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INTERNET-DELIVERED COGNITIVE BEHAVIOUR THERAPY FOR PAEDIATRIC ANXIETY DISORDERS IN CLINICAL SETTINGS: INCREASING ACCESS TO EVIDENCE-BASED TREATMENTS

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Internet-delivered cognitive behaviour therapy for paediatric anxiety disorders in clinical settings: increasing access to evidence-based treatments

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SAMMANFATTNING

Bakgrund

Ångest bland barn är vanligt förekommande och kan vara associerat med ett stort lidande hos barnet. Trots att det finns effektiva psykologiska behandlingar, så är det endast ett fåtal som har tillgång till dem. Internetbaserad kognitiv beteendeterapi (IKBT) skulle kunna vara ett effektivt och kostnadsbesparande sätt att öka tillgången till evidensbaserade behandlingar för barn med ångestsjukdomar.

Syfte och metod

Syftet med denna avhandling var att utvärdera IKBT för barn med ångestsjukdomar i två kliniska miljöer; som del av en specialenhet i Region Stockholm inom barn- och ungdomspsykiatrin (BUP), samt som del av en öppenvårdsenhet i Region Jämtland Härjedalens BUP. Specifikt utvärderades (1) effekten och kostnadseffektiviteten av IKBT, (2) långtidseffekten av IKBT där de som hade kvar sin diagnos efter behandling erbjöds ytterligare behandling, samt (3) möjligheten och effekten av att erbjuda IKBT inom en öppenvårdsenhet i landsbygden.

Resultat

Resultatet visade att IKBT var en effektiv och kostnadsbesparande behandling. Behandlingseffekterna kvarstod upp till 12 månader efter avslutad behandling. De med diagnosen separationsångest samt de som i större utsträckning var engagerade i att arbeta med beteendeförändring var sannolika att gynnas av behandling. De med svår ångest var i mindre utsträckning sannolika att gynnas av behandlingen. För de som fick mer behandling efter avslutad IKBT minskade symtomen ytterligare. Däremot var det mer än hälften av deltagarna som tackade nej till mer behandling då de påbörjat en kontakt med lokal öppenvård för huvudsakligen annan problematik än ångest. IKBT tycks dessutom gå att sprida genom en BUP öppenvårdsenhet på landsbygden. De familjer och lokala kliniker som deltog i studien var nöjda och ångestsymtomen hos barnen minskade.

Slutsats

IKBT för barn med ångestsjukdomar är en effektiv och kostnadsbesparande behandling, åtminstone för de med måttlig ångestproblematik. IKBT skulle kunna erbjudas som ett förstahandsalternativ inom reguljär vård (d.v.s., innan traditionell ansikte-mot-ansikte behandling). Däremot behövs mer information om vilka som bör erbjudas IKBT samt vid vilken tidpunkt. IKBT bör ingå som del av en specialiserad verksamhet för att säkerställa kvalitet och kompetens. Däremot kan andra sätt vara nödvändiga i t.ex. landsbygden.

ABSTRACT

Background

Paediatric anxiety disorders are common, impairing and associated with a societal and economic burden. Even though there are efficacious treatments to treat these disorders, access to them are limited. Internet-delivered cognitive behaviour therapy (ICBT) has gained support for being an efficacious treatment for paediatric anxiety disorders and is suggested as one possible solution to increase access to evidence-based treatments.

Aims and methods

The main aim of this thesis was to evaluate the BiP Anxiety programme, for children aged 8 to 12 years old with an anxiety disorder, in two clinical settings. First by conducting a randomised controlled trial within a specialised ICBT clinic part of the child and adolescent mental health services (CAMHS) in Stockholm. Secondly by conducting a pilot feasibility trial at a CAMHS outpatient clinic in rural Sweden. Specific aims were to evaluate (1) the effects and cost-effectiveness of ICBT compared to an active placebo control, (2) the long term effect of ICBT within a stepped-care model where non-remitters of treatment were offered additional treatment, (3) predictors of treatment outcome, and (4) the feasibility and potential effectiveness of ICBT when disseminated in an outpatient clinic in rural Sweden.

Results

ICBT was effective in reducing anxiety symptoms in a cost-effective manner when compared to a placebo condition controlling for non-specific therapeutic factors such as attention and weekly homework assignments. Treatment gains were maintained up to 12 months after the end of the treatment. Participants with a principal diagnosis of separation anxiety disorder, and those more engaged in behaviour change were more likely to be in remission at the three-months follow-up. Participants with more severe anxiety were less likely of being in remission. Additional face-to-face treatment for non-remitters of ICBT was efficacious for those receiving it. The majority of non-remitters however declined this offer down, mostly due to already receiving treatment for other mental health disorders (e.g., depression) at their local CAMHS. Also, ICBT seemed to be feasible and potentially also effective when disseminated to an outpatient clinic in rural Sweden.

Conclusion

ICBT is an effective treatment, at least for children with moderate anxiety disorders. ICBT could be suitable as a first-line treatment, but a greater understanding about to whom it should be offered and when the treatment should be stepped up is needed. ICBT should be implemented as part of a specialised clinic to ensure the necessary education, support and supervision. However, other models of implementation might be required in rural areas where the resources needed for a specialised clinic cannot be motivated.

LIST OF SCIENTIFIC PAPERS

I. Jolstedt, M., Wahlund, T., Lenhard, F., Ljótsson, B., Mataix-Cols, D., Nord, M., ... & Vigerland, S. (2018). Efficacy and cost-effectiveness of therapist-guided internet cognitive behavioural therapy for paediatric anxiety disorders: a single-centre, single-blind, randomised controlled trial. *The Lancet Child & Adolescent Health, 2*(11), 792-801.

II. Jolstedt, M., Högström, J., Ljótsson, B., Mataix-Cols, D., Wahlund, T., Nord, M., … & Vigerland, S. *Predicting outcome of internet-delivered cognitive behaviour therapy for paediatric anxiety disorders*. Unpublished manuscript.

III. Jolstedt, M., Vigerland, S., Mataix-Cols, D., Ljótsson, B., Wahlund, T., Nord, M., … & Serlachius, E. *Long-term outcomes of internet-delivered cognitive behaviour therapy for paediatric anxiety disorders: Towards a stepped care model of health care delivery.* Unpublished manuscript.

IV. Jolstedt, M., Ljótsson, B., Fredlander, S., Tedgård, T., Hallberg, A., Ekeljung, A., ... & Vigerland, S. (2018). Implementation of internet-delivered CBT for children with anxiety disorders in a rural area: A feasibility trial. *Internet interventions, 12,* 121-129.

CONTENTS

LIST OF ABBREVIATIONS

3MFU	Three months follow-up
12MFU	Twelve months follow-up
ADIS	Anxiety disorder interview schedule
BiP	"*Barninternetprojektet*" [The child internet project]
CAMHS	Child and adolescent mental health services
CBT	Cognitive behaviour therapy
CSR	Clinician severity rating
DSM	Diagnostic and statistical manual of mental disorders
F2F	Face-to-face
GAD	Generalized anxiety disorder
ICBT	Internet-delivered cognitive behaviour therapy
ICDP	Internet-delivered child-directed play
PD	Panic disorder
RCT	Randomised controlled trial
SeAD	Separation anxiety disorder
SoAD	Social anxiety disorder
SP	Specific phobia
SSRI	Selective serotonin reuptake inhibitors

1 INTRODUCTION

Mental disorders are common, impairing and associated with increased societal costs (Kessler et al., 2009). They are globally the fifth leading disorder category with regards to overall disease burden, with depression having the highest disease burden, followed by anxiety disorders (Whiteford et al., 2013). Anxiety disorders are however the most prevalent mental health disorders (Wittchen et al., 2011) and have the earliest age of onset (Kessler et al., 2005).

