LUND UNIVERSITY

The Effectiveness and Acceptability of Internet-Delivered Cognitive Behavioral Therapy for Depression and Anxiety in Routine Clinical Care

Johansson, Olof

2023

Total number of authors:
1

The Effectiveness and Acceptability of Internet-Delivered Cognitive Behavioral Therapy for Depression and Anxiety in Routine Clinical Care

OLOF JOHANSSON

DEPARTMENT OF PSYCHOLOGY | FACULTY OF SOCIAL SCIENCES | LUND UNIVERSITY

The Effectiveness and Acceptability of Internet-Delivered Cognitive Behavioral Therapy for Depression and Anxiety in Routine Clinical Care
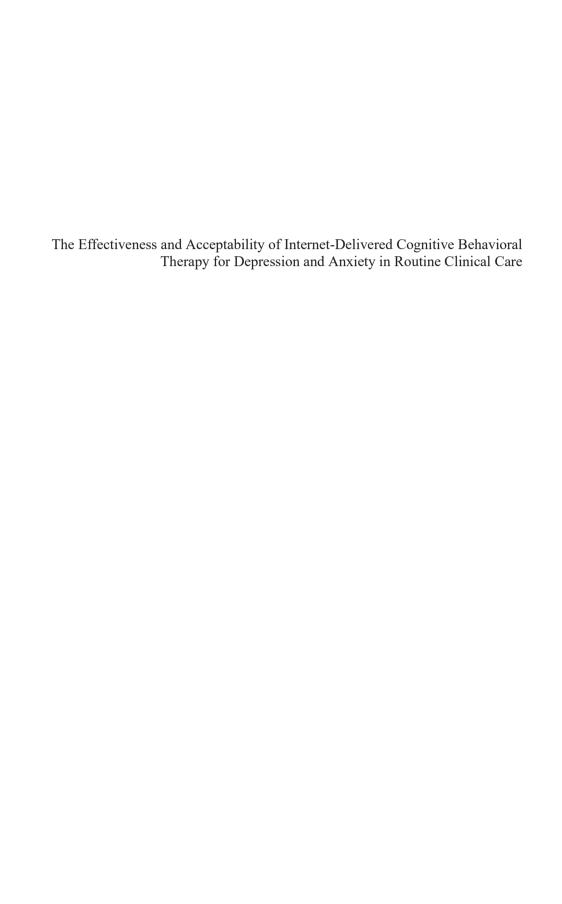
The Effectiveness and Acceptability of Internet-Delivered Cognitive Behavioral Therapy for Depression and Anxiety in Routine Clinical Care

Olof Johansson

LUND
UNIVERSITY

Organization: LUND UNIVERSITY

Document name: DOCTORAL DISSERTATION   **Date of issue** September 15, 2023

Author: Olof Johansson   **Sponsoring organization:**

Title and subtitle: The Effectiveness and Acceptability of Internet-Delivered Cognitive Behavioral Therapy for Depression and Anxiety in Routine Clinical Care

Abstract:

Evidence-based psychological interventions delivered via the internet and mobile technologies (Digital Mental Health) hold the promise of reducing barriers to care, including difficulties accessing treatment because of distance, cost, work and family commitments, and limited provider capacity. Such barriers represent a particular challenge for individuals with depression and anxiety, that tend to co-occur and to recur following treatment cessation, and which are among the most common and burdensome illnesses worldwide. Numerous randomized controlled trials have shown that internet-delivered cognitive behavioral therapy (ICBT) for depression and anxiety is highly effective in reducing the severity and impact of symptoms and improving overall functioning when compared to no-treatment in individuals recruited online. However, important knowledge gaps remain about the acceptability and effectiveness of ICBT when delivered in routine psychiatric care settings. Bridging these knowledge gaps is especially important now as ICBT is being disseminated at a rapid pace in Sweden. The current program of research was carried out with the purpose of investigating the usefulness, acceptability, and effectiveness of ICBT when delivered in a routine psychiatric care setting to adults. Study I was a naturalistic evaluation of the sustained effectiveness of treatment for depression in a psychiatric out-patient setting and examination of psychosocial and clinical predictors of symptom recurrence and relapse to a depression diagnosis. Study II was a randomized waitlist controlled trial evaluating the acceptability and effectiveness of an 8-week ICBT program for depression delivered in a routine psychiatric setting. Study III was a qualitative study that sought to identify why patients with mixed symptoms of generalized anxiety disorder (GAD) and depression had non-adhered to an ICBT program for GAD. Overall, the findings indicate that ICBT for depression delivered in a routine outpatient psychiatric care setting is acceptable and effective in reducing depressive symptoms as well as mitigating anxiety. However, the study also highlights challenges related to treatment adherence and the need for more effective interventions to prevent relapse and recurrence in psychiatric depression treatment. Further research and improvements in ICBT delivery are warranted to address these issues and enhance mental health care outcomes in such settings.

Key words:

Effectivenesss, Internet-Delivered Cognitive Behavioral Therapy, Depression, Anxiety, Non-adherence, Acceptability, Psychiatry

Language English   **ISSN and key title**:

ISBN:

978-91-8039-785-8 (print)

978-91-8039-786-5 (digital)

Recipient's notes   **Number of pages**: 69

Price   Security classification

Signature   Date 2022-08-21

The Effectiveness and Acceptability of Internet-Delivered Cognitive Behavioral Therapy for Depression and Anxiety in Routine Clinical Care

Olof Johansson

LUND
UNIVERSITY

Table of Contents

Acknowledgements

Abstract

Evidence-based psychological interventions delivered via the internet and mobile technologies (Digital Mental Health) hold the promise of reducing barriers to care, including difficulties accessing treatment because of distance, cost, work and family commitments, and limited provider capacity. Such barriers represent a particular challenge for individuals with depression and anxiety, that tend to co-occur and to recur following treatment cessation, and which are among the most common and burdensome illnesses worldwide. Numerous randomized controlled trials have shown that internet-delivered cognitive behavioral therapy (ICBT) for depression and anxiety is highly effective in reducing the severity and impact of symptoms and improving overall functioning when compared to no-treatment in individuals recruited online. However, important knowledge gaps remain about the acceptability and effectiveness of ICBT when delivered in routine psychiatric care settings. Bridging these knowledge gaps is especially important now as ICBT is being disseminated at a rapid pace in Sweden. The current program of research was carried out with the purpose of investigating the usefulness, acceptability, and effectiveness of ICBT when delivered in a routine psychiatric care setting to adults. Study I was a naturalistic evaluation of the sustained effectiveness of treatment for depression in a psychiatric out-patient setting and examination of psychosocial and clinical predictors of symptom recurrence and relapse to a depression diagnosis. Study II was a randomized waitlist-controlled trial evaluating the acceptability and effectiveness of an 8-week ICBT program for depression delivered in a routine psychiatric setting. Study III was a qualitative study that sought to identify why patients with mixed symptoms of generalized anxiety disorder (GAD) and depression had non-adhered to an ICBT program for GAD. Overall, the findings indicate that ICBT for depression delivered in a routine outpatient psychiatric care setting is acceptable and effective in reducing depressive symptoms as well as mitigating anxiety. However, the study also highlights challenges related to treatment adherence and the need for more effective interventions to prevent relapse and recurrence in psychiatric depression treatment. Further research and improvements in ICBT delivery are warranted to address these issues and enhance mental health care outcomes in such settings.

Summary in Swedish

Psykologiska evidensbaserade interventioner som förmedlas via internet och mobila teknologier (Digital Mental Health) har potential att minska tröskeln för att få vård, samt minska svårigheter att få tillgång till behandling på grund av avstånd, kostnader, arbete och familjekonflikter eller begränsad kapacitet hos vårdgivare. Den här typen av hinder utgör en särskild utmaning för personer med depression och ångest, besvär som tenderar att förekomma samtidigt och dessutom återkomma efter behandlingsavslut, och som är bland de vanligaste och mest påfrestande sjukdomarna i ett globalt perspektiv. Ett stort antal randomiserade kontrollerade studier har visat att internetbaserad kognitiv beteendeterapi (IKBT) för depression och ångest är mycket effektivt för att minska svårighetsgraden och påverkan av symtomen samt för att förbättra den övergripande funktionsförmågan jämfört med ingen behandling hos individer som rekryterats online. Det finns dock fortfarande viktiga kunskapsluckor kring metodens acceptabilitet och effektivitet när den förmedlas inom psykiatrisk rutinvård. Att överbrygga dessa kunskapsluckor är särskilt viktigt nu när IKBT sprids snabbt i Sverige. Den aktuella avhandlingen genomfördes med syfte att undersöka användbarheten, acceptabiliteten och effektiviteten av IKBT när det används inom psykiatrisk rutinvård för vuxna. Studie I var en naturalistisk utvärdering av den långsiktiga effekten av depressionsbehandling på en psykiatrisk öppenvårdsmottagning, dessutom undersöktes i vilken utsträckning psykosociala och kliniska faktorer predicerar återfall och tillbakagång till en depressionsdiagnos. Studie II var en randomiserad studie med väntliste-kontrollgrupp som utvärderade acceptabiliteten och effektiviteten av ett 8-veckors IKBT-program för depression, förmedlat inom psykiatrisk rutinvård. Studie III var en kvalitativ studie som syftade till att identifiera varför patienter med blandade symtom på generaliserat ångestsyndrom (GAD) och depression inte fullföljde ett IKBT-program för GAD. Sammanfattningsvis tyder resultaten på att IKBT för depression, förmedlat inom psykiatrisk öppenvård, är acceptabelt och effektivt för att minska depression- och ångestsymtom. Resultaten belyser dock även utmaningar såsom problem med följsamhet till behandling och behovet av mer effektiva interventioner för att förhindra återfall i depression inom psykiatrisk vård. Ytterligare forskning och förbättringar av IKBT behövs för att hantera dessa frågor och förbättra utfallet av psykiatrisk vård.

List of Studies

I.   Johansson, O., Lundh, L.-G., & Bjärehed, J. (2015). 12-Month Outcome and Predictors of Recurrence in Psychiatric Treatment of Depression: A Retrospective Study. *Psychiatric Quarterly, 1–11*. DOI: 10.1007/s11126-015-9341-y

II.   Johansson, O., Bjärehed, J., Andersson, G., Carlbring, P., & Lundh, L.-G. (2019). Effectiveness of guided internet-delivered cognitive behavior therapy for depression in routine psychiatry: A randomized controlled trial. *Internet Interventions, 17*, 100247. DOI: 10.1016/j.invent.2019.100247

III.   Johansson, O., Michel, T., Andersson, G., & Paxling, B. (2015). Experiences of non-adherence to Internet-delivered cognitive behavior therapy: A qualitative study. *Internet Interventions, 2*(2), 137–142. DOI: 10.1016/j.invent.2015.02.006

Abbreviations

ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CBT	Cognitive Behavior Therapy
DSM	Diagnostic and Statistical Manual of Mental Disorders
GAD	Generalized Anxiety Disorder
GAD-Q-IV	Generalized Anxiety Disorder Questionnaire-IV
GT	Grounded Theory
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale - Anxiety
HADS-D	Hospital Anxiety and Depression Scale - Depression
ICBT	Internet-Delivered Cognitive Behavior Therapy
ICD	International Classification of Diseases
IKBT	Internetbaserad Kognitiv Beteendeterapi
IPT	Interpersonal Therapy
MADRS-S	Montomery Åsberg Depression Rating Scale – Self-Report Version
MDD	Major Depressive Disorder
OQ-45	Outcome Questionnaire-45
PSWQ	Penn State Worry Questionnaire
RCT	Randomized Controlled Trial
SCID-I	Structured Clinical Interview for DSM-IV
WHO	World Health Organization

Introduction

Major Depressive Disorder

Major Depressive Disorder (MDD) is one of the eight depressive disorders listed in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2022). DSM-5 defines MDD by the presence of either a depressed mood or loss of interest in activities for most of the day, nearly every day, over a two-week period, along with four additional symptoms from a list of six: weight loss/gain, slowed thinking/movements, fatigue, feelings of worthlessness/excessive guilt, diminished concentration/indecisiveness, and recurrent thoughts of death, suicidal ideation, or attempted suicide. The International Classification of Diseases ICD-11 (World Health Organization, 2019), the latest version, uses almost identical criteria to define what is referred to as "Depression." For the purpose of this investigation, the term "depression" will be used to encompass both MDD in DSM-5 and Depression in ICD-11.

Depression is the fourth most common health problem worldwide, affecting approximately 6% of the world population at any given time and close to 20% over the course of a lifetime, placing it on par with diabetes (Bromet et al., 2011; Ferrari et al., 2013; Whiteford et al., 2015). The World Health Organization (WHO) estimates that as many as 350 million people worldwide suffer from depression in a single year (Whiteford et al., 2015).

Depression is about twice as common among women compared to men (Seedat et al., 2009). Apart from constituting a significant burden of disease, depression is also associated with an increased risk of developing somatic disorders such as heart disease, stroke, and diabetes, thereby further complicating the treatment of depression and related health issues (Whooley & Wong, 2013). Depression is strongly linked to the risk of suicide, with psychiatric disorders present in 90% of suicide cases, and depression being the most prevalent among these disorders, occurring in up to two-thirds of the cases (Hawton et al., 2013). It is estimated that the rate of suicide is approximately twenty times higher among people with depression than in the general population (Chesney et al., 2014).

Etiology

Depression is considered a complex condition with a wide range of factors that contribute and interact in its development, and no single model can explain all aspects of the disease (Otte et al., 2016). The genetic component, or heritability, of the disorder has been estimated at approximately 35% (Flint & Kendler, 2014). Various environmental risk factors have been extensively researched and linked to depression, although many of these factors remain inconclusive and potentially bidirectional in their causality. For instance, loneliness may lead to depression, but depression itself can also make it more challenging to establish and maintain relationships. Studies have found that life stressors increase susceptibility to psychopathology (Lewis & Rudolph, 2014). Simultaneously, individuals' behavior and choices play an active role in causing negative life events (Rnic et al., 2023). This interaction creates a potentially accelerating negative cycle of mental illness.

In a comprehensive umbrella review conducted by Köhler et al. (2018), which included 134 meta-analyses applying strict evidence criteria for risk factors, several noteworthy risk factors for depression were identified. These factors include widowhood, physical abuse during childhood, obesity, having 4-5 metabolic risk factors, sexual dysfunction, and job strain. These findings represent some of the strongest and most clearly established risk factors for depression.

A commonly used model to describe the development of depression involves the interaction between genes and the environment, which can lead to depression. This model suggests that genetic vulnerability, in combination with environmental risk factors mentioned earlier, and the absence of protective factors like social support and exercise, contribute to the onset of depression (Otte et al., 2016). However, it is important to note that no single model can explain all aspects of the disease. The choice of a model is often based on pragmatism, focusing on specific aspects of depression that can be influenced by the intervention being studied. In this dissertation, the cognitive and behavioral models of depression are of particular importance as they provide a framework for interventions. The behavioral model of depression connects avoidance (the attempt to escape, prevent, or minimize contact with aversive stimuli) to depression. By avoiding situations, interactions, and behaviors that are perceived as aversive, individuals engage in more passive behavior and withdraw from situations that could produce positive stimuli. This pattern reinforces and sustains a state of depressed and passive behavior (Carvalho & Hopko, 2011; Ferster, 1973; Lewinsohn, 1974; Martell et al., 2001). The behavioral model is complemented by the cognitive behavioral model proposed by Beck and colleagues (Beck et al., 1979), which suggests that early life events influence thought patterns, leading to negative interpretations of oneself, the world, and the future. These negative cognitive distortions or biases affect attention and reasoning, creating pessimistic and depressed thought patterns. The cognitive behavioral model was later developed and expanded to highlight the crucial role of

rumination and repetitive negative thoughts in the development and maintenance of depression (Watkins, 2016). The cognitive and behavioral models are influential and of wide clinical use, simultaneously though it can be argued that these models represent pieces of a larger puzzle in the context of depressive etiology (Otte et al., 2016). Nonetheless, they play a crucial role in the development of interventions for depression.

The available evidence suggests multiple potential etiologies for depression, with a common pathway involving individuals experiencing trauma, bereavements, or repeated exposure to aversive stressors. These stressors can be either internal, such as chronic pain, or external, such as poverty and exposure to violence. These experiences, in combination with genetic and psychological vulnerabilities, contribute to the development of depression. Over the years, research has provided a more detailed understanding of the pathways leading to depression. For instance, studies have identified specific genes associated with depression (Pantelis et al., 2014) and have delineated the types of stressors that increase the risk for depression (Köhler et al., 2018). Additionally, the integration of knowledge about the personality trait neuroticism has enhanced our understanding of how it moderates the pathogenic effects of stress exposure in the development of depression (Barlow et al., 2014; Kendler et al., 2004).

