General introduction
Major depressive disorder (MDD) is a prevalent mental disorder\(^1\), associated with a high risk of relapse and recurrence\(^2\), and with frequently incomplete remission between episodes\(^3\)–\(^5\). It is considered to be among the most disabling illnesses\(^6\), and negatively affects many aspects of life\(^7\)–\(^9\). MDD was the second leading cause of the total burden of disease in 2010\(^{10}\), 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 MDD\(^{11}\). Treating MDD in the Netherlands costs almost a billion euro (€966 million) per year\(^{12}\). Decision makers seem to have become increasingly aware of the disease burden and healthcare costs associated with MDD due to the current economic down-turn and an expenditure for mental health care that is unlikely to be sustainable\(^{13}\). However, decision makers in health care are confronting a host of challenges because the healthcare environment, both in the Netherlands and globally, is changing rapidly. There are many catalysts for change, including government regulations, increased utilization of health care, patients’ expectations, competition, declining reimbursement and technological developments. Therefore, the question decision makers have to ask themselves is how healthcare for major contributors of disease burden and healthcare costs, like 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.

An important part of the healthcare for MDD is the prevention of relapse and recurrence. The proactive management that is currently mostly used is the continuation of antidepressant medication (ADM). This may not be most optimal strategy\(^{14}\)–\(^{19}\). Another approach to the prevention of relapse and recurrence in MDD, is the use of preventive psychological interventions. Research demonstrates that these interventions can be effective in reducing the risk of relapse and recurrence\(^{20}\)–\(^{23}\).

There are several knowledge gaps regarding recurrent MDD and the prevention of relapse and recurrence by psychological interventions in people with a history of depression. First of all, only little attention is paid in literature to what part of the burden of disease of MDD is attributable to single episode depression compared to recurrent depression. Secondly, the effectiveness of all types of currently available, preventive psychological interventions compared to treatment-as-usual (TAU) and ADM is unknown. Thirdly, as the majority of the psychological interventions is offered in secondary care, often relying on intensive use of therapist’s time, these interventions are costly. Also, therapists are scarce. A minimally supported self-help intervention may help to overcome these problems and has already proved as effective as face-to-face treatment in acute depressed patients\(^{24}\). The integration of such an intervention into current longitudinal primary care systems, would fit best with the recurrent character of MDD. Besides, the prevalence of patients with MDD or depressive feelings in primary practice is high, around 21%\(^{25}\). So far, it is unknown if supported self-help for recurrent MDD, offered in primary care, is more effective than usual care. Finally,
it is the combination of data on effects and costs of interventions that will inform decision makers, who are forced to allocate limited resources to interventions that maximise cost-effectiveness. Data on both effects and costs is often lacking.

In this thesis we try to close these knowledge gaps by answering 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?

In this chapter we present background information relevant to recurrent MDD. Furthermore, we present the main concepts and assumptions that motivate the aims and the design of our studies.

Major depressive disorder; definition and epidemiology

According to the most recent Diagnostic and Statistical Manual of Mental Disorders (DSM-5)\textsuperscript{26}, for a diagnosis of MDD, at least five of the symptoms, mentioned in Table 1 have to be present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms is either depressed mood or loss of interest or pleasure. In other words, MDD is not just having a bad day or a bad mood. It is a lasting and overwhelming sad feeling that does not resolve after a few weeks and, more importantly, interferes with daily life. It is a serious illness that is common, unfortunately, affecting no less than 18.7\% of the population on a lifetime basis and 5.2\% of the population over 12 months\textsuperscript{1}. MDD has a detrimental impact on social, family and professional role functioning and is a leading cause of burden of disease\textsuperscript{10,11,27,28}.
Table 1. DSM-5 criteria for major depressive episode

<table>
<thead>
<tr>
<th>DSM-5 criteria for major depressive episode</th>
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<tr>
<td>Depressed mood</td>
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<td>Loss of interest or pleasure</td>
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<td>Significant weight loss or gain</td>
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<tr>
<td>Insomnia or hypersomnia</td>
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<td>Psychomotor agitation or retardation</td>
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<td>Fatigue or loss of energy</td>
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<td>Feelings of worthlessness or excessive or inappropriate guilt</td>
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<td>Diminished ability to think or concentrate, or indecisiveness and</td>
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<td>Recurrent thoughts of death or suicidal ideation</td>
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1 American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders (DSM-V)

The course of depression

MDD is characterized by a dynamic course. To describe the course of depression, the operational criteria of Frank et al. (1991) are often cited (Figure 1). According to these criteria the course of depression is described as a series of disease stages in which a person can move from a symptom-free stage, to a stage characterized by some symptoms but not meeting the diagnostic criteria, to a stage with the full-blown disorder, after which the person can go into remission. When a person stays in remission for a minimum of six months, he or she is considered to be recovered. Subsequently, a relapse is defined as a depressive episode that occurs during remission and before recovery while a recurrence is defined as a depressive episode that occurs after recovery. Unfortunately, definitions of relapse, recurrence, remission and recovery are generally not being used in a consistent manner in the literature. Therefore, caution should be paid when interpreting results of studies on recurrent MDD.

