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Blended CBT for Depression

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CHAPTER 7

GENERAL DISCUSSION



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; Høifødt 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; Demyttenaere 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; Wilhelmsen 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.

Reflection on the Main Findings

Treatment Dose and Duration

Our blended CBT protocol was designed to facilitate patients and their therapists in establishing a CBT dose of two sessions per week: one face-to-face session and one online session accompanied by online therapist feedback. The intended duration of the blended CBT was approximately ten weeks. As previously discussed, the aim of providing two sessions per week was based on the 2013 meta-regression analysis by Cuijpers and colleagues (2013), which indicated that an increase from one to two sessions per week could enhance the clinical effect of adult depression treatment.

In both treatment groups in our trial, the average treatment duration extended beyond the intended duration. Among patients who started treatment, the duration in blended CBT

($n = 49$) was 18.5 weeks on average (SD 6.5, range 5 to 35)¹, compared with 35 weeks (SD 22.5, range 4 to 82)² in face-to-face CBT ($n = 47$). Interestingly, patients in face-to-face CBT averaged 14 face-to-face sessions (SD 6, range 3 to 27) in that time frame, fewer than the planned 16 to 20 sessions recommended by the treatment protocol. Adherence rates were higher for blended CBT, with patients receiving an average of one more face-to-face and one more online session than planned (a mean of 11 face-to-face sessions, SD 3.5, range 2 to 16; and 10.5 online sessions SD 3.4, range 2 to 30). In total, this translated to a mean of 21.5 sessions in the blended CBT group (SD 5.8, range 5 to 31).

Regarding treatment dose, the RCT results were mixed. Patients who started with blended CBT ($n = 49$) received on average about two thirds of the protocolled face-to-face and online sessions in the first ten weeks of treatment (mean 13 out of 19, SD 6). Combined with treatment duration, the average number of sessions per week was 1.3 (SD 0.5, range 0.2 to 2.5), or roughly one session every five days. In the face-to-face CBT group, patients received significantly fewer sessions per week, with a mean of 0.5 (SD 0.3, range 0.1 to 1.3), or an average of one session per two weeks. This suggests that, while the goal of offering two sessions per week was not met in blended CBT, blended treatment still facilitated the delivery of more sessions per week than face-to-face CBT, resulting in shorter treatment duration. One possible explanation may be that the blended online sessions provided a focused and transparent treatment structure, encouraging patients and therapists to specifically *focus on depression* and work through the *core components of CBT* (psychoeducation, behavioral activation, cognitive therapy, and relapse prevention) in a fixed order.

Therapist Time

Results on the aim of blended CBT to reduce therapist time per patient were not conclusive. As was previously discussed, blended CBT was designed to reduce the number of face-to-face sessions needed to deliver the treatment protocol, and results indeed showed that patients received fewer face-to-face sessions in blended CBT than in face-to-face CBT. However, after inclusion of time spent on online therapist feedback, the average per-patient therapist time did not differ significantly between the two treatment groups. Our main explanation for this finding was the fact that patients in the face-to-face CBT group received considerably fewer sessions on average than the 15 to 20 sessions we had anticipated from the CBT manuals used (J. S. Beck, 2011; Bockting & Huibers, 2011). That limited the margin for relative change in therapist time. Another aspect to consider is that therapist time spent on online feedback in blended CBT was estimated at 30 minutes per feedback message, because online therapist feedback was a relatively new treatment method at that time in specialized mental health care. In the future, therapists will probably need less time, as they become more adept at giving online feedback. To obtain accurate estimates of per-patient

¹ This excludes two outliers with a treatment duration of 69 weeks. That duration was not related to the time needed to deliver blended CBT (12 to 16 face-to-face sessions, 8 to 10 online sessions, 7 to 10 feedback messages), but to delayed treatment onset at the beginning of the study. The mean number of weeks including outliers was 20.5 (SD 11.8, range 5 to 69).

² No non-treatment-related outliers in treatment duration were found in face-to-face CBT.

therapist time, future studies are advised to include measures of actual time spent on therapy, both for the online and the face-to-face elements.

