General discussion
Background and research questions

Major Depressive Disorder (MDD) is prevalent\(^1\), has a high risk of relapse and recurrence\(^2\) and is therefore potentially, a chronic, lifelong illness for many people\(^3\). In order to stop the rhythm of MDD, prevention of relapse and recurrence is of importance. Though continuation of antidepressant medication (ADM) is recommended for the prevention of relapse and recurrence\(^4\), and therefore is the mostly used strategy, it may not be the most optimal preventive strategy\(^5-10\). Preventive psychological interventions\(^4\) might be a better option.

There were several knowledge gaps regarding recurrent MDD and the prevention of relapse and recurrence by psychological interventions in people with a history of depression. To add to the knowledge about prevention of relapse and recurrence in recurrent MDD we tried to answer the following research questions:

1) What is the burden of disease of recurrent depression compared to single episode depression?
2) What is the effectiveness of existing psychological interventions compared both to usual care and the continuation of ADM, to prevent relapse and recurrence in recurrent depression?
3) What is the cost-effectiveness of existing psychological interventions to prevent relapse and recurrence in recurrent depression, compared to enhanced usual care?
4) What is the (cost-)effectiveness of supported self-help in primary care, for the prevention of relapse and recurrence in recurrent depression?

Outline of discussion

In the present chapter, we summarise the main findings, thereby answering the research questions. Further, the main findings are described in light of previous research and we comment on some methodological considerations, associated with the studies in this thesis. Finally, we reflect on the implications for clinical practice and conclude with recommendations for further research.
Chapter 8

MAIN FINDINGS

Chapter 2, research question 1

Single depressive episodes emerge as a key driver of disease burden from an individual perspective. From a population perspective, recurrent depressions emerge as a key driver. For this study, we used data from the first wave of the second Netherlands-Mental-Health-Survey-and-Incidence-Study\textsuperscript{11} (NEMESIS-2, n=6,646; single episode DSM-IV depression, n=115; recurrent depression, n=246). Disease burden from an individual perspective was assessed as ‘disability weight * time spent in depression’ for each person in the dataset, resulting in Quality Adjusted Life Year (QALY) decrements. We found that a single episode poses a greater burden on individuals than a recurrent depressive episode (QALY decrement=0.111 and 0.078 respectively). From a population perspective, disease burden was assessed as ‘disability weight * time spent in depression * number of people affected’ resulting in Years Lived with Disease (YLD). From this perspective, recurrent depression causes a larger disease burden than single episode depression (YLD/mln= 2,782 and 1,882 respectively. This implies that the burden of disease differs between subtypes of depression and depends much on the choice of perspective. Both perspectives serve different purposes and should be made explicit to avoid misunderstandings between policy makers and clinicians.

Chapter 3, research question 2

Preventive psychological interventions are significantly better than treatment-as-usual (TAU) in reducing the risk of relapse or recurrence and also more successful than the continuation of ADM.

For this meta-analysis and meta-regression, we systematically reviewed the pertinent trial literature until May 2014 and found 25 studies that met inclusion criteria; a) a randomised controlled trial b) examining adult patients in the age bracket of 18-64 year c) with recurrent MDD d) who were in remission (according to their own definition in the individual trial-paper) at randomisation e) receiving a preventive psychological intervention f) with the aim of reducing the risk of relapse or recurrence and g) with a comparison to a control condition. Control conditions could be classed as TAU (routine clinical management, assessments only, no treatment and waiting-list control with unrestricted access to TAU) or anti-depressant medication (ADM). The psychological interventions were diverse and consisted of Internet-based treatments, booster sessions, group and individual treatment. We included trials on Cognitive (Behavioural) Therapy, Interpersonal Therapy (IPT) and Mindfulness Based CT (MBCT). We found no randomised controlled trials on other psychotherapies such as problem-solving therapy and psychodynamic therapy.
Preventive psychological interventions were significantly better than TAU in reducing the risk of relapse or recurrence (RR=0.64, 95%CI=0.53-0.76, z= 4.89, p<0.001, NNT=5) and also more successful than ADM (RR=0.83, 95%CI=0.70-0.97, z=2.40, p=0.017, NNT=13). Meta-regression showed that the preventive effect of psychological interventions was usually better, when the prevention was preceded by treatment in the acute phase (b=-1.94, SEb=0.68, z=-2.84, p=0.005).

