

## Summary

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Major Depressive Disorder (MDD) is prevalent, has a high risk of relapse and recurrence and is therefore potentially, a chronic, lifelong illness for many people. MDD was the second leading cause of total burden of disease in 2010, 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. Due to the current economic downturn and an expenditure for mental health care that is unlikely to be sustainable, decision-makers seem to have become increasingly aware of the disease burden and healthcare costs that are associated with MDD. In order to stop the rhythm of recurrent MDD, prevention of relapse and recurrence should play a major role. The proactive management that is currently mostly used, continuation of antidepressant medication (ADM), may not be the most optimal strategy. Research demonstrates that preventive psychological interventions are also effective in reducing the risk of relapse and recurrence.

There are several knowledge gaps regarding recurrent MDD and the prevention of relapse and recurrence by psychological interventions in people with recurrent MDD. 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 **Chapter 2 (Research question 1)** we estimated the non-fatal disease burden of both single episode and recurrent depression, from both an individual and a population perspective. We used data from the first wave of the second Netherlands-Mental-Health-Survey-and-Incidence-Study (NEMESIS-2, n=6,646; *single episode DSM-IV depression*, n=115; *recurrent depression*, n=246). Results indicated that single depressive episodes emerged as a key driver of disease burden from an individual perspective. From a population perspective, recurrent depressions emerged as a key driver.

Our meta-analysis and meta-regression in **Chapter 3 (Research question 2)** provided more insight in the effectiveness of existing available psychological interventions, aimed at the prevention of relapse and recurrence in major depressive disorder. We systematically reviewed the pertinent trial literature until May 2014. A distinction was made between

R1 two comparator conditions: (1) treatment-as-usual and (TAU) (2) the use of antidepressants  
R2 (ADM). Twenty-five randomised trials met inclusion criteria. Preventive psychological  
R3 interventions were significantly better than TAU in reducing the risk of relapse or recurrence  
R4 and also more successful than ADM over 2 years, with a relative risk of 0.64 and 0.83,  
R5 respectively. Meta-regression showed that the preventive effect of psychological intervention  
R6 was usually better when the intervention was preceded by treatment in the acute phase.  
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R8 The aim of our study in **Chapter 4 (Research question 3)** was to investigate whether  
R9 offering preventive psychological interventions would improve the cost-effectiveness of  
R10 the Dutch health care system for recurrent MDD. A health economic model was used to  
R11 assess return on investments (ROI). We compared a base-case scenario (enhanced TAU)  
R12 with four scenarios in terms of cost-effectiveness: enhanced TAU plus A) cognitive therapy,  
R13 CT; B) mindfulness-based CT, MBCT; C) interpersonal therapy, IPT and D) a hypothetical  
R14 supported self-help based on PCT. Enhanced TAU is an evidence-based healthcare system  
R15 for depressive disorder in full agreement with the Dutch clinical guidelines for the treatment  
R16 of depression. The study showed that augmenting enhanced TAU (ROI=€1.30) with CT  
R17 (ROI=€1.43) or MBCT (ROI=€1.45) might make the healthcare system for recurrent  
R18 depression more cost-effective compared to enhanced TAU only. In order to reach the most  
R19 competitive ROI (€1.45), the supported self-help needs to reach a moderate relative risk  
R20 reduction (0.71).  
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R22 In **Chapter 5** we presented the design of the PARADE-study, a randomised controlled  
R23 clinical trial (n=248) with the aim to prevent relapse and recurrence in MDD. Participants  
R24 had a lifetime history of at least 2 depressive episodes and were remitted for at least 2  
R25 weeks at the start of the trial. Participants were randomised to receive either TAU (n=124)  
R26 plus our intervention or TAU alone (n=124). The intervention consisted of a supported Self-  
R27 help Preventive Cognitive Therapy (S-PCT) consisting of a printed self-help book with eight  
R28 modules, minimally supported by a counsellor. Participants were contacted weekly for the  
R29 course of 8 weeks to evaluate progress and understanding of the self-help. The follow-up  
R30 was 12 months.  
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R32 The effectiveness of S-PCT was presented in **Chapter 6 (Research question 4)**. S-PCT  
R33 significantly reduced relapse and recurrence over 12 months compared with TAU (risk-  
R34 difference 14%). Compared to the TAU group, the S-PCT group showed a significant  
R35 improvement in symptoms of depression and in quality of life (EQ-5D). The intervention  
R36 had no effect on co-morbid psychopathology, self-efficacy and quality of life based on the  
R37 SF12.  
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A cost-evaluation of S-PCT compared to TAU was presented in **Chapter 7 (Research question 4)**. Clinical outcomes, costs and incremental cost-effectiveness ratios were calculated both from a societal perspective and from a healthcare perspective. Mean total societal costs in the S-PCT group were higher than in the TAU group. Willingness-to-pay values should be quite high to reach an acceptable probability that S-PCT is considered cost-effective in comparison with TAU. Sensitivity analyses showed similar results.

