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## Short-term psychotherapy for depression

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# Part IV

Conclusions and summary



# 10

General discussion

## Introduction

Major depressive disorder is a highly prevalent mental disorder characterized by depressed mood and markedly diminished interest or pleasure in (almost) all activities, which is both very impairing for the patient and carries a tremendous financial burden to society. Major depressive disorder can be treated with antidepressant medications and with psychological treatments, such as short-term psychodynamic psychotherapies (STPPs) and cognitive behavioral therapy (CBT). Psychodynamic psychotherapies are based on the notion that vulnerability to depression is created for an important part by early attachment relations and significant experiences in early childhood, which influence a person's perception of himself and others. Gaining insight into these patterns is considered to be curative in this psychotherapy method. CBT on the other hand, assumes that depression is caused and maintained by maladaptive thought schemata and by a lack of satisfactory activities. Changing these maladaptive schemata and errors in thinking in combination with engaging in more activities that affect mood positively is assumed to alleviate depressive symptoms in this psychotherapy method.

212 Since the early 1960s, studies have examined the efficacy of psychological treatments for depression and major advances have been made since. Psychological treatments have been found to be efficacious in the treatment of depression to about the same degree as antidepressant medications, with few differences in efficacy found between different psychotherapy methods. Nevertheless, the field of psychological treatment for depression outcome research is an evolving one with numerous issues unresolved and major research questions remaining to be answered. The main objective of this thesis is to broaden the field of psychological treatment for depression efficacy research by adding research findings to five issues in the field, which represent current and important topics in order to improve clinical practice. In this chapter, the main findings of this thesis with regard to each of these five topics are summarized, considering methodological issues that need to be taken into account when interpreting the findings. Next, the implications of the findings for clinical practice, policy making and future research are discussed, and the conclusions are stated.

## Key findings and methodological considerations

### Psychotherapy for depression in general

#### *A. It is unclear whether depression severity moderates efficacy*

Recent studies have suggested that the efficacy of antidepressant medication is moderated by depression severity, with antidepressants having clinically significant effects only for patients with more severe depressions (Khan, Leventhal, Kahn, & Brown, 2002; Kirsch et al., 2008; Fournier et al., 2010). With regard to psychological

treatment of depression, it is also believed that efficacy is moderated by depression severity, but in the opposite direction, such that psychological treatment has little effect on more severely depressed patients. However, the relation between pretreatment depression severity and psychological treatment outcomes has not yet been studied in depth systematically. The aim of this thesis was to conduct a study that systematically assessed whether pretreatment severity is related to the outcome of psychological treatment relative to controls conditions by means of different meta-analytic techniques (Chapter 2).

Chapter 2 describes a meta-analysis including 132 RCTs (totaling 10,134 participants) in each of which the effects of psychological treatment for adult outpatients with a depressive disorder or depressive symptoms were compared with a control condition. Meta-regression analyses showed no indication that pretreatment mean depression scores predicted psychological treatment versus control condition posttreatment effect size, but among the smaller subset of studies that reported within-study severity analyses, posttreatment effect sizes were higher for high-severity patients ( $d=0.63$ ) than for low-severity patients ( $d=0.22$ ) when psychological treatment was efficacious relative to a more stringent control. These latter findings suggest that the specificity of efficacy of psychological treatment for depression is higher for high-severity than it is for low-severity patients and are in line with what has been found with regard to antidepressant medication.

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The major strength of this study is that it systematically examined the relationship between pretreatment depression severity and psychological treatment outcomes in depth in a large set of studies. The main limitation of this study is that only a small number of studies reported within-study severity analyses, so that the abovementioned findings were based on a small subset of the total body of studies available. In sum, this thesis provides indications that the specificity of efficacy of psychological treatment for depression is higher for high-severity than it is for low-severity patients that need to be replicated.

### *B. Efficacy might be overestimated due to publication bias*

It has been shown that the efficacy of pharmacotherapy for depression has been overestimated due to selective publication of positive outcomes (Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008), also referred to as publication bias, but this has only been inferred with regard to psychological treatments for depression. This thesis aimed to do a true test for study publication bias with regard to the efficacy of psychological treatment for depression by identifying a cohort of studies and directly ascertaining the frequency with which studies conducted were not published. Moreover, this thesis aimed to provide an estimate of the efficacy of psychological treatment for depression adjusted for study publication bias by adding the unpublished findings to the published data (Chapter 3).