Figure 1. Overview of criteria for remission, relapse, recurrence and recovery modified after Tohen et al.
Recurrent depression; a chronic disorder?

The risk of relapse and recurrence of MDD is high. A long term follow-up study in the general population demonstrated that 38% of all people experienced a recurrence over a ten-year period. The Netherlands Mental Health Survey and Incidence Study (NEMESIS), conducted in the general population, showed a similar percentage. The National Institute of Mental Health Collaborative Study of the Psychobiology of Depression (NIMH) demonstrated the probability of recurrence to be 67% after 10 years and 85% after 15 years. Other studies present recurrence rates ranging from 26.8%-33.5% over two years and 40%-60% over five years. While the course of depression is portrayed somewhat inconsistently in the literature, the general picture is as follows: of all people with a first episode of MDD, at least 45% experience recurrences, typically with seven to eight depressive episodes over the course of their lifetime and spending as much as 21% of their lifetime in a depressed condition. The risk of relapse and recurrence increases with every other episode. Based on these findings, MDD should perhaps no longer be considered as an episodic, but as a chronic and lifelong disorder for many people, with much of its disease burden stemming from its recurrent nature.

The disease burden associated with subtypes of depression (i.e. a single episode and a recurrent episode) has received remarkably little attention in research. Therefore, research question 1 of this thesis addresses the burden of disease per subtype of MDD (Chapter 2).

Risk factors for relapse

Possible risk factors for relapse and recurrence according to the American Psychiatric Association, are summarized in Table 2. Evidence for these predictors is inconsistent although the number of previous episodes and the level of residual symptoms have been found to consistently increase the risk of relapse and recurrence. There is growing recognition that recurrently depressed people often experience residual symptoms during remission; approximately one third of these people fails to achieve full remission, defined as an absence of symptoms for at least two months. ‘Partial remission’ is defined in numerous ways in the literature. Most commonly used is a 7-13 score on the Hamilton Rating Scale for Depression (HAM-D) but it is also frequently defined as the remitted state before full remission is achieved. Residual symptoms of depression probably reflect persistence of the original disorder in a milder form in partially remitted persons and cause significant functional impairment.
The information on course of depression and risk factors for relapse and recurrence can be used for ‘profiling and staging’, which is a diagnostic strategy that takes the heterogeneity of depression into account. By profiling (what risk factors for relapse or recurrence does a person have, e.g. prior history of multiple episodes of major depressive disorder or early age at onset) and staging (in which phase is a person: acute, remission or recovery), more targeted interventions can be offered, in an early stage, to depressed people.

What treatment works best for people with recurrent depression

As mentioned, the course of depression can be described as a series of disease stages. Treatment stages can be defined accordingly: acute-phase treatment is given to patients meeting the diagnostic criteria of MDD and its aim is to restore function and shorten episode duration, or equivalently, to promote remission. During remission, continuation treatment can be offered, which has the aim to sustain remission and to prevent relapse. Finally, during recovery, maintenance treatment can be offered, which has the aim to reduce the risk of recurrence (Figure 1). Similar to relapse, recurrence, remission and recovery, the terms continuation and maintenance are often used interchangeably in the literature.

Table 2. Risk factors for relapse and recurrence in MDD

<table>
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<tr>
<th>Risk factor</th>
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<tr>
<td>Prior history of multiple episodes of major depressive disorder</td>
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<td>Persistence of sub threshold depressive symptoms</td>
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<td>Severity of initial and any subsequent episodes</td>
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<td>Earlier age at onset</td>
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<td>Presence of an additional non-affective psychiatric diagnosis</td>
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<td>Presence of a chronic somatic medical disorder</td>
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<td>Family history of psychiatric illness, particularly mood disorder</td>
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<td>Ongoing psychosocial stressors or impairment</td>
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<tr>
<td>Negative cognitive style</td>
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<tr>
<td>Persistent sleep disturbances</td>
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1 American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)