Intervention-focused models, such as the behavioral and cognitive models, have also made efforts to integrate distinct psychiatric conditions described in diagnostic manuals (e.g., American Psychiatric Association, 2022) into more comprehensive models of emotional problems, as seen in Barlow's Unified Protocol (Barlow et al., 2004, 2014). Barlow's model recognizes the commonalities in etiology, shared vulnerability, and similarities in psychological processes across different disorders. It presents an overarching process that leads to various psychiatric disorders, differing primarily in their outward manifestations, while sharing many underlying risk and maintenance factors. These factors include genetic predisposition, familial and social environment, negative life events or trauma, hyperarousal, irritability, biased attention to threat or loss cues, avoidance tendencies, and perseverative or negative thinking styles. This perspective is bolstered by a growing body of evidence supporting substantial overlap in genetic and psychosocial risk and maintenance factors across diverse psychiatric disorders (Arango et al., 2021; Martin et al., 2018).

Anxiety and Depression

Depression rarely occurs in isolation, as evidenced by population-based studies indicating that approximately 70% of adults who meet diagnostic criteria for depression also experience at least one additional somatic or mental illness. The

most prevalent form of psychiatric comorbidity is clinically significant symptoms of anxiety (>70%) or one or more anxiety disorders (>50%) (Hasin et al., 2018; Steffen et al., 2020). Researchers widely acknowledge the shared or overlapping etiologies, both genetic and psychosocial, between depression and anxiety. For the majority of individuals affected, these two conditions are interconnected (Kalin, 2020). This recognition led to the addition of an additional specifier ("With Anxious Distress") to the DSM-5 criteria for Major Depressive Disorder (American Psychiatric Association, 2013). Throughout this thesis, unless otherwise stated, it is assumed that individuals identified and offered treatment for depression are highly likely to also experience clinically significant symptoms of anxiety, and vice versa.

Treatment

Fortunately, there is now a substantial body of evidence from randomized controlled trials (RCTs) demonstrating that psychotherapies and pharmacotherapies are moderately to strongly effective compared to no treatment, and moderately effective compared to care-as-usual or pill placebo in treating depression and comorbid symptoms of anxiety (Cuijpers et al., 2009; Cuijpers, 2017; Gartlehner et al., 2017). While various forms of psychotherapy have shown effectiveness, cognitive-behavioral therapy (CBT) has been extensively studied and consistently identified as the most effective treatment, with a mean pooled effect size from RCTs of Hedges' g = 0.67 (95% CI [0.60, 0.75]). CBT has demonstrated efficacy in individual or group formats, as well as through telehealth interventions (Cuijpers, 2017). Moreover, recent meta-analyses have found that internet-delivered CBT (ICBT), both therapist-guided and unguided, is effective for individuals with depression (Karyotaki et al., 2021). Treatment outcomes are influenced by factors such as the type of treatment (e.g., antidepressant medication, pill placebo, psychotherapy) and patient clinical and demographic characteristics (Burcusa & Iacono, 2007; Moriarty et al., 2022; Sim et al., 2016; Vittengl et al., 2007; Williams et al., 2009).

It is important to acknowledge that Cognitive Behavioral Therapy (CBT) and Internet-delivered CBT (ICBT) for depression encompass a wide range of interventions aimed at addressing symptoms of depression and anxiety. These interventions include: 1) providing psychoeducation about mental health; 2) teaching stress reduction techniques and enhancing emotion regulation skills (e.g., goal-setting, problem-solving, relaxation, mindfulness); 3) identifying and modifying dysfunctional beliefs and behaviors that trigger or maintain negative mood states and impair overall functioning (e.g., cognitive restructuring); 4) promoting engagement in activities that can improve mood (e.g., behavioral activation); and 5) encouraging broader healthy lifestyle changes (e.g., increasing

exercise, reducing alcohol and substance use) (Cuijpers, 2017; Karyotaki et al., 2021).

Challenges in Treatment Research

While there is international consensus on the efficacy of CBT and somewhat a general agreement regarding the necessary content of CBT protocols, two significant challenges persist in relation to this treatment for depression. Firstly, there is a need to understand how and for whom CBT works best to enhance treatment effectiveness. Secondly, efforts must be made to increase access to CBT in routine care settings while maintaining the efficacy levels achieved in research conditions, in order to reduce the massive burden of disease linked to depressive disorders.

Despite decades of research on psychotherapy for depression, including CBT, there has been no substantial improvement in the effectiveness of psychotherapies for depression (Patel et al., 2018). This may be due to the fact that we still lack knowledge about how different psychotherapies, or their individual components, lead to clinical improvements (Furukawa et al., 2016). Indeed, researchers have argued from meta-analytic findings that the effects of psychotherapy for depression, including CBT, are over-estimated, in part because of the significant heterogeneity in symptoms of individuals presenting for depression treatment (Cuijpers et al., 2010, 2020). Randomized controlled trials (RCTs) and meta-analyses provide group-level statistics, which do not provide insights into why more than one-third of patients fail to recover within a 3-6 month treatment period, while 53% naturally recover within 12 months without treatment. Similarly, comparing average outcomes of 66% recovery for CBT to the 35-40% recovery for pill placebo (Cuijpers et al., 2020) does not explain the individual-level variations in treatment outcomes. Lack of significant progress in treatment efficacy, coupled with emerging evidence suggesting similar outcomes among various types of therapies, has prompted some researchers to advocate for a key focus in depression research: reducing the burden of illness for example by increasing access to guided self-help, such as ICBT, rather than comparing different treatment protocols against each other (Cuijpers, 2017).

Help-Seeking

While clinical researchers make continued efforts to better understand how psychotherapies for depression work and for whom, there remains a need to increase access to existing treatments for depression, with CBT still being the primary

indicated form of psychotherapy around the world (Cuijpers et al. 2020). The available evidence suggests that only a small proportion of the individuals suffering from depression globally receive adequate treatment (Thornicroft et al., 2017). Numerous barriers to care have been identified, including a pervasive sense of stigma associated with diagnosis and help-seeking, insufficient screening for mental illnesses, difficulties physically accessing care (including the burden of work and child/family care), low treatment capacity, and the cost of healthcare (Wainberg et al., 2017). Even in a wealthy country like Sweden, which has made sustained efforts over several decades to reduce such barriers to care, population surveys find that only 50% of those diagnosed with depression during a 12-month period received adequate treatment during that period, indicating that depression remains an undertreated condition in Sweden (Johansson et al., 2013; Olsson et al., 2021).

Relapse and Recurrence

Despite successful treatment for depression, the risk of relapse (new depressive episodes) remains high, with rates varying significantly in different settings. On average, approximately half of patients will experience a relapse or recurrence within a year (Ali et al., 2017; Beshai et al., 2011, p. 2017; Hollon et al., 2005; Moriarty et al., 2022; Shapiro et al., 1995; Sim et al., 2016). Relapse refers to the re-emergence of depressive symptoms after some level of improvement but before full recovery, while recurrence involves the onset of a new depressive episode after recovery (Frank et al., 1991). Meta-analyses suggest that rates of recurrence and relapse are lower among individuals receiving pharmacological treatments compared to placebo, and even lower when treatment is continued after recovery. However, there is insufficient evidence to draw firm conclusions about the efficacy of psychosocial treatments in reducing the risk of recurrence and relapse (Sim et al., 2016).

In a systematic review investigating the recurrence of depression in specialized mental health care settings (Hardeveld et al., 2010), recurrence rates of up to 40% within a year after remission were observed. Different outcomes in terms of recurrence rates are reported in primary and specialized health care. In a Swedish primary care sample, Åkerblad et al. (2006) reported a relapse/recurrence rate of 34% over a follow-up period of two years. A Finnish study examining recurrence in primary and psychiatric care patients reported recurrence rates of 42% and 61%, respectively, over a 7-year follow-up period (Poutanen et al., 2007). The large variation between studies suggests that this is an area that needs to be explored further. Recurrence and relapse of depression are common in individuals treated with medication and CBT for depression. Therefore, it is crucial to incorporate these aspects when investigating the effectiveness of therapies in routine care, particularly

during the first year following treatment completion, as this period appears to be particularly important.

Previous research has suggested several patient-level risk factors for depression relapse, unrelated to treatment, including the number of previous depressive episodes, severity of the index episode, residual symptoms after treatment of the index episode, and childhood maltreatment (Buckman et al., 2018; Burcusa & Iacono, 2007; Moriarty et al., 2022; Paykel et al., 1995). However, research to date has not conclusively identified demographic variables that reliably predict the risk of depression relapse and recurrence (Buckman et al., 2018; Burcusa & Iacono, 2007; van Bronswijk et al., 2019). Although some studies have included demographic factors, such as age and marital status, among other patient factors in prognostic models of long-term depression outcomes (Angstman et al., 2017) findings for individual risk factors vary depending on whether the study samples are recruited from the community or clinical populations. Further longitudinal studies in both populations are needed to better understand the impact of demographic variables on depression relapse and recurrence (Buckman et al., 2018).

Swedish Mental Health Care

In Sweden, CBT is the recommended treatment for depression (Socialstyrelsen, 2021). All residents in Sweden have access to subsidized healthcare services, including CBT for depression, at a minimal cost. For individuals with mild to moderate depression, treatment is typically offered through first-line services, particularly primary health care providers (Vårdcentral). Swedish policy mandates that individuals requiring assessment and treatment through primary care for mental health conditions should receive their first assessment within three days (Socialstyrelsen, 2008). After the initial assessment, the waiting time for psychological treatment is usually at least a month. If a patient requires care at a specialist psychiatric outpatient service, the assessment is to be performed within 90 days.

As in other countries, there are several potential obstacles to receiving and benefiting from CBT for depression. Among the most common are: 1) the availability of a CBT therapist where the individual needs to be seen, and 2) the patient's willingness and ability to attend face-to-face treatment sessions on a weekly basis. The latter obstacle can be influenced by various factors, including concerns about potential stigma associated with attending a mental health service or treatment, the therapist's available time and schedule, taking time off work to attend psychotherapy sessions, availability of childcare support for attending sessions, and the patient's comfort level with their therapist (Andrade et al., 2014; Johansson et al., 2013; Patel et al., 2018; Rowan et al., 2013). Moreover, studies show that

patients who require and desire mental health care but face long wait-lists for their care tend to have more severe symptoms, including depression and anxiety, and are at a greater risk of relapse (Gagliardi et al., 2021; Sareen et al., 2005; van Beljouw et al., 2010). Importantly, patients who wait longer than expected for mental health care are more likely to disengage from treatment-seeking (Gallucci et al., 2005; Reitzel et al., 2006).

Internet-Delivered Treatment

One potential solution to address the service- and patient-level obstacles to CBT for depression is the delivery of treatment via the internet. Following an appropriate assessment and suitability, individuals can be provided access to a secure digital platform where they can access the treatment. The treatment is delivered in a written format, often with video-based demonstrations and instructions, and offers opportunities to communicate with a therapist via the platform, phone, or video links. This approach is generally referred to as eHealth or digital health (Smoktunowicz et al., 2020).

Since its introduction in the 1990s, internet-delivered CBT (ICBT) has gained popularity due to its potential for increasing access to and reducing the cost of mental health care (Andersson et al., 2019). A large number of RCTs examining ICBT for depression provide evidence of its efficacy and cost-effectiveness (Andersson et al., 2016; Andrews et al., 2018; Carlbring et al., 2018; Donker et al., 2015; Hedman-Lagerlöf et al., 2023; Karyotaki et al., 2021). However, and as with medication and face-to-face mental health treatments more broadly, adherence to and completion of treatment remains a significant challenge for ICBT (Christensen et al., 2009; Dunn et al., 2012; Eysenbach, 2005). Systematic reviews suggest that non-adherence to ICBT (irrespective of disorder focus) is somewhat higher than for other forms of CBT (Etzelmueller et al., 2020; Fernandez et al., 2015).

Providing participants with online contact with a therapist to help guide and support them during internet-delivered treatments has been found to increase adherence and effect sizes (Andersson, 2009; Andrews et al., 2018; Baumeister et al., 2014; Christensen et al., 2009). In addition to online therapist support, researchers have explored the effects on adherence and outcome of adding telephone calls from the therapist (Clarke et al., 2005), increasing the frequency of e-mails from the therapist (Klein et al., 2009), allowing choice of treatment course and timing, adding face-to-face contact with a clinician and varying the economic cost for the patients (Hilvert-Bruce et al., 2012). This research, while still preliminary suggests that regular and more frequent therapist contact, whether digitally (email, phone, video) or face-to-face, the use of digital reminders to access/use the internet intervention, and more frequent or planned (intended) usage by the patient are associated with greater

adherence levels (Kelders et al., 2012). However, as noted by Postel et al. (2011) the success of specific adherence initiatives seems in part to be related to the setting in which they are performed, e.g. adding telephone prompts yields different effects in different studies (Clarke et al., 2005; Farrer et al., 2011). As mentioned, adding e-mail support from a therapist increases adherence but increasing therapist e-mail support (from one to three times a week) did not affect adherence significantly in the study by Klein et al. (2009). The heterogeneity in results possibly highlighting the need for more refined methods for identifying and giving support specifically to patients that are at risk for non-adherence (Forsell et al., 2019).

Adherence in ICBT

Baseline predictors of adherence in internet-delivered treatments also vary between studies (Beatty & Binnion, 2016). One systematic review (Christensen et al., 2009) found that factors such as disease severity, treatment length, and chronicity predicted adherence in internet-delivered CBT. Treatment credibility has also been shown to predict and influence adherence as well as outcomes in ICBT (Alfonsson et al., 2016; El Alaoui et al., 2015)

While there are previous studies that describe aspects of prematurely exiting a psychological treatment (Wierzbicki & Pekarik, 1993), few studies elaborate on why individuals choose not to adhere. In a study on the reasons for non-adherence in an eating disorder treatment (Vandereycken & Devidt, 2010), the authors found that several patients did not complete treatment because they believed that they had achieved "sufficient progress." Similarly, lack of progress is not necessarily related to non-adherence in several studies (Christensen et al., 2009; Klein et al., 2009). When reasons for non-adherence are studied, common answers often concern personal reasons (Christensen et al., 2009).

Non-adherence to psychological treatment can impede recovery, as individuals generally do not improve on their own without further treatment (Beumont et al., 1993; Fairburn et al., 1993). Considering the ambiguous results of research on predictors of adherence and strategies for improving it, there is a need for further investigation into the reasons and circumstances surrounding non-adherence. Specifically, the literature lacks an in-depth exploration of the subjective reasons for not adhering to online psychological treatments.

Integrating ICBT Into Routine Settings

As noted above, internet-delivered CBT is gradually being integrated into routine mental health care settings (Titov et al., 2018, 2020). In Sweden, this has involved the development of a publicly funded national digital platform for ICBT and other forms of internet-delivered treatments under the name "Stöd och behandling" (Inera, 2022). The platform was introduced in 2016 and monthly activity has increased at least tenfold since then (Inera, 2021). While "monthly activity" (e.g., usage) may be interpreted as a crude indicator of the acceptability of ICBT to patients in routine care, further studies are needed to better understand how patients experience ICBT. This will help in modifying the treatment interface, the content of the individual ICBT programs, and the ways in which the programs are delivered (e.g., levels of therapist support) to improve their acceptability and effectiveness.

Apart from issues of acceptability, another important aspect of interest is the extent to which patients in routine health care, who are offered and accept ICBT, share similar sociodemographic and clinical characteristics as patients recruited in RCTs of ICBT. These characteristics may be relevant to both treatment acceptability and outcomes (Westen et al., 2004).

ICBT and the Psychiatric Setting

The studies in this dissertation were conducted in a psychiatric setting, which, in Sweden, refers to a second-line mental health service. This is in contrast to first-line care, which in Sweden, includes primary care settings such as local, state-supported/subsidized, and general medical practices, where the majority of depressed patients are seen (Sundquist et al., 2017). Generally, patients in second-line mental health services constitute a more socially vulnerable group in terms of demographics compared to those seen in first-line services. They have lower levels of education, higher rates of unemployment, higher symptom severity and comorbidity, a longer history of psychiatric illness, and more frequent relapses post-treatment. These differences may help to explain why treatment outcomes in second-line psychiatric clinics are generally poorer than in primary care (Hansson et al., 2013; Sun et al., 2018; Wahlbeck et al., 2011).

Most trials of ICBT for depression studies have recruited patients online or from first-line mental health services (Romijn et al., 2019) and thus it remains unclear whether ICBT will achieve similar outcomes in second-line services. As previously mentioned, patients in second-line services are more likely to exhibit sociodemographic and clinical characteristics associated with poorer treatment outcomes compared to patients in first-line care. Furthermore, individuals who consent to participate in RCTs of ICBT, regardless of their recruitment source, may

differ from those who do not consent or receive ICBT outside of a trial in routine care.