Access to evidence-based treatment for mental health disorders is limited and internet-delivered therapies have been suggested as an efficient and cost-effective solution that could help increase availability (Andersson, Titov, Dear, Rozental, & Carlbring, 2019; Kazdin, 2019). The efficacy of internet-delivered cognitive behaviour therapy (ICBT) for adults is well known (Andersson, Carlbring, Titov, & Lindefors, 2019), and research on ICBT for paediatric mental health disorders has increased immensely in the last decade, showing promising results (Hollis et al., 2017; Vigerland, Lenhard, et al., 2016).

Even though several randomised controlled trials (RCTs) have been conducted to evaluate the efficacy of ICBT for paediatric anxiety disorders (e.g., March, Spence, & Donovan, 2009; Vigerland, Ljótsson, et al., 2016), the efficacy and cost-effectiveness of treatment when compared to active control conditions, and whether treatment gains are maintained in the long run are questions that remain unanswered. Also, knowledge about for whom ICBT is efficient, how it could be disseminated, and whether it is effective when conducted in regular care is limited.

2 BACKGROUND

2.1 Normal fear and anxiety

Fear and anxiety are normal reactions to real or imagined threats (Gullone, 1996). They are considered adaptive and evolutionary processes protecting us from potentially harmful situations (Nesse & Ellsworth, 2009). Fear and anxiety are overlapping but different emotions. Fear is short-lived and disappears when the threat is removed, whereas anxiety arises when being faced with uncertain and ambiguous threats, and persists even when the threat is removed (Sylvers, Lilienfeld, & LaPrairie, 2011).

All children experience feelings of fear and anxiety and they are often transitory (Craske, 1997). During childhood, the content of fear and anxiety naturally differs depending on the age of the child. Fear regarding concrete and approximate objects, supernatural phenomena and darkness are common among younger children, whereas anticipatory and imaginary fears are more common among older children (Gullone, 2000). Even though fear and anxiety are normal and common, childhood anxiety should be taken seriously, since for a proportion of children the fear and anxiety persists and starts to interfere with their everyday life (Costello, Egger, & Angold, 2005).

2.2 Anxiety disorders

2.2.1 Definition

The Diagnostic and Statistical Manual of Mental Disorders – Fifth edition (DSM-5; APA, 2013) is a diagnostic system which can be helpful to distinguish normal, age-appropriate, and adaptive fear and anxiety from a clinically impairing and persisting anxiety disorder. In the DSM-5, fear and anxiety are structured into factors/dimensions that group symptoms and expressions together based on the most current research (Regier, Kuhl, & Kupfer, 2013). The most prevalent and frequently evaluated anxiety disorders in children are separation anxiety disorder (SeAD), specific phobia (SP), social anxiety disorder (SoAD), generalized anxiety disorder (GAD), and panic disorder (PD).

Anxiety disorders are differentiated from each other based on the core content of the anxiety. In SeAD, the anxiety is primarily focused on being separated from the primary caregiver; SP is characterized as an irrational fear towards specific objects or situations; SoAD is when the anxiety revolves around being negatively evaluated by others and the fear of being humiliated; GAD is characterized as excessive and uncontrollable worry in several different areas such as family, school, or health; and PD is when there are recurrent panic attacks with physiological and/or cognitive symptoms that cause fear and distress.

2.2.2 Aetiology

There are a wide range of different scientific theories, ranging from biological to psychological, describing how anxiety disorders develop. The development of anxiety disorders is probably best explained by the complex interaction of e.g., neurological, temperamental, genetic and environmental influences (Muris, 2006; Muris, Merckelbach, de Jong, & Ollendick, 2002; Murray, Creswell, & Cooper, 2009). A complete description of this intricate interaction is beyond the scope of this thesis. Instead, a brief overview of relevant theories is provided below.

Firstly, the limbic system in the brain, particularly increased activity in the amygdala, has a strong association with anxiety (Albaugh et al., 2017). The activity in the limbic system is in turn known to influence differences in reactivity and self-regulation, i.e., temperaments and/or traits (Schwartz, Wright, Shin, Kagan, & Rauch, 2003). Behaviour inhibition (Pérez-Edgar & Fox, 2005), failure to inhibit threat-related attention bias (Puliafico & Kendall, 2006), and dysfunctional emotional regulation (Cisler, Olatunji, Feldner, & Forsyth, 2010) are examples that are known to moderate the development of anxiety disorders.

Anxiety disorders are hereditary and genes play an important role in their development (Gregory & Eley, 2007). However, the interaction between genes and the environment is not fully understood and environmental factors are considered equally important as genetic influences (Eley et al., 2015). Parents own anxiety, as well as parental responses towards the child's anxiety are examples of environmental factors associated with increased risk of developing anxiety disorders (Lebowitz, Leckman, Silverman, & Feldman, 2016; Yap & Jorm, 2015). Parental rejection, control, warmth, and autonomy granting are also considered environmental factors that moderate childhood anxiety (McLeod, Wood, & Weisz, 2007).

2.2.3 Prevalence and onset

Anxiety disorders are the most prevalent mental health disorders among children and adolescents (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012; Merikangas et al., 2010) with approximately 6.5% children and young people meeting diagnostic criteria for an anxiety disorder (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). Approximately 60% will have met diagnostic criteria for an anxiety disorder by the time they reach adulthood (Kessler et al., 2005). The most prevalent disorders (i.e., life-time prevalence) are SP (15%), SoAD (10%) and SeAD (5%), whereas GAD, and PD have a lower prevalence of approximately 2% (Beesdo-Baum & Knappe, 2012). The median age for the onset of anxiety disorders are around 11 years where SP and SeAD have the earliest age of onset around 7 years (Bandelow & Michaelis, 2015).

2.2.4 Impairment and progression

Childhood anxiety disorders are highly impairing and are associated with poorer functioning in school as well as higher school absenteeism (Mychailyszyn, Méndez, & Kendall, 2010). These children also have a higher likelihood of meeting diagnostic criteria for other anxiety disorders, as well as for major depressive disorder and attention-deficit/hyperactivity disorder (Spence, Zubrick, & Lawrence, 2018).

If left untreated, paediatric anxiety disorder could have a chronic course persisting into adulthood (Beesdo, Knappe, & Pine, 2009; Bittner et al., 2007; Cohen, Andrews, Davis, & Rudolph, 2018). Untreated paediatric anxiety disorders are associated with increased risk of developing secondary depressive disorders (Finsaas, Bufferd, Dougherty, Carlson, & Klein, 2018) and poor functioning in important life domains later in life (Comer et al., 2011; Copeland, Angold, Shanahan, & Costello, 2014). Even though approximately half of the children with anxiety disorders seem to naturally recover before reaching adulthood, these adults have more difficulties in functioning, compared to adults without any history of mental disorders (Costello & Maughan, 2015). Also, children with early onset anxiety disorders, compared to late onset, have a higher likelihood of developing subsequent comorbid and secondary anxiety disorders (Ramsawh, Weisberg, Dyck, Stout, & Keller, 2011). Early interventions are therefore imperative and could help reduce severity and persistency of the disorder as well as to prevent secondary disorders (De Girolamo, Dagani, Purcell, Cocchi, & McGorry, 2012). Early interventions could also help reduce societal costs related to impairments associated with these disorders (Gustavsson et al., 2011).

2.3 Treating paediatric anxiety disorders

2.3.1 Cognitive behaviour therapy

Cognitive behaviour therapy (CBT) for children with anxiety disorders is considered an effective treatment (James, James, Cowdrey, Soler, & Choke, 2015; Warwick et al., 2017) and is suggested as the first-line psychological treatment in national and international guidelines (e.g., NICE, 2014; Socialstyrelsen, 2016). CBT can be delivered in different modalities, such as individually, in groups, via the internet, as a self-help treatment, or via the parents/legal guardians. There are several manualised treatments for paediatric anxiety disorders (e.g., Kendall & Hedtke, 2006; Rapee et al., 2006), all of which tend to include five basic components: (1) psychoeducation, (2) stress management, (3) challenging negative beliefs, (4) exposure to the feared stimuli, and (5) relapse prevention. The aim of treatment is not only to decrease anxiety symptoms, but also to increase functioning and quality of life (Swan & Kendall, 2016). CBT treatments for children are often transdiagnostic in the sense that several anxiety disorders are targeted by the intervention (Ewing, Monsen, Thompson, Cartwright-Hatton, & Field, 2015).