**Chapter 4, research question 3**

*Adding preventive Cognitive Therapy (CT) and Mindfulness Based Cognitive Therapy (MBCT) to enhanced TAU, might make the healthcare system for recurrent depression more cost-effective compared to enhanced TAU alone.*

A health economic (Markov) model that synthesizes clinical, economic and epidemiological evidence was used to assess return on investments (ROI). The model calculated the total healthcare costs and health gains by comparing a base-case scenario (enhanced TAU) with four scenarios in terms of cost-effectiveness: enhanced TAU plus A) CT; B) MBCT and C) IPT. Enhanced TAU is a hypothetical, evidence-based healthcare system for depressive disorder in full agreement with the Dutch clinical guidelines for the treatment of depression. We used clinical effectiveness data from our review on the effectiveness of psychological interventions on relapse and recurrence. Costs were estimated by mapping the total time of one intervention (hours) multiplied by the appropriate full economic costs of the healthcare professional according to the Dutch guidelines for health economic evaluations. The ROI of enhanced TAU is €1.30 while the ROI of adding CT, MBCT or IPT is €1.43, €1.45 and €1.31 respectively.

**Chapter 6, research question 4**

*Adding a supported self-help preventive cognitive therapy (S-PCT) to TAU for people with a history of depressions is more effective than TAU alone in the prevention of relapse and recurrence over 12 months.*

We conducted a randomised controlled trial, evaluating the (cost-)effectiveness of TAU augmented with S-PCT, compared with TAU alone for people with a history of depressions, currently in remission (n=248). Details of this study are described in Chapter 5. We found that in the S-PCT group, 44/124 participants (35.5%) relapsed compared to 62/124 participants (50.0%) in the TAU group. Therefore, our analyses showed a significant risk difference in relapse rate of 14% (95%CI 2-24, number needed to treat=8) in favour of the S-PCT group after 12 months (incidence rate ratio=0.71, 95%CI 0.52 to 0.97).
The cost-effectiveness of S-PCT was assessed in two ways, which resulted in two (different) findings.

**A) Chapter 4, research question 4**

*In order to reach the most competitive ROI (€1.45), a hypothetical S-PCT needs to reach a relative risk reduction of 0.71. This relative risk reduction is feasible (Chapter 6).*

A hypothetical S-PCT was added to the health economic Markov model. We found that in order to reach the most competitive ROI (MBCT, €1.45), the hypothetical S-PCT needs to reach a relative risk reduction of 0.71. *Chapter 6, assessing the real-life effectiveness of S-PCT in a pragmatic randomised controlled trial (RCT), shows that a relative risk reduction of 0.71 is feasible.*

**B) Chapter 7, research question 4**

*Adding S-PCT to TAU for people with a history of depressions is not cost-effective compared to TAU alone, in the prevention of relapse and recurrence over 12 months.*

An economic evaluation alongside a RCT was performed over a 12-month follow-up. Mean total societal costs were €2,114 higher (95%CI -112;4261). From a societal perspective, the ICER for recurrence of depression was 13,515. At a Willingness To Pay (WTP) of 22,000 €/relapse or recurrence prevented, the probability that S-PCT is cost-effective, in comparison with TAU, is 80%. From a healthcare perspective, the WTP at a probability of 80% should be 11,500 €/relapse or recurrence prevented. The ICER for QALYs was 63,051. The cost-effectiveness acceptability curve indicated that at a WTP of 30,000 €/QALY gained, the probability that S-PCT is cost-effective in comparison with TAU is 21%. From a healthcare perspective, at a WTP of 30,000 €/QALY gained, the probability that S-PCT is cost-effective in comparison with TAU is 46%.
INTERPRETATION AND EXPLANATION OF MAIN FINDINGS

