

Chapter 9

Summary

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Depressive disorders are highly prevalent, have a detrimental impact on the quality of life of patients and their relatives and are associated with increased mortality rates, high levels of service use and substantial economic costs. Current treatments are estimated to only reduce about one-third of the disease burden of depressive disorders. Prevention may be an alternative strategy to further reduce the disease burden of depression.

In **chapter 2**, we found a pooled incidence rate ratio of 0.79 (95% CI 0.69 - 0.91), indicating a 21% decrease in incidence of major depressive disorders in intervention groups compared with control groups. Heterogeneity was low ($I^2 = 24\%$). The number needed to treat (NNT) to prevent one new case of depressive disorder was 20. Sensitivity analyses revealed no differences between type of prevention (i.e., selective, indicated or universal) nor between type of intervention (i.e., cognitive behavioural therapy, interpersonal psychotherapy or other). Prevention of depression seems feasible and may, in addition to treatment, be an effective way to delay or prevent the onset of depressive disorders. Preventing or delaying these disorders may contribute to the further reduction of the disease burden and the economic costs associated with depressive disorders.

Web-based interventions have shown to be effective in reducing depressive symptom severity. However, it is not known whether web-based interventions may also be effective in preventing the onset of major depressive disorder. In **chapter 3**, we described the design of a randomised controlled trial. The aim of the study was to evaluate the (cost-) effectiveness of an indicated web-based guided self-help intervention (GET.ON Mood Enhancer Prevention) on the onset of major depressive disorder. Adults with subthreshold depression (N = 406) were recruited from the general population and randomised to either the web-based intervention or enhanced usual care. The primary outcome was time to onset of major depressive disorder within a 12-month follow-up period. Major depressive disorder was assessed according to DSM-IV criteria as assessed by the telephone-administered Structured Clinical Interview for DSM-IV (SCID). Time to onset of major depressive disorder was assessed using life charts. Secondary outcomes included changes on various indicators of depressive symptom severity, anxiety and quality of life from baseline to post-treatment, to a 6-month and a 12-month follow up. Additionally, we conducted an economic evaluation from a societal and public health care perspective, respectively.

In **chapter 4**, we evaluated the effectiveness of the web-based intervention in the treatment of subthreshold depression. In total, 406 participants were enrolled in the trial. The mean treatment duration was 5.84 weeks (SD = 4.37). On average, participants completed 4.93 of 6 sessions. Participants in the intervention group showed a significantly greater pre-post

reduction in depressive symptom severity ($d = 1.06$; 95% CI 0.86 - 1.27) as compared to the control condition ($d = 0.29$; 95% CI 0.10 - 0.49). The corresponding between-group effect size was $d = 0.69$ (95% CI 0.49 - 0.89). At 6-month follow-up the effect was reduced to $d=0.28$ (95% CI 0.09 - 0.48) but was still statistically significant [$F(1, 403) = 9.240$; $p = .003$]. The findings lend support to the idea that problem-solving coupled with behavioural activation is an effective treatment for subthreshold depression. In addition, the delivery of the intervention over the Internet might be a promising strategy for the dissemination of psychological interventions for subthreshold depression on a large scale.

In **chapter 5**, the aim was to evaluate the effectiveness of the web-based guided self-help intervention on the onset of major depressive disorder. Among 406 randomised patients (mean age 45, 73.9% women), 335 (82%) completed the telephone follow-up at 12 months. In the intervention group, 55 participants (34%) and 84 participants (49%) in the control group experienced an major depressive episode. Cox regression analyses controlling for baseline depressive symptom severity showed a hazard ratio of 0.59 (95% CI 0.42 - 0.82, $p = .002$) at 12-month follow-up. The number need to treat to avoid one new case of MDD was 6.5 (95% CI 4.2 - 18.5). Among patients with subthreshold depression, the use of a web-based guided self-help intervention compared to enhanced usual care reduced the incidence of major depressive disorder over 12 months. Further research is needed to understand whether the effects are generalizable to both first depression onset and depression recurrence as well as effectiveness without the use of an eCoach.

In **chapter 6**, we evaluated whether the web-based intervention represent good value for money. The main outcome in the cost-effectiveness analysis was depression-free years (DFYs). DFYs were based on the number of depression-free weeks up to the onset of a major depressive episode within the 12-month follow-up period. Significantly more DFYs were gained in the intervention group (0.82 vs 0.70). Quality-adjusted life years (QALYs) were used as the outcome in the cost-utility analysis. QALYs were based on the EQ-5D-3L (EuroQol) and SF-6D (a subset of items of the SF-12v1). QALY health gains were also in favour of the intervention, but only statistically significant when measured with the more sensitive SF-6D. The incremental per-participant costs were €136 (£116). Taking the health care perspective and assuming a willingness-to-pay of €20,000 (£17,000), the intervention's likelihood of being cost-effective was 99% for gaining a DFY, 64% or 99% for gaining an EQ-5D or a SF-6D QALY. Our study supports guidelines recommending web-based treatment for subthreshold depression and adds that this may not only restore health in people with subthreshold depression, but in addition reduces the risk of developing a MDD. Offering the intervention has an acceptable likelihood of being more cost-effective than enhanced usual care and could therefore reach community members on a wider scale.

