Summary
As described in Chapter 1, mental disorders are among the most disabling illnesses worldwide, and the associated burden is even expected to increase in coming decades. The studies in this thesis specifically focused on major depressive disorder and schizophrenia, both associated with wide ranging consequences for the lives of patients and their social environment. In addition, the economic consequences of mental illness are substantial as well. It has been estimated that between 2% and 5% of healthcare expenses in Western countries is spent on the treatment of depressive disorders and schizophrenia. In the last decades, decision-makers seem to have become increasingly aware of the burden and rising healthcare costs related to mental illness. Detailed information on economic aspects of interventions in mental healthcare was required for policy decisions. However, this information was practically absent for the Netherlands. The main objective of the studies presented in this thesis was therefore to assess the cost-effectiveness of various interventions focusing on patients with major depressive disorder and schizophrenia in the context of the Dutch healthcare system.

Although there are various treatment options available for people suffering from schizophrenia, most continue to have disabling residual symptoms and remain handicapped in social functioning. Hallucination focused Integrative Treatment (HIT) was developed to improve the well-being of patients with persistent auditory hallucinations by combining various treatment modalities. The cost-effectiveness analysis of HIT presented in Chapter 2 was an integral part of a clinical study on the effectiveness of HIT in patients with schizophrenia and persistent auditory hallucinations. The study compared two interventions; HIT and care as usual (CAU). Main outcome measure of the cost-effectiveness analysis was the aggregated score on the Positive And Negative Syndrome Scale (PANSS). The study was performed from a societal perspective. Costs and outcomes were registered prospectively during a period of 18 months. In total 63 patients were included in the study, 31 in the HIT group and 32 in CAU. Mean total costs per patient were $18,237 in the HIT group, and $21,436 in the CAU group. Total costs in both groups were largely influenced by the costs of sheltered accommodations and admissions to psychiatric hospitals. Results of the PANSS were more positive for the HIT intervention, but did not differ significantly from CAU. It was indicated that both costs and health outcomes were in favour of HIT, but a statistically significant cost-effectiveness advantage could not be found. Positive outcomes on additional clinical outcome measures could not directly be included in the conducted cost-effectiveness analysis. It was concluded that it seemed most likely that future application of the HIT intervention in patients with chronic schizophrenia would have positive economic consequences.
Many patients suffering from depression and anxiety disorders can not adequately be treated in secondary care due to a limited number of available therapists. Self-therapy interventions appear to be effective for various forms of mental illness and could provide a solution for this healthcare problem. The cost-effectiveness of Cognitive Self-Therapy (CST) in patients with depression and anxiety disorders was assessed in the study described in Chapter 3. The economic evaluation was part of an 18-month clinical study on the effectiveness of CST. In total 151 patients were randomly assigned to two intervention arms, CST (n=75) or treatment as usual (TAU, n=76). The economic evaluation was performed from a societal perspective. The primary outcome measure of the cost-effectiveness analysis was the Symptom Checklist 90 (SCL-90). Measurement took place at six-month intervals, starting at the time of inclusion until the end of the follow-up period 18 months later. Results indicated that the mean total costs during the entire study period were €4028 per patient in the CST group and €4837 per patient in the TAU group. Results of the SCL-90 showed improvements in both groups over time, differences between conditions were modest but in favour of CST. Additional analyses indicated that when decision-makers are willing to pay €100 per point improvement on the SCL-90, the probability that CST will be cost-effective increases up to 83%. It was concluded that CST appears to have positive economic consequences and could be applied to relieve the burden of many patients with depression or anxiety disorders who currently do not receive the necessary care due to a limited number of available therapists.