Exposure is crucial when treating children with anxiety disorders (Peris et al., 2015) and the aim of exposure is extinction (i.e., changing the perception of fear; Waters & Craske, 2016). The amount of exposure tasks, as well as the time spent on more difficult tasks, has been shown to have a positive effect on perceived fear (Peris et al., 2017). There are primarily two theories on the mechanisms of extinction; emotional process theory (EPT) and inhibitory learning theory (ILT). In EPT, extinction is primarily reached through fear reduction (i.e., habituation; Kendall et al., 2005) compared to ILT where extinction is reached by gaining new associations adding to previous learning (Craske, 2015).

The addition of parental involvement in treatment does not seem to enhance the effects of treatment outcome for paediatric anxiety disorders (e.g., Carnes, Matthewson, & Boer, 2019; Thulin, Svirsky, Serlachius, Andersson, & Öst, 2014). However, none of these reviews took type of parental involvement in treatment into consideration. A meta-analysis looking specifically at type of involvement in treatment found that parental participation focusing on the parent being a co-therapist, transferring treatment content to the child, had a positive effect on outcome (Manassis et al., 2014). Also, family conflicts, negative communication within the family and inconsequent parental behaviours have been found to have a negative effect on childhood anxiety symptoms and could therefore be targeted in treatment (Breinholst, Esbjørn, Reinholdt-Dunne, and Stallard, 2012). Moreover, a review specifically evaluating family treatments for paediatric anxiety disorders found that parental involvement in treatment could be particularly important when parents themselves are anxious (Creswell & Cartwright-Hatton, 2007).

2.3.2 Pharmacological treatment

Selective serotonin reuptake inhibitors (SSRIs) are the first-line pharmacological treatment for paediatric anxiety disorder (Locher et al., 2017; Strawn, Welge, Wehry, Keeshin, & Rynn, 2015). Even though there is support for SSRIs, the mechanisms behind its effects are unclear (Farb & Ratner, 2014) and its effects are to some extent explained by placebo effects (Koechlin, Kossowsky, Gaab, & Locher, 2018). The effects of the single treatment with SSRIs or CBT for paediatric anxiety disorders are comparable (Walkup et al., 2008). However, SSRIs are associated with adverse events such as gastric distress, behaviour agitation, mood swings, sleep difficulties, and suicidal ideation (Patel, Feucht, Brown, & Ramsay, 2018), whereas adverse events related to CBT are uncommon (Wang et al., 2017). Families also seem to prefer CBT over pharmacological treatments and perceive it as more credible and acceptable (Brown, Deacon, Abramowitz, Dammann, & Whiteside, 2007).

SSRIs in combination with CBT have shown to have a superior effect over single-treatment with either SSRIs or CBT (Walkup et al., 2008). Sub-analyses have however shown the combination treatment is more effective only for those children

with severe anxiety, not for the children with less severe symptoms (Taylor et al., 2018). Also, when comparing the combination treatment of SSRIs and CBT with the combination of pill placebo and CBT, no significant differences were detected (Hudson, McLellan, Eapen, & Rapee, 2019). Hence, one could argue that CBT is a better first line intervention, at least for those with mild to moderate anxiety disorders. This is particularly relevant in Sweden, for example, where treatments with SSRI for paediatric anxiety disorders are not approved by the Swedish medical products agency (Ivarsson & Westholm, 2016).

2.3.3 Accessibility

Even though there are known effective treatments for paediatric anxiety disorders, only a small proportion have access to services and clinicians providing them (Merikangas et al., 2011; Wang et al., 2005). The shortage of trained therapists (particularly in remote areas), long waiting-lists, and underfunded clinics have been suggested by Comer and Barlow (2014) as important factors limiting accessibility to evidence-based treatments. Also, youth most often receive treatments based on practitioners' preferences rather than based on supported research (Garland et al., 2013). Moreover, only a minority of CBT therapists use exposure when treating anxiety disorders limiting the access to the core component of CBT (Whiteside, Deacon, Benito, & Stewart, 2016). ICBT has been suggested as a solution to increase access to evidence-based treatments in a cost-effective (Ophuis et al., 2017) and feasible way (Andersson, Titov, et al., 2019; Kazdin, 2019).

2.4 Internet-delivered cognitive behaviour therapy

2.4.1 Definition

ICBT is when at least a part of the CBT treatment is delivered through texts, videos, and/or audio-files either via a computer or a mobile device (Hill et al., 2018). The type and amount of therapist support varies considerably, ranging from using technology as a complement to traditional face-to-face (F2F) CBT (e.g., Khanna & Kendall, 2010) or with the add-on of telephone sessions (e.g., Wuthrich et al., 2012), to programmes with limited therapist-support only via messages within the treatment platform (e.g., March et al., 2009). ICBT could also be delivered as a preventive programme (e.g., Morgan et al., 2017) and delivered to the parent only (e.g., Donovan & March, 2014).

ICBT has several advantages compared to F2F CBT such as (1) being geographically independent increasing access in remote areas, (2) requiring one third of the therapist time compared with traditional F2F CBT, (3) treatment format being standardised guaranteeing that key components are kept and reducing the risk for therapist-drift, and (4) helping to consolidate learning and increasing self-efficacy since participants have constant access to the treatment and have the possibility to return to material (Titov et al., 2015).

2.4.2 Efficacy

There is evident support for ICBT for adults with a range of mental disorders (Andersson, Carlbring, et al., 2019). However, research on ICBT for children and adolescents are lagging behind but slowly growing showing promising effects when compared to wait-list conditions (Bennett et al., 2019; Hollis et al., 2017; Vigerland, Lenhard, et al., 2016). Treatment gains of ICBT also seem to be maintained up to 12 months after completion of the treatment (e.g., Vigerland et al., 2017), which is in similarity with what is typically seen in F2F CBT for children (Gibby, Casline, & Ginsburg, 2017; Kodal et al., 2018; Piacentini et al., 2014).

However, even though ICBT often is suggested as a cost-effective treatment alternative, having the potential to be delivered within a stepped-care model, few trials have evaluated such approaches for children (Creswell & Waite, 2016; Ollendick, Öst, & Farrell, 2018). One trial evaluating ICBT as part of a stepped-care model found such an approach feasible (Rapee et al., 2017) and potentially also cost-effective (Chatterton et al., 2019). No studies have yet been fully powered to detect differences between ICBT and an active control condition (Khanna, Carper, Harris, & Kendall, 2017; Spence et al., 2011; Spence, Donovan, March, Kenardy, & Hearn, 2017). Only three trials have examined the question of for whom ICBT for paediatric anxiety disorder seems to work most efficiently (Morgan, Rapee, Salim, & Bayer, 2018; Stjerneklar, Hougaard, & Thastum, 2019; Vigerland et al., 2017), with mixed results. A much larger body of research has been conducted on predictors of F2F CBT for paediatric anxiety disorders, showing that severity of the disorders, comorbidity, parental psychopathology, and a diagnosis of SoAD affects treatment negatively (e.g., Hudson et al., 2015; Wergeland et al., 2016).

2.5 Towards implementation in clinical settings

The effects of a treatment cannot be guaranteed when changing setting, for instance when wanting to implement a new treatment programme in regular care (Victora, Habicht, & Bryce, 2004). Differences in patient characteristics, clinicians' motivation to follow evidence-based treatments, and organisational resources have been suggested to differ when moving from research to clinical setting (Weisz, Krumholz, Santucci, Thomassin, & Ng, 2015). Other issues when implementing treatment in regular care have been lack of treatment fidelity and support (Novins, Green, Legha, & Aarons, 2013), where the implementation of exposure has been suggested to be particularly difficult (Ringle et al., 2015).