Human resources to deliver psychological treatments are limited. In **chapter 7**, we therefore evaluated the effectiveness of the web-based intervention with adherence-focused guidance in the treatment of subthreshold depression. Participants with subthreshold depression (CES-D \geq 16, no Major Depressive Disorder according to DSM-IV criteria, N = 204) recruited via a large statutory health insurance fund were randomly allocated to the web-based intervention or to a waitlist control condition with unrestricted access to usual care. The primary outcome was the reduction in depressive symptom severity as measured by blind diagnostic raters using the Quick Inventory of Depressive Symptomatology (QIDS) at post-treatment. There was a statistically significant between-group difference in QIDS scores at post-treatment in favour of the intervention group [$F(1,201) = 11.31$; $p = .001$] corresponding to a medium effect size of $d = 0.40$ (95%-CI 0.12 - 0.68) and a number needed to treat (NNT) of 7 (95%-CI 3.7 - 41.2). Significant effects in favour of the intervention group were also found for secondary outcomes, such as quality of life, anxiety, and insomnia severity. We found that a web-based self-help intervention with adherence-focused guidance could be an acceptable and effective approach to reduce a range of negative consequences associated with subclinical depression.

The primary aim of this thesis was to evaluate the clinical and cost-effectiveness of a web-based guided self-help intervention on the onset of diagnosed major depression in adults with subthreshold depression. **Chapter 8** summarised and integrated the main findings of both studies. Results of our meta-analysis showed that prevention of depression using psychological interventions seems feasible and it might in conjunction to treatment be an effective way to prevent or at least delay the onset of major depressive disorder (chapter 2). Results from our first randomised controlled trial indicated a greater reduction in depressive symptom severity in the intervention as compared to the control group at post-treatment. These effects were sustained at 6- and 12-month follow-up (chapter 4). Findings from the first study also suggested that the web-based guided self-help intervention could effectively reduce the risk of depression onset, or at least delay its onset. The number-needed-to-treat (NNT) to prevent one new case of major depressive disorder was comparable to NNTs in the treatment of major depression (chapter 5). In addition, the intervention has an appealing likelihood of being more cost-effective than enhanced usual care (chapter 6). Findings from the second trial showed that, compared with a waitlist control group, the same web-based intervention using an adherence-focussed guidance concept was effective in reducing observer-rated and self-reported depressive symptom severity compared with a waitlist control condition (chapter 7).

We noted some limitations of the randomised controlled trials. (1) We did not assess lifetime history of major depressive disorder at baseline. Findings from the first study likely refer to a mixed sample of first depression onsets and depression recurrences. Hence, we cannot draw conclusion about whether the intervention is equally effective in both subsamples. In addition,

we did not assess (chronic) medical conditions. Experiencing (chronic) medical conditions might also be a risk indicator for the onset of a major depressive disorder. (2) We did not standardize care-as-usual across GPs, which added noise to the studies. (3) We permitted the use of antidepressant medication as part of usual care. Thus, we cannot rule out that for some participants the web-based intervention was an adjunct to concurrent antidepressant treatment (i.e., secondary prevention). (4) The first randomised controlled trial had only a 12-month follow-up period. Therefore, it is not without doubt whether the web-based guided self-help intervention actually prevented the onset of major depressive disorders or just delayed its onset. (5) In the first trial, study conditions were not balanced with regard to human attention as no eCoach was involved in the web-based psychoeducational intervention. Therefore, it cannot be ruled out that parts of the observed preventive effects were caused by human attention. With regard to the second trial, we cannot rule out a potential placebo effect in the control condition even though patients in the control group had full access to usual care. (6) In the first study, we assessed depressive symptom severity exclusively with self-report measures. (7) We did not assess the duration of depressive symptoms at baseline meaning that we do not know whether depressive symptoms were first onset or persistent. Consequently, we do not know whether the reduction in depressive symptom severity was influenced by the duration of depressive symptoms. (8) Participants in our trials were better educated as compared to the general population and were predominately female. It might be that by virtue of increased levels of education, study participants are more motivated to engage in a web-based intervention, and are, therefore, more responsive.

Then some implications for clinical practice and opportunities and risks of translating the web-based intervention to a population level were discussed. For example, both studies add to the existing evidence that psychological interventions for subthreshold depression could result in substantial and clinically significant effects. In addition, while the majority of non-web-based psychological interventions evaluated so far consist of 10 or more sessions, we achieved similar effect sizes with a brief intervention consisting of six sessions. However, (1) more research is needed to replicate the findings before a nation-wide implementation could be considered. (2) The individual eCoach feedback provided in this web-based intervention hinders a scale-up. (3) The same technical resources available in the research setting (i.e., reasonable Internet connections) may not be available when the intervention is scaled up. (4) Dissemination into primary care does not only depend on the target group's willingness to use such intervention and the availability of technical requirements, but also on the willingness of practitioners to refer patients to a web-based intervention. (5) It is not clear how web-based interventions could be rolled out to the population.

Finally, I discussed some directions for future research. For example, how much guidance is needed in web-based interventions, how acceptable are web-based interventions in the target group, who benefits most from preventive (web-based) interventions, what do we know about negative effects of web-based interventions, and how could men be reached to engage in (web-based) preventive interventions.

In conclusion, both trials have shown that GET.ON Mood Enhancer Prevention is effective in treating subthreshold depression and in preventing the onset of major depressive disorder. Also, the web-based intervention represented good value for money. The intervention can result in clinically meaningful changes also in the long-term using different guidance concepts. Our studies support recommendations given in clinical guidelines on depression treatment that low-intensity psychosocial interventions should be offered to manage (persistent) subthreshold depressive symptoms and mild to moderate depression. Web-based interventions might be a complement to face-to-face mental health services. Large-scale dissemination of web-based preventive interventions might be a promising strategy to alleviate depression's disease burden on a wide scale in an affordable way.

