Objectives

At the time the studies conducted for this thesis commenced, no other articles on blended depression treatment in specialized care had been published to our knowledge. Available studies focused on combined treatment, whereby an online intervention had been added to treatment-as-usual (Hickie et al., 2010; Heifedt et al., 2013; D. Kessler et al., 2009; Månsson et al., 2013; Robertson et al., 2006). This thesis chose a more integrated approach to blended treatment, replacing some of the face-to-face sessions normally provided at the clinic with online sessions. The rationale for choosing integration of the two components above an add-on approach was that this would facilitate the delivery of two sessions per week (one online and one face-to-face), thereby shortening treatment duration as compared with face-to-face cognitive behavioral therapy (CBT), as well as possibly enhancing treatment effects (based on Cuijpers, Huibers, et al., 2013). By reducing the number of face-to-face sessions, integrated blended CBT was also hypothesized to reduce the costs of treatment in comparison with face-to-face CBT (Kooistra et al., 2014). The funding for this thesis was granted by the Netherlands Organisation for Health Research (ZonMw) within one of its health economics funding frameworks. Its focus was on exploring the potential cost-effectiveness of interventions not yet found equally clinically effective to established treatments, but with potentials to reduce costs in comparison with alternatives. This explains the explorative nature of our randomized controlled trial, which focused on the initial evaluation of costs, effectiveness, and working alliance in blended CBT versus face-to-face CBT. Results are intended to inform future clinical and cost-effectiveness studies of blended CBT for depression.

A second aim of the thesis was to gain a better understanding of the patient population that is seen in specialized mental health services. We assessed possible predictors of why patients reach specialized mental health care services, and determined how such predictors corresponded to patient characteristics contained in formal referral guidelines, such as suicidal behavior, co-morbid mental or physical disorders, chronicity and recurring episodes (National Institute for Health and Care Excellence (NICE), 2011; Piek, van der Meer, Penninx, et al., 2011; Spijker et al., 2013; van Balkom et al., 2013; van Hemert et al., 2012).

Background

Depression is a common and debilitating mental health disorder, affecting more than 300 million people worldwide (World Health Organization (WHO), 2018). Fortunately, there are effective pharmacological and psychological treatment options available, which can be offered separately or in combination to each other (Cuijpers, 2017; Cuijpers et al., 2008; Cuijpers et al., 2020). However, access to mental health care is often limited by increasingly insufficient mental health care budgets (Bremmer & van Es, 2013; Demytenaere et al., 2004; Kohn et al., 2004). To manage this challenge, there is a high need for mental health care that is both effective and efficient (Higgins et al., 2017). The problem is especially relevant in specialized mental health care, where the multidisciplinary treatment approaches and longer treatment durations required for more severe patient populations can lead to substantial
costs and long waiting-lists (Araya et al., 2018; Bremmer & van Es, 2013; Demyttenaere et al., 2004; Kohn et al., 2004).

Online treatment is often discussed for its potential to reduce costs of treatment and make treatment more readily available (Andersson, 2010; Andrews et al., 2018; Emmelkamp et al., 2014; Ruwaard & Kok, 2015), and numerous studies have shown online treatment to be 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). Recipients seem to benefit most when the online treatment involves professional guidance (Andersson et al., 2014, 2017; Cuijpers et al., 2011; Karyotaki et al., 2018), and therapist-guided online treatment may be equally as effective as standard face-to-face therapy (Carlbring et al., 2018; Webb et al., 2017). Most often, online treatment is based on cognitive behavioral therapy (CBT).

Considering the severity of depressive disorders and their comorbid disorders that are treated in specialized mental health care, stand-alone guided online interventions – where patients’ sole contact with their therapists takes place via an online environment – may not provide adequate treatment as compared with face-to-face therapies. A blended treatment format, in which part of the therapy is provided online and part face-to-face, may therefore be a more feasible and desirable option. The hopes of blended treatment are to retain the positive aspects associated with online treatment, such as reduced therapist time (van der Vaart et al., 2014) and increased patient self-management (Andersson & Cuijpers, 2008; Cuijpers et al., 2015; Thase et al., 2018), while at the same time 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 may also be attractive to patients as an alternative to standard face-to-face treatment, for example those who need to travel long distances to the clinic or experience time-related difficulties due to work or home responsibilities.