Chapter 3 reports the findings of a systematic review and meta-analysis of 38 United States National Institute of Health grants approved to conduct randomized controlled trials (RCTs) comparing psychological treatment to controls or other treatments in adult or geriatric patients diagnosed with major depressive disorder. Seven of the 36

funded grants that began trials did not result in publications and two others never started. Effect sizes were found to be significantly lower ( $p=0.04$ ) in unpublished ( $g=0.16$ ) than in published ( $g=0.50$ ) comparisons to control conditions, resulting in a 14% decrease in effect size when the two were pooled ( $g=0.43$ ). The proportion of unpublished psychological treatment trials (7/36=19%) did not differ from what has been found with regard to antidepressant medications (23/74=31%) ( $p=0.54$ ). These findings show that the efficacy of psychological interventions for depression when compared to control conditions has been overestimated in the published literature, just as it has been for pharmacotherapy. Both treatments are efficacious and specific, but not to the extent that the published literature would suggest.

The major strength of this study is that it provides a direct assessment of the extent of study publication bias (non-publication of studies) in the psychological treatment for depression literature, in stead of relying on an inferred estimate based on statistical procedures. The major limitation of the study is that it was not possible to ascertain the extent to which the published results might have been inflated by outcome reporting bias (inflation of published results) and our findings may overestimate the “true” effect of psychological treatment for depression as outcome reporting bias currently cannot be examined quantitatively.

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### *C. Equal efficacy is based on superiority rather than equivalence trials*

Different psychotherapy methods for depression are generally considered to be equally efficacious. At the same time, the psychotherapy efficacy literature is dominated by superiority trials, which are designed to show the superiority of one treatment over another and cannot demonstrate equal efficacy. This thesis aimed to add to the field of psychological treatment for depression outcome research by means of comparing CBT and STPP in the outpatient treatment of depression in an RCT employing a non-inferiority design from which non-inferiority of STPP to CBT can be demonstrated (Chapter 7).

Chapter 7 concerns an RCT comparing the efficacy of STPP with CBT in a group of 341 adult patients seeking treatment for major depressive episode in non-academic routine outpatient clinics. No statistically significant treatment differences were found for any of the outcome measures scores at both post-treatment and follow-up. Noninferiority of STPP to CBT was shown for post-treatment observer-rated as well as post-treatment patient-rated depression scores, but could not be demonstrated for post-treatment remission rates and any of the follow-up measures. A major strength of this study in this regard is that it was the first to apply noninferiority margins in a CBT to STPP comparison for depression, which allowed the examination of potential noninferiority of STPP to CBT. A limitation of the study in this respect is that, although noninferiority margins were carefully thought through and based on clinical expert opinion, they remain arbitrarily set. Although no significant differences were found on any of the outcome measures, noninferiority was not shown on all outcome measures, which underlines the notion that the absence of significant differences is not necessarily the same as equivalence or noninferiority.

## STPP for depression

### *D. STPP has a limited evidence-base*

When compared to other forms of psychotherapy for depression, such as cognitive behavioral therapy, there is a limited evidence-base for STPP, although this form of treatment is applied in clinical practice. In addition, although studies have provided initial support for the STPP variant short psychodynamic supportive psychotherapy (SPSP) in the outpatient treatment of depression, SPSP has not yet been directly compared to other forms of psychotherapy. It therefore remains unknown how SPSP compares to evidence-based psychotherapy methods. This thesis aimed to add to this issue by summarizing the available efficacy research with regard to STPP for depression in a meta-analysis (Chapter 4) and by comparing the efficacy of SPSP as a STPP variant with CBT in a randomized clinical trial (Chapters 6, 7, and 8).

Chapter 4 reports a meta-analysis of 23 studies examining the efficacy of STPP for depression totaling 1365 subjects. STPP was found to be significantly more effective than control conditions at post-treatment ( $d=0.69$ ). STPP pre-treatment to post-treatment changes in depression level were large ( $d=1.34$ ), and these changes were maintained until 1-year follow-up. Compared to other psychotherapies, a small but statistically significant effect size ( $d=-0.30$ ) was found, indicating the superiority of other treatments immediately post-treatment, but no significant differences were found at 3-month ( $d=-0.05$ ) and 12-month ( $d=-0.29$ ) follow-up. Studies examining individual STPPs ( $d=1.43$ ) found significantly larger pre- to post-treatment effect sizes than studies examining STPP in group format ( $d=0.83$ ), and no significant differences were found between individual STPP and other individual psychotherapies at post-treatment ( $d=-0.19$ ), 3- and 12-month follow-up ( $d=-0.05$  and  $-0.31$ ; all non-significant). These findings indicate that STPP is effective in the treatment of depression in adults and add to the evidence-base of STPP for depression.