The burden of disease of recurrent depression compared to single episode depression
MDD was the second leading cause of total burden of disease in 2010\textsuperscript{15}, accounting for 8.2% of the global burden of disease, behind low back pain. Within the group of mental and substance use disorders, 41% of the global burden of disease was caused by depressive disorders\textsuperscript{16}. However, depressive disorder is not a homogenous condition and burden of disease estimates might vary across subtypes (e.g. single and recurrent episodes). Kruijshaar et al.\textsuperscript{17} studied the associations of type of depression with functional impairment of the individual in a Dutch general population sample. They concluded that recurrent depression was not associated with more impairment than single episode depression. In contrast, Vos et al.\textsuperscript{18} found that recurrent depression is the key driver of disease burden and that depression should be treated as a chronic episodic disorder in order to reduce this great burden of disease. These studies took either the individual- or the population perspective when assessing burden of disease. From an individual perspective, clinicians tend to give priority to the disorders that exact the heaviest toll on their patients, while from a population perspective the disease burden might be driven by the number of people affected, in addition to case severity and disease duration. Both perspectives may lead to difference results in terms of burden of disease. Indeed, a study by Lokkerbol et al.\textsuperscript{19} into the non-fatal burden of several mental disorders showed that the rank order of disease burden of several disorders at an individual level is often different from the rank order at the population level. Using data of the second Netherlands Mental Health Survey and Incidence Study (NEMESIS-2, n=6,646)\textsuperscript{11}, we showed that single depressive episodes emerge as a key driver of disease burden from an individual perspective and that recurrent depressions emerge as a key driver from a population perspective (Chapter 2). Both perspectives serve different purposes and may require careful alignment when being used jointly. Such an alignment may result in the optimal balance between an individual approach directed, for example, at the episodic treatment of acute single episode depressions, in combination with a public health care approach with an emphasis on the longer-term preventive management of recurrences.

In the study in Chapter 2, we assessed the burden of disease due to depressive relapse or recurrence. However, we know that approximately one third of the recurrently depressed people experience residual symptoms during remission or recovery\textsuperscript{20-22}. Residual symptoms of depression probably reflect persistence of the original disorder in a milder form and cause significant functional impairment\textsuperscript{23,24}. Unfortunately, we had no data on burden of disease due to residual symptoms of depression during remission or recovery. In future studies, when assessing the burden of disease of recurrent depression it would be interesting to take the burden of disease due to all stages (i.e. acute phase, remission, recovery) into account.
Effectiveness of preventive psychological interventions

Preventive psychological interventions were effective in reducing relapse and recurrence over a mean follow up of two years versus TAU and ADM treatment with a relative risk of 0.64 and 0.83, respectively (Chapter 3). These results are an extension to previous research which demonstrated that C(B)T, including MBCT, after remission might be equally effective in reducing the risk of depressive relapse and recurrence as ADM and more effective than TAU25–30. Further, we found that the effectiveness of the psychological interventions increased when the interventions directly followed acute phase treatment.

Previous research demonstrated that the effectiveness of MBCT and preventive C(B)T was limited to patients with a higher number of previous episodes27,28,30–35. An explanation for this might be that preventive treatments function to disrupt the internal depressive associations which the sufferer tends to make during the course of his condition36. Our findings, both in the meta-analysis (Chapter 3) and in the RCT (Chapter 6), did not demonstrate this; preventive psychological interventions were effective, irrespective of the number of previous episodes. Current national and international clinical practice guidelines state that prevention of relapse with preventive C(B)T of MBCT is especially effective in patients with three or more episodes and that the number of previous depressive episodes should be taken into account when deciding on relapse prevention25,27,28,37–39. Our results suggest that prevention of relapse and recurrence can be advised to all patients with recurrent MDD, irrespective of their depression history.

Cost-effectiveness of preventive psychological interventions

The return on investments (ROI) of enhanced TAU was €1.30 while the ROI of adding CT, MCT or IPT was €1.43, €1.45 and €1.31 respectively. In other words, we found that adding CT or MCT might make the healthcare system for recurrent MDD more cost-effective than enhanced TAU. It should be noted that assumptions in the model are conservative and that the base-case scenario is likely to be more effective than the current Dutch healthcare system. As a consequence, the ROI of the base-case scenario (€1.30) is likely to over-estimate the ROI of the present health care system for depressive disorders in the Netherlands. This implies that results might be more optimistic.

As far as we know, this is the first modelling article on the cost-effectiveness of preventive psychological interventions. With regard to real-life effectiveness, only few RCTs on the cost-effectiveness of preventive psychological interventions versus TAU and ADM have been assessed and results of these studies are mixed29,40–41. As the substantial economic consequences of MDD are largely due to its recurrent character44–47, cost-effective interventions for the prevention of relapse and recurrence are sorely needed. Therefore, we strongly recommend to conduct real-life studies on the cost-effectiveness of preventive interventions for relapse and recurrence.
Supported self-help for recurrent depression

Effectiveness of S-PCT

Many randomised trials and meta-analyses have shown that (supported) self-help is effective in the treatment of acute depression and other disorders\(^{48-56}\). Our study is the first showing that a self-help for remitted patients in primary care is effective in preventing relapse and recurrence compared to TAU. The effect was even more pronounced in participants that completed a higher number of modules (≥5) (risk difference=15%, 95%CI 4-24, NNT=7). The latter finding fits previous research on acute treatment of depression demonstrating that the effectiveness of minimally supported interventions might depend on treatment adherence\(^{57}\).