As noted, blended treatment is a relatively new concept. Most studies to date have focused combinations of online treatment and face-to-face treatments. These suggested that blended treatment may be an adequate treatment option in primary care (Høifødt et al., 2013; Wilhelmson et al., 2013), outpatient specialized care (Berger et al., 2018), and inpatient specialized care (Zwerenz et al., 2017). One more recent study has suggested that a more integrated approach to blended depression treatment, reducing therapist time by half, can lead to non-inferior results compared with face-to-face CBT (Thase et al., 2018). However, that study focused on medication-free adults in university clinics, thus limiting its generalizability to specialized mental health care.

This chapter will continue with a summary of the main findings of each study included in this thesis. The findings will then be assessed in relation to our initial expectations with respect to blended CBT in specialized mental health care and will be discussed in the context of the current literature on blended CBT for depression. Methodological considerations, implications for clinical practice, and perspectives on future research will be examined, and the chapter will end with closing remarks.
Main Findings

Chapter 2 described the process of developing a blended CBT protocol for patients with major depressive disorder (MDD) in specialized mental health care. The treatment protocol was based on existing face-to-face CBT protocols (A. T. Beck, Rush, et al., 1979; J. S. Beck, 2011; Bockting & Huibers, 2011), as well as on input from patients (n = 3) who had received CBT for depression in specialized care, therapists (n = 18) who were experienced in working with the face-to-face CBT protocol in specialized mental health care, and our research team (see also van der Vaart et al., 2014). After integration of all information, the resulting blended CBT protocol included ten face-to-face sessions and nine online sessions, starting with a face-to-face session. After completion of an online session, patients received written online feedback from their therapist. The intended treatment duration was ten weeks, offering one face-to-face session, one online session and one online feedback message per week. That decision was based on the 2013 meta-regression analysis by Cuijpers and colleagues (2013), which focused on the amount of psychotherapy required to treat depression. The study suggested that, rather than treatment duration and dosage, the number of sessions provided per week (the treatment intensity) was positively associated with the effect of treatment. Results indicated that increasing the number of sessions from one to two per week increased the effect size by $g = 0.45$.

After the development of the blended CBT protocol, it was tested in an uncontrolled pilot study among patients (n = 9) and therapists (n = 7). Seven of the nine patients started treatment and five completed the blended protocol, with a treatment duration ranging from 10 to 13 weeks. The study results suggested that depressive symptoms were adequately addressed in the blended protocol. In addition, blended CBT had the potential to shorten treatment duration and was acceptable to both patients and therapists. Based on these findings, we continued the development and evaluation of blended CBT by conducting a randomized controlled trial (RCT).

Chapter 3 described the study protocol for that trial. Blended CBT for major depression in routine specialized mental health care had not yet been studied at the time. We therefore chose to conduct a pilot RCT in order to explore the potential cost-effectiveness of blended CBT in comparison with face-to-face CBT. The study was funded by the Netherlands Organisation for Health Research and Development (ZonMw) within a program specifically designed to explore cost-effectiveness of innovative treatments on which few studies had been conducted (ZonMw Doelmatigheid, project number 837001007). The trial focused on comparative costs and clinical effects (cost-effectiveness) of blended CBT in relation to face-to-face (standard) CBT. Participants were followed for up to 30 weeks. The intended treatment duration of blended CBT was 10 weeks (10 face-to-face sessions and 9 online sessions); for face-to-face CBT this was 16 to 20 weeks (16 to 20 weekly face-to-face sessions). Costs were calculated from the societal perspective (including medical costs and costs associated with informal care and productivity losses) and the health care provider perspective (including medical costs only). Clinical effect measures included reliable change in depression severity, based on the Inventory of Depressive Symptomatology (IDS-SR);
occurrence of depressive episodes as evaluated by clinicians using the MINI-Plus diagnostic interview, and quality of life years (QALYs) gained, measured with the EQ-5D-3L questionnaire.