ICBT has successfully been implemented for adults in regular care in Australia, Canada, Denmark, Norway, and Sweden by having specialised units only delivering ICBT (Titov et al., 2018). A recent meta-analysis of ICBT for adults however found that the effects of ICBT were smaller when evaluated in clinical settings compared to research settings (Romijn et al., 2019). Only two trials have evaluated the effects of ICBT for children and young people in regular care. One large

study (*N*=1026) disseminating ICBT for paediatric anxiety disorders in a primary care setting in New Zealand have shown positive results (Moor et al., 2019). The other large trial (*N*=4425), making an ICBT programme without any therapist support publicly available in Australia, showed low adherence rates and modest effects (March, Spence, Donovan, & Kenardy, 2018). The way in which ICBT for paediatric anxiety disorders should be disseminated to regular care remains unclear. Also, there is a need to better understand if any adaptations are required to ensure feasibility and efficacy of treatment when changing setting.

2.6 Summary

Internet-delivered CBT has been suggested as one way to increase access to evidence-based treatments. Research on ICBT for paediatric anxiety disorders has increased during the last decade and the results indicate that ICBT is effective when compared to waitlist conditions. There is an increasing interest for internet and mobile treatment options, however, more knowledge regarding the efficacy and cost-effectiveness of ICBT when compared to active placebo conditions is needed to control for potential confounders. Also, a better understanding of for whom ICBT is effective is needed before implementation in clinical settings. Furthermore, the ways in which ICBT could and should be disseminated remains unclear and there is a need to evaluate ICBT in different contexts before taking steps towards implementation.

3 OBJECTIVE AND RESEARCH QUESTIONS

3.1 Overall objective

The overall objective of this thesis was to examine the effects of the BiP Anxiety programme, an internet-delivered CBT treatment for paediatric anxiety disorders, in two different clinical settings. Firstly, a large randomised trial was conducted at a clinical research unit, part of the CAMHS in Region Stockholm, Sweden (Studies I to III). Secondly, a pilot feasibility trial was conducted in an outpatient CAMHS clinic in rural Sweden, Region Jämtland Härjedalen (Study IV).

3.2 Specific research questions

This thesis had six specific research questions, which Studies I to IV aimed to answer:

3.2.1 Is ICBT effective in reducing anxiety symptoms when compared to an active placebo control condition?

In Study I, ICBT was compared to an active placebo condition that controlled for modality of treatment delivery and the potential effect of confounding non-specific treatment variables such as therapist contact, homework assignments, and general behaviour change. The effects of ICBT when delivered within a potential future specialised ICBT clinic were evaluated. It was hypothesised that ICBT would be more effective than the control condition and also that delivering treatment in a specialised unit would be feasible.

3.2.2 Is ICBT cost-effective when compared to an active control condition?

In Study I, ICBT was also compared to the active condition described above with regards to health-economic benefits, such as health care and medical consumption as well as school and work absenteeism. It was hypothesised that ICBT would be more cost-effective than the control condition.

3.2.3 Do certain patient characteristics and clinical features predict treatment outcome of ICBT?

In Study II, demographic and clinical variables measured at pre-treatment, as well as in-treatment variables measured early during treatment, were explored to investigate whether ICBT is more suitable for certain subgroups of participants and whether non-responders could be detected early in treatment.

3.2.4 What are the long-term effects of ICBT 12-months after completing treatment?

In Study III, the long-term effects of ICBT, 12-months after completed treatment, was evaluated to investigate whether treatment benefits were maintained. It was hypothesised that the majority of participants would maintain their treatment gains, and that some would improve further.

3.2.5 Is additional F2F CBT for non-remitters of ICBT feasible and effective?

In Study III, ICBT was also evaluated within a stepped-care model of delivery. Traditional F2F CBT was offered to those participants not benefiting sufficiently from ICBT three months after completing treatment. It was hypothesised that additional F2F treatment for non-remitters of ICBT would be effective.

3.2.6 Is ICBT a feasible and potentially effective treatment when disseminated within a CAMHS outpatient clinic in rural Sweden?

In Study IV, the feasibility and potential effectiveness of ICBT was evaluated when delivered as part of a CAMHS outpatient clinic in rural Sweden. Feasibility was defined as participants accepting, completing, and being satisfied with treatment, as well as clinicians finding the treatment acceptable as part of their everyday work. It was hypothesised that ICBT would be feasible and potentially also effective in this clinical setting, at least for a subgroup of participants.

4 THE EMPIRICAL STUDIES

Studies I, II, and III were all part of a large (*N*=131) randomised controlled trial (ethical review numbers 2014/1885-31 and 2015/316-31/1) aiming to evaluate ICBT when delivered in a potential future specialised ICBT clinic part of the CAMHS in Region Stockholm. See Figure 1 for an overview of participant flow for the clinical trial comprising Studies I to III.

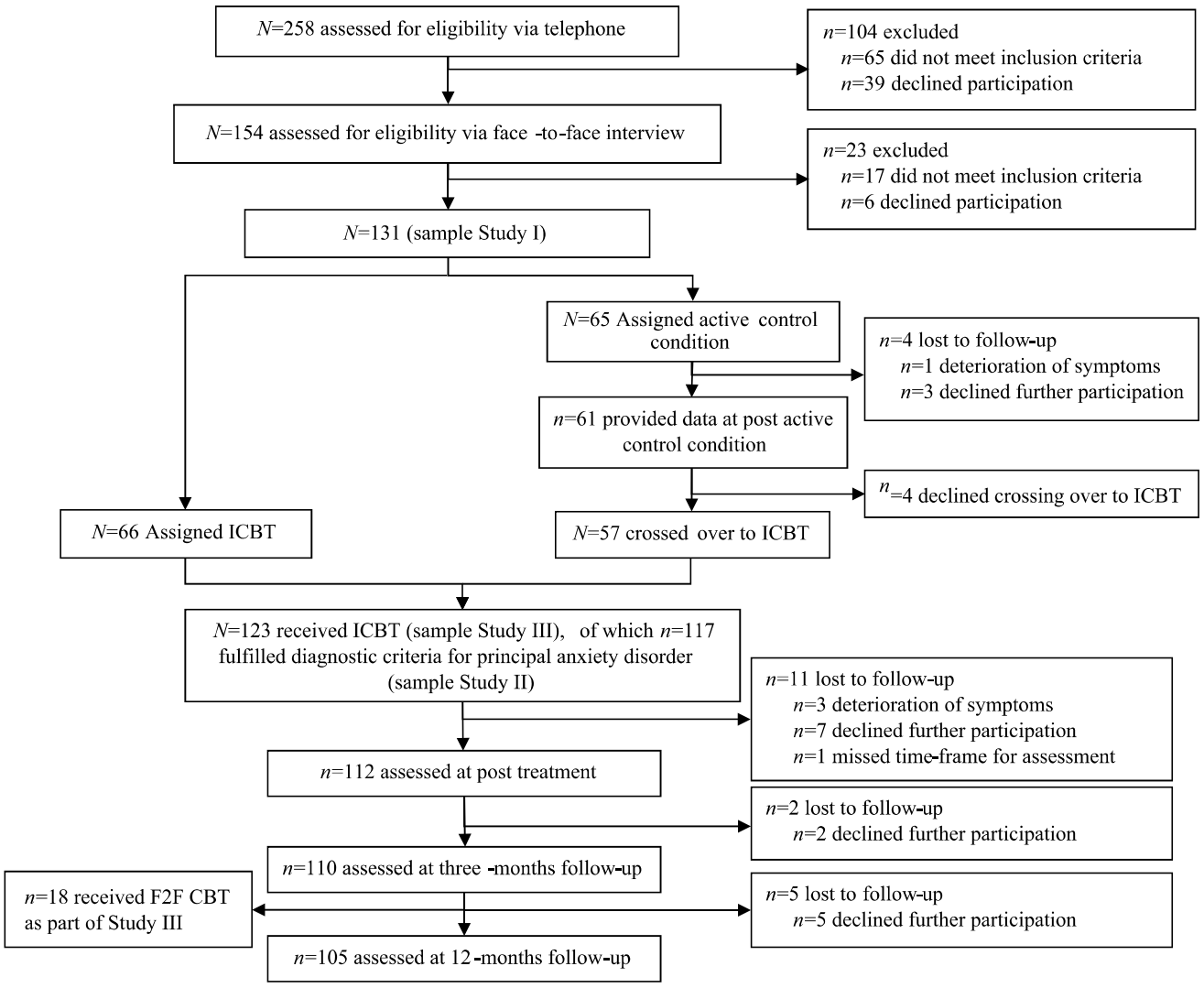

Figure 1. *Participant flow for participants in Studies I, II and III. Abbreviations. ICBT = Internet-delivered cognitive behaviour therapy; F2F CBT = Face-to-face cognitive behaviour therapy.*

Study IV was a small (*N*=19) feasibility trial (ethical review number 2014/1225-31/4) aiming to evaluate ICBT when delivered in a CAMHS outpatient clinic in Region Jämtland Härjedalen, a rural area in northern Sweden. See Figure 2 for an overview of participant flow for Study IV.