The self-help in this study was supported by primary care mental health nurses and clinical psychologists. Studies already showed that mental health nurses are capable of providing high quality psychological interventions in primary care\(^{58-60}\). We think the type of counsellor might not have impacted findings on a large scale for three reasons. First, in a meta-analysis on moderators of self-help interventions, Gellatly et al.\(^{51}\) found that there were no significant relationships between effect size and personnel type, content of the guidance and mode of the guidance. Second, the backgrounds and educational level of nurses is diverse as both literature\(^{61-63}\) and our study showed. Finally, the support given by the counsellor was primarily of supportive and facilitative nature and meant to support the participant in working through the manual. Also, the support of the intervention was strictly protocolled leaving no room for personal contributions.

Cost-effectiveness of S-PCT

In this thesis, we assessed the cost-effectiveness of S-PCT in two ways. The positive results of our modelling work did not correspond to the negative results of the cost-effectiveness analysis (CEA) alongside the RCT. We found two possible explanations for these different results. Pragmatic RCTs are designed to evaluate the effectiveness of interventions in real-life routine practice conditions, whereas modelling studies aim to test whether an intervention works under certain conditions. Assumptions in our model were as conservative as possible. Still, these assumptions may have portrayed an overly optimistic outcome scenario and might not have resembled clinical practice in a credible way. Another explanation may be the different cost-price of S-PCT between the studies which is €178 per participant in the modelling study and €388.15 per participant in the CEA. This difference is caused by a different approach in calculating these costs. However, an additional analysis showed that replacing the higher costs of €388.15 by €178 euro in the CEA, did not impact much on the results. To end with, in the CEA costs of the S-PCT group were substantially higher. An obvious explanation for these higher costs is lacking. As a consequence, an explanation for the different results between the modelling study and the CEA is also lacking.
Enrolment

Only 4.5% (248 out of 5,489) of the persons that were invited, were enrolled. Both methodological (selecting the ‘right’ patient) and motivational (motivating a patient to participate) problems may have played a role here. The methodological problems should be placed in the context of conducting a trial while motivational problems might play a role in the context of conducting a trial but also in the context of offering a preventive intervention for recurrent depression in clinical practice.

Medical records of primary care practices and mental health care practices were screened for eligible persons. Obviously, selecting persons who are in remission of recovery from a database is quite difficult and therefore, many non-eligible persons (e.g. chronically depressed patients) were invited. Direct referral of primary are patients into the trial by the general practitioner after an acute phase treatment would have been preferred, because relapse prevention shows better results when offered directly after acute phase treatment\(^{13}\) (Chapter 3) and because there are some indications that patients referred to self-help by their general practitioner benefit most from these treatments, compared with patients who are referred by mental health professionals and self-referrals from the community\(^{64}\). However, due to time restraints, we chose to screen medical records of primary care practices and mental health care practices.

Poor recruitment to RCTs is a widespread problem\(^{65}\). The decision to enter a trial or accept a treatment involves a judgement between risk and reward by the patient\(^{66}\). A combination of depressive feelings with positive expectations about the outcomes of the trial, will probably positively affect recruitment\(^{67}\). However, participants considered for a prevention trial or treatment are not currently diagnosed as having an illness. Typically, they are at risk of a disorder and may not be aware of this. This may influence their attitudes towards a trial or treatment and hence their behaviour\(^{68}\). A self-help intervention might facilitate the judgement between risk and reward by lowering the threshold of requesting for help for those who are not aware of their risk of a disorder or unwilling to participate in formal methods of treatment. Finally, due to the very same reasons that constitute their vulnerability for depression\(^{69}\), such as lack of concentration and confidence and low motivation, it might be difficult for remitted patients to enrol in a trial or to accept a treatment.

Adherence and acceptability

In pragmatic trials, an important outcome is the level to which the intervention was implemented according to protocol\(^{70}\). We found that adherence to the intervention protocol by the counsellors was high. The mean duration of weekly calls of 13.8 minutes seems to imply that the counsellors kept to the protocol and that the support was only motivational without an in-depth and therapeutic conversation. However, some counsellors needed
extra support to keep the ‘supporting trail’ and not to go into detail with a participant (based on feedback during supervision.