The main strength of this meta-analysis is that, due to its thorough literature search and wide inclusion criteria, it provides a good overview of the total field of STPP for depression outcome research. However, the abovementioned results must be interpreted bearing in mind the limitations of the study and of the body of literature that it reviewed. Most importantly, the quality of the included studies was not optimal. Only 13 of the 23 included studies were RCTs and various studies lacked quality standards, such as employing a treatment integrity check or using a treatment manual. Although the meta-analyses' results including RCTs only were similar to the results of the meta-analyses including non-RCT studies as well and subgroup analyses revealed no indications that different quality criteria influenced effect sizes significantly, STPP efficacy estimates are based on studies with a rather low quality. Since low study quality has been associated with higher effect sizes in a meta-analysis of psychotherapy for depression studies (Cuijpers, van Straten, Bohlmeijer, Hollon, & Andersson, 2010), it is possible that the STPP effect sizes found in this study are overestimated. Secondly, STPP efficacy estimates are based on studies employing different STPP methods, with numbers of studies using the same STPP variant being too small to conduct subgroup analyses. Although subgroup analyses indicated no



significant differences between supportive and expressive STPP modes in term of efficacy, this meta-analysis' results might not generalize to any given STPP mode. Finally, this meta-analysis used depression level as the sole outcome measure. Reliable effect sizes could not be computed for other outcome measures due to the diverse use of these measures in the primary studies, but examining the efficacy of STPP on additional outcome measures (e.g., social functioning, personality functioning, general psychopathology, and quality of life) would be desirable.

Chapters 6, 7, and 8 describe an RCT comparing the efficacy of SPSP with CBT in a group of 341 adults seeking treatment for a major depressive episode in non-academic routine outpatient clinics. Post-treatment remission rates were 24.3% for CBT and 21.1% for SPSP. No statistically significant treatment differences were found for any of the outcome measures scores at both post-treatment and follow-up. Noninferiority was shown for post-treatment observer-rated as well as post-treatment patient-rated depression scores, but could not be demonstrated for post-treatment remission rates and any of the follow-up measures. These findings, which suggest that SPSP is not inferior to CBT on two out of three outcome measures at post-treatment and does not result in significantly different outcomes than CBT on the other outcome measures, add to the evidence-base of SPSP for depression. At the same time, these findings show that time-limited treatment is insufficient for a substantial number of patients encountered in non-academic routine outpatient clinics to reach remission.

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This study has a couple of strengths, the most important one being a number of aspects that add to the generalizability of this study's findings, such as the non-academic routine outpatient setting in which a large number of therapists with different experience levels treated patients with relatively low socio-economic statuses. Second, in terms of sample size this study is a large addition to the field of STPP for depression outcome research, including 341 participants. In comparison, the 6 CBT-STPP RCTs included in the abovementioned STPP for depression meta-analysis totaled 421 participants. Third, it is the first study that directly compares SPSP to another (evidence-based) psychotherapy for depression.

However, these study's findings must also be considered in the light of the limitations of the design. First of all, follow-up findings must be considered with caution, as help-seeking in the follow-up period was not controlled and a trend-level difference suggested that patients in the CBT condition might have sought more additional treatment during the follow-up period than patients in the SPSP condition. This might have suppressed differences favoring SPSP at follow-up. Secondly, this study has the following methodological limitations: 1) a substantial number of patients did not complete treatment or were lost to assessment, 2) treatment adherence was not assessed objectively, 3) HDRS assessors were not blind to patient grouping, 4) research assistants enrolling participants were aware of the allocation sequence, and 5) no control group was included, making it difficult to examine to what extent both of the treatments were more efficacious than no-treatment or non-specific factors.

With regard to the first limitation, we aimed to minimize the influence of attrition by means of applying statistical measures robust to missing data. With regard to limitations 2 to 4, we tried to assess the extent to which these factors might have

influenced results and a number of different sensitivity analyses that showed no indications that this was the case. Nevertheless, we cannot rule out the possibility that our findings were affected by observer bias or selection bias. With regard to the fifth limitation, we designed the study in such a way that it was similar to other studies that did compare CBT to a placebo-control condition in terms of inclusion criteria and treatment content in order to facilitate the comparison of findings. So that, if CBT in our study would result in similar outcomes as the CBT condition in those studies, it could be argued that CBT as conducted in our study might also be more efficacious than a placebo-control condition. However, we found lower remission rates in the CBT condition of our study than in the CBT conditions of these other studies using the similar remission criteria (21% in our study versus 36%-50% reported in Dimidjian et al., 2006, Elkin et al., 1989, DeRubeis et al., 2005). It is hard to make out what exactly caused these lower remission rates in our study, with options including the sample's relatively low socio-economic status and income levels as well as the use a large group of therapists with different experience levels. Notwithstanding the exact cause, the lower remission rates found make it difficult to make the case that both treatments in our study performed better than control conditions, especially in the light of a study recently published by Barber and colleagues (Barber, Barrett, Gallop, Rynn, & Rickels, 2012), in which the superiority of emotion-focused PDT over pill-placebo was not demonstrated.