To receive ICBT for depression in an RCT, potential participants must undergo lengthy inclusion assessments before having the option to consent to randomization. They are also made aware, before these assessments begin, that if eligible, they may be randomized to a delayed treatment condition or a different treatment than ICBT. Their willingness to undergo this process and accept the risk of being randomized to delayed treatment or a less preferred treatment may indicate high expectancies for a positive outcome in treatment as usual, as well as sufficient coping resources to deal with any delay. Positive treatment expectancies are known to significantly contribute to treatment outcomes in depression (B. Meyer et al., 2002). Additionally, individuals in RCTs who are randomized to their preferred treatment tend to have lower drop-out rates and improved outcomes, with an average preference effect size of cohen's $d = 0.28$ (Swift et al., 2018).

The above contrasts with the range of treatment expectancies and preferences observed in patients receiving second-line care, which may also influence outcomes, including for ICBT once introduced. In secondary mental health care services in Sweden, the majority of individuals have previously undergone medication and/or face-to-face psychotherapy, either in first- or second-line care. However, their previous psychotherapy might not have been their preferred or recommended form of treatment due to imbalances between demand and capacity at the clinic level. Moreover, the psychotherapy they received is unlikely to have followed the rigorous quality control protocols used in RCTs. In RCTs, the treatment content is clearly specified, therapists are trained to deliver the treatment according to standards, often using a session-by-session manual, and they receive regular supervision from a clinician trained in the same treatment. Therapists in RCTs may also need to record treatment sessions, complete treatment adherence forms after each session, and are aware of close monitoring of treatment fidelity by their supervisor and researchers. As a result, patients in secondary care may have varied levels of positive or negative expectancies about treatment outcomes due to considerable variability in the quality of the treatment they received and whether it aligned with their preferences.

Given the expected variability in procedures and patient characteristics in a clinical psychiatric setting, effectiveness studies in this context offer an excellent opportunity to observe how the effect sizes of ICBT delivered in psychiatric care compare to published effect sizes from RCTs with online participant recruitment. Several uncontrolled studies of ICBT for anxiety and depression in routine care have been carried out in different countries, generally finding large effect sizes at post-treatment, which remained stable up to 6 to 12 months post-treatment, with high patient satisfaction rates (Titov et al., 2018). However, in Sweden, only one large effectiveness study of ICBT for depression has been conducted (Hedman et al., 2014). This study evaluated the effectiveness of a 10-module ICBT program in 1203 adults recruited from a single outpatient psychiatry clinic at a university hospital in

Stockholm (routine care, first-line mental health care). Pre-treatment attrition (participants refusing ICBT) was not reported, and 24.7% dropped out before completing five sessions. While the intent-to-treat analyses revealed a large treatment effect size (Cohen's d = 1.27), and satisfaction rates for treatment completers were high, the absence of information on pre-treatment attrition and a control condition limits the inferences that can be drawn about the effectiveness of ICBT for depression in routine care. To the best of our knowledge, very few, if any, ICBT studies have been entirely conducted in a second-line mental health service in Sweden.

It is important to note that the drop-out rates reported by Hedman et al. (2014) compare favorably to the average drop-out rates for all forms of CBT for depression (34.2%) reported in a meta-analysis by Fernandez et al. (2015). Interestingly, this same meta-analysis reported that pre-treatment attrition was higher for ICBT than for individual and group CBT (24.2% versus 9.7% and 14.5%, respectively). However, the authors did not specify whether treatment setting (routine care versus other) moderated this variable. Given the relative scarcity of controlled studies of ICBT for depression in routine psychiatric care, randomized controlled trials carried out in routine care settings are needed. Moreover, while there is evidence supporting the relative acceptability of ICBT versus in-person CBT (Fernandez et al., 2015), much of that data has been obtained during trials of ICBT conducted by research groups with individuals who meet inclusion criteria but have been recruited via social media. By conducting the effectiveness study of ICBT in this dissertation in a second-line mental health service, the aim is to explore the acceptability and effectiveness of ICBT in various settings.

The psychiatric context is well-suited to truly test the acceptability and tolerance for variance in both clinical and sociodemographic variables of the ICBT treatment modality. More studies are needed to evaluate the acceptability of ICBT for depression among patients recruited in routine care. This would also introduce the psychiatric outpatient setting to a type of treatment that is more consistent in content and delivery across patients, which is one of the benefits of ICBT. This consistency has proven to be important in routine care settings in general, as there are relatively high levels of variance in outcomes between therapists (Firth et al., 2019).

General and Specific Aims

In summary, depression is an extremely common, often chronic, and burdensome condition that is frequently accompanied by some form of comorbidity, particularly anxiety. While moderately effective treatments are available, not all individuals offered treatment accept, adhere to, or complete the treatment successfully,

achieving clinically meaningful responses or sustaining symptom improvements after treatment completion.

There is a clear need to enhance the effectiveness of treatments for depression and disseminate interventions that improve caregivers' capacity, thereby decreasing the burden of the disease. Achieving this goal requires identifying individual-level predictors or moderators of treatment outcomes to better match individuals to specific treatments or modify treatment components and delivery methods for improved results. This objective remains crucial for research conducted in routine psychiatric care contexts. Simultaneously, ensuring swift access to existing evidence-based treatments for individuals with depression is equally important. Such access may significantly reduce the duration and burden of depressive episodes on individuals, their families, and society as a whole.

The overall aim of this thesis was to investigate the acceptability and effectiveness of ICBT for depression and anxiety when delivered in a routine outpatient psychiatric care setting where the investigator was employed. To provide context, the first study aimed to gain a better understanding of outcomes for depression treatment among individuals seen in this service. The second study focused on investigating the effectiveness of ICBT for depression delivered in the service and explored whether patient-level characteristics and treatment adherence influenced the outcome. Lastly, the third study aimed to qualitatively explore patients' reasons for non-adherence to an ICBT program targeting generalized anxiety disorder (GAD), with the majority of the patients also experiencing clinically significant symptoms of depression.

Method

Design and Setting

The present investigation was conducted within a psychiatric outpatient clinic situated in Malmö, a city located in the southern region of Sweden. This particular clinical environment represents a second-line mental health service, denoting a secondary tier of care within the Swedish healthcare system. In Sweden, the assessment and treatment of psychiatric disorders predominantly occur within primary care settings, known as first-line mental health services. Nevertheless, patients with severe or urgent psychiatric conditions, as well as those enduring particularly challenging social circumstances, are commonly referred to second-line mental health services. Moreover, individuals with moderate levels of anxiety and depression that do not exhibit satisfactory responses to initial treatment interventions may also be directed to a psychiatric clinic for further evaluation and management. Second-line mental health care encompasses both inpatient and outpatient facilities, along with the provision of emergency services to address acute mental health crises.

Participants

Participants in this investigation were exclusively recruited from the aforementioned psychiatric outpatient clinic, where they had either been currently or previously registered. The inclusion criteria stipulated that participants must have attained a minimum age of 18 years and received a diagnosis of either depression or anxiety during their course of treatment at the clinic. The data in this dissertation was collected between 2010 and 2018.

Inclusion and Exclusion Criteria

The patients under investigation underwent comprehensive evaluations conducted by therapists or psychiatrists affiliated with the clinic. All participants were diagnosed with either depression or anxiety as their primary condition during the

course of receiving treatment at the clinic. Study I specifically required individuals to have achieved a state of remission from their primary diagnosis for at least 12 months prior to their inclusion in the study. In study II, participants with a primary diagnosis of depressive episode or recurrent depressive disorder were included. Study III targeted participants who exhibited non-adherence to their prescribed treatment regimen. The exclusion criteria were primarily established to ensure that participants requiring alternative interventions, such as individuals with eating disorders or those exhibiting high-risk suicidal tendencies, were not included in the study. Additionally, individuals with conditions sharing similar symptoms but following distinct trajectories, such as bipolar disorder, were also excluded. The aim of these criteria was to strike a balance, carefully avoiding excessive exclusions that could potentially limit the external validity of the findings. By implementing a judicious approach to participant selection, the research sought to maximize the generalizability of the results while maintaining the necessary rigor in study design. A comprehensive account of the specific inclusion and exclusion criteria employed in this research can be found in the Research Studies section.

Interventions

The interventions utilized and studied in this dissertation, specifically in Study II and Study III, are referred to as internet-delivered cognitive behavior therapy (ICBT). Previous reports, such as those by Andersson, Carlbring, et al. (2013) and Andersson et al. (2019), have thoroughly described the methods employed in this dissertation.

Following the initial assessments, participants are allocated to an encrypted web-platform (Vlaescu et al., 2016) accessible upon login. Various devices, including desktop computers, mobile phones, and tablets, are utilized to access the platform's content. The platform presents treatment content and questionnaires in a coherent and comprehensible manner, enabling text-based asynchronous communication between the participant and the therapist.

In this investigation, the intervention was guided, meaning therapeutic support was involved in the intervention. Distinguishing between guided and unguided ICBT has been shown to be relevant, as studies suggest that therapeutic support enhances the effectiveness of the intervention, particularly among individuals experiencing moderate to severe symptoms

Therapist support can be carried out in different manners. In the studies encompassed in this thesis, support consisted of a weekly asynchronous message from the therapist. Generally, the feedback (guidance) was focused on validating the participants, as well as supporting and encouraging them to remain focused on the tasks. While the treatment content primarily comprised text, video and audio

formats were also utilized to convey information. The treatment was organized into chapters, with participants advised to complete one chapter per week. Each chapter included assignments to be completed and symptom questionnaires to be regularly filled out. The therapist employed information from these assignments and questionnaires to provide weekly feedback on the participants' progress.

The treatment content employed in study II was originally developed by Andersson and colleagues (Andersson et al., 2005), and has been utilized and described in several other studies (Andersson, Hesser, Hummerdal, et al., 2013; Andersson, Hesser, Veilord, et al., 2013; Hedman et al., 2014; Jakobsen et al., 2017; Johansson et al., 2012; Vernmark et al., 2010). The treatment content in study III is described in the following studies (Andersson et al., 2012; Paxling et al., 2011). Both treatments consist of eight weekly chapters, with each chapter comprising approximately 10-20 pages of text, illustrations, and assignments.

Ethics

Ethical approval was obtained from the Regional Ethical Review Board in Lund (Reference numbers: 2011775, 2010459. Informed consent was obtained from all participants

Measures

Structured Clinical Interview for DSM-IV (SCID-I)

The Structured Clinical Interview for DSM-IV, SCID-I developed by First and Gibbon (1997) was utilized in study I to establish a diagnosis and identify potential psychiatric comorbidities. The SCID-I have been found to possess robust psychometric properties and serve as a valid assessment tool for psychiatric disorders (Lobbestael et al., 2011)

Montomery Åsberg Depression Rating Scale (MADRS-S)

For the assessment of depressive symptoms, the Montgomery Åsberg Depression Rating Scale, self-rating version (MADRS-S), created by Montgomery and Åsberg (1979), was employed. This questionnaire comprises nine items designed to measure depression symptoms experienced within the past three days. Each item is rated on a scale of 0 to 6, with higher scores indicating a greater severity of depressive symptoms. A total score ranging from 0 to 54 is calculated, and a

MADRS score of 11 or below has been suggested as indicative of remission from depression (Bandelow et al., 2006).

In study I, the paper and pencil version of the MADRS-S was administered, while in study II, the digital version was utilized. A comparison of the digital version's psychometric properties with the paper and pencil version was conducted by Holländare et al. (2010), revealing similar levels of internal consistency (Cronbach's α between 0.73 and 0.81). Furthermore, the self-rating version of the MADRS-S has demonstrated a strong correlation with expert ratings (Svanborg & Asberg, 2001)

Hospital Anxiety and Depression Scale (HADS)

In study II, the Hospital Anxiety and Depression Scale (HADS), developed by Zigmond and Snaith (1983), was also used. The HADS encompasses two distinct subscales, namely the Depression subscale (HADS-D) and the Anxiety subscale (HADS-A). Each subscale consists of seven items that assess symptoms of depression and anxiety, respectively, using a rating scale ranging from 0 to 3. A score below 8 on both the HADS-D and HADS-A subscales is commonly interpreted as indicative of non-clinical levels of depressive and anxiety symptoms (Lisspers et al., 1997; Zigmond & Snaith, 1983). The psychometric properties for HADS in a Swedish sample have been examined by Lisspers et al. (1997), reporting Cronbach's α 0.84 for HADS-A and 0.82 for HADS-D.

Outcome Questionnaire-45 (OQ-45)

In study II, the Outcome Questionnaire-45 (OQ-45), developed by Lambert et al. (1996), was employed as a comprehensive measure of psychiatric symptoms. The OQ-45 is specifically designed to assess a broad range of psychiatric symptoms, making it a valuable tool for evaluating overall symptomatology. Comprising 45 items that examines symptoms during the last week, each rated on a scale of 0 to 4, the questionnaire encompasses three subscales that measure symptom distress, interpersonal relations, and social role functioning (including challenges in the workplace, school, or home duties). For the purposes of study II, however, only the total score of the OQ-45 was utilized as an indicator of general psychiatric symptoms. The OQ-45 exhibits good reliability and demonstrates high test-retest reliability (Beckstead et al., 2003; Lambert et al., 1996). The psychometric properties for OQ-45 in a Swedish sample have been examined by Strid et al. (2014), reporting Cronbach's α 0.88 for the total OQ-45.

Generalized Anxiety Disorder Questionnaire-IV (GAD-Q-IV)

The Generalized Anxiety Disorder Questionnaire-IV (Newman et al., 2002), reported in study III, is a questionnaire consisting of 9 items that measures prevalence and impact of excessive worry during the last 6 months. The participant also registers their own description of symptoms which are common among patients with GAD, hence clinical interpretation is needed for scoring. A cut-off of 5.7 points (83% sensitivity and 89% specificity) on the GAD-Q-IV has been reported to indicate the presence of GAD (Newman et al., 2002).

Penn State Worry Questionnaire (PSWQ)

The Penn State Worry Questionnaire, reported in study III, was developed by Meyer and colleagues (1990). The PSWQ consists of 16 items that measure the frequency and intensity of worry (without any specific time frame). Each item is rated on a scale from 1 - 5, and several items have reversed scoring. A total scare falls in the range of 16 – 80, although the instrument is good for measuring worry, no clear cut-off for distinguishing pathological worry has been established. A value between 62 – 65 has been suggested for distinguishing GAD from other anxiety disorders (Fresco et al., 2003).

Data Analysis

Quantitative Measures

In study I Chi-square tests and t-tests were used to compare included participants with excluded on relevant variables. To analyze predictors of relapse/recurrence, logistic regression was used.

Study II employed analysis of variance and chi-square tests to detect potential systematic differences between the control group and the intervention group with regard to clinical and demographic variables. Multiple imputation was used to replace missing post treatment values, however missing follow-up measures (6-month, and 12-month) were not replaced, as these follow-ups were performed outside of the experimental design (both groups had then received treatment and were therefore treated as one group). Main outcomes were calculated using one-way analyses of covariance (ANCOVA) with group variable as independent variable and outcome variables as fixed factors. The pre-treatment measures were used as covariates. Analysis of variance (ANOVA) was used to compare group means at follow up (6-month and 12-month) to pretreatment means.

Qualitative Measures

In study III a qualitative approach was used based on Charmaz (2006) interpretation of grounded theory, a method originally developed and described by Glaser and Strauss (1967). After data collection the data analysis involves several steps and principals. The first step involves analyzing the data using various techniques. In study III specifically patterns, concepts and categories were identified from the data collected using an open approach minimizing the use of predetermined theories or concepts, the focus was on the experiences of the participants. The analysis is an iterative process aiming on refining the theory being developed, theory development was the last step of the analysis where a tentative theory was developed for summarizing and explaining the experiences of non-adherence to Internet-delivered treatment in this context.

Research Studies

Study I - 12-Month Outcome and Predictors of Recurrence in Psychiatric Treatment of Depression: A Retrospective Study

Background

Many individuals treated for depression suffer from relapse or recurrence after treatment. Known risk factors include the number of previous depressive episodes and residual symptoms after treatment. However, both relapse and recurrence rates, as well as predictors of relapse/recurrence, may differ between various settings. Different studies report considerably different rates of recurrence/relapse, varying between about 30% to 60%, and very few studies report from a naturalistic setting (Hollon et al., 2005; Shapiro et al., 1995). The large variation between studies suggests that this is an area that needs to be explored further. This exploration should include investigating recurrence rates among different populations and contexts, as well as identifying factors that affect the risk of recurrence in depression. Naturalistic follow-up studies are an effective way to examine the actual effectiveness of treatment in healthcare settings regarding depressive recurrence and to study variables influencing recurrence in different clinical settings.

Aims and Purpose

The purpose of this study was to conduct a naturalistic evaluation of the sustained effectiveness of treatment for adult clinical depression in a psychiatric outpatient setting during the first year after discharge. The study also aimed to examine psychosocial and depression-related predictors of depressive relapse/recurrence during this period.