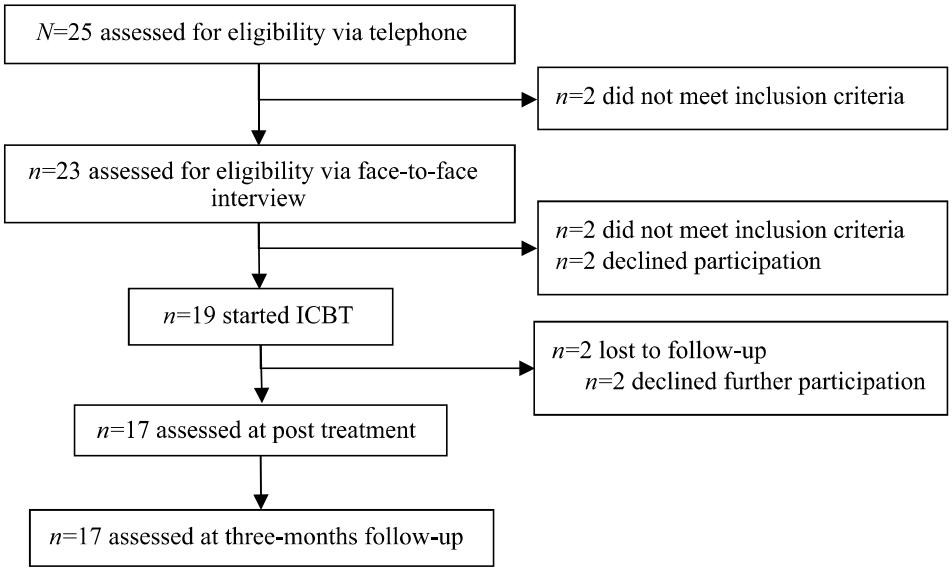

Figure 2. *Participant flow for participants in Study IV. Abbreviations. ICBT = Internet-delivered cognitive behaviour therapy.*

4.1 The BiP Anxiety programme

The BiP Anxiety programme is a generic ICBT programme for children with anxiety disorders (either SeAD, GAD, SoAD, SP, and PD). BiP Anxiety has previously been evaluated in two clinical trials showing positive results (Vigerland, Ljótsson, et al., 2016; Vigerland et al., 2013). BiP Anxiety is completely web-based and consists of 12 modules for the child and the parent to conduct together, and 12 additional modules for the parent only. The treatment duration is 12 weeks long and participants are encouraged to work with one module each week. Access to the next module is only given if the prior is completed. Module 12 is provided at week 12 of treatment, regardless of how many modules the family has conducted during the treatment period.

BiP Anxiety consists of texts, pictures, and short videos. Figure 3 shows screenshots of the treatment platform to illustrate its layout. In modules 1 to 3, participants are given psychoeducation about anxiety disorders, the rationale for exposure, and are instructed to create exposure hierarchies. In modules 4 to 11, participants are instructed to start working with exposure and create homework assignments based on chosen hierarchies. Moreover, participants also learn about stress management techniques (e.g., breathing, relaxation), cognitive techniques (e.g., cognitive restructuring), reward systems, and problem solving to facilitate exposure. Module 12 is about how to maintain treatment gains and prevent relapses. Therapist support is asynchronous and provided on a weekly basis, mainly through standardised forms and messages within the programme. The main role of the therapist is to make sure that participants log in and work with the programme, encourage the work conducted, answer questions regarding treatment content and homework assignments, and also, if needed, clarify the rationale for treatment by referring back to treatment content.

Figure 3. *Screenshots from the BiP Anxiety programme.*

4.2 Study I: Efficacy and cost-effectiveness

4.2.1 Aims

The main aim of Study I was to evaluate the efficacy and cost-effectiveness of ICBT for paediatric anxiety disorders when delivered in a specialised unit within the CAMHS in Region Stockholm.

4.2.2 Methods

A total number of 131 children with anxiety disorders (either SeAD, SoAD, SP, GAD, or PD), aged 8 to 12 years, and their parents were randomised (1:1) to either receive ICBT (n=66) or an active placebo control condition, internet-delivered child-directed play (ICDP; n=65). ICDP was inspired by components from parent management training (Kaminski, Valle, Filene, & Boyle, 2008) and was designed to control for mode of delivery, therapist attention, conducting homework assignments, and time passing. The primary outcome measure was the clinician severity rating (CSR) derived from the Anxiety Disorder Interview Schedule (ADIS-IV; Silverman & Albano, 1996). CSR is rated from 0=Absence of symptoms/No disturbance in functioning/No disability to 8=Very Severe Symptoms/Very severe disturbance in functioning/Very severely disabling. A rating of four or higher on the CSR indicates that diagnostic criteria for a disorder is met. Primary endpoint was after treatment completion (week 12). Participants in the control condition crossed over to receive ICBT directly after primary end-point. Cost-effectiveness was analysed from a societal perspective including e.g., health care consumption, medication use, and school and work absenteeism.

4.2.3 Results

Intent-to-treat analyses showed that participants improved significantly from pre- to post-treatment, regardless of treatment allocation (Cohen's d for ICBT=1.22; for ICDP=0.72). Participants in ICBT improved significantly more than those in the active control condition (between group effect size d=0.77). Twenty-nine participants (48%) in ICBT were in remission (i.e., not fulfilling diagnostic criteria for their principal anxiety disorder) at post-treatment, compared to nine participants (15%) in the control condition. The total societal costs were 493.05€ lower in ICBT compared to the control condition. The ratio of cost and effect differences indicated that ICBT was cost-effective with regards to improvement in anxiety symptoms, but not with regards to improvements in quality of life.

4.3 Study II: Predicting outcome

4.3.1 Aims

The main aim of Study II was to explore whether demographic, clinical, and in-treatment process-related variables could predict non-remitters of the BiP Anxiety programme.

4.3.2 Methods

Study II presents secondary analyses of data from Study I. Participants were 117 children with an anxiety disorder who had undergone ICBT (either directly allocated to ICBT or crossed over to ICBT after completing the active control condition). The primary outcome measure was remission status (i.e., whether or not diagnostic criteria for the principal anxiety disorder was fulfilled) three months after completion of the ICBT programme. Predictor variables were categorised as either (1) demographic (i.e., gender, age of onset of the anxiety symptoms, parental psychopathology, parental sick leave, and school absenteeism), (2) clinical (i.e., severity of the principal anxiety disorder, type of principal anxiety disorder, type and number of comorbid anxiety disorders, clinicians' prediction at baseline of how well the treatment would work for the participant, and levels of anxiety and impairment), or (3) in-treatment process-related (i.e., early symptom reduction and treatment adherence).

4.3.3 Results

Three clinical variables and one in-treatment process-related variable remained in the final multivariate regression model best predicting remission status at 3MFU. This model explained 39.7% of variance in the sample. Principal diagnosis of SeAD (OR=3.988, p=0.042) and higher engagement in exposure practice (OR=2.314, p=0.004) were associated with a higher likelihood of being in remission. A more positive clinician prediction of treatment outcome also affected treatment outcome positively, but this effect was non-significant (OR=1.482, p=0.121). Severity of the principal anxiety disorder affected treatment outcome negatively (OR=0.325, p=0.005), whereby participants with higher severity were less likely to be in remission three months after having completed ICBT.