Most people in the Western world who seek help for their acute depression, receive ADM. Not surprisingly, the most commonly used strategy to prevent relapse during remission is continuation of ADM. This is in line with guidelines of the National Institute of Health and Clinical Excellence (NICE), which recommend to encourage a person who has benefited from taking ADM in the acute phase to continue ADM for at least 6 months during remission on the dose that achieved remission. However, continuing ADM may not always be the preferred option. First, ADM may have side effects such as weight gain and loss of libido. Second, the optimal duration of the use of ADM has not been studied well enough. Third, there is divergent information on the relation between tapering ADM and relapse or recurrence. As a consequence, reported levels of non-adherence have been consistently high. Psychosocial interventions may therefore be a valuable alternative to ADM.
In various meta-analyses acute phase psychological interventions proved to have a sustained ‘prophylactic’ effect, that reduces the risk of relapse or recurrence\textsuperscript{1,66,67}. Still, there is a high proportion of people who experience a relapse or recurrence. Therefore, longer-term strategies, integrated into current longitudinal primary care systems, would fit better with the recurrent and chronic character of depression. Research demonstrates that psychological interventions, specifically aimed at the prevention of relapse and recurrence offered during the continuation- or maintenance phase, are effective in reducing the risk of relapse and recurrence\textsuperscript{20–23}. These interventions are mostly based on CBT, but add strategies such as modifying dysfunctional meta-cognitions in PCT\textsuperscript{68–70} and meditation in MBCT\textsuperscript{71–73}. The psychological interventions target issues untouched by pharmacological treatments such as awareness and understanding of the disorder, early identification of prodromal symptoms and coping skills. Therefore, they may enable individuals to take a more active role in the management of their disorder. NICE guidelines\textsuperscript{65} recommend that people with recurrent MDD who are considered to be at significant risk of relapse or recurrence should be offered one of the following psychological interventions: 1) individual CBT for people who have relapsed despite antidepressant medication and for people with a at least 3 depressive episodes and residual symptoms despite treatment or 2) MBCT for people who are currently in remission or recovery, but have experienced three or more previous episodes of depression.

The question we asked ourselves is what preventive psychological interventions currently exist for the prevention of relapse and recurrence, thereby including all types of interventions and all types of delivery modes (e.g. booster sessions and over the Internet). Furthermore, we are interested in what interventions works best. We addressed this research question, by conducting a meta-analysis on the effectiveness of existing preventive psychological interventions offered in the continuation or maintenance phase aimed at the prevention of relapse or recurrence in depressive disorder (Research question 2, Chapter 3).

**Economic consequences of recurrent depression**

MDD is one of the leading causes of health care expenditure. These substantial economic consequences of MDD are mainly due to its recurrent nature\textsuperscript{74–77}. The total annual cost of depression in Europe was estimated at €118 billion in 2004, which corresponds to a cost of €253 per inhabitant and 1% of the total economy of Europe\textsuperscript{78}. Treating MDD in the Netherlands costs almost a billion euro (€966 million) per year\textsuperscript{12}. Research has shown that depressed patients are more often absent from work (absenteeism) and work less effectively while being present at work (presenteeism) than non-depressed people\textsuperscript{27,79,80}. The costs of both absenteeism and presenteeism due to MDD are over €1,8 billion annually, in the Netherlands. The general tendency is that the costs due to depression are largely caused by costs due to lost productivity and that treatment costs comprise a smaller portion.
Besides a need for clinical evidence for the prevention of relapse, there is an additional need for economic evidence due to the current economic down-turn and an expenditure for mental health care that is unlikely to be sustainable\textsuperscript{13}. It is the combination of data on effects and costs that will inform decision makers, who are forced to allocate limited resources to interventions that maximise cost-effectiveness. Therefore, in Chapter 4, we assess the cost-effectiveness of existing psychological interventions to prevent relapse and recurrence in recurrent depression, compared to enhanced usual care (Research question 3).