Method

All participants met the following criteria: (a) they were outpatients with a primary diagnosis of depressive episode or recurrent depressive disorder based on ICD-10

criteria; (b) they were at least 18 years of age; and (c) they were in remission at the time of discharge. The assessment of remission status involved both confirmation from the treating psychiatrist at discharge and validation during a structured interview before inclusion in the study.

Participants' depressive status was assessed 12-14 months after treatment termination through structured telephone interviews, during which relapse/recurrence was evaluated retrospectively, along with the validation of remission status at discharge. These interviews were conducted by a clinical psychologist and two clinical psychology students at the master's level, all of whom had prior training and experience with the diagnostic instrument. Current symptomology at the follow-up was assessed using a self-rating form (MADRS-S).

Results and Discussion

The overall average score on MADRS-S at follow-up was 18. Out of the 51 participants, 31 (61%) reported having suffered a new depressive episode during the 12 months following discharge from the psychiatric clinic. Of these, 7 (23%) participants were categorized as having relapsed (experiencing a new depressive episode within two months of discharge), and another 24 (77%) participants were categorized as having a recurrence of depression (suffering a depressive episode after at least two months of sustained treatment effect). Furthermore, in the total sample, 15 participants (29%) were categorized as suffering from an ongoing depressive episode at follow-up, 23 participants (45%) were categorized as being in partial remission at the 12-month follow-up, and 13 (26%) were categorized as being in full remission. Out of the 51 participants, 11 (22%) were categorized as having a sustained treatment response (in full remission and with no relapse or recurrence of depression during the follow-up period).

In this study, a greater number of previous depressive episodes and not having a partner were identified as predictors of depressive relapse/recurrence. The number of previous episodes is a well-established moderator of depressive relapse/recurrence (Berlanga et al., 1999; O'Leary & Lee, 1996). Additionally, having a partner at the time of discharge appeared to be a variable that seemed to protect against depressive relapse/recurrence. Previous results pertaining to the impact of having a partner on depressive relapse/recurrence are not conclusive (Gonzales et al., 1985; Kessing et al., 1998; Mueller et al., 1999). Usually, "marital status" is investigated rather than having a partner. Not having a partner is arguably a more general description and may, as such, be connected to other social variables that influence depressive relapse/recurrence, such as the level of social support, which has been shown to predict relapse/recurrence (Lewinsohn et al., 1988; Wilhelm et al., 1999).

This sample of individuals treated within a Swedish psychiatric context has a noticeably high prevalence of depression and partially remitted depression at the 12-month follow-up. A large proportion of the sample would likely benefit from commencing active treatment for depression again. A comparison with other research suggests the hypothesis that relapse/recurrence rates are higher in psychiatric settings than in primary care. If so, this would indicate a need for a different treatment strategy in the psychiatric care of depression, where emphasis on long-term management of depression should be the primary concern for treatment, rather than focusing resources strictly on acute treatment. This study also demonstrates the need for future research to identify methods for relapse/recurrence prevention that are easily integrated into routine psychiatric care. With limited resources, outpatient clinics in this study seem to prioritize acute treatment of depressed individuals over different types of continuation interventions. Therefore, in addition to enhanced risk identification methods (for optimal use of resources), there is a need for easily accessible and easily disseminated prevention methods, such as possibly physical exercise or internet-delivered CBT.

Tabel 1. Descriptive characteristics of the sample in study I

	Mean	SD	Range
Age (years)	47	17.0	20-86
Age at depressive onset (years)	34	17.6	9-85
MADRS-S at 12-month follow-up	18	10.2	2-48

	Frequencies
Gender (female/male)	36/15
Occupational status (employed / unemployed)	30/21
Having a partner (yes/no)	30/21
Type of treatment (Pharmacotherapy/Psychotherapy/Combined)	17/8/26
Previous episodes (None/One/Two/Three or more)	8/7/8/28
Sought treatment during follow-up (Yes/No)	15/36
Remission status at 12-month follow-up (Full/Partial)	13/23

Study II - Effectiveness of Guided Internet-Delivered Cognitive Behavior Therapy for Depression in Routine Psychiatry: A Randomized Controlled Trial

Background

Since its introduction in the early 1990s, Cognitive Behavioral Therapy delivered via the internet (ICBT) has gained popularity due to its acceptability, effectiveness, and feasibility (Andersson et al., 2019). Numerous randomized controlled trials examining ICBT for depression have consistently established the method as an effective and viable treatment option for major depressive disorder . I Overall, ICBT holds promise as a treatment for a condition that is often undertreated.

As ICBT transitions from research settings to routine care (Titov et al., 2018).), certain risks need to be considered. One risk is that participants in efficacy trials may differ from patients in routine health care in characteristics that are relevant to treatment outcomes (Westen et al., 2004), such as baseline severity, comorbidity, education level, or treatment expectations. Another risk is the variation in procedures between settings, which can hinder the generalizability of findings from efficacy studies. For instance, there is a difference between self-selected samples (commonly used in research settings) and referral samples (a more traditional recruitment strategy in clinical settings).

Aims and Hypotheses

The purpose of this study was to investigate the effectiveness of ICBT on depressive symptoms, building upon the evidence from multiple efficacy trials, by implementing the treatment in an outpatient psychiatric clinic and using the clinic's routine practices. Unlike previous studies that often used self-selected samples, this study utilized a psychiatric referral sample. Additionally, a control group was included in the study design.

The main hypothesis was that participants in the treatment group would experience a reduction in depressive symptoms compared to those in the waitlist control group at the end of the treatment. Furthermore, it was anticipated that there would be reductions in anxiety-related symptoms and overall psychiatric symptoms. Additionally, the study aimed to examine the participants' symptom levels at the 6- and 12-month follow-ups after the completion of ICBT treatment.

Method

A randomized controlled design was employed, where participants were randomly assigned to either the experimental group receiving therapist-supported internet-delivered CBT for depression or the waitlist control group (which later received the treatment). Initially, 108 patients from the outpatient clinic were referred, and ultimately, 54 were included in the randomization process for either ICBT or the waitlist.

The treatment program consisted of 8 weekly modules to be completed over an 8-week period. The program was primarily based on Beck's cognitive therapy for depression and behavioral activation. Outcome measures, including depressive symptoms, anxiety, and general psychiatric symptoms, were collected digitally. The data was collected at baseline, after treatment/waitlist completion (at 8 weeks), 6 months, and finally, 12 months after the treatment was completed. It's important to note that both groups had received treatment at the 6- and 12-month follow-up.

Results and Discussion

The sample in this study differed from samples in similar trials, where the same treatment program was used, in several ways: they were less educated, had a higher rate of sick leave, more severe symptoms at baseline, and a history of more previous depressive episodes. The aim of this study was to examine the effectiveness of ICBT on depressive symptoms when treating patients in a psychiatric setting using the clinic's routine practices.

The results on the primary outcome measure (MADRS-S) revealed a significant decrease in depressive symptoms in the experimental group compared to the control group, with a large between-group effect size (Cohen's $d = 1.6$). Similar results were observed for depressive symptoms as measured with HADS-D (Cohen's $d = 1.6$). Furthermore, the results showed significantly reduced symptoms on the secondary outcome measures HADS-A and OQ-45, with large between-group effect sizes (Cohen's $d = 1.5$ and 1.3 respectively). These gains were maintained at the 6- and 12-month follow-ups.

Clinical significance was calculated using the Jacobson and Truax reliable change index-method for assessing clinically significant change (Jacobson & Truax, 1991), which revealed that 58% of the sample reached the status of "recovered" or "improved" when assessing depressive symptoms with MADRS-S. About 4% of the participants were classified as "deteriorated" on the main outcome variable at the post-treatment assessment using the Jacobson and Truax methodology.

Rozental and colleagues (2017) utilized the identical definition of deterioration in their comprehensive meta-analysis concerning participants undergoing ICBT.

Within this analysis 5.8% of the individuals studied experienced deterioration during the treatment process.

Comparing the outcomes of this trial to earlier studies that used the same ICBT treatment program, the results are similar but not entirely equivalent. The treatment effect size in the current study was Cohen's d = 1.6 (depressive symptoms), while effect sizes in the reference trials ranged from d = 1.27 to d = 2.11. The proportion of participants considered "recovered" was somewhat lower in this study (29% at post-treatment). Prior trials reported recovery rates ranging from 26.5% to 56%.

Moreover, when comparing adherence rates among these studies, it was found that 54% completed all modules in this study, compared to 65–94% in prior trials. The treatment was generally somewhat less effective when compared to earlier studies using the same treatment program, but the results still compare well, considering it was performed in a naturalistic setting with a referral sample. The study shows that the version of ICBT used in this trial can be effective when delivered in routine psychiatry using standard practices, such as internal referral for recruiting patients.

Tabel 2. Description of clinical significance according to Jacobson and Truax (1991) criteria, study II

Measure	n	Recovered (n)	Improved (n)	No change (n)	Deteriorated (n)
MADRS-S					
Post	24	29% (7)	29% (7)	38% (9)	4% (1)
6-Month	42	50% (21)	17% (7)	29% (12)	5% (2)
12-Month	41	54% (22)	17% (7)	29% (12)	2% (1)

Study III - Experiences of Non-Adherence to Internet-Delivered Cognitive Behavior Therapy: A Qualitative Study

Background

Numerous published trials on internet-delivered psychological treatments have faced challenges with a high degree of non-adherence (Christensen et al., 2009; Dunn et al., 2012; Eysenbach, 2005). While web-based psychological treatments have proven effective (Andersson et al., 2019), increasing treatment completion rates remains a crucial aspect in further enhancing their effectiveness. Providing participants with therapist contact for online guidance and support during treatment has been shown to improve adherence and effect sizes (Andrews et al., 2018; van

Ballegooijen et al., 2014). However, despite added therapist support, the proportion of non-completers remains a significant factor for web-based treatment programs. Several other strategies have been explored to enhance adherence to Internet-delivered treatment programs. Generally, more frequent therapist contact, regular reminders, and increased intended usage have been associated with better adherence (Kelders et al., 2012). Nevertheless, the success of these specific initiatives appears to be partly influenced by the setting in which they are implemented (Postel et al., 2011).

Aims and Hypotheses

Although there have been previous studies describing aspects of prematurely exiting psychological treatment, few have elaborated on the reasons why individuals choose not to adhere to treatment. For instance, in a study on non-adherence in an eating disorder treatment (Vandereycken & Devidt, 2010), some patients did not complete treatment because they believed they had achieved "sufficient progress." Similarly, lack of progress is not consistently associated with non-adherence in several other studies (Christensen et al., 2009; Klein et al., 2009). When reasons for non-adherence are studied, common answers often concern personal reasons (Christensen et al., 2009). Salmoiraghi and Sambhi concluded in a literature review (2010) that no single strong predictor of treatment discontinuation exists. Given the ambiguous results of research on predictors of adherence and strategies for improving adherence, there is a need to further investigate the reasons and circumstances surrounding non-adherence. Specifically, there is a gap in the literature concerning an in-depth exploration of the subjective reasons for not adhering to internet-delivered psychological treatments.

Few, if any, studies have examined experiences of non-adherence to guided ICBT. This study focuses on an internet-delivered, guided self-help program for generalized anxiety disorder, aiming to gain more knowledge about the factors that might play a role in the decision not to complete an ICBT treatment more generally. By interviewing and qualitatively analyzing the participants' experiences of non-adherence, the study aims to generate a new theoretical working model on how non-adherence occurs in internet-delivered treatments.

Method

The participants in this study consisted of six women and one man, recruited from the psychiatric clinic. They were contacted via letter and telephone and informed about the purpose of the study. All participants initially started the same ICBT treatment for generalized anxiety disorder but left the treatment prematurely. The study was conducted as part of a randomized controlled trial in a psychiatric setting in Sweden in 2010. Data were collected through semi-structured interviews with

individual participants. The theory-generating method grounded theory, developed by Glaser and Strauss (B. Glaser & Strauss, 1967), served as an inspiration for the study design. An informed approach of grounded theory was utilized for the analyses.

Grounded theory (GT) is an inductive qualitative method where the researcher seeks to derive new theoretical models from empirical data. The theory-generating process of GT is based on conceptualizing the currently collected empirical data. This approach is well-suited for the purpose of the presented study, which aims to openly explore participants' experiences of non-adherence to Internet-delivered therapy.

Results and Discussion

A working model theory was generated, consisting of five specific underlying concepts or reasons for non-adherence. This model describes a process where certain treatment features, such as workload, text-content complexity, and treatment process, don't align with personal prerequisites, including daily routines, language skills, and treatment expectations, respectively. Negative effects of the treatment were also prominent as a reason for non-adherence, along with a desire for face-to-face contact. Each concept was derived from participants' experiences of the treatment process. The participants reported that the decision to not adhere to the treatment was taken when certain dimensions of the treatment process were perceived as incompatible with their personal capabilities, constraints, or perceived needs.

Importantly, a treatment aspect only caused problems if certain characteristics of the patient were present, and vice versa. For instance, the text modules were not necessarily always perceived as difficult, but they turned out to be so if the patients experienced themselves as having lower reading or writing capabilities. These different conditions and characteristics, presented in interplaying pairs, seem to play a role in non-adherence to Internet-delivered therapy. The concepts that collided with personal constraints, needs, or conceptions in this study were: extensive treatment content, demands of reading and writing capabilities, perceived side effects of treatment, lack of face-to-face contact, and limited prior information/knowledge about the treatment.

Some of the common strategies used within ICBT to increase adherence in general appear to be related to the reasons given for non-adherence by the participants in this study (such as high intended usage and a modular treatment approach). Other common strategies, such as increasing prior knowledge about treatment, were regarded as important for adherence by the participants in this study.

Discussion

Principal Findings

The overall aim of this thesis was to investigate the acceptability and effectiveness of ICBT for depression and anxiety when delivered in a routine outpatient psychiatric care setting.

To provide context for studies II and III, study I involved a retrospective review of medical records from 51 individuals who had successfully completed a depression treatment course and were discharged from the clinic. In the year following treatment, 61% experienced relapse or a recurrent depressive episode. At the 12-month follow-up, 29% were still experiencing a depressive episode, 45% were in partial remission, and 26% were in full remission. The risk of relapse/recurrence was significantly predicted by a higher number of previous depressive episodes and the absence of a partner. The proportion of individuals experiencing relapse and recurrence was higher than rates reported in meta-analyses for depression treatments (Moriarty et al., 2022; Sim et al., 2016). These findings suggest that additional or more effective treatments are likely needed in the clinic, further straining an already limited treatment capacity.

Study II involved a randomized controlled trial comparing an 8-module ICBT for depression, guided by therapists with weekly text feedback, to a waitlist control for depression in 54 adults recruited from the same outpatient psychiatric service as study I. Regarding adherence, participants in the ICBT completed an average of 6.3 out of the 8 modules, with 46% successfully completing all eight treatment modules. Furthermore, 89% rated the ICBT as either satisfactory or very satisfactory. Although these ratings were uncorrelated with improvement, they do indicate an overall acceptability of the treatment. In terms of effectiveness, significant and substantial reductions in self-reported depression were observed in the ICBT group compared to the treatment-as-usual group (Cohen's d = 1.6), with 58% showing improvement or recovery after treatment. These improvements were maintained at the 6- and 12-month follow-ups.

In study III, a qualitative study, seven adults who had prematurely terminated their participation in the ICBT group for Generalized Anxiety Disorder (GAD) in the same clinic as studies I and II were interviewed. Several themes emerged regarding their decision to discontinue the treatment, including the extensive treatment

content, demands of reading and writing capabilities, perceived side effects of treatment, lack of face-to-face contact, and limited prior information/knowledge about the treatment. Overall, the results suggest that adherence and completion of this ICBT treatment were influenced by a negative interaction between patient perceptions of their own resources/needs, the demands of the treatment, and a lack of perceived progress.

Ethical Considerations

Ethical considerations play a crucial role in the scientific process, and they are briefly described here. Firstly, prior to participation, all participants provided written informed consent. They were presented with a written description of the study and its potential contributions to the scientific literature. Moreover, they were informed that they had the right to withdraw themselves and their data from the three studies at any time without affecting their access to further treatment.

Secondly, all procedures and materials were described in detail to, and fully approved by, the independent regional ethics committee in Lund, Sweden.

In any research involving human participants, it is essential that the knowledge gained from the study outweighs any potential risks associated with participation. The present studies were specifically designed to address critical knowledge gaps in the depression literature, with the overarching goal of improving outcomes for adults receiving psychotherapy for depression and anxiety. The well-being of the participants was of utmost importance, and every effort was made to minimize any possible negative effects of study participation, ensuring that no lasting harm was caused.

During study II, which focused on an intervention, it was revealed that approximately 4% of participants experienced deterioration in the primary outcome measure over the course of the intervention. It is noteworthy that this rate of deterioration aligns closely with findings from an earlier mentioned comprehensive investigation (Rozental et al., 2017) examining deterioration rates in ICBT.