Of all 124 participants in the S-PCT group, 101 participants completed at least 5 modules and no participant dropped-out of the intervention after module 5. Therefore, adherence, defined as the proportion of participants that started the first module of and completed the final module, was 81.5% (101 out of 124 participants). This adherence was much higher than the adherence rate of self-help psychological interventions over the Internet, reporting adherence rates of ‘only’ 65.2%-72%72. The relatively high adherence rate of S-PCT might be explained by the total counsellor support time per participant which was moderately to high in our study (110.2 minutes), compared to other studies in depressed patients and patients in partial remission of depression (21-150 minutes)73–76. It might also be explained by the intervention being developed in such a way that each module could be completed in someone’s own time and place within approximately 60 min and without the need for a computer with access to the Internet.

According to the checklist of the counsellors, in 6% of all contacts, the participant had not read the literature belonging to that week’s module. In 11% of all contacts, the participants declared they did not complete the assignments for that week’s module. These numbers suggest that the acceptability of the therapy was high.
METHODOLOGICAL CONSIDERATIONS

Deviations from the study protocol
Between April 2012 and April 2014, we sent 5,489 letters and enrolled 248 patients from 22 primary care practices and 4 specialized mental health care practices. One major deviation from the protocol (Chapter 5) occurred in the first part of the study. The inclusion of participants in primary care, as intended, proved difficult. Explanations for this can be found in the previous paragraph (Interpretation and explanation of main findings; enrolment). The number of patients per practice that was both eligible and willing to participate was very low (1-5 per practice). In order to reach the numbers needed to be able to study the effect of the intervention, we decided to recruit patients from secondary care as well. A meaningful distinction between characteristics of participants from primary care or secondary care could not be made; participants that were selected in a primary care database might have been under treatment in secondary care and vice-versa. Also, selected participants might not have been under treatment at all.

Another deviation concerns the support of the self-help intervention. It proved difficult to involve primary care mental health nurses that were willing to support the self-help in this trial. In the Netherlands, a primary care mental health nurse is operative to a maximum of 9 hours per week per average general practice of 2,350 patients\(^77\). Because of this restraint, nurses, and the general practitioners they work with, need to set priorities in the allocation of their time spent on mentally ill patients. As a direct consequence, we experienced problems involving mental health nurses for our trial on relapse prevention. Approaching clinical psychologists to support the intervention, proved a successful strategy.

Patient selection
With regard to the generalizability of the findings, the participants recruited within the context of our RCT were willing to accept help for the prevention of relapse or recurrence. Therefore, this sample might not reflect the whole population with recurrent depression. We think our inclusion criteria, (i.e. at least 2 previous episodes, the last one ending no longer than 5 years ago, age 18+, fluent in Dutch) maximised generalizability of the results, because there were no restrictions with respect to the level of depressive symptoms, contrary to other prevention studies\(^28,31,78\). Finally, we should keep in mind that most participants that dropped out of follow-up are the ones with poorer outcomes\(^79\). Leaving these patients out of the analyses may cause bias and, because not all data are used, reduced statistical power. Fortunately, because ‘missingness’ of data, i.e. due to drop out, could be predicted from available data, both multiple imputation and linear mixed models including all patients, yielded unbiased results.
**Time horizon**

For trials on (cost-)effectiveness it is recommended to choose a follow-up period that is long enough to capture all (costs and) effects\(^8\). In our RCT, a follow-up of 12 months was chosen. Information on time to relapse or recurrence is divergent. Besides, the level of residual symptoms proved to influence the time to relapse or recurrence. A 12-year study by Judd and colleagues\(^8\), showed that patients with residual sub threshold symptoms, when compared with asymptomatic patients, had a relapse or recurrence of the next major depressive episode more than 3 times faster. A study by van Londen et al. found that patients with residual symptoms particularly relapse in the first 4 months after remission, while patients without residual symptoms mainly experience a recurrence after 12 months of remission\(^8\). Two studies showed that about 90% of the patients who remitted rapidly and fully with CT remained well for at least 1 year after acute phase therapy\(^8\). These findings possibly imply that we have missed the interventions’ and TAU’s impact on later recurrences. Therefore, it would be valuable to find out if the positive clinical effects of the intervention change or sustain over a longer time. Sustained positive effects in favour of PCT over 5, 5 and 10 years were found in a previous study on the long term effects of PCT in group format\(^8\). Another preliminary study suggested long-term effects of cognitive therapy over 6 years as applied in remitted recurrently depressed patients (n=40)\(^8\). Also, it would be valuable to assess the health-economic consequences (such as productivity and health care use) that are associated with these longer term effects.

