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## Blended CBT for Depression

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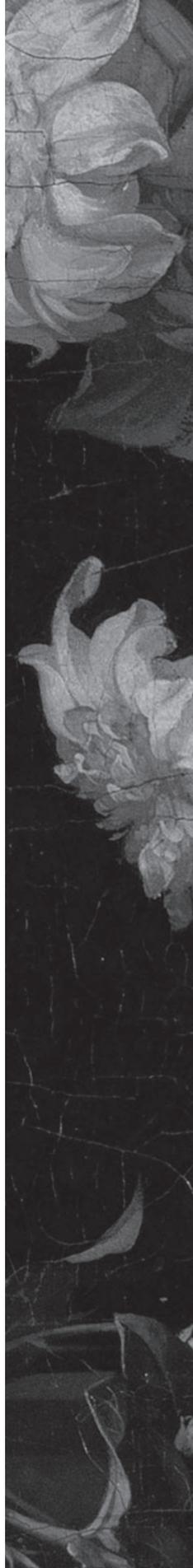
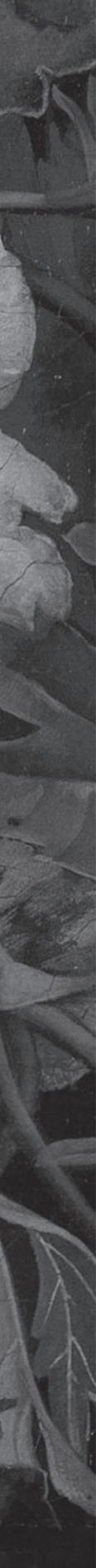
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# **CHAPTER 1**

## **GENERAL INTRODUCTION**



Depression is a common and debilitating mental health disorder, affecting more than 300 million people worldwide (World Health Organization (WHO), 2018). Fortunately, a number of treatments approaches for depression have proven efficacious, including psychotherapy and pharmacotherapy (Cuijpers, 2017; Cuijpers et al., 2008; Cuijpers et al., 2020). However, access to mental health care and trained therapists is often limited (Bremmer & van Es, 2013; Demyttenaere et al., 2004; Kohn et al., 2004), which is explained in part by increasingly insufficient mental health care budgets (Bremmer & van Es, 2013). This has caused a discrepancy between treatment availability and treatment demand. Individuals experiencing depression often do not receive treatment, or they are placed on waiting lists rather than having immediate access to mental health care (Araya et al., 2018; Kohn et al., 2004). There is a widespread need for cost-effective mental health care to manage this problem (Higgins et al., 2017). This thesis examines whether digitizing some parts of cognitive behavioral therapy for depression, also known as blended treatment, can contribute to the solution.

### **Depression**

A depressive episode is characterized by a depressed mood or anhedonia (loss of interest), which a person experiences for most of the day, almost every day, for a period of at least two weeks. Other symptoms associated with depression include a change in weight or appetite (loss or increase), sleep difficulties (insomnia or hypersomnia), fatigue or loss of energy, psychomotor agitation or retardation, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate, and suicidality. For a diagnosis of depression, also known as major depressive disorder (MDD), five such symptoms need to be present, at least one of them being depressed mood or anhedonia (American Psychiatric Association (APA), 2013). Depression is one of the most common mental health disorders, with an estimated lifetime prevalence of 15% (Wittchen et al., 2011) in the EU population. Many people will experience relapse or multiple episodes (recurrence) of depression. For about a third of people with depression, the condition has a chronic course, with symptoms persisting for two years or longer (Köhler et al., 2019; Murphy & Byrne, 2012). Based on the number and severity of symptoms, a depressive episode can be categorized as mild, moderate, or severe. As depression severity increases, it significantly impacts a person's health, quality of life, and ability to engage in social, work, or domestic activities.

### **Treatment for Mental Health Problems**

In the Netherlands, people with common mental health problems have access to several levels of mental health care. Mild problems can be treated by a general practitioner (GP), often with additional support from a general practice mental health worker (in Dutch: POH-GGZ). If mental health problems do not sufficiently respond to that level of treatment, people can be referred to primary (basic) or specialized (secondary) mental health services. The primary care services are intended for mild to moderate mental health problems and provide short-duration treatment (5 to 10 sessions). If patients experience serious or complex symptoms, or do not respond to treatment in primary care, they may be referred to specialized care. At that level, treatment tends to be of longer duration, and often takes a more multidisciplinary

approach, for example with combined psychotherapy and pharmacotherapy or with added forms of treatment such as body-oriented therapy. Many specialized mental health care centers also offer day-treatment or inpatient treatment programs (Government of the Netherlands, 2019; Kooistra et al., 2018).

### **Treatment for Depression**

Numerous studies, including randomized controlled trials (RCTs), meta-analyses and individual patient data meta-analyses (IPDMAs), which combine raw data from several RCTs, have established that both pharmacotherapy and psychological treatment for depression can be effective in reducing symptom severity. Within the domain of psychotherapy, treatment options include behavioral activation (BA), cognitive behavioral therapy (CBT), interpersonal therapy (IPT), and psychodynamic therapy, with evidence suggesting that the different treatment options have comparable effects (Barth et al., 2013; Cuijpers, 2017).