The need for a low-cost preventive intervention in primary care

The emphasis on cost-effectiveness puts pressure on primary and secondary mental health care, to deliver high quality care at affordable cost. As a consequence, decision makers in the mental health care system are well aware of the need for organizational change. In the Netherlands, the government supports a shift of patients with mild mental problems from secondary care towards primary care by introducing a primary care mental health nurse and a ‘generalistic basic mental health care’ (basis GGZ). Technological developments, such as Internet and mobile apps, and patient-empowering may also play an important role here. In this dynamic environment, a cost-effective, preventive intervention for recurrent depression is sorely needed. Existing psychological interventions often rely on intensive use of therapist’s time in secondary care and are therefore costly. Primary care might be a better setting to offer preventive interventions\textsuperscript{81}. In the Netherlands, as in most western countries, it is the primary care professional who has regular contact with the vast majority of the population, knows about the patients’ social situation and provides low access, continuous care\textsuperscript{82}. Besides, the prevalence of patients with MDD or depressive feelings in primary practice is high, around 21\%\textsuperscript{25}. Therefore, a previously evaluated face-to-face PCT\textsuperscript{23,68} and mobile PCT\textsuperscript{70}, developed by Bockting et al, was redeveloped into a supported self-help PCT (S-PCT) offered in primary care to persons with a history of depression. Even over 10 years, face-to-face PCT in remitted people with multiple prior episodes, has shown preventive effects on time to recurrence, compared to usual care. Mobile PCT\textsuperscript{70} has shown a more favourable course over 3 months in the mobile CT group compared to usual care with regard to residual symptoms during remission. A barrier might be that primary care practitioners claim they do not have enough time to perform preventive services. Therefore, the self-help is supported by para-professionals like mental health nurses or social workers in primary care. Growing evidence shows that these para-professionals can effectively deliver self-help treatment protocols for depression, particularly in chronic care models\textsuperscript{83,84}.

First, we add S-PCT as hypothetical intervention to our health economic model in Chapter 4. We ask ourselves how effective this intervention needs to be, to become competitive in terms of its cost-effectiveness relative to existing psychological interventions.
Second, in order to evaluate the real-life effectiveness and cost-effectiveness of S-PCT, we conducted a pragmatic randomised controlled trial (RCT) - the Parade study - to evaluate this intervention. Details of this study are outlined in the next paragraph.

The PARADE-study; an economic evaluation alongside an effectiveness trial
In the PARADE-study, we made a comparison between usual care augmented with S-PCT, and usual care alone, in terms of terms of both their costs and effects\(^9\). (Research question 3, Chapters 5, 6, 7).

S-PCT is a manualised PCT-based bibliotherapy consisting of a printed self-help book with eight modules, with minimal guidance by a counsellor in primary care\(^8\). It is an adapted type of cognitive therapy for acute depression\(^7\) and aims to prevent relapse and recurrence in remitted people with a history of depressive episodes. Like regular CT, PCT follows a fixed structure, with agenda setting, review of homework, explanation of the rationale of each session, and the assignment of homework. Participants complete one module per week. Each module includes reading homework plus assignments to be completed in approximately 60 minutes. In the first meeting (by phone or face-to-face), the counsellor explained the rationale of PCT and coming week’s planning. Each week, the counsellor contacted the participant by phone to evaluate progress and understanding. This call was strictly protocolled and was designed to last no longer than 15 minutes. The nature of the contact was solely to support and counsel the participant and not to actively engage in a therapeutic relationship. Each week, the counsellor completed a checklist with 4 items; (1) the number of that week’s module (1-8), (2) did the participants read the literature of that week (yes/no plus reason), (3) did the participant do the assignments (yes/no plus reason) and (4) time spent on the call (minutes).

The PARADE-study is carried out among 248 persons with a history of depression, currently in remission or recovery, in the Netherlands. Primary outcome is the incidence of relapse or recurrence of depression over a 12-months follow-up period.

Outline of this thesis
In Chapter 2, data from the first wave of the second Netherlands-Mental-Health-Survey-and-Incidence-Study\(^8\) (NEMESIS-2) are used to estimate the non-fatal disease burden for both single episode and recurrent depressions. The estimates are assessed from an individual and a population perspective. The estimates are presented as unadjusted, raw estimates and as estimates adjusted for comorbidity. Chapter 3 presents a review with the aim to meta-analytically examine the effectiveness of psychological interventions aimed at the prevention of relapse or recurrence. The health-economic modelling study presented in Chapter 4 assesses how offering preventive psychological interventions would improve the cost-effectiveness of the Dutch health care system for depressive disorders.
Also, we addressed the question how effective a self-help Preventive Cognitive Therapy (S-PCT) needs to be, to become competitive in terms of its cost-effectiveness relative to existing psychological interventions. In Chapter 5 the study protocol of the PARADE-study is presented. This protocol includes a description of S-PCT and the procedure for recruiting people with a history of recurrent depressions, currently in remission. Chapter 6 evaluates the effectiveness of augmenting usual care with S-PCT compared with usual care alone at 12 months post baseline. Chapter 7 describes the cost-effectiveness and cost-utility of S-PCT compared with usual care.

In Chapter 8, we summarise the main findings, thereby answering the four 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.
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General introduction


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