**Pragmatic trial**

The pragmatic study that is evaluated in this thesis resembled clinical practice to a high degree. This increases the generalizability of the results to broader populations. Because usual care is offered in both arms, the contrast between the intervention group and the control group may be small. Even in these circumstances, S-PCT significantly reduced relapse and recurrence compared to usual care. However, the results from the cost-effectiveness analysis were less convincing and a clear explanation for the results was lacking. One option is to change the design of the study to find out if a clearer contrast between the intervention group (e.g. S-PCT only) and the control group (MBCT or ADM only) would result in other effect and costs and thus, economic outcomes. However, the growing number of economic evaluations is not only caused by a widespread interest in both economic and clinical information on medical interventions, but also by reimbursement requirements in many countries. To make sure that policy decisions are made that apply to clinical practice, policy makers need both economic and clinical information on the outcomes of a new medical intervention in the ‘real world’. Therefore it is recommended to employ a pragmatic study design for economic evaluation\(^8\), like we did.
Supported self-help

We do not know whether it was the intervention part of S-PCT, the counsellors’ support or a combination that caused the positive effect. The examination of the effectiveness of the separate parts may help deciding on which treatments strategy to apply. An additional complicating factor for usability is that patients could drop-out of the intervention group, from the counsellors’ support, and the assessments. It would be important to differentiate between these different types of drop-outs to examine which factors influence treatment outcome. Further, while we estimated modules to be completed in 60 minutes per week, we have no information available on the exact amount of time participants spent per module. Neither do we know what proportion of the completers finished the 8 modules within 8 weeks or e.g. 3 months. Gathering information on the time needed to finish modules is relevant because in face-to-face psychotherapy, there are indications that a higher intensity of treatment is associated with a higher effect size.

Assessments

The number of previous episodes of depression was retrospectively assessed with the SCID-1 and recall could have been affected by memory bias. Depressive symptoms were assessed at fixed time points, and therefore, variations in-between could have been missed. Finally, many variables, others than the once studied, could be of importance. For example, information on genes, family history or social support could help throwing light on the pathways to specific outcomes in recurrent depression.

There are several ways to collect cost data in cost-effectiveness studies alongside clinical trials, such as insurance data, medical records, interviews with patients, questionnaires and cost diaries. Because insurance data or medical records do not cover all medical resource utilisation of study patients, information on resource utilisation should preferably be obtained through self-reporting. Since questionnaires and interviews are by nature retrospective, they are subject to recall bias. Cost diaries are completed prospectively and, therefore, less subject to recall bias and the most reliable estimate of resource use. However, it is questionable whether depressed patients are up to completing the diaries prospectively, since depression is associated with loss of energy and a diminished ability to think and concentrate. Since residual symptoms of depression during remission or recovery are prevalent and probably reflect persistence of the original disorder in a milder form, this probably also counts for the participants in our trial.

In our RCT we made use of self-report questionnaires (Tic-P) to measure resource use. These questionnaires were assessed every three months. Recall periods of 1 and 2 months are mentioned as the optimal recall period in the literature. Therefore, the three months-interval between interviews might have caused some recall-bias.
CLINICAL IMPLICATIONS

Current guidelines on the prevention of relapse and recurrence recommend to encourage a person who has benefited from taking ADM, to continue ADM for at least 6 months after remission of an episode of depression. With respect to psychological interventions, guidelines recommend to offer CBT to persons with a significant history of depression plus residual symptoms, and MBCT to patients with a history of at least three episodes of depression\(^4\). Our studies\(^13\) confirm that C(B)T and MBCT should be offered to all remitted persons, however, irrespective of the type of previous acute-phase treatment, the previous numbers of depressive episodes (at least 2), and the level of residual symptoms. In addition, IPT can be advised as well (Chapter 3). Also, it is recommended to offer C(B)T, MBCT and IPT, directly after the acute-phase treatment to increase effectiveness. Further, a self-help intervention like S-PCT can be offered in primary care and might be an effective way for the prevention of relapse and recurrence in persons with at least 2 depressive episodes, with or without residual symptoms during remission or recovery (Chapter 6). With respect to cost-effectiveness, CT and MBCT could be recommended when added to usual care (Chapter 4).

What works for whom

The prevention of relapse and recurrence of depression is highly important for persons who are in remission of recovery. However, the treatment needs of a person may depend on his risk factors profile for relapse (e.g. number of previous episodes and level of residual symptoms) and may vary on the stage of the depressive disorder (i.e. acute phase, remission, recovery). On the basis of the information gathered by profiling and staging, the best treatment can be matched to patients in order to improve outcomes and reduce the burden of depression.