Alternatively, depression can be treated with pharmacotherapy (Cuijpers et al., 2008). This includes selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCIs), and monoamine oxidase inhibitors (MAIOs). Meta-analyses have shown that psychotherapy and pharmacotherapy can be equally effective in the treatment of depression, with a recent IPDMA (N = 1700) suggesting that this even applies for severely depressed individuals (Weitz et al., 2015). A meta-analysis pooling data from 23 randomized controlled trials has suggested that a combination of pharmacotherapy and psychotherapy is superior to pharmacotherapy alone, and that psychotherapy alone can lead to effects similar to those of combined treatment in the long term (Karyotaki et al., 2016).

### **Moving Towards Online Treatment Formats**

Psychotherapy is typically delivered in face-to-face sessions, in either individual or group settings. Given the limited access to mental health care, alternative delivery formats have been developed that require less therapist involvement, such as self-help manuals (Cuijpers et al., 2010; van 't Hof et al., 2009) and telephone-administered treatment (Mohr et al., 2005).

As internet-access and smartphones become more and more a part of daily life, the focus has shifted towards methods of online (or web-based) treatment delivery. Most evidence-based online treatment for depression and other common mental health disorders is based on traditional cognitive behavioral therapy manuals. Online treatment thus typically involves structured sessions or modules that (1) provide information on depression and explain the core principles of CBT (psychoeducation, behavioral activation, cognitive restructuring and relapse prevention) and (2) provide exercises that encourage patients to master these techniques and integrate them into their daily lives (Titov, 2011; Webb et al., 2017). Usually, online interventions in routine practice consist of text, supported by graphics, patient vignettes, or video material.

Many online treatments also monitor some types of symptoms, such as sleep, medication intake or mood, and provide the user with graphic feedback on changes over time. With the

emergence of new technologies, these functionalities are more and more accessible via mobile applications.

Within the domain of online treatment, a distinction is made between unguided (self-help) and guided treatment. In unguided or self-guided online treatment, individuals work through the online material autonomously and receive no feedback, or fully automated feedback, rather than personalized therapeutic support. A benefit of unguided online treatment is that it is easily accessible, and can be offered as a first step in mental health care (Karyotaki et al., 2017). However, unguided interventions often have high dropout rates. A recent IPDMA (N = 2705), for instance, showed that about 70% of patients discontinued unguided online treatment interventions for depression before completing 75% of the treatment protocol (Karyotaki et al., 2017). To help patients work through treatment, online treatment can also be guided. Guidance usually involves written feedback messages, which are sent by a professional, after a patient completes an online session. Alternatively, feedback can be provided in real-time via audio, instant messaging (chat), or video-calling. A number of forms of guidance exist, ranging from technical support to motivational messages or therapeutic feedback from a coach or therapist.

Various studies have shown that online interventions are effective in reducing symptom severity in depression and other common mental disorders (Andersson et al., 2014; Andrews et al., 2018; Carlbring et al., 2018; Cuijpers & Riper, 2014; Richards & Richardson, 2012; Webb et al., 2017), especially when patients receive professional guidance (Andersson et al., 2014, 2017; Cuijpers et al., 2011; Karyotaki et al., 2018; van 't Hof et al., 2009). Most available studies have focused on the efficacy of online depression treatment in homogeneous community samples and self-referred participants. Less is known about its effectiveness in routine mental health care. In routine care, patient populations are generally more heterogeneous than those represented in efficacy studies, for example in terms of demographic characteristics, such as age and education, or clinical characteristics such as symptom severity and comorbid disorders. At the time the study described in this thesis was started (2013), very little was known about the applicability of guided online treatment in specialized mental health care. More recent findings have indicated that effects in routine care do appear comparable to those in the general population (Andersson et al., 2016). Recent studies have also suggested that therapist-guided online treatment may be equally as effective as standard face-to-face therapy (Carlbring et al., 2018; Webb et al., 2017). However, direct comparisons of online treatment with face-to-face treatment are still scarce, and most studies to date have focused on patients with mild to moderate depression severity (Andersson et al., 2016).

### **Blended Treatment**

For patients being treated for depression in routine specialized mental health settings, a *blended treatment format* may be a promising way of delivering online treatment. The rationale of blended treatment is that the combination of face-to-face and online therapy could lead to a “best of both worlds” approach (Erbe et al., 2017; van der Vaart et al., 2014). The assumption is that blended treatment retains positive aspects associated with online treatment – such as increased patient self-management, lower costs compared with standard

treatment, and a reduction of therapist time required to deliver the treatment (Åndersson & Cuijpers, 2008; Cuijpers et al., 2015; Thase et al., 2018) – while still allowing therapists to closely monitor and guide their patients, both in face-to-face sessions at the clinic and in an online environment.