4.4 Study III: Long-term effects within a stepped-care model

4.4.1 Aims

The aim of Study III was to investigate whether the effects of ICBT were maintained 12 months after completion of the treatment and to evaluate the effect of additional F2F CBT for participants who did not benefit sufficiently from ICBT (i.e., non-remitters).

4.4.2 Methods

Study III also presents secondary analyses of data from Study I. Participants in this study were all the 123 children who had undergone the BiP Anxiety treatment protocol, either directly allocated to ICBT or crossing over after completing the active control condition. *N*=117 met diagnostic criteria for their principal anxiety disorder prior to starting ICBT. The primary outcome measure was change in symptom severity over time measured with the CSR. Participants were assessed at post-ICBT as well as three and 12 months after completion of ICBT (3MFU and 12MFU, respectively). Participants assessed as non-remitters (i.e., still fulfilling diagnostic criteria for their principal anxiety disorder) at 3MFU were offered up to 10 sessions of traditional F2F CBT delivered over a period of ten weeks. Participants receiving F2F CBT were assessed directly after treatment completion.

4.4.3 Results

The majority of participants were assessed as being in remission at 3MFU (62.4%; *n*=73) and they continued to improve from 3MFU to 12MFU (*d*=0.42; 95% CI 0.17 to 0.68). Considering the whole trial time period (pre-treatment to 12MFU), those classified as remitters improved with a large effect (*d*=2.42; 95% CI 1.78 to 3.07). This effect remained statistically unchanged when controlling for the use of supplementary service use during the trial period (*t*=0.163; *p*=0.871). Of the 43 participants assessed as non-remitters at 3MFU, 41.9% (*n*=18) accepted the offer to receive additional F2F CBT. Directly after the end of the F2F treatment, 70.6% (*n*=12) were assessed as being in remission. Considering the whole trial time period, these participants improved with a large effect (*d*=2.27; 95% CI 1.03 to 3.50). The participants who turned down the offer to receive F2F CBT (*n*=12) did so due to already receiving additional treatment at their local CAMHS. Of these 12 children, only four received treatments at their local CAMHS for their anxiety disorder. Participants turning down the offer to receive additional treatment also improved with a large effect (*d*=1.51; 95% CI 0.69 to 2.34).

4.5 Study IV: Dissemination in rural Sweden

4.5.1 Aims

The aim of Study IV was to evaluate the feasibility and potential effectiveness of ICBT when delivered in an outpatient CAMHS clinic in rural Sweden, Region Jämtland Härjedalen.

4.5.2 Methods

Participants (*N*=19) were 8 to 12 years old with a principal diagnosis of either SeAD, GAD or SP assessed with Mini International Neuropsychiatric Interview (M.I.N.I.) for children (Sheehan et al., 1998). All participants underwent the BiP Anxiety programme and local clinicians provided the treatment. The primary outcome measure was the Clinician Global Impression – Severity scale (CGI-S; Guy, 1976). Secondary measures included treatment completion/adherence, as well as treatment satisfaction and acceptability from both participating families and clinicians. Clinicians had weekly supervision from a researcher at Karolinska Institutet who also documented possible needed adaptations for a future larger trial.

4.5.3 Results

Of the initial 19 participants, 17 (89%) remained in treatment and completed on average six (*SD*=3) out of the total 12 modules. Thus, the majority of participants started with, or at least were given the rationale for, exposure. Missing data on secondary outcome measures were high due to participants forgetting to log in to fill in questionnaires and clinicians forgetting to report their assessments. Participants and clinicians were generally satisfied with treatment finding it acceptable. Participants improved significantly (t=4.371, p<0.001) with a large effect (d=1.51, 95% CI 0.75 to 2.28) from pre- to post treatment. Treatment gains were maintained up to three months after treatment completion. At follow-up, 13 participants (68%) no longer needed further treatment for any disorder and were discharged from the clinic.

5 DISCUSSION

5.1 Effects of ICBT for paediatric anxiety disorders

5.1.1 Efficacy of ICBT compared to an active control condition

Study I (Jolstedt, Wahlund, et al., 2018) was the second study to compare ICBT for paediatric anxiety disorders with a placebo-like condition (Khanna, Carper, Harris, & Kendall, 2017), but the first study to be adequately powered to detect differences between ICBT and the active control condition. The control condition in Study I was designed to act as a placebo condition, controlling for mode of delivery and non-specific therapeutic variables such as therapist attention and conducting homework assignments. Results clearly showed that ICBT was more efficacious than the control condition with regards to both remission status and clinician- and parent-rated child anxiety symptoms. The results in Study I support ICBT as an effective treatment for paediatric anxiety disorders.

5.1.2 Cost-effectiveness

Study I was the first to evaluate the cost-effectiveness of ICBT for paediatric anxiety disorders, and results showed that ICBT was more cost-efficient than the placebo control condition with regards to remission-status. More recently, Chatterton et al. (2019) also were able to show that ICBT was cost-effective when compared to F2F CBT, adding to the adoption of ICBT being a cost-effective treatment alternative for paediatric anxiety disorders.

5.1.3 Long-term effects

Study III showed that treatment gains received during ICBT were maintained up to 12 months after treatment completion. These results are comparable to those seen in previous trials investigating ICBT for paediatric anxiety disorders (March et al., 2009; Spence et al., 2011; Vigerland et al., 2017). Remission rates were however higher in Study III and effects smaller when compared to the mentioned trials. The long-term effects remained when controlling for supplementary mental health service use, which had not been done in any previous trial evaluating the long-term effects of ICBT for paediatric anxiety disorders.

5.1.4 Preliminary effectiveness when disseminated in rural Sweden

In Study IV (Jolstedt, Ljótsson, et al., 2018) BiP Anxiety was evaluated when delivered within an outpatient CAMHS clinic in rural Sweden. Anxiety symptoms were reduced and functional impairment improved with large effects indicating that treatment effects of the BiP Anxiety programme could be maintained when moving from research to clinical settings.

5.1.5 Methodological considerations

In Study I, ICBT was cost-effective when looking at remission, but not in measures of quality of life. Improvements in quality of life might not occur directly after treatment completion which was the primary endpoint of Study I. In CBT, children are asked to change their behaviours in a way that may increase anxiety in the short-term, which might be associated with a decrease in quality of life, or at least a lack of improvement. Supporting this hypothesis, in Study III, improvement in quality of life actually occurred between 3MFU and 12MFU. This is however only a hypothesis and must be further examined, for example by having the primary endpoint at a later assessment point in future trials. Quality of life in the cost-effectiveness analyses were based on child-reports only which could have affected the results. Disagreement between child and parent reports are well-known (Robitail, Siméoni, Ravens-Sieberer, Bruil, & Auquier, 2007), and it is therefore suggested that both reports should be taken into consideration when assessing symptoms in paediatric anxiety disorders (Comer & Kendall, 2004). Future cost-effectiveness evaluations of ICBT should also consider objective resource use data, for example from medical records instead of retrospective self-reports which was used in Study I. Lack of improvement in quality of life could also be due to limitations in the measure of quality of life. The measure of quality of life used in Study I, KIDSCREEN-10, is a valid measure of general health-related quality of life but not good at detecting specific changes, for example in psychosocial domains (Ravens-Sieberer et al., 2010)

The control group crossing over to receive ICBT directly after the end of treatment limits the conclusions that can be drawn about the outcomes at follow-up as seen in Study III. The assessments during the follow-up, three and 12 months after the end of the ICBT treatment, were not blind, which makes it unclear whether effects at follow-up are due to the treatment or to other confounding variables. It could however be ethically problematic to withhold potentially effective treatment from children for the whole follow-up period. Future studies evaluating the long-term effects of ICBT should consider using treatment-as-usual or pharmacological treatments as comparators for ICBT. This would potentially be credible control conditions that would allow for longer controlled follow-up periods.