Profiling Preventive interventions are most likely to be effective when targeted at those with a high a priori risk profile of developing the disorder\(^9\). For example, research demonstrated that in patients with less than 5 episodes, psycho-education led to the same reduction in risk or relapse or recurrence as preventive CBT\(^14\). However, in patients with 5 or more previous episodes, preventive CBT resulted in lower relapse and recurrence rates than psycho-education. While replication is needed, this might indicate that more specific treatment is required when patients are at higher risk for relapse or recurrence\(^2,21,31,94-97\). Applying personalised prevention strategies, with the choice of treatment depending on the presence of risk factors to depressive relapse or recurrence, might increase the effectiveness of treatment. Current specific preventive interventions like PCT and MBCT might be implemented to prevent depressive relapse and recurrence when an ultra-high risk for relapse or recurrence is present, whereas a less specific intervention, such as psycho-education or perhaps even only monitoring of mood, might be enough to prevent relapse when the risk of relapse or recurrence is relatively less high\(^9\).
Staging Besides by profiling, we also suggest that the type of treatment should match the current stage of the disorder. For example, during remission there is more room for training the recall of positive experiences, and the need for support is suggested to be lower during remission than during acute-phase of depression. In this case, a minimally supported intervention like S-PCT, may benefit persons while in the acute phase, face-to-face MBCT might be the best approach.

Finally, it is questionable whether the response to treatment will remain stable across different episodes of depression\(^9\). For example, response to a specific ADM during the first episode is no guarantee for response to the same ADM during the fourth episode. Everything we experience changes us as a person\(^1\) and risk factors for relapse or recurrence might change with each consecutive episode. This fits a dynamic treatment approach, where the choice of treatment is not predetermined but depends on the needs of individuals, the stage of the disorder\(^2\) and also previous experiences.

In our RCT, we did not have information on the exact number of previous episodes which is a main risk factor for relapse and recurrence. Besides, it was unclear if participants were in remission or recovery at the moment they enrolled. In the future, it is important to make profiling and staging of participants, a routine part of conducting trials.

Implementation of S-PCT for recurrent depression in primary care

Instead of replacing existing therapies, S-PCT could be part of a blended care approach. Offering blended care broadens the options when matching treatment strategies to treatment needs. For example, dependent on the results of profiling and staging, one could vary the amount and type of support. Face-to-face contacts might be added or reduced and other technologies, such as self-help manuals, the Internet, text messages and telephone support might be considered. Before implementation, the cost-effectiveness of this blended care approach should be evaluated to assesses the added (monetary) value of this approach.

According to Vanhaecht et al.\(^1\), the success of adding a new intervention to the current healthcare system largely depends on three items before the actual implementation can take place.

1) Commitment of the healthcare system (top-down)

This thesis argues that the Dutch healthcare system may be insufficiently prepared for the high volume, high costs and high risk of chronic problems such as recurrent depression. In the Netherlands, the healthcare sector has started showing commitment to the problem of recurrent depression by several top-down initiatives. For example, the Department of Health, Welfare and Sports has given priority to the prevention of depression in its health policy in 2014. The introduction of ‘generalistic basic mental health care’ including several preventive treatments, and the introduction of a primary care mental health care nurse (POH-GGZ) in 2007 are another examples of attempts to make the mental health care
system more accessible and more affordable. Also, ongoing research on relapse prevention (e.g. this thesis) is stimulated and sponsored by governments and related institutions. A final example is the gradual introduction of guideline-recommendations on relapse prevention which are now more part of the continued care for patients with recurrent depression. Unfortunately, guidelines on relapse prevention in primary care are still rather unspecific and deserve attention. Our trial results add to this knowledge base.

2) Ownership of the problem is clear (bottom-up)