Major depression often runs a chronic-recurrent course and is highly disabling for patients. Recurrence is an important factor contributing to the substantial societal costs associated with depression, but only few (economic) studies specifically focused on the actual prevention of these recurrences. The study described in Chapter 4 examined the cost-effectiveness of a Psycho-Educational Prevention programme (PEP) aimed at depression in primary care settings in the Netherlands. Patients with depression were randomly assigned to four intervention arms; PEP only, PEP with psychiatric consultation (psychiatrist-enhanced PEP), PEP with cognitive behavioural therapy (CBT-enhanced PEP), and care as usual (CAU). Primary outcome measure in the cost-effectiveness analysis was the proportion of depression-free time. The economic analysis was performed from a societal perspective. Costs and health outcomes were registered at 3-month intervals during a period of 36 months. The Expectation Maximisation algorithm with a bootstrap approach was applied to handle missing data. Longitudinal analyses were based on the data of 226 patients. Mean estimated costs during the 36 months of the study were €8200 in the CAU group, €9816 in the PEP group, €9844 in the psychiatrist-
enhanced PEP group, and €9254 in the CBT-enhanced PEP group. Results of the primary health outcome in the basic PEP condition were worse than in the CAU group. In the psychiatrist-enhanced PEP and CBT-enhanced PEP groups, health outcomes were slightly better. It was concluded that the basic PEP intervention was not cost-effective in comparison with CAU. For the other variants of PEP, costs were higher and health outcomes were only slightly better. Results of this study seem to provide little support for the implementation of PEP in current healthcare systems.

Guidelines for the treatment of first episode psychosis generally recommend maintenance treatment, defined as the prolonged use of antipsychotic drugs following remission. Although this approach appears to be successful in preventing relapses, it is also associated with disabling side effects. Guided discontinuation strategy appears to be less intrusive, but is associated with more relapses. The economic evaluation presented in Chapter 5 compared the costs and health outcomes of discontinuation strategy with the results of maintenance treatment in patients with first episode psychosis. The included patients were randomly assigned to two treatment conditions, guided discontinuation strategy (n=65) and maintenance treatment (n=63). Subsequently, patients were prospectively followed for 18 months after a period of stable remission. The economic evaluation was conducted from a societal perspective. Quality-Adjusted Life Years (QALYs) were used as primary outcome measure. A wide range of secondary outcomes was also assessed, including relapse rates. Results indicated that there were no relevant differences between groups in terms of mean total costs during the main study phase of 18 months. Furthermore, no differences between groups were found for QALY results. The relapse rate in the discontinuation strategy group (42%) was twice as high as in maintenance treatment (21%). Discontinuation strategy did not lead to the advantages that were expected on other secondary outcomes. It was concluded that there were no indications that either of the examined medication strategies in first episode patients is superior to the other in terms of economic outcomes. For a minority of remitted first episode patients, guided discontinuation strategy could form a feasible alternative to maintenance treatment.

It is generally recommended to use preference-based health outcomes in economic evaluations, in particular Quality-Adjusted Life Years (QALYs). However, by far the most economic studies in mental healthcare were designed as cost-effectiveness analyses focusing on a specific aspect of health. Chapter 6 demonstrated the potentially negative consequences of (arbitrarily) choosing between outcome measures in mental healthcare. Data collected in the context of the HIT study
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(Chapter 2) was used for illustrative purposes. Economic analyses based on the initially selected single primary health outcome were compared to analyses based on various other relevant health outcomes assessed during the study, including social functioning, quality of life, and QALYs. Relevant and significant differences were identified on three of the four additionally assessed health outcomes, in contrast to moderate differences on the originally selected primary outcome. Cost-effectiveness analyses and acceptability curves were more strongly in favour of the HIT intervention when focusing on these three additional instruments. However, QALY results did not show relevant differences between groups, nor did additional economic analyses based on this outcome. It was concluded that the selection of a single primary outcome measure in cost-effectiveness analysis may lead to various problems in the field of mental healthcare. Decision-makers could be provided with incomplete and eventually incorrect information. It was suggested to use (disease-specific or generic) QoL instruments for assessing health outcomes in studies where the described problems may arise, at least until there is consensus on a valid preference-based instrument suited for mental healthcare.

In Chapter 7, an overview was provided of the main findings of the presented studies. Two of the four examined interventions were eventually recommended for reimbursement in the Dutch healthcare system. Furthermore, various methodological issues that seem highly relevant for economic evaluations in mental healthcare were discussed. These included the use of QALYs versus (disease-)specific outcome measures, power analyses and alternative study designs, length of follow-up periods, inclusion and quantification of productivity losses, and handling missing data in economic studies. Several suggestions for the design of economic evaluations in mental healthcare were formulated based on the discussed methodological issues. Recent (inter)national developments and outcomes of various other interventions studied in mental healthcare were discussed in light of the present findings. It seems that more (research) attention should be focused on the actual implementation of cost-effective interventions in mental healthcare, to optimise associated economic and clinical benefits for both society and patients involved.