The results in Study III showing smaller effects regarding symptom reduction and larger effects regarding remisson status could be due to the relatively low ratings of CSR at baseline. The mean CSR for the pooled sample in Study III prior to receiving ICBT was 4.64 (*SD*=0.75) compared to 6.07 (*SD*=0.58) seen in the trial by March et al. (2009). Since CSR is both a continuous measure of symptom severity (from 0 to 8) as well as a categorical measure of diagnostic status (a cut-off of 4), this could lead to an inflated effect with regards to remission-status if the participant has a low CSR at baseline. This is due to a low CSR at baseline only requiring a small improvement (i.e., decrease from CSR 4 to 3) to reach remission-

status, whereas a high CSR at baseline could improve largely (i.e., decrease from CSR 7 to 4) and still not reach remission-status. Despite this limitation, the CSR is commonly used and considered to be "gold standard"' in paediatric anxiety disorder research and it has shown good psychometric properties with regards to both remission status and symptom reduction (Silverman, Saavedra, & Pina, 2001).

A common methodological issue with effectiveness trials is the use of an open design, as in Study IV. This limits the internal validity and makes the results highly susceptible to confounders. It could be considered unethical to randomise participants to control conditions that are not recommended by the national guidelines in regular care, making robust trial designs in regular care more complex. However, the use of treatment as usual or medication as control conditions should make RCTs more feasible in regular care. Also, since only a small sample was used, and since participants were chosen by clinicians involved in the trial (i.e., not systematically), the generalisability of the results becomes greatly limited.

The participants in the Studies I to IV were less severe than those in previous trials evaluating ICBT with regards to the primary outcome measure, clinician assessed functional impairment and child and parent reported child-anxiety symptoms (see e.g., March et al., 2009). However, in the case of dissemination in Sweden, ICBT would probably primarily target those with mild- to moderate anxiety disorders and those who have the capacity to work more independently. Hence, one could argue that the results in Studies I to IV are generalizable to the sample it aims to target.

The active control condition was created specifically for Study I, making the results not directly comparable to any already existing treatments. However, these results still give valuable knowledge about the efficacy and cost-effectiveness of ICBT when compared to a psychosocial intervention, with similar therapist contact and delivery method.

5.2 Understanding for whom ICBT is suitable

5.2.1 Predicting treatment outcome

Study II showed that the children with higher levels of clinician rated anxiety symptoms (measured with CSR) were less likely to be in remission three months after completion of ICBT which is in line with the findings by Morgan et al. (2018). The negative impact of symptom severity on treatment outcome are well known, at least for F2F CBT (e.g., Knight, McLellan, Jones, & Hudson, 2014). Additionally, Taylor et al. (2018) were able to show that the single treatment of F2F CBT was appropriate for children with mild to moderate severity, but not for those with severe anxiety disorders. Hudson et al. (2013) further found that an accumulated risk (e.g., severity, comorbidity, parental psychopathology) was associated with less likelihood of being in remission after receiving F2F CBT.

It is likely that ICBT is less suitable for severe anxiety disorders compared to F2F CBT since it is to a greater extent based on self-support. Higher motivation and less family stressors might be required to benefit from ICBT. Motivation (Kodal et al., 2018; Wergeland et al., 2016) and compliance (Lee et al., 2019 in F2F CBT) have previously been suggested to predict positive outcome for paediatric anxiety disorders. Similar results are seen in Study II were higher engagement in exposure, i.e., higher motivation to conduct behaviour change had a positive impact on treatment outcome. These results could indicate that motivation and treatment compliance could be assessed early in treatment to detect those at risk of becoming non-remitters. Also, if low motivation is detected early, this could specifically be targeted as part of treatment, potentially increasing the likelihood of a more positive treatment outcome.

Study II also found that participants with the principal anxiety disorder of SeAD were more likely to be in remission compared to participants with any other anxiety disorder. Study II did however not find that the diagnosis of SoAD had a negative impact on treatment outcome, which has been suggested in previous trials exploring predictors of outcome for F2F CBT (e.g., Knight, McLellan, Jones, & Hudson, 2014). This discrepancy could be due to Study II having a relatively homogenious sample, not including the most severe children with anxiety disorders.

5.2.2 Non-remitters of ICBT

The non-remitters at 3MFU in Study III were given the option to receive additional treatment, however, less than half accepted this offer. Participants who declined the offer to receive additional treatment were more severe with regards to their principal anxiety disorder and were more likely to have a principal diagnosis of SoAD compared to those being in remission. These participants also had a higher number of comorbid disorders compared to both participants in remission as well as the non-remitters accepting the offer to receive additional treatment. The main reason for declining treatment were due to already receiving treatment at the local CAMHS prior to 3MFU, for either severe anxiety symptoms or other comorbid diagnoses (e.g., depression, suspected neurodevelopmental disorder). This could indicate that ICBT is least suitable for those with more severe conditions.

5.2.3 Missing and attrition

Missing data and drop-out in all studies (Study I to IV) was associated with higher symptom severity and, in some cases, higher functional impairment. Apart from limiting the generalisability of the findings, these results also imply that ICBT might not be ideal for participants with more severe anxiety disorders.

5.2.4 Methodological considerations

Trials investigating predictors of treatment outcome are usually secondary analyses of conducted RCTs powered to detect differences between two groups. Therefore, few trials examining predictors of outcome have enough power to detect more complex interactions. Understanding for whom treatment works is clinically relevant, especially when taking steps towards implementation in regular care. These types of trials should therefore be prioritised in the future. Also, the statistical analyses most often used to predict outcomes (i.e., regression analyses) might not be best suited, due to the risk of over-fitting the data and thus confounding results (Fusar-Poli, Hijazi, Stahl, & Steyerberg, 2018). More complex analyses, such as machine learning approaches (e.g., Lenhard et al., 2018), should be adopted to better understand predictors of outcomes in clinical trials.

The use of different outcome measures (e.g., remission-status or change in symptoms severity) and time-points (e.g., three or 12 months after completed treatment) between studies that aim to predict outcome could be a problem in understanding for whom treatment is most beneficial (Knight, McLellan, Jones, & Hudson, 2014; Nielsen, Vangkilde, Wolitzky-Taylor, Daniel, & Hageman, 2016; Walczak, Ollendick, Ryan, & Esbjørn, 2018). A consensus about which outcome measures to use, and at which time-points, are needed to allow comparisons between trials.

5.3 How ICBT should be disseminated

The aim of ICBT is to increase access to evidence-based psychological treatments. However, the way in which ICBT should be disseminated, implemented, and organised in regular care remains unclear, at least for paediatric anxiety disorders.

Three potential ways to disseminate ICBT for children with anxiety disorders have been investigated as part of this thesis: (1) within a specialised unit part of the CAMHS, (2) in an already existing CAMHS outpatient clinic, and (3) within a stepped-care model of delivery, which is possible in both a specialised ICBT clinic as well as part of a CAMHS outpatient clinic.

5.3.1 Specialised ICBT clinic

In Study I, ICBT was evaluated and delivered as part of a potential future specialised ICBT clinic within the CAMHS in Region Stockholm. The clinic primarily received children and families via self-referrals, but also referrals from general practitioners (GPs) and other CAMHS. The staff at the clinic were clinicians from CAMHS and the administrative work within the trial had been harmonized with what is required at regular outpatient clinics.

Only few referrals came from GPs and CAMHS which could indicate that a specialised clinic does not increase access to CBT for those already in contact with mental health care practitioners. However, recruitment was not difficult in Study I and only participants fulfilling diagnostic criteria for a principal anxiety disorder (i.e., had at least moderate severity/functional impairment/disability) were included. This indicates that a specialised clinic does increase access to evidence-based treatment for a population in need.

There are some possible benefits to have a specialised clinic in the region of Stockholm, where the CAMHS are heavily burdened and have a large turn-over of employees. This will allow for the specific ICBT competence and knowledge to be maintained. Such a model of delivery could also facilitate research on ICBT for paediatric mental health disorders, integrating clinic and research which has been suggested as an important factor in the implementation of evidence-based treatments (Lilienfeld, Ritschel, Lynn, Cautin, & Latzman, 2013).