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In conclusion, the findings of a meta-analysis summarizing the available research so far and an RCT comparing STPP to CBT both add to the evidence-base of STPP for depression. STPP was found more efficacious than control conditions and no significant differences between individual STPPs (including SPSP) and other psychotherapies (including CBT) were found. However, the quality of the studies on which these findings are based is suboptimal, which limits the interpretation of the findings. Furthermore, it is unclear to what extent these findings generalize to specific STPP types. Finally, the notion that SPSP is shown to be noninferior to CBT on some outcome measures and does not result in significantly different outcomes than CBT on the other outcome measures is currently based on one study with methodological limitations and without a control condition.

#### *E. It is unclear what factors moderate differential efficacy of STPP*

If studies comparing different psychotherapies for depression generally fail to find significant efficacy differences in larger patient samples (e.g., Cuijpers, van Straten, Andersson, van Oppen, 2008), the question can be raised as to whether specific types of patients might benefit from one treatment over the other. A useful distinction in this regard can be made between prognostic and prescriptive factors. Prognostic factors (or non-specific predictors of treatment outcome; Kraemer, Wilson, Fairburn, & Agras, 2002), predict outcome to a given treatment (or treatment in general) and can be used to determine which patients are more likely to respond to that given treatment relative to other patients. Although such prognostic factors can help shape expectations when starting treatment, they are of little use in deciding what treatment to select. On the other hand, prescriptive information (or moderators; Kraemer et al.,

2002) relate to different patterns of outcomes between different treatments for different types of patients and provide a basis for choosing the best treatment for a given patient.

With regard to prognostic factors associated with STPP efficacy, Van, Schoevers, and Dekker (2008), for instance, identified female gender, younger age, and duration of the depressive episode shorter than one year as prognostic factors associated with better response to psychodynamic therapy relative to patients of male gender, older age, and with longer episode duration. Similarly, it was reported in Chapter 2 that studies employing STPP in groups ( $d=0.83$ ) found significantly lower pre-treatment to post-treatment effect sizes than studies using an individual format ( $d=1.48$ ), suggesting that group format might be a prognostic factor with regard to STPP efficacy. However, a major limitation of that study is that moderator analyses in the context of a meta-analysis are observational and cannot be taken to imply causality. For example, it is possible that the lower effect size found in the subgroup of studies employing STPP in groups relative to studies examining individual STPP formats was due to the use of a different group format. However, it is also possible that the group of studies examining group-STPP differed in another systematic way (e.g., were more likely to include STPP as a “control condition” to compare another new therapy to) from the studies using an individual format and that the effect size difference was due to this factor.

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With regard to prognostic factors of CBT efficacy, Chapter 5 revealed that patients who are married, are younger, have higher intelligence levels or show low levels of pretreatment dysfunctional attitudes seem to be more likely to respond to CBT than patients who are unmarried or older, have lower intelligence levels or show high levels of dysfunctional attitudes. Depression chronicity and severity were also prognostic factors found to be associated with poorer response to CBT, while factors such as brief duration of the current episode, a later age of depression onset, an absence of family history of affective disorder, and a history of more previous episodes of depression were associated with good response to CBT.

Although research has focused on prognostic factors of STPP and CBT efficacy, little is known about prescriptive factors that are associated with differential efficacy to CBT and psychodynamic therapy for depression. Given the lack of research findings in this regard, the National Institute for Health and Clinical Excellence (NICE, 2009, p.46) called for the examination of moderators of response to CBT and psychodynamic therapy in the treatment of moderate and severe depression as a research recommendation in order to improve patient care. The aim of this thesis is to add to this aspect of psychotherapy for depression outcome research by means of trying to identify moderators associated with differential outcomes of STPP versus other psychotherapies in a meta-analytic review (Chapter 2). Furthermore, this thesis aims to identify factors associated with differential response to CBT or SPSP within the context of a randomized clinical trial (Chapter 9). In addition, prescriptive CBT moderator research is reviewed in Chapter 5.

In Chapter 5, unemployment, more antecedent life events, more previous antidepressant medication exposures, the absence of Axis II comorbidity, and being

married were found to be prescriptive factors associated with better response to CBT compared with medications. Furthermore, Chapter 5 reported consistent indications that presence of personality disorder dimensions may be prescriptive; although the exact nature of that prediction may depend on the specific comparison (CBT was found to be superior to IPT for patients with avoidant personality traits and inferior to antidepressant medication for patients with Axis II personality disorders). Finally, patients with lower levels of dysfunctional attitudes were found to do better in CBT relative to pill-placebo (but not to antidepressant medication). No findings with regard to prescriptive factors of differential efficacy to CBT compared with STPP were identified in Chapter 5.