Study I involved a retrospective review of patients' electronic records in the psychiatric service where they received treatment, posing no immediate risk of harm from participation. The author conducted the review on the clinic premises, entering patient data into a spreadsheet for analysis. However, names and person numbers were removed and replaced with a research identifier number. Additionally, a separate digital file containing patient names and research identifier numbers was encrypted with a password known only to the author and stored on a computer in the clinic, which was not connected to the internet. The data file for analysis was also encrypted with a password known only to the author.

In study II, a randomized controlled treatment trial, a GDPR secure platform was utilized, and only the author had access to participant data on the platform. Data necessary for analysis were downloaded without patient names or person numbers and stored in an encrypted file, accessible only to the author. Participants in study II received a treatment whose components had been previously tested in numerous controlled and uncontrolled trials, both in-person and digitally, and proven to be safe and effective. Throughout the treatment, the severity of participants' symptoms was closely monitored, and they were assured of access to the author in case of any concerns. Additionally, they were informed about statutory services (e.g., 112 and the psychiatric clinic) they could reach out to in case of any sudden increase in their symptoms or concerns about personal safety. While participation in the trial diverted participants from the routine care pathway, it did not prevent them from receiving other supports or treatments from the clinic where they were recruited, either after the trial was completed or if they decided to withdraw during the ongoing trial. Although study II imposed an additional assessment burden on participants, the self-report measures used were comparable to (or included) those employed in routine psychiatric care, and there is no evidence indicating that their use is associated with increased distress in the short or long-term.

Study III involved a qualitative assessment through a single interview, scheduled at the participant's convenience and lasting up to two hours. The interviews took place on the clinic premises, and they focused on the participant's treatment experience. During the interviews, participants' responses were recorded, and the information stored in an encrypted audio file for analysis purposes, with names and person numbers replaced by research identifier numbers. These numbers and patient names were kept in a separate encrypted data file stored on a password-protected clinic computer in the author's clinic office, which was not connected to the internet. To the best of our knowledge, there is no evidence from the literature suggesting any negative effects arising from participation in qualitative interviews about treatment experiences.

Brief Overview of Limitations

The above findings should be considered in light of several methodological limitations. The overall attrition in the studies has an impact on the inferences that can be drawn from the data. Studies conducted in a clinical care context may experience higher attrition compared to those in more controlled settings (Swift & Greenberg, 2012), attrition has been discussed in more detail above in connection with the individual studies. Nevertheless, the clinical context adds to the external validity, which is considered a strength in this dissertation.

In this dissertation, no measure entirely dedicated to quality of life has been used. Instead, a wide range of clinical measures was employed to focus more deeply on psychiatric symptoms. The primary reason for not including more follow-up variables was to decrease the assessment burden among the participants. High assessment burden can lead to disengagement and non-compliance, especially among patients with severe symptoms such as depression, who may have particularly low motivation (Aiyegbusi et al., 2022). A meta-analysis by Hofmann et al. (2017) has shown that when quality of life is measured in depression trials, treatments typically affect quality of life to a lesser degree than depression and anxiety symptoms. However, while the use of quality of life measures is recommended, there is much debate in the literature about what existing measures actually assess and what they should measure (Carr, 2001).

Regarding study I, it employed a retrospective analysis of medical records, and it is not guaranteed that the medical records were complete or accurate, nor that the identified sample represents individuals who are routinely treated for depression at this clinic or the wider population of patients referred for depression treatment to a community-based psychiatric service. The sample may, therefore, be biased, such that those agreeing to participate belong to a subgroup with either higher or lower depressive symptoms. Several variables potentially influencing the results, particularly depression symptoms at baseline (discharge from psychiatric care), were not measured or controlled for. The results, indicating the sample had high depression symptoms at the 12-month follow-up, could be attributed to a high degree of depressive symptoms at discharge or a recurrence of depressive symptoms.

Although study II was a randomized controlled trial, the sample size was relatively small. Studies with smaller sample sizes tend to report larger effect sizes. The small sample size meant that the study was underpowered to detect treatment moderator effects. Systematic differences between the groups in terms of medication were not controlled for (except for the proportion using antidepressant medication), such as dosage or type of medication used. Participants were not restricted regarding further treatment for depression during the follow-up period, and results at the follow-up may not solely be attributable to the ICBT intervetion. Using a waitlist control group can be problematic from a methodological perspective. Several studies have indicated that a waitlist control group can result in larger effects for the therapy studied when compared to other types of control groups (Furukawa et al., 2014; Mohr et al., 2014). While a majority in the control group did receive pharmacological treatment (which, in this case, was treatment as usual except psychotherapy), they were also randomized to a waitlist for ICBT, making the study design vulnerable to possible shortcomings of the waitlist control group design. At the same time, it is worth discussing and refining the type of control group used, considering whether the control group receives no intervention or some form of intervention. As discussed by Goldberg et al. (2023), different types of waitlist

control groups can differ in ways that influence the validity of the study design. The control condition in study II involved (for most participants) an active intervention (antidepressant medication), which constitutes an important distinction compared to a control condition with no active intervention and no intended antidepressant effect. Goldberg et al. (2023), refer to this as "treatment as usual active," thereby distinguishing it from control groups receiving no intervention or interventions with no expected antidepressant effect.

Participants in study III were selected from a larger sample of individuals who had prematurely terminated their participation in ICBT for GAD. Choosing a qualitative design, in this case grounded theory, for interpreting interview data means that the interviewer and participant together form themes during the interview. Grounded theory involves several steps or iterations that transform themes discussed into higher-order concepts and theories. The process is intended to create clear and overarching concepts and theories, but there is also a risk of distorting the original content in some way (Lingard et al., 2008). This means that objective data, such as baseline symptoms, is not controlled for, while the participant's ideas, in this case, the subjective reasons for dropout, are explored. Generalizability is not the central guiding principle in qualitative research as in quantitative research. Rather, the goal for using this methodology is to explore concepts that could be difficult to discover using only quantitative methods (Korstjens & Moser, 2017). Qualitative work and its potential limitations are discussed within a qualitative framework, rather than comparing quantitative and qualitative methodology. Due to its characteristics, the method used introduces some general limitations compared to other qualitative methods of exploring concepts. For example, in this method, the participants and interviewer together form concepts, which means that there is a risk that the interviewer introduces ideas and concepts to the participant, potentially influencing the reasons given for not completing the treatment. The aim was to minimize these risks by conducting the interviews in a way that the participants were not introduced to novel concepts, and it was emphasized that the important issue was to explore their unique experience, regardless if it meant criticizing the intervention.

The grounded theory method is a theory-inducing approach, and researchers strive for data saturation, which means that additional input from participants no longer adds new insights to the theory being formed(Lingard et al., 2008). Given the relatively low number of participants in this study, there is a risk that data saturation may not have been fully achieved (Morse, 2015).

Another concern when using grounded theory is the potential for the generated theory to be too closely linked to the specific setting in which the interviews were conducted, which could decrease the external validity of the study(B. G. Glaser, 2002).

Results in Context

In study I, the sample had received treatment as usual for depression, and 12 months later, the average MADRS-S score in that group was 18. A score above 12 has been suggested to distinguish individuals with depression from the non-depressed (Svanborg & Ekselius, 2003). These findings provide further evidence that depression is a recurrent condition, even among individuals successfully treated in routine psychiatric services. Therefore, for most depressed patients, a single episode of care/treatment is unlikely to be sufficient to maintain recovery and prevent relapse. As a result, previously treated individuals are likely to be referred back for further treatment, placing additional demands on psychiatric services already struggling with long waiting lists and pressure to provide timely treatment to depressed individuals. ICBT has been at the forefront of trying to address the ever-increasing demand for psychological treatments for depression and anxiety, but its dissemination into routine care is still relatively new.

Over the past two decades, one of the most distinctive characteristics of CBT dissemination has been its digital aspect. Digital and internet-delivered interventions, including ICBT, offer the possibility of rapid clinical innovation (Andersson et al., 2019). Online advertising and sign-up facilitate recruitment and bridge geographical and practical distances. Digital tools also streamline the handling of large samples, minimizing clinician resources and thereby addressing the challenge of underpowered studies (Andersson et al., 2019; Schuster et al., 2021). Both in clinical contexts and RCTs, ICBT has proven to be a powerful tool that significantly expedites dissemination. The transition from research to clinical practice is well underway and is substantially changing the way CBT is delivered. In Sweden, a government-funded ICBT platform, Stöd och behandling (Inera, 2022) has been developed and is used nationwide for treatment with different content, primarily CBT programs for anxiety and depression. ICBT appears to be one answer to the challenge of disseminating CBT.

Moving ICBT from a highly controlled RCT setting to a regular clinical setting raises questions about how different aspects of the method generalize to clinical practice. Conducting an ICBT trial at a psychiatric outpatient clinic emphasize external validity, as patients in psychiatric care often exhibit more comorbid symptoms, greater symptom severity, and a higher proportion of individuals using psychiatric medication. Additionally, a larger proportion may be on sick leave or unemployed compared to the community samples or open recruitment samples used in many ICBTs that examine treatment effects using the same treatment program as in study II. Apart from patient-related clinical variables, other factors concerning the treatment process, such as referral procedures vs. self-selection, patient motivation, treatment expectations, and treatment experience, also come into play. Although few investigations on referral procedures exist, the ones conducted

indicate that relevant differences may exist between participants recruited through different procedures (Lindner et al., 2015).

When transitioning ICBT from a research setting to a clinical setting, effect sizes tend to decrease (Etzelmueller et al., 2020; Romijn et al., 2019). While ICBT remains effective in clinical routine practice, the effect sizes appear to be smaller when compared to community samples recruited through open recruitment, such as advertisements. Romijn and colleagues (2019) suggest that the lower effect sizes could be related to adherence differences, as well as different recruitment strategies that may lead to variations in effectiveness. The results from study II demonstrate a similar trend, where ICBT is effective but with lower effect sizes and lower adherence, contributing to the growing body of research pointing in the same direction. However, the specific reasons why effect sizes tend to diminish have not been clearly established, and addressing this in future research could significantly enhance the knowledge base of ICBT.

It is important to acknowledge that this is, to some extent, a general challenge when working with patients in this context. Effectiveness studies conducted in second-line mental health care demonstrate that therapy generally produces slightly more moderate results compared to efficacy studies, including both face-to-face CBT and other effective forms of therapy, such as Interpersonal Therapy (IPT) (Ekeblad et al., 2016). Moreover, recurrence and relapse are highly common among these patients, leading to a significant burden of disease. In study I, there are indications that factors like loneliness and previous episodes of mental illness (which are extremely common, with 89% of participants in study II having experienced three or more depressive episodes) could contribute to this phenomenon. Research also shows that a history of mental illness can be a strong predictor of future need for psychiatric care (Sun et al., 2018). Typically, more severe symptoms increase the likelihood of future psychiatric care. However, this correlation is not present among individuals with a history of psychiatric care utilization – in this group, the likelihood for future psychiatric care remains high across all levels of symptom severity (Sun et al., 2018), indicating a general vulnerability. Although this poses challenges for treatment efforts, highly structured interventions seem to generate positive treatment effects. For instance, in 2013, Hansson and colleagues (Hansson et al., 2013) conducted an RCT at the same outpatient clinic using mixed treatment protocols and a heterogeneous sample, with a special type of therapist feedback as the common framework. That intervention did not produce a significant symptom reduction among the participating patients.

In comparison to more unstructured care, highly structured interventions, such as ICBT, appear to have their place. However, it is also crucial to emphasize the need for more than a one-time treatment series, especially considering the outcomes in study I, where a large proportion of the sample, one year after treatment termination, still have a significant need for further psychiatric care. The results in this dissertation partly demonstrate that depression, for many people, is a recurrent and,

to some extent, lifelong condition. Structured interventions are effective, but in a real-life setting, an intervention of this kind seems to be just one piece in the puzzle of managing mental health. Similarly, the cognitive and behavioral theories of depressive pathways only depict a part of a potentially more complicated picture, where genetic vulnerability interacts with personality and social factors such as loneliness, exposure to traumatic life events, and unemployment.

Another relevant aspect to consider when transitioning interventions into routine care is the proportion of individuals who deteriorate during the intervention—an aspect sometimes overlooked in psychotherapy but investigated by Rozental et al. (2017) regarding ICBT. The proportion that deteriorated in study II was similar to the proportion found in the meta-analysis by Rozental et al. (2017) which, in turn, showed that deterioration rates could be somewhat lower for ICBT than for psychotherapy in general. While the deterioration rate was at an expected level, it remains an important aspect to continuously monitor to prevent any negative trends.

As demonstrated in several investigations, study II also revealed higher attrition rates when moving from randomized trials to routine care. Understanding attrition is crucial when considering the effectiveness and acceptability of a treatment. If patients seek treatment for depression but encounter barriers that prevent them from starting and/or completing a recommended treatment, it becomes problematic both for the individual patient, who misses out on effective treatment, and for the community, as a large proportion of the population in need of treatment may not receive the necessary symptom relief. Another issue arises when other potentially more resource-demanding treatments need to be initiated if patients drop out from ICBT. Fernandez and colleagues (2015) discussed the problem of attrition, emphasizing that it is most strongly influenced by diagnosis and treatment format, with depression and "e-therapies" showing the highest degree of attrition in their meta-analysis. However, aside from these variables, there are few clear-cut factors that influence dropout. And perhaps more importantly, the factors that do emerge as influencing attrition (such as treatment credibility and intrinsic motivation among patients) are not easily manipulated (Alfonsson, 2016). In his dissertation on adherence to ICBT, Alfonsson (2016) concludes that overall, it is difficult to identify distinct treatment features that can be manipulated to increase adherence. This might be why the qualitative analysis of reasons for non-adherence performed in study III is the most cited article in this thesis.

Using ICBT in a clinical setting carries a potential risk, as seen in the results of study III and from the experience of treating patients in such a context. There is a higher risk that patients, in digital treatment (as compared to face-to-face treatment), feel they can decide for themselves which parts of the treatment they want to actively engage in. This might be a consequence of psychological treatment being presented in the format of any other online service, giving the impression that it can be used at will rather than requiring dedicated and consistent engagement for treatment success. In contrast, certain studies demonstrate promising results by providing

additional therapist attention specifically to patients who are assessed as being at risk for treatment failure, using treatment progress as an indicator of the need for such attention and personalization (Forsell et al., 2019). This approach further underscores the importance of actively dedicating extra attention to patients at risk of treatment failure (where treatment dropout is one type of failure), rather than relying on patients to determine their level of commitment based on their treatment experience.

In study II, a rather significant percentage (25%) of the patients recommended for ICBT did not respond when contacted by the treating clinicians about starting the treatment. While these patients are not actively refusing treatment, the proportion not starting treatment is very close to the numbers reported in the meta-analysis by Fernandez and colleagues (2015) as pretreatment dropout (24.2%) for "e-therapy." When examining the clinical usefulness of ICBT, it appears to be of great importance to also measure pretreatment attrition and possibly gain an understanding of how it can be avoided. When using open recruitment and participants are recruited via online ads, it's extremely difficult to measure the proportion that for different reasons don't reach a recommended treatment. This part of attrition is therefore at times left out when examining the clinical effectiveness of ICBT (Etzelmueller et al., 2020). Nevertheless, this type of pretreatment dropout is common in psychiatric care, and research in this area indicates that it's a general problem rather than a treatment protocol-specific issue (Glyngdal et al., 2002), but it still poses a challenge that needs to be addressed and understood.

Considering the problem of attrition, the reasons for attrition, and the serious challenge it poses for the dissemination of ICBT, future research is needed. The experience from this dissertation suggests that the field would benefit if such research were directed at the context in which ICBT is delivered—how patients are educated and informed about the intervention, how the importance of adherence is conveyed to the patient, and how the quality is thoroughly followed up to maintain effectiveness.

The overall results from this dissertation underscore the need for further efforts to increase treatment capacity for depression and anxiety in routine care, especially considering the cyclic nature of many mental health problems – an aspect that must be taken into account when structuring mental health care. Simultaneously, there is a necessity to ensure the acceptability and improve the effectiveness of the offered treatments. Regardless of the treatment type and its acceptability to patients, a significant proportion of treatment completers are likely to experience a recurrence or relapse of depression. This emphasizes the importance of both short- and long-term management of mental health among patients at psychiatric outpatient clinics. Ideally, patients who experience recurrence or relapse will seek or be re-referred for treatment, but these factors place added pressure on providers who may already be struggling to meet the demand for treatment.

The present results contribute to the literature by suggesting that further integration and testing of ICBT in routine care are essential for widespread dissemination of CBT. This will help determine whether ICBT can fulfill its promise of providing increased access to an efficacious and cost-effective treatment that is less burdensome for both patients and providers.

Efforts are imperative to enhance the acceptance and effectiveness of ICBT programs. This involves optimizing the treatment programs and their delivery within the specific contexts where they are utilized, thereby maximizing the use of this highly structured intervention in a broader treatment chain. Placing the ICBT intervention in a broader treatment context recognizes its role alongside other therapeutic methods for managing depression and anxiety. By finding the right place for highly structured interventions, we can better meet the sometimes-lifelong needs of individuals facing these challenges.