Comparison with other studies on blended CBT for depression in specialized mental health care is not yet possible. The most similar research to date is the Thase study (Thase et al., 2018), which focused on medication-free depressed adults receiving treatment in a university clinic. It compared conventional 16-week, 20-session CBT ($n = 77$) with 16-week blended CBT ($n = 77$) consisting of twelve 25-minute face-to-face sessions and a pre-existing nine-session online therapy protocol (the Good Days Ahead program). Therapists reviewed the online material before each face-to-face session but did not provide online feedback. Completion rates were similar in the two treatment groups (79% for conventional CBT and 82% for blended CBT). In blended CBT, patients received on average 8 online sessions (SD 2.1) and 11 face-to-face sessions (SD 3.0), versus 16 sessions (SD 5.0) in the face-to-face CBT group. In the blended group, patients received about 37% less therapist time on average than those in the face-to-face CBT group, consistent with the initial goal of reducing therapist time by one third. This might imply that achieving a time reduction could require an even more stringent blended treatment protocol than the one we applied.

In specialized mental health care, however, it may not be advisable or desirable to both omit online feedback and shorten face-to-face sessions in order to reduce therapist time. In one way, shorter sessions might sharpen the focus on the protocol and might still be adequate to help patients formulate goals or exercises. However, shorter sessions could hinder a therapist in adequately detecting or responding to suicidality, and they could complicate therapeutic interventions such as practicing through role play. Shorter face-to-face sessions would also place a greater emphasis on the online sessions, thus requiring active patient participation. That could be seen as either a benefit or a potential pitfall.

Reconsidering the use of online therapist feedback may be a more viable option to reduce therapist time in blended treatment. Mol and colleagues (2018) studied online feedback in blended CBT for patients with depression ($n = 45$) in specialized mental health care. Therapists in that study received instructions for providing feedback that were similar to those in our trial. The study found that therapists, in their online feedback, appeared to focus on offering positive reinforcement and showing an interest in patients' thoughts, emotions, and behaviors (informing, encouraging, and affirming). Those supportive online feedback elements showed no relation, however, to completion rates of online sessions or to change in depression severity.

Hence, while feedback is crucial in stand-alone online treatment (Andersson et al., 2014, 2017; Cuijpers et al., 2011; van 't Hof et al., 2009), it may suffice in a blended format to have therapists monitor their patients' online homework and discuss the content in the weekly face-to-face sessions. In a more dynamic approach, online sessions with online therapist feedback could be used to phase out treatment, allowing patients to practice with self-therapy and with implementing their relapse prevention techniques, and supporting them in this process while no longer offering face-to-face sessions.

Costs and Effects

The results from our trial suggest that blended CBT and face-to-face CBT are associated with similar clinical effects. This is a promising finding, as it suggests that the clinical effects of CBT can be retained while significantly reducing the number of face-to-face sessions at the clinic and replacing these with online sessions and online therapist feedback. Our results are in line with those of the above-mentioned study by Thase and colleagues (2018), where blended CBT was found non-inferior to face-to-face CBT after 16 weeks of treatment, as measured by the Hamilton Depression Rating Scale (Hamilton, 1960).

In the studies conducted for this thesis, no additional clinical effect of the higher treatment intensity in blended CBT was found in comparison with face-to-face CBT, although it should be noted that the studies described in this thesis were not designed to test that hypothesis. A recent study by Bruijniks and colleagues (2020) was designed to compare weekly sessions of CBT ($n = 49$) or interpersonal therapy (IPT, $n = 55$) with twice-weekly sessions of CBT ($n = 49$) or IPT ($n = 47$) for adults with depression in specialized mental health care. It showed a significant effect of session frequency over time in favor of twice-weekly sessions (estimated mean difference 3.85 points, difference in effect size $d = 0.55$) in terms of the Beck Depression Inventory-II (BDI-II) (A. T. Beck et al., 1996) at six-month follow-up. No differences were found in the effectiveness of CBT versus IPT. It therefore seems worthwhile to further explore the role that blended CBT could play in increasing the number of sessions per week, as blended CBT did appear to facilitate the delivery of CBT sessions.

When considering the clinical effects of CBT and the potential to enhance these effects in specialized mental health care, it should be noted that many patients still experience residual symptoms at the end of CBT. In our trial, patients on average reported experiencing severe symptoms on the IDS-SR at the start of treatment and mild to moderate symptom severity after 30 weeks (estimated means in blended CBT: 43.1, 95% CI 41.0 to 44.7, reducing to 27.5, 95% CI 22.1 to 32.9; in face-to-face CBT: 42.9, 95% CI 41.0 to 44.7, reducing to 25.0, 95% CI 19.1 to 30.9). These findings match those of other studies that focused on CBT in specialized mental health care (Bruijniks et al., 2020; Driessen et al., 2013). For example, in the Bruijniks (2020) study discussed in the previous section, the reduction of estimated mean scores on the BDI-II from baseline to six-month follow-up showed a similar pattern to that in our trial, moving from severe to moderate depression (estimated means in once-weekly CBT: 31.05, 95% CI 29.29 to 32.81, reducing to 23.01, 95% CI 19.45 to 26.57; twice-weekly CBT: 32.58, 95% CI 30.84 to 34.32, reducing to 20.69, 95% CI 17.18-24.21).