Chapter 5 provides a narrative review of research examining predictive factors for CBT. A major strength of this paper is that it gives an overview of the findings of high-quality studies. Although it includes the most important studies in the field of CBT efficacy research known to the authors, it must be noted that this review was not based on a systematic literature search and that relevant studies might have been missed. Related, the summarizing conclusions are drawn qualitatively rather than quantitatively and it cannot be ruled out that publication bias left unpublished studies that found nonsignificant relations between CBT efficacy and the factors described above. Finally, the prognostic and prescriptive factors reported were typically found in small numbers of studies and need to be replicated before they can be used to guide treatment selection.

In Chapter 4, moderator analyses in the context of a meta-analysis are described in an effort to detect study, participant and intervention characteristics associated differential outcomes of STPP versus other psychotherapies. No significant relationship was found between any of the moderating variables examined and the effect size of STPP versus other psychotherapies at post-treatment. In addition to the strengths and limitations of this meta-analysis described in section D above, it can be noted in this regard that this study is the first which conducts subgroup analyses in order to identify STPP treatment moderators for depression. An additional major limitation is that the power of subgroup analyses and meta-regression analyses is often low and that failure to detect significant findings cannot be taken to imply that there is no relationship between the effect size and the factor examined. Furthermore, the efficacy of STPP was compared to a combination of different other psychotherapies, which might have obscured possible prescriptive relations between STPP and a specific type of other psychotherapy (e.g., CBT).

In Chapter 9, potential prescriptive factors associated with differential efficacy of CBT and SPSP were examined. While treatment differences were minimal in the total sample of patients ( $d=0.04$ ), model-based recursive partitioning indicated differential treatment efficacy in certain subgroups of patients. Psychodynamic therapy was found more efficacious among moderately depressed patients receiving psychotherapy only that showed low baseline comorbid anxiety levels ( $d=-0.40$ ) and among severely depressed patients receiving combined treatment that reported a duration of the depressive episode of one year or longer ( $d=-0.31$ ), while cognitive behavioral therapy was found more efficacious for such patients reporting a duration shorter than one

year ( $d=0.83$ ). In addition to strengths of the RCT described in section D above, strengths of this study are that it is one of few examining prescriptive factors associated with differential efficacy of CBT and psychodynamic therapy for depression, that it is the first that considered demographic and illness characteristic as potential prescriptive factors, and that it is the first to apply model-based recursive partitioning in this regard, which provides the benefits of reducing the number of prescriptive factors and selecting the most important ones. The most important limitation of this study is its post-hoc nature. The findings are observational and can be the consequence of chance findings in the sample studied. They should, therefore, be validated before being used to guide treatment selection.

In sum, a number of factors have been associated with prescriptive CBT efficacy when compared to with medications, IPT and pill-placebo, but not in comparison with STPP. When moderator analyses were applied in the context of a meta-analysis, no prescriptive factors associated with differential efficacy of STPP and other psychotherapies were found, but given the low power of these analyses and the combined other psychotherapies examined, it cannot be ruled out that other prescriptive factors are related to STPP efficacy in comparison with other specific psychotherapies. Post-hoc analyses alongside a randomized clinical trial suggested comorbid anxiety level and depressive episode duration as possible prescriptive factors associated with differential efficacy of CBT and SPSP. These findings are observational and need validation before they can be used to guide treatment selection, but suggest that knowledge of prescriptive factors can help improving the efficacy of psychotherapy for depression.

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## Recommendations for clinical practice and policy making

The findings presented in this thesis have implications for public health and science policy making as well as for clinical practice and lead to the following five recommendations in this regard.

### **Clinicians, guidelines developers, and decision makers should be aware of overestimated effects of both the predominant treatments for depression**

The findings presented in Chapter 3 show that the efficacy of psychological interventions for depression when compared to control conditions as reflected in the published literature is overestimated due to study publication bias, as is the case for antidepressant medication. Both psychotherapy and antidepressant medication are efficacious in the treatment of major depression, but not to the extent that the published literature would suggest. Clinicians, guideline developers and policy makers, who base their decisions upon (systematic reviews or meta-analyses of) published findings should be aware of the overestimated effects of both the predominant treatments for depression.

**Third party payers and policy makers need to contemplate on the current pressure to limit depression treatment duration.**

The findings presented in Chapter 7 show that less than a quarter of the patients treated for a major depressive episode achieved remission after 22 weeks of CBT or SPSP treatment, with 40% seeking additional treatment afterwards. Similar remission rates have been reported for major depressive disorder after individual psychotherapy in routine clinical practice (27%; van der Lem, van der Wee, van Veen, & Zitman, 2012). These findings indicate that the majority of patients encountered in non-academic routine outpatient clinics require more than a time-limited treatment to achieve remission and show that depression, as it is encountered in Dutch secondary care, can be characterized as a difficult-to-treat disorder. As residual depressive symptoms have been found to be a predictor for future relapse (Paykel, 1998), the majority of patients would have been undertreated if not provided additional health care.