In 2013, the Dutch King Willem-Alexander said in his yearly message to the Dutch people from the government that the Dutch ‘welfare’ state of the 20th century is on its way out. He said that in its place a “participation society” is emerging, in which people must take responsibility for their own future and create their own social and financial safety nets, with less help from the national government. The self-help type of intervention that we evaluated in our RCT, fits well within such a society. Still, for effectiveness reasons, self-help needs to be embedded in the current healthcare system. Our meta-analysis of 25 studies (Chapter 3), did not provide clarification on the optimal provider or place of a preventive intervention; the setting of these studies was heterogeneous, varying from primary care and secondary care to a community setting. In the Netherlands, as in most western countries, primary care professionals have regular contact with the vast majority of the population, learn about the patients’ social situation and provide continuous care. Besides, the prevalence of patients with depression or depressive feelings in primary practice is around 21%\(^1\). Therefore, primary practice is the ideal institution to offer a preventive self-help for depression. However, primary care practitioners still refer more, and particularly the more severe, patients to a more expensive form of care in specialty care than to psychologists and social workers in primary care. Also, patients treated in secondary care may not return to primary care quickly enough\(^2\). Because mental health expenditures exceed budget in many European countries, a budgetary desire for secondary-primary care substitution is understandable. The policy incentive to strengthen the capacities of primary mental health care under the responsibility of the general practitioners by introducing a primary care mental health care nurse (POH-GGZ) so far has had limited effects\(^3\)–\(^5\).

Unfortunately, in our trial, we notified that relapse prevention is currently not their key-priority.

Further work is needed to define their workload and priorities. A nurse guideline for relapse could help here. In sum, we conclude that, besides the patient him- or herself, primary care may be the best place to provide chronic care for people with recurrent depression. However, primary care might currently not be fully resourced (yet) to respond to this challenge.
3) Practical issues of integrating a clear concept in the current healthcare system

Previous research showed that integration of depression care and primary care faces several barriers including patient factors and organizational issues\(^{106}\). For example, moving patients into a prevention treatment might be difficult (see Discussion/Enrolment) and referral to a counsellor in primary care requires a careful and timely coordination between health care groups. Still, we think that the addition of S-PCT to primary care seems a strategy that should be relatively easy implemented into current longitudinal primary care systems. Collaboration between primary and secondary care is in line with Dutch developments in mental health care. Besides, primary care psychologists and mental health nurses could act as case managers in a model for continued care for recurrent depression.

To end with

This thesis started with an overview of the burden of recurrent MDD, both for patients and society, and the challenges that decision makers in health care are confronted with these days. We suggested that decision makers should ask themselves how healthcare for major contributors of disease burden and healthcare costs, like recurrent MDD, is to be organised; how it is to be channelled to the right people, and how the right services can be delivered at the right time, at the right place and at bearable costs.

This thesis showed that recurrent MDD causes a major burden for society. It also showed that a minimally supported self-help intervention offered in primary care to patients with a history of depression can reduce this burden. Still, the prevention of relapse and recurrence of MDD proved complicated, both with regard to reaching high-risk patients as well as to offering personalised, cost-effective strategies to support these high-risk patients. By the ongoing studying of data on processes and outcomes, reflect on them, learn and act, it must be possible to improve the continuous care for people with recurrent MDD. For the well-being of these patients and the sound allocation of available budgets, this improvement process will be crucial for the years to come.
RECOMMENDATIONS FOR FUTURE RESEARCH

In this thesis, we tried to contribute to the research area of relapse and recurrence in major depressive disorder. However, more research in this area is needed.

- The follow-up of trials, e.g. on S-PCT, should be extended to evaluate outcomes on the longer term.
- The continuation of ADM is the mostly used strategy in the prevention of relapse and recurrence. Therefore, an RCT evaluating supported self-help compared to ADM would be clinically relevant.
- To gain a better picture of the total burden of disease of recurrent depression, it would be interesting both to take the burden of disease due to relapse and recurrence and due to residual symptoms during remission of recovery into account.
- In order to move from the current ‘one size fits all’ approach to more tailored care, future research should identify which components of the intervention work best for whom.
- As in many trials, recruitment proved difficult in this prevention trial. Therefore, research should also focus on understanding and addressing the facilitators and barriers to participation of eligible patients in (depression) prevention interventions trials.
- In our RCT (Chapter 6), we included participants in either remission or recovery and we did not differentiate between depressive relapse or recurrence. As a consequence, it is not clear what part of our findings refers to relapse and what part to recurrence. As treatment strategies for prevention of relapse and recurrence of depression serve different goals, it is important to differentiate between relapse and recurrence whenever possible. Therefore, future scientific research should use appropriate terminology.
- Finally, the primary outcome in this study was relapse or recurrence over a 12-month follow-up period. In our CEA we saw that the majority of costs over 12 months were due to absenteeism. Therefore, it might be interesting to adjust depression treatment goals. Return to work and social activities despite residual depressive symptoms might be valuable alternatives. Also patient adjusted outcomes ‘What do patients themselves find important?’ might be relevant.
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Chapter 8


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General discussion


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