5.3.2 Part of outpatient clinic in rural area

In Study IV, another model of dissemination was tested. Region Jämtland Härjedalen is approximately the size of Denmark with only one CAMHS clinic, making remote delivery of treatments necessary. The preliminary results regarding the effectiveness of ICBT in this particular setting showed that treatment effects were kept. Supervision, training and support were however essential, which have previously been found to be important in facilitating the implementation of new treatments (Reid et al., 2017; Ringle et al., 2015). Delivering ICBT as part of an outpatient clinic might be necessary in small regions who do not have the resources to create a specialised unit for ICBT. Also, such an approach might be imperative in rural areas where long distances to health care facilities is a struggle. Implementation directly to an outpatient clinic could help ensure that children visiting these health care facilities are provided with a standardised treatment that is known to be effective.

5.3.3 Stepped-care model of delivery

The majority of participants in Study III who accepted the offer to receive F2F CBT at 3MFU improved significantly indicating that additional treatment within a stepped-care approach is feasible. A large proportion of participants continued to improve from post-treatment to 3MFU, which could indicate that stepping up treatment at 3MFU is a good time-point. However, there is a need to better understand for whom ICBT is effective, since a large proportion of non-remitters could not wait until 3MFU to receive additional treatment. Stepping up could be conducted earlier for participants in risk of not benefiting sufficiently, either by changing modality or intensity of treatment. The use of telephone sessions when stepping up treatment could be considered, since this modality allows for treatment to be geographically

independent. Such an approach, where early detection of non-responders of ICBT are given additional telephone-support, has been evaluated for adults with insomnia with promising results (Forsell et al., 2019). This has however not yet been done in paediatric ICBT research. Trials designed to evaluate when treatment should be stepped up and/or intensified could help make models of delivering ICBT efficient and cost-effective.

5.3.4 Methodological considerations

None of the studies in this thesis were specifically designed to evaluate the effects of implementation (i.e., not based on implementation science, Williams & Beidas, 2019). Instead, the two trials were primarily designed to investigate the efficacy and feasibility of ICBT in different clinical settings. However, information regarding possibilities and difficulties in the implementation of ICBT have still been acquired. For instance, a clear advantage of ICBT is that the treatment is manualised to a great extent, which limits therapist drift and hence increases fidelity to treatment, which has been proposed as one of the major difficulties when implementing evidence-based treatment to regular care (Novins et al., 2013). Also, in Study IV, clinicians asked for more support and supervision, which is considered important in implementation science (Ringle et al., 2015). The pilot feasibility design of Study IV was created to collect information about needed adjustments before conducting a larger trial. Adapting treatment to better suit clinical settings and then evaluating it has been done in F2F CBT trials for paediatric anxiety disorders with promising results (Weisz, Bearman, Santucci, & Jensen-Doss, 2017).

Study III was a naturalistic evaluation of a stepped-care approach. The observed similarities and differences at 12MFU after treatment completion could not be compared since participants chose and ended up receiving treatment based on personal characteristics (such as symptom severity) rather than by chance (i.e., by randomisation). However, the stepped-care approach investigated in Study III still could provide decision makers with knowledge about the effects of additional treatment for those accepting the offer of further treatment within the trial. It also provided information on which characteristics were associated with not being able to wait until the 3MFU time point to receive additional treatment.

5.4 Ethical considerations

5.4.1 Informed consent/assent

When conducting research that involves children, the element of informed consent becomes more complex since it is generally harder for the researcher to make sure that the child fully understands what it means to be part of a research study

or even to be part of a psychological treatment. The children in Studies I to IV were between 8 and 12 years and did not have to give written consent, but instead gave oral assent, which is when the child verbally expresses his/her willingness to participate (WMA, 2001).

Two separate documents were used to inform families about the trial; one written document for the parents/legal guardians and child version with less text (bullet-points when possible) and a schematic, visual overview of the study design. The child was thoroughly informed about the study and treatment in an age appropriate manner, and was encouraged to ask questions. The clinician presenting the study emphasised the child's autonomy and that he or she could say "no" to participation even though the primary caregivers would think otherwise, and that the researcher would not be upset or disappointed if the child declined participation. The child was also informed during the meeting that, in case they wanted to withdraw from the trial, he/she would not have to explain why they had chosen to do so.

5.4.2 Randomisation

An ethical consideration in the large RCTs (i.e., Studies I to III) was that children could be allocated to receive the active placebo control treatment, a treatment that, to the best of our knowledge, at that time was less effective than ICBT in reducing anxiety symptoms. However, to ensure the relative contribution of a new treatment, an RCT design is necessary (Akobeng, 2005), and hence having a control group that withholds potentially efficient treatment can be motivated.

In this trial, an active control condition that could be beneficial for participating families was chosen. The active control condition was based on a parent management training component known to have positive effects on parent-child relationship and the child's self-esteem (Kaminsky & Valle, 2008). Participants were clearly informed about the chance (1:1) of being allocated to either intervention, and about the current knowledge about both conditions (i.e., possible benefits), which could have affected the credibility of the control condition. Double-blinded studies could eliminate this bias, but are difficult and potentially impossible to conduct in research evaluating psychological treatment.

Also, the trial was designed to have a primary endpoint directly after treatment completion (i.e., after 12 weeks) so that children randomised to the control group would be crossed over to ICBT as soon as possible. Nonetheless, having the primary endpoint directly after treatment limits the conclusions on the long-term effects of ICBT, since these effects no longer are controlled for (i.e., increased risk of confounding variables).

5.4.3 Assessing symptoms before and during treatment

In ICBT there is a potential risk of not detecting deterioration in psychiatric symptoms (e.g., anxiety and/or depression), since the clinician does not meet the child in person during treatment. Participants were instructed to fill out online questionnaires every three weeks regarding anxiety and depressive symptoms to systematically monitor the participants throughout the treatment period. Also, participants were asked about their week at the beginning of each chapter and questioned about whether there was anything that had happened that they wished to discuss with their clinician. Inactive families (families who did not log in to the platform according to plan) were contacted via telephone to make sure that inactivity was not due to deterioration of symptoms.

Having conservative inclusion and exclusion criteria could help reduce complexity in the included sample, minimising the risk of including the most severely ill children. It is however important with regards to generalisability (external validity) and to be able to make a fair estimation of the efficacy of ICBT, to include all patients meeting relevant inclusion criteria and not to refer patients to other treatment options too easily. Having weekly clinical supervision allows for discussion regarding different clinical issues that arise before, during, and after treatment.

6 CONCLUSIONS

ICBT is an effective treatment for paediatric anxiety disorders, leading to reduction in anxiety symptoms and functional impairment, when compared to an active placebo control condition. ICBT has also shown to be cost-effective, at least with regards to remission status. Children seem to further improve their symptoms up to three-months after treatment completion, and treatment gains are maintained up to 12 months after treatment completion. ICBT also seems to be effective when delivered in an outpatient CAMHS clinic in rural Sweden, where local clinicians provide the treatment as part of regular care.

ICBT appears to be best suited for children with mild to moderate anxiety disorders which should be taken into consideration when offering ICBT in regular care. Also, engagement in exposure could be an important process-related variable to assess early in treatment to detect potential non-remitters.

ICBT should be implemented as part of a specialised clinic to ensure the nessessary education, support and supervision, and also to facilitate research. However, other models of implementation might be required in rural areas where resources are limitied, making it difficult having a specialised clinic. ICBT seems to be suitable as a first-line treatment option within a stepped-care model of treatment delivery, for at least a subgroup of individuals. Novel ways of detecting non-remitters or patients in need of other or more enhanced interventions early in ICBT should be explored in future trials.

In summary, ICBT is a clinically efficacious and cost-effective treatment for children with moderately severe anxiety disorders. ICBT is standardised and scalable which makes it ideal for dissemination to regular care, as long as adequate support and supervision is provided.

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