adolescent OCD, leading to significant symptom reductions in primary measures of OCD symptom severity and secondary measures of OCD symptoms, impairment, and comorbid symptoms
- ICBT is a highly satisfactory treatment from the patients' point of view
- ICBT is a safe intervention
- ICBT has the potential to save clinician time, requiring on average below 20 min per patient and week
- ICBT is less costly for society than leaving patients untreated on a waitlist
- ICBT treatment outcome could accurately be predicted by machine learning algorithms

This initial evaluation of ICBT for pediatric OCD is encouraging, but warrants replication in larger, clinical samples and should be extended to active control trials or non-inferiority trials that include not only an efficacy but also a cost-effectiveness component.

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