The residual symptoms are worrisome, as they have been shown to increase the likelihood that the disorder will return (Keller, 2003; Paykel et al., 1995). Furthermore, prior research has shown that about a third of patients experience treatment-resistant depression (Fekadu et al., 2009; Trivedi et al., 2006). More research is needed to determine underlying factors that influence treatment effects. For example, Bruijniks and colleagues (2020) stress the importance of evaluating and improving the quality of the provided treatments.

Also, certain subgroups of people with depressive disorders may benefit from additional or other depression treatment, such as cognitive behavioral analysis system of psychotherapy (CBASP) (McCullough, 1999), or may need therapy to focus on other problems, such as personality disorders.

Pairing information on the differences in clinical effects and costs between blended CBT and face-to-face CBT, the economic analyses in this thesis suggest that blended CBT was not cost-effective in comparison with face-to-face CBT from a societal perspective (with inclusion of medical costs, costs due to productivity loss, and costs associated with informal care). The difference in societal costs appeared to be driven mainly by productivity loss (estimated means at 30-week follow-up in blended CBT €6497, 95% CI 5009 to 7986; in face-to-face CBT €4003, 95% CI 2348 to 5659). This finding is not uncommon. For example, a recent individual patient data meta-analysis (IPDMA) (Kolovos et al., 2018) also found productivity losses to be the largest contributor to total costs when examining data from five RCTs that compared stand-alone guided online interventions with control groups (treatment-as-usual, $n = 4$, or waitlist, $n = 1$). When considering the between-group difference in costs associated with productivity loss, we should note that throughout our RCT there were no significant between-group differences in the numbers of missed or unproductive work hours due to absenteeism or presenteeism. This suggests that the difference in costs was not related to the type of treatment received but possibly to chance.

In terms of the health care provider perspective, which includes medical costs only, blended CBT did have an acceptable probability of being cost-effective as compared with face-to-face CBT. This suggests that providing blended CBT can potentially reduce the costs of treating depression in specialized mental health care.

Working Alliance

After ten weeks of treatment, the working alliance ratings by both patients and therapists associated with blended CBT and face-to-face CBT were similarly high. This suggests that providing a proportion of treatment online, rather than face-to-face, did not have a negative impact on the working alliance between patients and therapists. This is an important finding, because therapists in previous research had voiced that concern as one of their hesitations about considering blended treatment (van der Vaart et al., 2014). In general, patients and therapists in our treatment groups were satisfied with the working alliance. The high alliance ratings are similar to those reported in other studies that examined patient- and therapist-rated alliance, for example the trial by Preschl and colleagues ($n = 53$), which compared online CBT with face-to-face CBT for depression (Preschl et al., 2011), and the uncontrolled study by Vernmark and colleagues ($n = 73$) on blended CBT for depression (Vernmark et al., 2019).

An interesting finding in our study was that, in blended CBT, no association was found between the patient-rated working alliance and depression severity during treatment, whereas in face-to-face CBT higher alliance ratings were related to lower depression severity. A possible explanation may be that in blended CBT more emphasis was placed on self-efficacy and autonomy by letting patients work through part of the treatment protocol on their own via the online treatment platform. Hence, patients in blended CBT may have felt

less dependent on their therapist to achieve a change in depression severity than patients in the face-to-face CBT group. How this relates to our finding that blended CBT and face-to-face CBT appear to be similarly effective, with no improved clinical effectiveness found for blended CBT, cannot be established in this thesis.

Methodological Considerations

In interpreting the findings in this thesis, it is important to keep a few considerations in mind. Including a large study sample in routine practice proved to be quite difficult. Consequently, 102 participants were included in the RCT instead of the 150 that the study originally aimed for. Extending the duration of the study would have increased the chance of including more patients, but it would have taken longer to collect the data and analyze and disseminate the results. In the case of blended CBT, there was a gap between evidence and practice, with many organizations already implementing this treatment even though little was known about costs and effects. The aim of this thesis was therefore to gain initial insights into blended CBT and determine whether further research was warranted, rather than to conduct a large controlled study. On that basis, the decision was made to start the analyses with a smaller group of patients in order to establish whether the new intervention was safe and feasible.