At the same time, there is a trend towards shortening depression treatment duration in (Dutch) public health care stimulated by third party payers. Although efforts to increase the efficiency of depression treatment can only be supported in the light of both the increasing health care costs and in order to decrease patient suffering, our findings underline that clinicians and policy makers ought to be modest about the expected outcome of time-limited depression treatments for major depression. In effect, third party payers currently mandate limits on duration that may lead to the under-treatment of depression.

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**High-quality research aimed at improving psychotherapy outcomes should be stimulated and financially supported.**

The findings presented in Chapter 7 show that less than a quarter of patients suffering from a major depressive episode encountered in a Dutch non-academic routine outpatient clinics are free of depressive symptoms after 22 weeks of CBT or SPSP treatment. Although the remission rates found in these studies are lower than found in other studies (Dimidjian et al., 2006, Elkin et al., 1989, de Jonghe et al., 2004), even high-quality studies with well-trained therapists do not report CBT remission rates higher than 50% (Dimidjian et al., 2006, Elkin et al., 1989, DeRubeis et al., 2005) and the same is true for antidepressant medication (Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). Given the high prevalence of the disorder and the increasing societal costs associated with it, these findings indicate that there is an urgent need to improve psychotherapy for depression outcomes. High-quality research aiming to do so should be stimulated and financially supported by governmental and public health institutions.

**Raw data from any psychotherapy for depression treatment trial should be archived**

The study described in Chapter 3 found that the efficacy of psychological interventions for depression when compared to control conditions as presented in the published literature is overestimated due to study publication bias and aimed to provide an estimate of the efficacy of psychological treatment for depression adjusted for study

publication bias (non-publication of studies). Although it was possible to provide such an estimate, we do not know to what extent this estimate reflects the “true” effect of psychological treatment for depression as this estimate might be overestimated due to outcome reporting bias (inflation of published results).

In order to assess the “true” effect of psychological treatment for depression both study publication bias and outcome reporting bias need to be assessed. The latter can be done qualitatively by comparing the methods proposed in study or grant protocols to those described in the publications to determine whether *a priori* plans had been followed, as is the aim of trial registries where a study protocols are collected that were provided before a trial started. Outcome reporting bias also can be assessed quantitatively by comparing outcomes of analyses done by an independent party using the study’s raw data to the published outcomes, as is the aim of the US Food and Drug Administration (FDA) repository for industry-funded pharmacotherapy trials. To be able to assess the “true” effects of psychotherapy for depression, our field will need more than just a clinical trials registry, it will need a data repository for psychotherapy trials similar to that of the FDA. Recommendations that funding agencies or journals should archive both original protocols and raw data from any trial (Alsheikh-Ali, Qureshi, Al-Mallah, & Ioannidis, 2011; Chan et al., 2006; Perneger, 2011; Smith & Roberts, 2006; Vickers, 2011) should also apply for studies examining the effects of psychological treatments for depression.

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The study described in Chapter 2 of this thesis provided indications that the specific efficacy of psychological treatment for depression is higher for high-severity than it is for low-severity patients. In addition, findings presented in Chapter 5 and Chapter 9 suggest that patient characteristics, such duration of the depressive episode and levels of comorbid anxiety levels, might be related to differential efficacy of psychotherapies. The main limitation of these studies is that these findings are based on a small number of studies. As replication of these findings in a larger set of studies could have important implications with regard to the treatment of depression, the question of moderation deserves further study and could be addressed by pooling data for individual patients from multiple randomized controlled trials in a mega-analysis. Archived and publically available raw patient-level data would provide the opportunity to do so.

### **The level of evidence for STPP can be raised to the highest level.**

The findings presented in Chapter 4, show that STPP is superior to control conditions at post-treatment and indicate that STPP is effective in the treatment of depression in adults. In addition, STPP pre-treatment to post-treatment changes in depression level were found to be large and these changes were found to be maintained through 1-year follow-ups. The findings all add to the evidence-base of STPP for depression.

The National Health and Medical Research Council (NHMRC; 1998) has provided criteria for levels of evidence for treatment methods as rated in clinical practice guidelines ranging from Level I (systematic review of all relevant randomized controlled trials) to Level V (expert opinion). Malhi et al., (2009) have rated the strength of evidence for STPP at Level II (one or more properly designed randomized

controlled trial) in their clinical practice recommendations for depression. However, as argued by Abbass and Driessen (2010), publication of the study presented in Chapter 2 may result in increasing the level of evidence for STPP in the treatment of depression to Level I.

## Recommendations for future research

In addition to implications for public health and science policy making, and clinical practice, the findings presented in this thesis also indicate a number of directions for further study. The following recommendations for future research can be made with regard to psychotherapy for depression in general and with regard to STPP for depression.