One crucial aspect of integrating an intervention into the broader scope of mental health care/routine care is to minimize pretreatment and treatment attrition, ensuring that all patients with treatment needs engage in and complete their treatments effectively. By optimizing attrition, effectiveness, and acceptability, we can reduce the risk of relapse, which is of particular importance among patients who are more vulnerable to mental illness due to socioeconomic circumstances, such as patients in second-line mental health care.

Collaboration between ICBT developers, clinicians, and patients is key. They should continuously adapt and test the ICBT programs to improve their effectiveness and address any shortcomings. This iterative process will enhance the programs' validity and reduce the risk of negative experiences with poorly validated ICBT offerings.

Furthermore, we must exercise caution when adopting ICBT programs that have only been tested in controlled environments or designed to mimic such protocols. Thorough evaluation is necessary before integrating them into clinical settings. This way, patients and providers can have confidence in the effectiveness of the ICBT programs they engage with, preventing broad negative perceptions due to inadequate exposure to properly validated interventions.

References

Aiyegbusi, O. L., Roydhouse, J., Rivera, S. C., Kamudoni, P., Schache, P., Wilson, R., Stephens, R., & Calvert, M. (2022). Key considerations to reduce or address respondent burden in patient-reported outcome (PRO) data collection. *Nature Communications*, *13*(1), 6026. https://doi.org/10.1038/s41467-022-33826-4

Akerblad, A.-C., Bengtsson, F., von Knorring, L., & Ekselius, L. (2006). Response, remission and relapse in relation to adherence in primary care treatment of depression: A 2-year outcome study. *International Clinical Psychopharmacology*, *21*(2), 117–124.

Alfonsson, S. (2016). *Treatment Adherence in Internet-Based CBT: The Effects of Presentation, Support and Motivation*.

Alfonsson, S., Olsson, E., & Hursti, T. (2016). Motivation and Treatment Credibility Predicts Dropout, Treatment Adherence, and Clinical Outcomes in an Internet-Based Cognitive Behavioral Relaxation Program: A Randomized Controlled Trial. *Journal of Medical Internet Research*, *18*(3), e52. https://doi.org/10.2196/jmir.5352

Ali, S., Rhodes, L., Moreea, O., McMillan, D., Gilbody, S., Leach, C., Lucock, M., Lutz, W., & Delgadillo, J. (2017). How durable is the effect of low intensity CBT for depression and anxiety? Remission and relapse in a longitudinal cohort study. *Behaviour Research and Therapy*, *94*, 1–8. https://doi.org/10.1016/j.brat.2017.04.006

American Psychiatric Association. (2022). *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5-TR). American Psychiatric Association Publishing. https://doi.org/10.1176/appi.books.9780890425787

American Psychiatric Association, & American Psychiatric Association (Eds.). (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed). American Psychiatric Association.

Andersson, G. (2009). Using the Internet to provide cognitive behaviour therapy. *Behaviour Research and Therapy*, *47*(3), 175–180. https://doi.org/16/j.brat.2009.01.010

Andersson, G., Bergstrom, J. A. N., Hollandare, F., Carlbring, P. E. R., Kaldo, V., & Ekselius, L. (2005). Internet-based self-help for depression: Randomised controlled trial. *British Journal of Psychiatry*, *187*(5), 456–461.

Andersson, G., Carlbring, P., Ljótsson, B., & Hedman, E. (2013). Guided Internet-Based CBT for Common Mental Disorders. *Journal of Contemporary Psychotherapy*, *43*(4), 223–233. https://doi.org/10.1007/s10879-013-9237-9

Andersson, G., Hesser, H., Hummerdal, D., Bergman-Nordgren, L., & Carlbring, P. (2013). A 3.5-year follow-up of Internet-delivered cognitive behavior therapy for major depression. *Journal of Mental Health*, *22*(2), 155–164. https://doi.org/10.3109/09638237.2011.608747

Andersson, G., Hesser, H., Veilord, A., Svedling, L., Andersson, F., Sleman, O., Mauritzson, L., Sarkohi, A., Claesson, E., Zetterqvist, V., Lamminen, M., Eriksson, T., & Carlbring, P. (2013). Randomised controlled non-inferiority trial with 3-year follow-up of internet-delivered versus face-to-face group cognitive behavioural therapy for depression. *Journal of Affective Disorders*. https://doi.org/10.1016/j.jad.2013.08.022

Andersson, G., Paxling, B., Roch-Norlund, P., Östman, G., Norgren, A., Almlöv, J., Georén, L., Breitholtz, E., Dahlin, M., Cuijpers, P., Carlbring, P., & Silverberg, F. (2012). Internet-based psychodynamic versus cognitive behavioral guided self-help for generalized anxiety disorder: A randomized controlled trial. *Psychotherapy and Psychosomatics*, *81*(6), 344–355. https://doi.org/10.1159/000339371

Andersson, G., Titov, N., Dear, B. F., Rozental, A., & Carlbring, P. (2019). Internet-delivered psychological treatments: From innovation to implementation. *World Psychiatry*, *18*(1), 20–28. https://doi.org/10.1002/wps.20610

Andersson, G., Topooco, N., Havik, O., & Nordgreen, T. (2016). Internet-supported versus face-to-face cognitive behavior therapy for depression. *Expert Review of Neurotherapeutics*, *16*(1), 55–60. https://doi.org/10.1586/14737175.2015.1125783

Andrade, L. H., Alonso, J., Mneimneh, Z., Wells, J. E., Al-Hamzawi, A., Borges, G., Bromet, E., Bruffaerts, R., Girolamo, G. de, Graaf, R. de, Florescu, S., Gureje, O., Hinkov, H. R., Hu, C., Huang, Y., Hwang, I., Jin, R., Karam, E. G., Kovess-Masfety, V., … Kessler, R. C. (2014). Barriers to mental health treatment: Results from the WHO World Mental Health surveys. *Psychological Medicine*, *44*(6), 1303–1317. https://doi.org/10.1017/S0033291713001943

Andrews, G., Basu, A., Cuijpers, P., Craske, M. G., McEvoy, P., English, C. L., & Newby, J. M. (2018). Computer therapy for the anxiety and depression disorders is effective, acceptable and practical health care: An updated meta-analysis. *Journal of Anxiety Disorders*. https://doi.org/10.1016/j.janxdis.2018.01.001

Angstman, K. B., Garrison, G. M., Gonzalez, C. A., Cozine, D. W., Cozine, E. W., & Katzelnick, D. J. (2017). Prediction of Primary Care Depression Outcomes at Six Months: Validation of DOC-6 ©. *The Journal of the American Board of Family Medicine*, *30*(3), 281–287. https://doi.org/10.3122/jabfm.2017.03.160313

Bandelow, B., Baldwin, D. S., Dolberg, O. T., Andersen, H. F., & Stein, D. J. (2006). What is the threshold for symptomatic response and remission for major depressive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder? *The Journal of Clinical Psychiatry*, *67*(9), 1428–1434.

Barlow, D. H., Allen, L. B., & Choate, M. L. (2004). Toward a unified treatment for emotional disorders. *Behavior Therapy*, *35*(2), 205–230. https://doi.org/10.1016/S0005-7894(04)80036-4

Barlow, D. H., Sauer-Zavala, S., Carl, J. R., Bullis, J. R., & Ellard, K. K. (2014). The Nature, Diagnosis, and Treatment of Neuroticism: Back to the Future. *Clinical Psychological Science*, *2*(3), 344–365. https://doi.org/10.1177/2167702613505532

Baumeister, H., Reichler, L., Munzinger, M., & Lin, J. (2014). The impact of guidance on Internet-based mental health interventions—A systematic review. *Internet Interventions*, *1*(4), 205–215. https://doi.org/10.1016/j.invent.2014.08.003

Beatty, L., & Binnion, C. (2016). A Systematic Review of Predictors of, and Reasons for, Adherence to Online Psychological Interventions. *International Journal of Behavioral Medicine*, *23*(6), 776–794. https://doi.org/10.1007/s12529-016-9556-9

Beck, A., Rush, J., Shaw, B., & Emery, G. (1979). *Cognitive Therapy of Depression* (1St Edition). The Guilford Press.

Beckstead, D. J., Hatch, A. L., Lambert, M. J., Eggett, D. L., Goates, M. K., & Vermeersch, D. A. (2003). Clinical significance of the Outcome Questionnaire (OQ-45.2). *The Behavior Analyst Today*, *4*(1), 86–97. https://doi.org/10.1037/h0100015

Berlanga, C., Heinze, G., Torres, M., Apiquián, R., & Caballero, A. (1999). Personality and clinical predictors of recurrence of depression. *Psychiatric Services (Washington, D.C.)*, *50*(3), 376–380.

Beshai, S., Dobson, K. S., Bockting, C. L. H., & Quigley, L. (2011). Relapse and recurrence prevention in depression: Current research and future prospects. *Clinical Psychology Review*, *31*(8), 1349–1360. https://doi.org/10.1016/j.cpr.2011.09.003

Beumont, P. J., Russell, J. D., & Touyz, S. W. (1993). Treatment of anorexia nervosa. *Lancet*, *341*(8861), 1635–1640.

Bromet, E., Andrade, L. H., Hwang, I., Sampson, N. A., Alonso, J., de Girolamo, G., de Graaf, R., Demyttenaere, K., Hu, C., Iwata, N., Karam, A. N., Kaur, J., Kostyuchenko, S., Lépine, J.-P., Levinson, D., Matschinger, H., Mora, M. E. M., Browne, M. O., Posada-Villa, J., … Kessler, R. C. (2011). Cross-national epidemiology of DSM-IV major depressive episode. *BMC Medicine*, *9*(1), 90. https://doi.org/10.1186/1741-7015-9-90

Buckman, J. E. J., Underwood, A., Clarke, K., Saunders, R., Hollon, S. D., Fearon, P., & Pilling, S. (2018). Risk factors for relapse and recurrence of depression in adults and how they operate: A four-phase systematic review and meta-synthesis. *Clinical Psychology Review*, *64*, 13–38. https://doi.org/10.1016/j.cpr.2018.07.005

Burcusa, S. L., & Iacono, W. G. (2007). Risk for Recurrence in Depression. *Clinical Psychology Review*, *27*(8), 959–985. https://doi.org/10.1016/j.cpr.2007.02.005

Carlbring, P., Andersson, G., Cuijpers, P., Riper, H., & Hedman-Lagerlöf, E. (2018). Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: An updated systematic review and meta-analysis. *Cognitive Behaviour Therapy*, *47*(1), 1–18. https://doi.org/10.1080/16506073.2017.1401115

Carr, A. J. (2001). Measuring quality of life: Is quality of life determined by expectations or experience? *BMJ*, *322*(7296), 1240–1243. https://doi.org/10.1136/bmj.322.7296.1240

Carvalho, J. P., & Hopko, D. R. (2011). Behavioral theory of depression: Reinforcement as a mediating variable between avoidance and depression. *Journal of Behavior Therapy and Experimental Psychiatry*, *42*(2), 154–162. https://doi.org/10.1016/j.jbtep.2010.10.001

Charmaz, K. C. (2006). *Constructing Grounded Theory: A Practical Guide through Qualitative Analysis*. Sage Publications Ltd.

Chesney, E., Goodwin, G. M., & Fazel, S. (2014). Risks of all-cause and suicide mortality in mental disorders: A meta-review. *World Psychiatry*, *13*(2), 153–160. https://doi.org/10.1002/wps.20128

Christensen, H., Griffiths, K. M., & Farrer, L. (2009). Adherence in Internet Interventions for Anxiety and Depression: Systematic Review. *Journal of Medical Internet Research*, *11*(2). https://doi.org/10.2196/jmir.1194

Clarke, G., Eubanks, D., Reid, E., Kelleher, C., O'Connor, E., DeBar, L. L., Lynch, F., Nunley, S., & Gullion, C. (2005). Overcoming Depression on the Internet (ODIN) (2): A Randomized Trial of a Self-Help Depression Skills Program With Reminders. *J Med Internet Res*, *7*(2), e16.

Cuijpers, P. (2017). Four decades of outcome research on psychotherapies for adult depression: An overview of a series of meta-analyses. *Canadian Psychology/Psychologie Canadienne*, *58*(1), 7–19. https://doi.org/10.1037/cap0000096

Cuijpers, P., Dekker, J., Hollon, S. D., & Andersson, G. (2009). Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: A meta-analysis. *The Journal of Clinical Psychiatry*, *70*(9), 1219–1229. https://doi.org/10.4088/JCP.09r05021

Cuijpers, P., Stringaris, A., & Wolpert, M. (2020). Treatment outcomes for depression: Challenges and opportunities. *The Lancet Psychiatry*, *7*(11), 925–927. https://doi.org/10.1016/S2215-0366(20)30036-5

Cuijpers, P., van Straten, A., Bohlmeijer, E., Hollon, S. D., & Andersson, G. (2010). The effects of psychotherapy for adult depression are overestimated: A meta-analysis of study quality and effect size. *Psychological Medicine*, *40*(2), 211–223. https://doi.org/10.1017/S0033291709006114

Donker, T., Blankers, M., Hedman, E., Ljótsson, B., Petrie, K., & Christensen, H. (2015). Economic evaluations of Internet interventions for mental health: A systematic review. *Psychological Medicine*, *45*(16), 3357–3376. https://doi.org/10.1017/S0033291715001427

Dunn, T. L., Casey, L. M., Sheffield, J., Newcombe, P., & Chang, A. B. (2012). Dropout from computer-based interventions for children and adolescents with chronic health conditions. *Journal of Health Psychology*, *17*(3), 429–442. https://doi.org/10.1177/1359105311415558

Ekeblad, A., Falkenström, F., Andersson, G., Vestberg, R., & Holmqvist, R. (2016). Randomized Trial of Interpersonal Psychotherapy and Cognitive Behavioral Therapy for Major Depressive Disorder in a Community-Based Psychiatric Outpatient Clinic: Research Article: IPT Compared to CBT for MDD-A Randomized Trial. *Depression and Anxiety*, *33*(12), 1090–1098. https://doi.org/10.1002/da.22495

El Alaoui, S., Ljótsson, B., Hedman, E., Kaldo, V., Andersson, E., Rück, C., Andersson, G., & Lindefors, N. (2015). Predictors of Symptomatic Change and Adherence in Internet-Based Cognitive Behaviour Therapy for Social Anxiety Disorder in Routine Psychiatric Care. *PLOS ONE*, *10*(4), e0124258. https://doi.org/10.1371/journal.pone.0124258

Etzelmueller, A., Vis, C., Karyotaki, E., Baumeister, H., Titov, N., Berking, M., Cuijpers, P., Riper, H., & Ebert, D. D. (2020). Effects of Internet-Based Cognitive Behavioral Therapy in Routine Care for Adults in Treatment for Depression and Anxiety: Systematic Review and Meta-Analysis. *Journal of Medical Internet Research*, *22*(8), e18100. https://doi.org/10.2196/18100

Eysenbach, G. (2005). The law of attrition. *Journal of Medical Internet Research*, *7*(1), e11. https://doi.org/10.2196/jmir.7.1.e11

Fairburn, C. G., Jones, R., Peveler, R. C., Hope, R. A., & O'Connor, M. (1993). Psychotherapy and bulimia nervosa. Longer-term effects of interpersonal psychotherapy, behavior therapy, and cognitive behavior therapy. *Archives of General Psychiatry*, *50*(6), 419–428.

Farrer, L., Christensen, H., Griffiths, K. M., & Mackinnon, A. (2011). Internet-based CBT for depression with and without telephone tracking in a national helpline: Randomised controlled trial. *PloS One*, *6*(11), e28099. https://doi.org/10.1371/journal.pone.0028099

Fernandez, E., Salem, D., Swift, J. K., & Ramtahal, N. (2015). Meta-analysis of dropout from cognitive behavioral therapy: Magnitude, timing, and moderators. *Journal of Consulting and Clinical Psychology*, *83*(6), 1108–1122. https://doi.org/10.1037/ccp0000044

Ferrari, A. J., Somerville, A. J., Baxter, A. J., Norman, R., Patten, S. B., Vos, T., & Whiteford, H. A. (2013). Global variation in the prevalence and incidence of major depressive disorder: A systematic review of the epidemiological literature. *Psychological Medicine*, *43*(3), 471–481. https://doi.org/10.1017/S0033291712001511

Ferster, C. B. (1973). A functional analysis of depression. *American Psychologist*, *28*(10), 857–870. https://doi.org/10.1037/h0035605

First, M. B., & Gibbon, M. (1997). *User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version*. American Psychiatric Pub.