In Chapter 4 we presented the main findings of our RCT. The trial included N = 102 patients with major depressive disorder in three specialized mental health care services (blended CBT n = 53; face-to-face CBT n = 49). The study originally aimed to include 150 patients, but that did not prove to be feasible within the set time frame, partly because fewer patients than expected were referred to specialized services. Before the start of treatment, 65% of the patients included in the trial (66 of 102) indicated a preference for receiving blended CBT over face-to-face CBT. Compared with patients allocated to the face-to-face CBT group, blended CBT patients received significantly more sessions in total (19 versus 13, \(t_{100} = -4.09, p < 0.001\)), but significantly fewer face-to-face sessions at the clinic (10 versus 13, \(t_{100} = 3.07, p = 0.003\)). With a cut-off of 14 sessions (75% of intended sessions) used as a marker for patients having received an adequate treatment dose, 43 patients in blended CBT (81%) and 22 patients in face-to-face CBT (22%) were considered treatment completers. As expected on the basis of the treatment protocol, mean treatment duration was significantly shorter in blended CBT than in face-to-face CBT, with an average of 19 (SD 13) weeks versus 33 (SD 23) weeks (\(t_{100} = 3.91, p < 0.001\)). Including the time spent on providing online feedback, the amount of therapist time did not differ between groups with an average of 14 (SD 6) hours for blended CBT and 13 (SD 6) hours for face-to-face CBT (\(t_{100} = -0.55, p = 0.58\)).

Over the 30-week study period, no significant differences in treatment effects were found between blended CBT and face-to-face CBT in treatment effects in terms of occurrence of depressive episodes (risk difference [RD] 0.06, 95% CI 0.05 to 0.19), reliable change in depression severity (RD 0.03, 95% CI 0.10 to 0.15), or QALYs gained (mean difference 0.01, 95% CI -0.03 to 0.04). Estimated mean scores on the Inventory of Depressive Symptomatology (IDS-SR) decreased from 43.1 (95% CI 41.0 to 44.7) to 27.5 (95% CI 22.1 to 32.9) in blended CBT and from 42.9 (95% CI 41.0 to 44.7) to 25.0 (95% CI 19.1 to 30.9) in face-to-face CBT. Analyses also revealed no significant cost differences between blended CBT and face-to-face CBT in terms of either societal costs (mean difference €1183, 95% CI -399 to 2765) or medical costs (health care provider perspective; mean difference €-176, 95% CI -659 to 343). When comparative costs and effects were combined in cost-effectiveness analyses, results showed that blended CBT was not cost-effective from the societal perspective (probability of 0.01 at €0 per additional unit of effect) but did have an acceptable probability of cost-effectiveness from the health care provider perspective in terms of response to treatment and QALYs (probability of 0.75 at €0 per additional unit of effect). On the basis of these findings, we concluded that blended CBT had the potential to be a promising treatment alternative to face-to-face CBT, and that conducting a fully powered RCT could be justified in the future.

In Chapter 5, the data from the trial was used to examine the working alliance between patients and therapists in blended CBT (n = 47) as compared with face-to-face CBT (n = 45). Working alliance was assessed by patients and therapists in both groups on the Working Alliance Inventory (WAI-SR; Task, Bond, Goal, and composite scores) after ten weeks,
corresponding with the intended treatment duration of blended CBT. Blended CBT and face-to-face CBT were associated with similarly high working alliance ratings by both patients and therapists. Replacement of a proportion of the face-to-face sessions with online sessions and online therapist feedback did not have a negative effect on the working alliance as perceived by patients and therapists. We found that a more positive patient-rated evaluation of working alliance was associated with lower depression severity in face-to-face CBT, whereas no such alliance–outcome association was seen in blended CBT. For therapist-rated alliance, no alliance–outcome association was found in both treatment groups.

In Chapter 6 we used longitudinal data from the Netherlands Study of Anxiety and Depression (NESDA, Penninx et al., 2008) to examine potential facilitators and barriers for people receiving specialized mental health care. We found that during a six-year period, roughly a quarter of individuals with a depression or anxiety diagnosis at baseline made the transition from no care or primary care to specialized mental health care (198 out of 701, 28.3%). Transition most often took place within two years of the start of the study (n = 124, 63%). With regard to the predictors of that transition, some clinical factors were confirmed that are included in formal referral guidelines (National Institute for Health and Care Excellence (NICE), 2011; Spijker et al., 2013; van Balkom et al., 2013; van Hemert et al., 2012), namely suicidal ideation and prior psychological or pharmacological treatment. Other clinical factors, such as severity of symptoms and comorbidity, did not appear to be predictive of transition, suggesting that some patients with depression or anxiety disorders may be at risk of undertreatment or overtreatment. Patients’ openness to experience and their perceived unmet need for help did increase the odds of transition to specialized mental health care, indicating that motivation for receiving treatment may be a more critical factor than the severity of symptoms. Finally, the non-clinical factors younger age and more years of education were found to be predictive of transition to specialized mental health care. This implies that older individuals and those with less formal education might be at risk of not reaching specialized services to the extent that this is warranted by their clinical profile.