Blended treatment is a relatively new concept, although results from several large studies have already been forthcoming (Kemmeren et al., 2016; Kleiboer et al., 2016; Vis et al., 2015). Most studies to date have evaluated the online component as an add-on to standard care, rather than as part of an integrated blended treatment protocol (Berger et al., 2018; Hickie et al., 2010; Høifødt et al., 2013; D. Kessler et al., 2009; Meyer et al., 2009; Zwerenz et al., 2017). Results of these studies are promising, and indicate that blended treatment may be a viable treatment option (van der Vaart et al., 2014). However, the add-on treatment format limits the margin for cost-effectiveness, as therapist time is not reduced and overall treatment dosage may even increase (Kenter et al., 2015; Kolovos et al., 2018). One recent study suggested that a more integrated approach to blended depression treatment, reducing therapist time by half, can lead to non-inferior results compared with standard CBT (Thase et al., 2018). However, that study focused on medication-free adults in university clinics, which limits generalizability to specialized mental health care.

### **Economic Evaluation**

As noted above, a potential reduction of treatment costs is often cited as an important incentive to develop or implement online and blended treatment formats (Åndersson, 2010; Andrews et al., 2018; Emmelkamp et al., 2014; Ruwaard & Kok, 2015). Establishing whether such reductions indeed occur falls within the domain of economic evaluation. An economic analysis focuses on the relative differences between one intervention and another, for example by comparing a new intervention with an existing treatment (status quo). Both costs and effects (consequences) are included and analyzed in relation to one another. The findings may then be used to inform decision makers about whether or not to offer or reimburse a particular treatment (Drummond, Sculpher, Claxton, Stoddart, & Torrance, 2015). For example, if a new intervention is less costly but also less effective than the alternative, one might still prefer the existing treatment. If the new treatment is more effective but at additional cost, one might be willing to make the extra investment and choose the new intervention over the existing one.

Currently, no information is available on the cost-effectiveness of blended CBT for depression. For guided online interventions for depression, a limited amount of information has been gathered. A recent IPDMA obtained participant data from five RCTs (N = 1426) that studied both costs and effects (Kolovos et al., 2018). It suggested that guided online treatment was more costly than the comparative offline treatment (most often treatment-as-usual), but that the difference was not statistically significant (12-month mean difference = €406, 95% CI - 611 to 1444), and no statistically significant differences were found in clinical outcomes. To reach an acceptable probability of cost-effectiveness for the online intervention compared to control, high investments would be needed. The conclusion was that online treatment was not considered cost-effective compared to the control.

In the present thesis, the economic evaluation consists of cost-effectiveness and cost-utility analyses. In a cost-effectiveness analysis (CEA), a clinical outcome is chosen that is relevant for the health domain of interest, such as remission of depression. In a cost-utility analysis (CUA), the focus lies on health-related well-being. The outcome of choice is quality-adjusted life-years (QALYs), calculated by combining the number of additional years of life gained by receiving an intervention and the quality of life in those years (Robinson, 1993). Several domains can be considered in evaluating costs. In this thesis, these include (1) the costs of health care utilization, such as visits to a GP or hospital, (2) care by informal caregivers, such as family and friends, and (3) productivity losses. To assess productivity losses, costs associated with days missed from work (absenteeism) and diminished work productivity while at work (presenteeism) are estimated for both paid and unpaid work (Drummond et al., 2015). The choice of which domains to include depends on the perspective chosen to evaluate costs. For example, from a societal perspective all costs are important. From the perspective of a health care provider, only medical costs are included in the analysis, because costs associated with work productivity do not influence policy making within that domain.

### **Aims and Outline of the Thesis**

The general objective of this thesis is to gain insights into the potential value of blended cognitive behavioral treatment (CBT) for depression. The focus is on routine practice and, more specifically, on outpatient specialized mental health care. This derives from the notion that the need for efficient care is especially high in specialized care in view of the high costs and long waiting-lists. The focus on blended CBT was chosen over stand-alone online treatment because the former was thought to be more acceptable and suitable for patients and therapists in specialized care, given the degree of symptom severity and complexity (van der Vaart et al., 2014). Blended CBT is compared with the existing treatment it was designed to substitute for, namely face-to-face (offline) CBT, and a specific focus is placed on routine practice (effectiveness), rather than on a selected group of patients (efficacy). **Chapter 2** describes the development and initial evaluation of blended CBT for depression. A study was then designed in which the costs and effectiveness of blended CBT were compared with existing face-to-face CBT, when provided to patients with depression who had sought treatment in specialized mental health care. The study protocol for this randomized controlled trial (RCT) is described in **Chapter 3**. In **Chapter 4** the results of the trial are presented. **Chapter 5** examines the trial data on working alliance between patients and therapists in blended CBT and in face-to-face CBT. **Chapter 6** identifies determinants of how patients find their way to specialized mental health care, using longitudinal data from the Netherlands Study of Depression and Anxiety (NESDA). Finally, the main findings from chapters 2 to 6 are summarized and discussed in **Chapter 7**.