A larger sample size would have facilitated more stable estimates of cost and effect differences. For example, the data on costs were characterized by outliers (patients with extreme scores). While this is not uncommon in economic evaluations, the impact of outliers increases as the sample size becomes smaller. Also, 25% of the desired observer-rated data and 40% of the self-reported data could not be collected, due to study dropout in both study groups. That meant that a significant amount of missing information needed to be estimated on the basis of the available data. Such estimates become less reliable as the sample size from the start of treatment decreases. Lastly, both in the trial and in the longitudinal study, large differences among patients in specialized mental health care were found in terms of both clinical and demographic characteristics. In the trial, those differences became apparent at baseline, where between-group differences could be seen in costs, quality of life, and depression severity. That may have contributed to between-group differences throughout the trial.

Concerning the cost-effectiveness analyses, it should be noted that data collection relied on a self-report measure (Trimbos/iMTA Questionnaire for Costs Associated with Psychiatric Illness, TiC-P) (Hakkaart-van Roijen et al., 2002), and that this may have resulted in recall bias. While patients have been shown to be able to reliably recall use of health care resources for periods up to three months (van den Brink et al., 2005), the estimation of absenteeism and presenteeism may be more complicated. To decrease the burden of filling in questionnaires and increase the chance of accurate recall of service use and productivity losses, we had patients provide information over four weeks, instead of the full ten-week assessment periods. To calculate cumulative costs, we estimated the costs in the intermediate weeks using linear interpolation. Assuming costs to be stable during each follow-up period.

Although this decision might have reduced recall bias, it might have also led to overestimation or underestimation of true costs. Finally, costs of using the online treatment platform, such as the costs of hosting and maintenance of the online environment, could not be included in the estimation of medical costs, which may have caused an underestimation of costs associated with the provision of blended CBT.

Future Research

In addition to the possible adaptations of blended CBT that were discussed earlier in this chapter, some next steps in the evaluation of blended CBT would be to study whether blended CBT and face-to-face CBT are indeed non-inferior to each other in terms of clinical effectiveness and to further examine cost-effectiveness. Answering these questions will require a large study sample. Also, to enable a better indication of the long-term effects of both treatment formats on costs and clinical effects, a longer follow-up period of at least a year would be advised. Fortunately, results from the E-COMPARED study are still forthcoming, comparing costs and effects of blended CBT with treatment-as-usual for patients with depression in routine practice in six European countries (Kleiboer et al., 2016).

Besides conducting large RCTs, one can also consider other research designs, such as data collection as part of routine practice. One important benefit would be that it may help to acquire information on a larger group of patients, thereby increasing external validity. In addition, it might provide a more accurate understanding of routine practice, and more insights in the flow of patients through specialized mental health care in general, rather than during the course of one treatment. Combining specific information on the type of treatment received, treatment response, and remission rates, could enhance knowledge about treatment availability and effectiveness. For example, it would be interesting to study how a focused depression treatment, such as the blended CBT protocol that was studied in this thesis, impacts patients' trajectories through mental health care.

Finally, it would be interesting to collect more information on the content and quality of face-to-face treatment provided in routine practice, in order to better assess the relationship between treatment and outcomes. In blended CBT, the number of finished online sessions provided a relatively reliable estimation of the CBT content that patients had received. For the face-to-face CBT group, in contrast, the information on the number of sessions and length of treatment provided less insight into the content of the treatment that was delivered. In the current study, no data could be collected on therapist adherence to the protocol, due to financial and time restraints. That is unfortunate, because some forms of 'therapist drift' from the protocol, such as omission of elements, can have negative effects on treatment outcomes (Bruijnicks et al., 2018; Wiltsey Stirman et al., 2015).

Concluding Remarks

This thesis is one of the first to examine the possibilities of blended cognitive behavioral therapy for depression in routine specialized mental health care. In comparison with face-to-face CBT, blended CBT showed a potential to produce comparable clinical effects, to enable therapists and patients to build a good working alliance, to shorten treatment duration, and to offer a transparent treatment protocol that helps patients and therapists to maintain the focus on depression. Because blended CBT increases the certainty that, after completion of the protocol, a CBT intervention targeting depression has actually been provided, it may also help patients and therapists in deciding what to do after blended CBT is completed. They may consider whether treatment can be stopped, whether a depression treatment other than individual CBT is indicated, or whether treatment focused on a comorbid disorder, such as an anxiety disorder, might be warranted. The question remains whether specialized mental health care for depression can become more efficient and what role blended CBT can play in this. To ensure delivery of blended CBT with less therapist involvement, adaptations to the protocol would be necessary, for example with decreased time spent on online therapist feedback. Whether this can be done without compromising treatment effects needs to be investigated in future studies.