Finally, **Chapter 8** provided an overview of the main findings in this thesis and answered the four research questions.

## INTERPRETATION AND EXPLANATION OF MAIN FINDINGS

### **The burden of disease of recurrent depression compared to single episode depression**

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. 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.

### **Effectiveness of preventive psychological interventions**

The results of our meta-analysis 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 TAU. However, previous research demonstrated that the effectiveness of MBCT and preventive C(B)T was limited to patients with a higher number of previous episodes. Our results, both from the meta-analysis and the RCT, 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**

As far as we know, we assessed the first modelling article on the cost-effectiveness of preventive psychological interventions. We found that adding CT or MCT might make the healthcare system for recurrent MDD more cost-effective than enhanced TAU. Assumptions in the model were conservative and that the base-case scenario is likely to be more effective than the current Dutch healthcare system. This implies that results might be more optimistic. With regard to real-life effectiveness, only few RCTs on the cost-

R1 effectiveness of preventive psychological interventions versus TAU and ADM have been  
R2 assessed and results of these studies are mixed.

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R4 **Supported self-help for recurrent depression**

R5 ***Effectiveness of S-PCT***

R6 Our study is the first showing that a self-help for remitted patients in primary care is effective  
R7 in preventing relapse and recurrence compared to TAU. The self-help in this study was  
R8 supported by primary care mental health nurses and clinical psychologists. Studies already  
R9 showed that mental health nurses are capable of providing high quality psychological  
R10 interventions in primary care. For several reasons, we think the type of counsellor might not  
R11 have impacted findings on a large scale.

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R13 ***Cost-effectiveness of S-PCT***

R14 The positive results of our modelling work did not correspond to the negative results of the  
R15 cost-effectiveness analysis (CEA) alongside the RCT. We found two explanations for these  
R16 different results. Pragmatic RCTs are designed to evaluate the effectiveness of interventions  
R17 in real-life routine practice conditions, whereas modelling studies aim to test whether an  
R18 intervention works under certain conditions. Another explanation may be the different cost-  
R19 price of S-PCT between the studies. As an obvious explanation for the higher costs in the  
R20 S-PCT group in the RCT is lacking, an explanation for the difference in results between the  
R21 modelling study and the CEA is also lacking.

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R24 **CLINICAL IMPLICATIONS**

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R26 Current guidelines on the prevention of relapse and recurrence recommend to encourage  
R27 a person who has benefited from taking ADM, to continue ADM for at least 6 months  
R28 after remission of an episode of depression. With respect to psychological interventions,  
R29 guidelines recommend to offer CBT to persons with a significant history of depression  
R30 plus residual symptoms, and MBCT to patients with a history of at least three episodes of  
R31 depression. Our studies confirm that C(B)T and MBCT should be offered to all remitted  
R32 persons, however, irrespective of the type of previous acute-phase treatment, the previous  
R33 numbers of depressive episodes (at least 2), and the level of residual symptoms. In addition,  
R34 IPT can be advised as well. Also, it is recommended to offer C(B)T, MBCT and IPT, directly  
R35 after the acute-phase treatment to increase effectiveness. Further, a self-help intervention  
R36 like S-PCT can be offered in primary care and might be an effective way for the prevention  
R37 of relapse and recurrence in persons with at least 2 depressive episodes, with or without  
R38 residual symptoms during remission or recovery. With respect to cost-effectiveness, CT and  
R39 MBCT could be recommended when added to usual care.

## FUTURE RESEARCH

Future trials on cost-effectiveness should extend follow-up, should evaluate what works for whom (by profiling and staging) and might adjust depression treatment goals to e.g. return to work or social activities despite residual depressive symptoms and should focus on understanding and addressing the facilitators and barriers to participation of eligible patients in relapse prevention interventions. Finally, as treatment strategies for prevention of relapse and recurrence of depression serve different goals, future studies should differentiate between relapse and recurrence whenever possible.



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