### Psychotherapy for depression in general

The findings presented in this thesis and from other high-quality studies of CBT and antidepressant medication (Dimidjian et al., 2006, Elkin et al., 1989, DeRubeis et al., 2005; Warden et al., 2007) show that less than half of the patients reach depression remission during short-term treatment. Given the high prevalence of the disorder and significant patient impairment as well as the increasing societal costs associated with it, these findings indicate that there is an urgent need to improve psychotherapy outcomes. A number of recommendations for future research in this regard can be made based on the findings of this thesis.

Findings presented in Chapter 2 provide indications that the specificity of efficacy of psychological treatment for depression is higher for high-severity than it is for low-severity patients that need to be replicated and might have important implications for the treatment of depression. These findings call for the inclusion of more severely depressed patients and stringent control conditions in trials examining the efficacy of psychological treatment for depression, stratification with regard to pre-treatment depression severity, and routinely testing severity-by-treatment interactions. The findings presented in Chapter 3 indicate the importance of publishing non-significant findings of psychological treatment to control condition comparisons, in the absence of a trial registry for raw data of psychotherapy RCTs. Although investigators or journal reviewers might consider such findings ‘not interesting’, they are of crucial importance in order not to overestimate the effects of psychological treatments for depression in general and in order to increase our knowledge of which specific types of psychotherapy might not work (for specific patient populations).

Research reviewed in Chapter 5 and the findings presented in Chapter 9 indicate that, while few efficacy differences have been found between different treatments for depression (psychotherapy versus psychotherapy as well as antidepressant medication versus psychotherapy), differential efficacy can be apparent in certain subgroups of patients. However, research in this regard needs replication and validation, before these potential prescriptive factors can be used to guide treatment selection. The field would benefit from RCTs routinely conducting hypothesis-generating examinations of



potential prescriptive factors (Kraemer et al., 2002). More importantly, future RCTs comparing psychological treatments or comparing psychotherapy with antidepressant medications need to use the known potential prescriptive factors as stratification variables and perform a priori specified tests to demonstrate potential moderation of variables (Kraemer et al., 2002). Such comparative studies should be based on a non-inferiority or equivalence design, so that non-significant differences can be differentiated from non-inferiority or equivalence of treatments.

In addition to optimizing psychotherapy for depression outcome by means of identifying subgroups of patients for which these treatments are particularly (in)effective, further study of working mechanisms through which the efficacy of different psychotherapies is realized is necessary. As described in Chapter 5, research examining mediators of CBT has been done, but causality has not been sufficiently demonstrated. Finally, research reviewed in Chapter 5 and the findings presented in Chapter 7 provide indications that efficacy of CBT, which is currently the most widely used psychotherapy for depression, can vary in relation to the skill with which it is implemented. Studies reporting the best CBT outcomes have typically selected experienced therapist, while studies that depended on more limited training typically produced less impressive findings. Therapist competence is even less likely to be assured in non-research settings. How much psychotherapy training and supervision is required to implement CBT optimally and whether this varies as a function of patient difficulty are issues that deserve further study in order to improve patient care.

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### **STPP for depression**

Although the findings presented in this thesis add to the evidence-base of STPP for depression and it can be argued that the level of evidence for this treatment method might be increased as a result of that, STPP is currently not a recommended psychotherapy in guidelines for the treatment of depression. In addition, the argument presented by Connolly-Gibbons, Crits-Christoph, and Hearon (2008) that STPP for depression does not meet the criteria for empirically supported psychological treatments formulated by Chambless and Hollon (1998) due to different STPP types studied and methodological quality of studies, still holds in the light of the findings presented in this thesis. At the same time, the findings with regard to the efficacy of STPP for depression presented in this thesis are promising and deserve further study.

In order to merit designation as an empirically supported treatment and to be included as a recommended psychotherapy in guidelines for the treatment of depression, more high-quality studies are necessary that assess the efficacy of the STPP variants compared to antidepressant medication and evidence-based psychotherapies such as interpersonal therapy (IPT) and CBT. Such trials should 1) apply rigorous methodological standards conform the CONSORT statement (CONSORT Group, 2010) including but not limited to concealment of allocation sequence, concealment of treatment condition to outcome assessors, objective assessment of treatment adherence; 2) include (more stringent) control conditions; 3) include non-inferiority or equivalence design if STPP is compared to another active treatment; 4) stratify with regard to pre-treatment depression severity and test for severity-by-STPP

interactions; 5) stratify with regard to comorbid anxiety level and episode duration (or any other known potential prescriptive factors) when comparing STPP to CBT and test for these moderator-by-treatment interactions; 6) include follow-up assessments; 7) include outcome measures other than depression, such as social functioning, personality functioning, general psychopathology, and quality of life; and 7) aiming to minimize patient drop-out. Again, in the absence of a trial registry for raw data of psychotherapy RCTs, any non-significant findings from such trials should be published.