Firth, N., Saxon, D., Stiles, W. B., & Barkham, M. (2019). Therapist and Clinic Effects in Psychotherapy: A Three-Level Model of Outcome Variability. *Journal of Consulting & Clinical Psychology*, *87*(4), 345–356. https://doi.org/10.1037/ccp0000388

Flint, J., & Kendler, K. S. (2014). The Genetics of Major Depression. *Neuron*, *81*(3), 484–503. https://doi.org/10.1016/j.neuron.2014.01.027

Forsell, E., Jernelöv, S., Blom, K., Kraepelien, M., Svanborg, C., Andersson, G., Lindefors, N., & Kaldo, V. (2019). Proof of Concept for an Adaptive Treatment Strategy to Prevent Failures in Internet-Delivered CBT: A Single-Blind Randomized Clinical Trial With Insomnia Patients. *American Journal of Psychiatry*, *176*(4), 315–323. https://doi.org/10.1176/appi.ajp.2018.18060699

Frank, E., Prien, R. F., Jarrett, R. B., Keller, M. B., Kupfer, D. J., Lavori, P. W., Rush, A. J., & Weissman, M. M. (1991). Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Archives of General Psychiatry*, *48*(9), 851–855.

Fresco, D. M., Mennin, D. S., Heimberg, R. G., & Turk, C. L. (2003). Using the Penn State Worry Questionnaire to identify individuals with generalized anxiety disorder: A receiver operating characteristic analysis. *Journal of Behavior Therapy and Experimental Psychiatry*, *34*(3–4), 283–291. https://doi.org/10.1016/j.jbtep.2003.09.001

Furukawa, T. A., Cipriani, A., Atkinson, L. Z., Leucht, S., Ogawa, Y., Takeshima, N., Hayasaka, Y., Chaimani, A., & Salanti, G. (2016). Placebo response rates in antidepressant trials: A systematic review of published and unpublished double-blind randomised controlled studies. *The Lancet Psychiatry*, *3*(11), 1059–1066. https://doi.org/10.1016/S2215-0366(16)30307-8

Furukawa, T. A., Noma, H., Caldwell, D. M., Honyashiki, M., Shinohara, K., Imai, H., Chen, P., Hunot, V., & Churchill, R. (2014). Waiting list may be a nocebo condition in psychotherapy trials: A contribution from network meta-analysis. *Acta Psychiatrica Scandinavica*, *130*(3), 181–192. https://doi.org/10.1111/acps.12275

Gagliardi, A. R., Yip, C. Y. Y., Irish, J., Wright, F. C., Rubin, B., Ross, H., Green, R., Abbey, S., McAndrews, M. P., & Stewart, D. E. (2021). The psychological burden of waiting for procedures and patient-centred strategies that could support the mental health of wait-listed patients and caregivers during the COVID-19 pandemic: A scoping review. *Health Expectations*, *24*(3), 978–990. https://doi.org/10.1111/hex.13241

Gallucci, G., Swartz, W., & Hackerman, F. (2005). Brief Reports: Impact of the Wait for an Initial Appointment on the Rate of Kept Appointments at a Mental Health Center. *Psychiatric Services*, *56*(3), 344–346. https://doi.org/10.1176/appi.ps.56.3.344

Gartlehner, G., Wagner, G., Matyas, N., Titscher, V., Greimel, J., Lux, L., Gaynes, B. N., Viswanathan, M., Patel, S., & Lohr, K. N. (2017). Pharmacological and non-pharmacological treatments for major depressive disorder: Review of systematic reviews. *BMJ Open*, *7*(6), e014912. https://doi.org/10.1136/bmjopen-2016-014912

Glaser, B. G. (2002). Conceptualization: On Theory and Theorizing Using Grounded Theory. *International Journal of Qualitative Methods*, *1*(2), 23–38. https://doi.org/10.1177/160940690200100203

Glaser, B., & Strauss, A. (1967). *The discovery of grounded theory: Strategies for qualitative research*. Aldine Publishing Company.

Glyngdal, P., Sørensen, P., & Kistrup, K. (2002). Non-compliance in community psychiatry: Failed appointments in the referral system to psychiatric outpatient treatment. *Nordic Journal of Psychiatry*, *56*(2), 151–156. https://doi.org/10.1080/080394802753617980

Goldberg, S., Sun, S., Carlbring, P., & Torous, J. (2023). *Selecting and describing control conditions in mobile health randomized controlled trials: A proposed typology* [Preprint]. PsyArXiv. https://doi.org/10.31234/osf.io/h479x

Gonzales, L. R., Lewinsohn, P. M., & Clarke, G. N. (1985). Longitudinal follow-up of unipolar depressives: An investigation of predictors of relapse. *Journal of Consulting and Clinical Psychology*, *53*(4), 461–469.

Hansson, H., Rundberg, J., Österling, A., Öjehagen, A., & Berglund, M. (2013). Intervention with feedback using Outcome Questionnaire 45 (OQ-45) in a Swedish psychiatric outpatient population. A randomized controlled trial. *Nordic Journal of Psychiatry*, *67*(4), 274–281. https://doi.org/10.3109/08039488.2012.736534

Hardeveld, F., Spijker, J., De Graaf, R., Nolen, W. A., & Beekman, A. T. F. (2010). Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatrica Scandinavica*, *122*(3), 184–191. https://doi.org/10.1111/j.1600-0447.2009.01519.x

Hasin, D. S., Sarvet, A. L., Meyers, J. L., Saha, T. D., Ruan, W. J., Stohl, M., & Grant, B. F. (2018). Epidemiology of Adult *DSM-5* Major Depressive Disorder and Its Specifiers in the United States. *JAMA Psychiatry*, *75*(4), 336. https://doi.org/10.1001/jamapsychiatry.2017.4602

Hawton, K., Casañas i Comabella, C., Haw, C., & Saunders, K. (2013). Risk factors for suicide in individuals with depression: A systematic review. *Journal of Affective Disorders*, *147*(1–3), 17–28. https://doi.org/10.1016/j.jad.2013.01.004

Hedman, E., Ljótsson, B., Kaldo, V., Hesser, H., El Alaoui, S., Kraepelien, M., Andersson, E., Rück, C., Svanborg, C., Andersson, G., & Lindefors, N. (2014). Effectiveness of Internet-based cognitive behaviour therapy for depression in routine psychiatric care. *Journal of Affective Disorders*, *155*, 49–58. https://doi.org/10.1016/j.jad.2013.10.023

Hedman-Lagerlöf, E., Carlbring, P., Svärdman, F., Riper, H., Cuijpers, P., & Andersson, G. (2023). Therapist-supported Internet-based cognitive behaviour therapy yields similar effects as face-to-face therapy for psychiatric and somatic disorders: An updated systematic review and meta-analysis. *World Psychiatry*, *22*(2), 305–314. https://doi.org/10.1002/wps.21088

Hilvert-Bruce, Z., Rossouw, P. J., Wong, N., Sunderland, M., & Andrews, G. (2012). Adherence as a determinant of effectiveness of internet cognitive behavioural therapy for anxiety and depressive disorders. *Behaviour Research and Therapy*, *50*(7–8), 463–468. https://doi.org/10.1016/j.brat.2012.04.001

Hofmann, S. G., Curtiss, J., Carpenter, J. K., & Kind, S. (2017). Effect of treatments for depression on quality of life: A meta-analysis. *Cognitive Behaviour Therapy*, *46*(4), 265–286. https://doi.org/10.1080/16506073.2017.1304445

Holländare, F., Andersson, G., & Engström, I. (2010). A comparison of psychometric properties between internet and paper versions of two depression instruments (BDI-II and MADRS-S) administered to clinic patients. *Journal of Medical Internet Research*, *12*(5), e49. https://doi.org/10.2196/jmir.1392

Hollon, S. D., DeRubeis, R. J., Shelton, R. C., Amsterdam, J. D., Salomon, R. M., O'Reardon, J. P., Lovett, M. L., Young, P. R., Haman, K. L., Freeman, B. B., & Gallop, R. (2005). Prevention of relapse following cognitive therapy vs medications in moderate to severe depression. *Archives of General Psychiatry*, *62*(4), 417–422. https://doi.org/10.1001/archpsyc.62.4.417

Inera. (2021). *Statistik, användning av 1177 Vårdguidens e-tjänst Stöd och behandling*. Inera. https://www.inera.se/tjanster/statistik-for-ineras-tjanster/statistik-for-stod-och-behandling/oversikt/

Inera. (2022, June 30). *Stöd och behandling*. Inera. https://www.inera.se/tjanster/alla-tjanster-a-o/stod-och-behandling/

Jakobsen, H., Andersson, G., Havik, O. E., & Nordgreen, T. (2017). Guided Internet-based cognitive behavioral therapy for mild and moderate depression: A benchmarking study. *Internet Interventions*, *7*, 1–8. https://doi.org/10.1016/j.invent.2016.11.002

Johansson, R., Carlbring, P., Heedman, Å., Paxling, B., & Andersson, G. (2013). Depression, anxiety and their comorbidity in the Swedish general population: Point prevalence and the effect on health-related quality of life. *PeerJ*, *1*, e98. https://doi.org/10.7717/peerj.98

Johansson, R., Sjöberg, E., Sjögren, M., Johnsson, E., Carlbring, P., Andersson, T., Rousseau, A., & Andersson, G. (2012). Tailored vs. standardized internet-based cognitive behavior therapy for depression and comorbid symptoms: A randomized controlled trial. *PloS One*, *7*(5), e36905. https://doi.org/10.1371/journal.pone.0036905

Kalin, N. H. (2020). The Critical Relationship Between Anxiety and Depression. *The American Journal of Psychiatry*, *177*(5), 365–367. https://doi.org/10.1176/appi.ajp.2020.20030305

Karyotaki, E., Ebert, D. D., Donkin, L., Riper, H., Twisk, J., Burger, S., Rozental, A., Lange, A., Williams, A. D., Zarski, A. C., Geraedts, A., van Straten, A., Kleiboer, A., Meyer, B., Ünlü Ince, B. B., Buntrock, C., Lehr, D., Snoek, F. J., Andrews, G., … Cuijpers, P. (2018). Do guided internet-based interventions result in clinically relevant changes for patients with depression? An individual participant data meta-analysis. *Clinical Psychology Review*, *63*, 80–92. https://doi.org/10.1016/j.cpr.2018.06.007

Karyotaki, E., Efthimiou, O., Miguel, C., Bermpohl, F. M. genannt, Furukawa, T. A., Cuijpers, P., Individual Patient Data Meta-Analyses for Depression (IPDMA-DE) Collaboration, Riper, H., Patel, V., Mira, A., Gemmil, A. W., Yeung, A. S., Lange, A., Williams, A. D., Mackinnon, A., Geraedts, A., van Straten, A., Meyer, B., Björkelund, C., … Forsell, Y. (2021). Internet-Based Cognitive Behavioral Therapy for Depression: A Systematic Review and Individual Patient Data Network Meta-analysis. *JAMA Psychiatry*, *78*(4), 361. https://doi.org/10.1001/jamapsychiatry.2020.4364

Kelders, S. M., Kok, R. N., Ossebaard, H. C., & Van Gemert-Pijnen, J. E. W. C. (2012). Persuasive system design does matter: A systematic review of adherence to web-based interventions. *Journal of Medical Internet Research*, *14*(6), e152. https://doi.org/10.2196/jmir.2104

Kendler, K. S., Kuhn, J., & Prescott, C. A. (2004). The Interrelationship of Neuroticism, Sex, and Stressful Life Events in the Prediction of Episodes of Major Depression. *American Journal of Psychiatry*, *161*(4), 631–636. https://doi.org/10.1176/appi.ajp.161.4.631

Kessing, L. V., Andersen, P. K., & Mortensen, P. B. (1998). Predictors of recurrence in affective disorder. A case register study. *Journal of Affective Disorders*, *49*(2), 101–108.

Klein, B., Austin, D., Pier, C., Kiropoulos, L., Shandley, K., Mitchell, J., Gilson, K., & Ciechomski, L. (2009). Internet-Based Treatment for Panic Disorder: Does Frequency of Therapist Contact Make a Difference? *Cognitive Behaviour Therapy*, *38*(2), 100–113. https://doi.org/10.1080/16506070802561132

Köhler, C. A., Evangelou, E., Stubbs, B., Solmi, M., Veronese, N., Belbasis, L., Bortolato, B., Melo, M. C. A., Coelho, C. A., Fernandes, B. S., Olfson, M., Ioannidis, J. P. A., & Carvalho, A. F. (2018). Mapping risk factors for depression across the lifespan: An umbrella review of evidence from meta-analyses and Mendelian randomization studies. *Journal of Psychiatric Research*, *103*, 189–207. https://doi.org/10.1016/j.jpsychires.2018.05.020

Korstjens, I., & Moser, A. (2017). Series: Practical guidance to qualitative research. Part 2: Context, research questions and designs. *European Journal of General Practice*, *23*(1), 274–279. https://doi.org/10.1080/13814788.2017.1375090

Lambert, M. J., Burlingame, G. M., Umphress, V., Hansen, N. B., Vermeersch, D. A., Clouse, G. C., & Yanchar, S. C. (1996). The Reliability and Validity of the Outcome Questionnaire. *Clinical Psychology & Psychotherapy*, *3*(4), 249–258.

Lewinsohn, P. M. (1974). A behavioral approach to depression. *Essential Papers on Depression*, 150–172.

Lewinsohn, P. M., Hoberman, H. M., & Rosenbaum, M. (1988). A prospective study of risk factors for unipolar depression. *Journal of Abnormal Psychology*, *97*(3), 251–264.

Lewis, M., & Rudolph, K. D. (Eds.). (2014). *Handbook of developmental psychopathology* (Third edition). Springer.

Lindner, P., Nyström, M. B. T., Hassmén, P., Andersson, G., & Carlbring, P. (2015). Who seeks ICBT for depression and how do they get there? Effects of recruitment source on patient demographics and clinical characteristics. *Internet Interventions*, *2*(2), 221–225. https://doi.org/10.1016/j.invent.2015.04.002

Lingard, L., Albert, M., & Levinson, W. (2008). Grounded theory, mixed methods, and action research. *BMJ*, *337*(aug07 3), a567–a567. https://doi.org/10.1136/bmj.39602.690162.47

Lisspers, J., Nygren, A., & Söderman, E. (1997). Hospital Anxiety and Depression Scale (HAD): Some psychometric data for a Swedish sample. *Acta Psychiatrica Scandinavica*, *96*(4), 281–286. https://doi.org/10.1111/j.1600-0447.1997.tb10164.x

Lobbestael, J., Leurgans, M., & Arntz, A. (2011). Inter-rater reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). *Clinical Psychology & Psychotherapy*, *18*(1), 75–79. https://doi.org/10.1002/cpp.693

Martell, C. R., Addis, M. E., & Jacobson, N. S. (2001). *Depression in Context: Strategies for Guided Action*. W.W. Norton.

Martin, J., Taylor, M. J., & Lichtenstein, P. (2018). Assessing the evidence for shared genetic risks across psychiatric disorders and traits. *Psychological Medicine*, *48*(11), 1759–1774. https://doi.org/10.1017/S0033291717003440

Meyer, B., Pilkonis, P. A., Krupnick, J. L., Egan, M. K., Simmens, S. J., & Sotsky, S. M. (2002). Treatment expectancies, patient alliance and outcome: Further analyses from the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *Journal of Consulting and Clinical Psychology*, *70*(4), 1051–1055. https://doi.org/10.1037/0022-006X.70.4.1051

Meyer, T. J., Miller, M. L., Metzger, R. L., & Borkovec, T. D. (1990). Development and validation of the Penn State Worry Questionnaire. *Behaviour Research and Therapy*, *28*(6), 487–495.

Mohr, D. C., Ho, J., Hart, T. L., Baron, K. G., Berendsen, M., Beckner, V., Cai, X., Cuijpers, P., Spring, B., Kinsinger, S. W., Schroder, K. E., & Duffecy, J. (2014). Control condition design and implementation features in controlled trials: A meta-analysis of trials evaluating psychotherapy for depression. *Translational Behavioral Medicine*, *4*(4), 407–423. https://doi.org/10.1007/s13142-014-0262-3

Montgomery, S., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry*, *134*(4), 382–389. https://doi.org/10.1192/bjp.134.4.382

Moriarty, A. S., Meader, N., Snell, K. I. E., Riley, R. D., Paton, L. W., Dawson, S., Hendon, J., Chew-Graham, C. A., Gilbody, S., Churchill, R., Phillips, R. S., Ali, S., & McMillan, D. (2022). Predicting relapse or recurrence of depression: Systematic review of prognostic models. *The British Journal of Psychiatry*, 1–11. https://doi.org/10.1192/bjp.2021.218

Morse, J. M. (2015). "Data Were Saturated. . . ." *Qualitative Health Research*, *25*(5), 587–588. https://doi.org/10.1177/1049732315576699

Mueller, T. I., Leon, A. C., Keller, M. B., Solomon, D. A., Endicott, J., Coryell, W., Warshaw, M., & Maser, J. D. (1999). Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *The American Journal of Psychiatry*, *156*(7), 1000–1006.