As the more supportive STPP variants seem currently to be ones most often tested in empirical outcome research (Van, Driessen, & de Maat, 2012), the field would also benefit from studies examining the efficacy of the more expressive STPP types. The evidence-base of the STPP variant SPSP specifically would be further supported by replication of the trial described in this thesis by another research group that meets the abovementioned standards. Furthermore, it has been argued that, albeit different names, some STPP types might be very similar in terms of content and demonstrating that this is the case for two STPP methods, which have had their efficacy demonstrated in trials with adequate research methods by different research groups, would contradict the argument presented by Connolly-Gibbons et al. (2008).

In addition to the need for more high-quality research to support the evidence-base of STPP for depression, the field of STPP efficacy research needs further broadening. In Chapter 5, for instance, research regarding CBT to prevent relapse or recurrence was reviewed. To date only cognitive and behavioral interventions have found to have enduring effects, largely because other psychological treatments have gone untested in this regard. As psychodynamic therapy also aims at reducing vulnerability to depression, it seems worthwhile to examine its potential enduring effects when compared to CBT and antidepressant medication. Chapter 5 also reviewed CBT mediator research. This type of research needs to be further explored with regard to SPSP. Furthermore, providing psychological treatment by means of internet-guided self-help has the potential benefits of reaching patients who are less inclined to seek help in general mental health care and of reducing costs by requiring less therapist time. While a number of psychological treatments for depression, including CBT, have been studied extensively as internet-guided self-help for depression, STPP has not been one of them, presumably because it has been long thought that psychodynamic therapy could not be provided by means of internet. However, a first trial in this regard showed promising results comparing internet STPP to an active control group (Johansson et al., 2012). Given the benefits of internet-guided self-help relative to face-to-face treatment, this field of research deserves further exploration.

## Conclusions

This thesis aimed to add research findings to five current issues in the field of psychotherapy for depression outcome research, which resulted in the following main findings and recommendations for clinical practice, public health and policy making, and future research.

A) This thesis provided indications that the specific efficacy of psychological treatment for depression might be higher for high-severity than it is for low-severity patients that might have important implications for clinical practice, but that need to be replicated in (a mega-analysis of multiple) randomized controlled trials.

B) The findings included in this thesis show that the efficacy of psychological treatments for depression when compared to control conditions has been overestimated in the published literature, just as it has been the case with regard to antidepressant medication. Clinicians, guidelines developers, and decision makers should be aware of overestimated effects of both of the predominant treatments for depression. At the same time, the findings reported in this thesis may still overestimate the “true” effect of psychological treatment for depression as outcome reporting bias in psychotherapy for depression outcome research currently cannot be examined quantitatively. Both original protocols and raw data from any psychological depression treatment trial should be archived in order to facilitate this assessment.

C) This thesis showed that the absence of significant differences is not necessarily the same as equivalence or noninferiority of psychological treatments of depression, suggesting that non-inferiority or equivalence designs should be applied when comparing active treatments in this regard.

226 D) The findings of this thesis add to the evidence-base of STPP for depression in general and SPSP in particular. STPP was found to be more efficacious than control conditions and no significant differences between individual STPPs (including SPSP) and other psychotherapies (including CBT) were found. However, the suboptimal quality of the studies on which these findings are based, limit their interpretation. Furthermore, it is unclear to what extent these findings generalize to specific types of STPP. As a result of these findings, the level of evidence for STPP can be raised to the highest level, but more high-quality research is needed before STPP will be included as a recommended psychotherapy in guidelines for the treatment of depression. Additionally, the evidence-base of the STPP variant SPSP needs further support by replication of the trial described in this thesis by another research group applying rigorous methodological standards. Finally, STPP efficacy research needs further broadening, for instance by examining its enduring effects and the option of providing STPP through internet.

E) Comorbid anxiety level and depressive episode duration have been found possible prescriptive factors associated with differential efficacy of CBT and SPSP. These findings are observational and need validation before they can be used to guide treatment selection, but suggest that knowledge of prescriptive factors can help improving the efficacy of psychotherapy for depression and should be routinely examined in future clinical trials or mega-analyses of such studies.

In addition, the findings presented in this thesis show that time-limited treatment is insufficient for a substantial number of patients treated for depression. These findings indicate that third party payers and policy makers need to contemplate on the current pressure to limit depression treatment duration as this might lead to under-treatment. Given the high prevalence of the disorder and the significant impairments for patients as well as the increasing societal costs associated with it, these findings indicate an

urgent need to improve the efficacy of psychotherapy for depression. High-quality research aimed at doing so should be stimulated and financially supported.

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