Newman, M. G., Zuellig, A. R., & Kachin, K. E. (2002). Preliminary Reliability and Validity of the Generalized Anxiety Disorder Questionnaire—IV: A Revised Self Report Diagnostic Measure of Generalized Anxiety Disorder. *Behavior Therapy*, *33*(2), 215–234.

O'Leary, D. A., & Lee, A. S. (1996). Seven year prognosis in depression. Mortality and readmission risk in the Nottingham ECT cohort. *The British Journal of Psychiatry: The Journal of Mental Science*, *169*(4), 423–429.

Olsson, S., Hensing, G., Burström, B., & Löve, J. (2021). Unmet Need for Mental Healthcare in a Population Sample in Sweden: A Cross-Sectional Study of Inequalities Based on Gender, Education, and Country of Birth. *Community Mental Health Journal*, *57*(3), 470–481. https://doi.org/10.1007/s10597-020-00668-7

Otte, C., Gold, S. M., Penninx, B. W., Pariante, C. M., Etkin, A., Fava, M., Mohr, D. C., & Schatzberg, A. F. (2016). Major depressive disorder. *Nature Reviews Disease Primers*, *2*(1), 16065. https://doi.org/10.1038/nrdp.2016.65

Pantelis, C., Papadimitriou, G. N., Papiol, S., Parkhomenko, E., Pato, M. T., Paunio, T., Pejovic-Milovancevic, M., Perkins, D. O., & Pietiläinen, O. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, *511*(7510), 421–427.

Patel, V., Saxena, S., Lund, C., Thornicroft, G., Baingana, F., Bolton, P., Chisholm, D., Collins, P. Y., Cooper, J. L., Eaton, J., Herrman, H., Herzallah, M. M., Huang, Y., Jordans, M. J. D., Kleinman, A., Medina-Mora, M. E., Morgan, E., Niaz, U., Omigbodun, O., … UnÜtzer, Jü. (2018). The Lancet Commission on global mental health and sustainable development. *Lancet (London, England)*, *392*(10157), 1553–1598. https://doi.org/10.1016/S0140-6736(18)31612-X

Paxling, B., Almlöv, J., Dahlin, M., Carlbring, P., Breitholtz, E., Eriksson, T., & Andersson, G. (2011). Guided internet-delivered cognitive behavior therapy for generalized anxiety disorder: A randomized controlled trial. *Cognitive Behaviour Therapy*, *40*(3), 159–173. https://doi.org/10.1080/16506073.2011.576699

Paykel, E. S., Ramana, R., Cooper, Z., Hayhurst, H., Kerr, J., & Barocka, A. (1995). Residual symptoms after partial remission: An important outcome in depression. *Psychological Medicine*, *25*(6), 1171–1180.

Postel, M. G., de Haan, H. A., ter Huurne, E. D., van der Palen, J., Becker, E. S., & de Jong, C. A. (2011). Attrition in Web-Based Treatment for Problem Drinkers. *Journal of Medical Internet Research*, *13*(4). https://doi.org/10.2196/jmir.1811

Poutanen, O., Mattila, A., Seppälä, N. H., Groth, L., Koivisto, A.-M., & Salokangas, R. K. R. (2007). Seven-year outcome of depression in primary and psychiatric outpatient care: Results of the TADEP (Tampere Depression) II Study. *Nordic Journal of Psychiatry*, *61*(1), 62–70. https://doi.org/10.1080/08039480601135140

Reitzel, L. R., Stellrecht, N. E., Gordon, K. H., Lima, E. N., Wingate, L. R., Brown, J. S., Wolfe, A. S., Zenoz, L. M., & Joiner, T. E. (2006). Does time between application and case assignment predict therapy attendance or premature termination in outpatients? *Psychological Services*, *3*(1), 51–60. https://doi.org/10.1037/1541-1559.3.1.51

Rnic, K., Santee, A. C., Hoffmeister, J.-A., Liu, H., Chang, K. K., Chen, R. X., Neufeld, R. W. J., Machado, D. A., Starr, L. R., Dozois, D. J. A., & LeMoult, J. (2023). The vicious cycle of psychopathology and stressful life events: A meta-analytic review testing the stress generation model. *Psychological Bulletin*. https://doi.org/10.1037/bul0000390

Romijn, G., Batelaan, N., Kok, R., Koning, J., Balkom, A. van, Titov, N., & Riper, H. (2019). Internet-Delivered Cognitive Behavioral Therapy for Anxiety Disorders in Open Community Versus Clinical Service Recruitment: Meta-Analysis. *Journal of Medical Internet Research*, *21*(4), e11706. https://doi.org/10.2196/11706

Rowan, K., McAlpine, D., & Blewett, L. (2013). Access and Cost Barriers to Mental Health Care by Insurance Status, 1999 to 2010. *Health Affairs (Project Hope)*, *32*(10), 1723–1730. https://doi.org/10.1377/hlthaff.2013.0133

Rozental, A., Magnusson, K., Boettcher, J., Andersson, G., & Carlbring, P. (2017). For better or worse: An individual patient data meta-analysis of deterioration among participants receiving Internet-based cognitive behavior therapy. *Journal of Consulting and Clinical Psychology*, *85*(2), 160–177. https://doi.org/10.1037/ccp0000158

Salmoiraghi, A., & Sambhi, R. (2010). Early termination of cognitive-behavioural interventions: Literature review. *The Psychiatrist*, *34*(12), 529–532. https://doi.org/10.1192/pb.bp.110.030775

Sareen, J., Cox, B. J., Afifi, T. O., Clara, I., & Yu, B. N. (2005). Perceived Need for Mental Health Treatment in a Nationally Representative Canadian Sample. *The Canadian Journal of Psychiatry*, *50*(10), 643–651. https://doi.org/10.1177/070674370505001011

Schuster, R., Kaiser, T., Terhorst, Y., Messner, E. M., Strohmeier, L.-M., & Laireiter, A.-R. (2021). Sample size, sample size planning, and the impact of study context: Systematic review and recommendations by the example of psychological depression treatment. *Psychological Medicine*, *51*(6), 902–908. https://doi.org/10.1017/S003329172100129X

Seedat, S., Scott, K. M., Angermeyer, M. C., Berglund, P., Bromet, E. J., Brugha, T. S., Demyttenaere, K., de Girolamo, G., Haro, J. M., Jin, R., Karam, E. G., Kovess-Masfety, V., Levinson, D., Medina Mora, M. E., Ono, Y., Ormel, J., Pennell, B.-E., Posada-Villa, J., Sampson, N. A., … Kessler, R. C. (2009). Cross-National Associations Between Gender and Mental Disorders in the World Health Organization World Mental Health Surveys. *Archives of General Psychiatry*, *66*(7), 785. https://doi.org/10.1001/archgenpsychiatry.2009.36

Shapiro, D. A., Rees, A., Barkham, M., Hardy, G., Reynolds, S., & Startup, M. (1995). Effects of treatment duration and severity of depression on the maintenance of gains after cognitive-behavioral and psychodynamic-interpersonal psychotherapy. *Journal of Consulting and Clinical Psychology*, *63*(3), 378–387.

Sim, K., Lau, W. K., Sim, J., Sum, M. Y., & Baldessarini, R. J. (2016). Prevention of Relapse and Recurrence in Adults with Major Depressive Disorder: Systematic Review and Meta-Analyses of Controlled Trials. *International Journal of Neuropsychopharmacology*, *19*(2), pyv076. https://doi.org/10.1093/ijnp/pyv076

Smoktunowicz, E., Barak, A., Andersson, G., Banos, R. M., Berger, T., Botella, C., Dear, B. F., Donker, T., Ebert, D. D., Hadjistavropoulos, H., Hodgins, D. C., Kaldo, V., Mohr, D. C., Nordgreen, T., Powers, M. B., Riper, H., Ritterband, L. M., Rozental, A., Schueller, S. M., … Carlbring, P. (2020). Consensus statement on the problem of terminology in psychological interventions using the internet or digital components. *Internet Interventions*, *21*, 100331. https://doi.org/10.1016/j.invent.2020.100331

Socialstyrelsen. (2008). *Vård i rimlig tid*. http://www.vardguiden.se/Theme_Startpage.asp?c=2982

Socialstyrelsen. (2021). *Nationella riktlinjer för vård vid depression och ångestsyndrom*. https://www.socialstyrelsen.se/regler-och-riktlinjer/nationella-riktlinjer/riktlinjer-och-utvarderingar/depression-och-angest/

Steffen, A., Nübel, J., Jacobi, F., Bätzing, J., & Holstiege, J. (2020). Mental and somatic comorbidity of depression: A comprehensive cross-sectional analysis of 202 diagnosis groups using German nationwide ambulatory claims data. *BMC Psychiatry*, *20*(1), 142. https://doi.org/10.1186/s12888-020-02546-8

Sun, Y., Möller, J., Lundin, A., Wong, S. Y. S., Yip, B. H. K., & Forsell, Y. (2018). Utilization of psychiatric care and antidepressants among people with different severity of depression: A population-based cohort study in Stockholm, Sweden. *Social Psychiatry and Psychiatric Epidemiology*, *53*(6), 607–615. https://doi.org/10.1007/s00127-018-1515-0

Sundquist, J., Ohlsson, H., Sundquist, K., & Kendler, K. S. (2017). Common adult psychiatric disorders in Swedish primary care where most mental health patients are treated. *BMC Psychiatry*, *17*(1), 235. https://doi.org/10.1186/s12888-017-1381-4

Svanborg, P., & Asberg, M. (2001). A comparison between the Beck Depression Inventory (BDI) and the self-rating version of the Montgomery Asberg Depression Rating Scale (MADRS). *Journal of Affective Disorders*, *64*(2–3), 203–216.

Svanborg, P., & Ekselius, L. (2003). Self-assessment of DSM-IV criteria for major depression in psychiatric out- and inpatients *. *Nordic Journal of Psychiatry*, *57*(4), 291–296. https://doi.org/10.1080/08039480307281

Swift, J. K., Callahan, J. L., Cooper, M., & Parkin, S. R. (2018). The impact of accommodating client preference in psychotherapy: A meta-analysis: SWIFT et al. *Journal of Clinical Psychology*, *74*(11), 1924–1937. https://doi.org/10.1002/jclp.22680

Swift, J. K., & Greenberg, R. P. (2012). Premature Discontinuation in Adult Psychotherapy: A Meta-Analysis. *Journal of Consulting and Clinical Psychology*. https://doi.org/10.1037/a0028226

Thornicroft, G., Chatterji, S., Evans-Lacko, S., Gruber, M., Sampson, N., Aguilar-Gaxiola, S., Al-Hamzawi, A., Alonso, J., Andrade, L., Borges, G., Bruffaerts, R., Bunting, B., Almeida, J. M. C. de, Florescu, S., Girolamo, G. de, Gureje, O., Haro, J. M., He, Y., Hinkov, H., … Kessler, R. C. (2017). Undertreatment of people with major depressive disorder in 21 countries. *The British Journal of Psychiatry*, *210*(2), 119–124. https://doi.org/10.1192/bjp.bp.116.188078

Titov, N., Dear, B., Nielssen, O., Staples, L., Hadjistavropoulos, H., Nugent, M., Adlam, K., Nordgreen, T., Bruvik, K. H., Hovland, A., Repål, A., Mathiasen, K., Kraepelien, M., Blom, K., Svanborg, C., Lindefors, N., & Kaldo, V. (2018). ICBT in routine care: A descriptive analysis of successful clinics in five countries. *Internet Interventions*, *13*, 108–115. https://doi.org/10.1016/j.invent.2018.07.006

Titov, N., Rock, D., Bezuidenhout, G., Webb, N., Kayrouz, R., Nielssen, O., Williams, L., Purtell, C., Dear, B. F., & Staples, L. G. (2020). Evaluation of The Practitioner Online Referral and Treatment Service (PORTS): The first 18 months of a state-wide digital service for adults with anxiety, depression, or substance use problems. *Cognitive Behaviour Therapy*, *49*(4), 307–326. https://doi.org/10.1080/16506073.2019.1666162

van Ballegooijen, W., Cuijpers, P., van Straten, A., Karyotaki, E., Andersson, G., Smit, J. H., & Riper, H. (2014). Adherence to Internet-based and face-to-face cognitive behavioural therapy for depression: A meta-analysis. *PloS One*, *9*(7), e100674. https://doi.org/10.1371/journal.pone.0100674

van Beljouw, I. M., Verhaak, P. F., Cuijpers, P., van Marwijk, H. W., & Penninx, B. W. (2010). The course of untreated anxiety and depression, and determinants of poor one-year outcome: A one-year cohort study. *BMC Psychiatry*, *10*(1), 86. https://doi.org/10.1186/1471-244X-10-86

van Bronswijk, S. C., Lemmens, L. H. J. M., Keefe, J. R., Huibers, M. J. H., DeRubeis, R. J., & Peeters, F. P. M. L. (2019). A prognostic index for long-term outcome after successful acute phase cognitive therapy and interpersonal psychotherapy for major depressive disorder. *Depression and Anxiety*, *36*(3), 252–261. https://doi.org/10.1002/da.22868

Vandereycken, W., & Devidt, K. (2010). Why Do Patients Drop Out of Therapy? *Eating Disorders Review*, *21*(2), 1–1.

Vernmark, K., Lenndin, J., Bjärehed, J., Carlsson, M., Karlsson, J., Oberg, J., Carlbring, P., Eriksson, T., & Andersson, G. (2010). Internet administered guided self-help versus individualized e-mail therapy: A randomized trial of two versions of CBT for major depression. *Behaviour Research and Therapy*, *48*(5), 368–376. https://doi.org/10.1016/j.brat.2010.01.005

Vittengl, J. R., Clark, L. A., Dunn, T. W., & Jarrett, R. B. (2007). Reducing relapse and recurrence in unipolar depression: A comparative meta-analysis of cognitive-behavioral therapy's effects. *Journal of Consulting and Clinical Psychology*, *75*(3), 475–488. https://doi.org/10.1037/0022-006X.75.3.475

Vlaescu, G., Alasjö, A., Miloff, A., Carlbring, P., & Andersson, G. (2016). Features and functionality of the Iterapi platform for internet-based psychological treatment. *Internet Interventions*, *6*, 107–114. https://doi.org/10.1016/j.invent.2016.09.006

Wahlbeck, K., Westman, J., Nordentoft, M., Gissler, M., & Laursen, T. M. (2011). Outcomes of Nordic mental health systems: Life expectancy of patients with mental disorders. *British Journal of Psychiatry*, *199*(6), 453–458. https://doi.org/10.1192/bjp.bp.110.085100

Wainberg, M. L., Scorza, P., Shultz, J. M., Helpman, L., Mootz, J. J., Johnson, K. A., Neria, Y., Bradford, J.-M. E., Oquendo, M. A., & Arbuckle, M. R. (2017). Challenges and Opportunities in Global Mental Health: A Research-to-Practice Perspective. *Current Psychiatry Reports*, *19*(5), 28. https://doi.org/10.1007/s11920-017-0780-z

Watkins, E. R. (2016). *Rumination-focused cognitive-behavioral therapy for depression*. The Guilford Press.

Westen, D., Novotny, C. M., & Thompson-Brenner, H. (2004). The Empirical Status of Empirically Supported Psychotherapies: Assumptions, Findings, and Reporting in Controlled Clinical Trials. *Psychological Bulletin*, *130*(4), 631–663. https://doi.org/10.1037/0033-2909.130.4.631

Whiteford, H. A., Ferrari, A. J., Degenhardt, L., Feigin, V., & Vos, T. (2015). The global burden of mental, neurological and substance use disorders: An analysis from the Global Burden of Disease Study 2010. *PloS One*, *10*(2), e0116820. https://doi.org/10.1371/journal.pone.0116820

Whooley, M. A., & Wong, J. M. (2013). Depression and Cardiovascular Disorders. *Annual Review of Clinical Psychology*, *9*(1), 327–354. https://doi.org/10.1146/annurev-clinpsy-050212-185526

Wierzbicki, M., & Pekarik, G. (1993). A meta-analysis of psychotherapy dropout. *Professional Psychology: Research and Practice*, *24*(2), 190–195. https://doi.org/10.1037/0735-7028.24.2.190

Wilhelm, K., Parker, G., Dewhurst-Savellis, J., & Asghari, A. (1999). Psychological predictors of single and recurrent major depressive episodes. *Journal of Affective Disorders*, *54*(1–2), 139–147.

Williams, N., Simpson, A. N., Simpson, K., & Nahas, Z. (2009). Relapse rates with long-term antidepressant drug therapy: A meta-analysis. *Human Psychopharmacology: Clinical and Experimental*, *24*(5), 401–408. https://doi.org/10.1002/hup.1033

World Health Organization. (2019). *International statistical classification of diseases and related health problems (11th ed.)* (Vol. 2019). orld Health Organization.

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x