Short-term psychotherapy for depression

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Summary

Part I
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 medication and psychological treatment, such as short-term psychodynamic psychotherapy (STPP) and cognitive behavioral therapy (CBT). Psychodynamic psychotherapies are based on the notion that vulnerability for 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 in these patterns is considered to be curative in this psychotherapy method. Cognitive behavioral therapy, on the other hand, assumes that depression is caused and maintained by maladaptive thought schemata and that changing these schemata and errors in thinking will alleviate depressive symptoms.

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 minimal differences found between the different types of psychotherapy. 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 of depression research, which represent current and important topics that can help improving clinical practice. Three of these issues relate to the efficacy of short-term psychotherapy for depression in general:

A) It is unclear whether depression severity moderates efficacy;
B) Efficacy might be overestimated due to publication bias;
C) Equal efficacy is based on 'superiority' rather than 'equivalence' trials.

The other two issues relate to the efficacy of STPP for depression specifically, as STPP is less extensively studied than other psychotherapies for depression:

D) STPP has a limited evidence-base;
E) It is unclear what factors moderate differential efficacy of STPP.

Part II
Reviews and meta-analyses

The first half of the thesis comprises four chapters that examine different research questions with regard to the abovementioned issues A, B, D, and E by means of (systematic) reviews and meta-analyses of available outcome research.

In **Chapter 2**, the possibility of a moderating relationship between pretreatment depression severity and the outcome of psychological treatment for depression is studied in depth by means of meta-analytic techniques (Issue A). The meta-analyses described in this chapter were based on 132 studies (encompassing 10,134 participants) in which the effects of psychological treatment for adult outpatients with a depressive disorder or an elevated level of depressive symptoms were compared with a control condition in a randomized controlled trial. Meta-regression analyses were conducted assessing whether mean pretreatment depression scores predicted psychological treatment versus control condition posttreatment effect size and provided no indications that this was the case. However, subgroup analyses summarizing the results of studies reporting within-study analyses of depression severity and psychological treatment outcome showed that 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 findings suggest that the specific efficacy of psychological treatment for depression might be higher for high-severity than it is for low-severity patients.

The extent of study publication bias in the psychological treatments for depression efficacy research is assessed by means of a systematic review and meta-analysis in **Chapter 3** (Issue B). In this study, United States National Institute of Health grants intended to fund randomized controlled trials comparing psychological treatments to control conditions or other treatments in patients diagnosed with major depressive disorder for the period 1972-2000 were identified and it was examined whether those grants led to publications. For studies that were not published, data were requested from investigators and included in the meta-analyses. In addition, the proportion of grants with unpublished findings was compared with the reported proportion of unpublished antidepressant studies. Seven of the 36 (19%) funded grants did not result in publications. Effect sizes were significantly lower in the unpublished (g=0.16) than in the published (g=0.50) comparisons to control conditions, resulting in a 14% decrease in effect size when the unpublished studies were added to the published ones (g=0.43). The proportion of unpublished psychological treatment trials (7/36=19%) did not differ from antidepressant medications (23/74=31%) (p=0.54). These findings indicate that study publication bias appears to be as much a problem for psychological treatment trials as it is for antidepressant trials and that the efficacy of both of the predominant treatments of depression when compared to control conditions is overestimated.

Chapter 4 reports a meta-analytic review of the efficacy of psychodynamic treatment for depression and efforts to identify moderating factors of this efficacy (Issues D and E). This meta-analysis included 23 studies 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 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 STPP (d=1.48) found larger pre- to post-treatment effect sizes than studies examining group STPP (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). In addition, no significant difference in effect sizes were found between supportive and expressive STPP modes (*d*=1.36 and *d*=1.30, respectively). These findings provide indications that STPP is effective in the treatment of depression in adults and add to the evidence-base of STPP for depression.

Finally, an overview of research concerning the efficacy of CBT for depression, and moderators and mediators of this efficacy is provided by a narrative review in **Chapter 5** (Issue E). It is concluded that CBT has been found superior to control conditions and at least as efficacious as other psychotherapies and antidepressant medication in the acute treatment of depression. It is argued that, when adequately implemented, CBT can be as efficacious as antidepressants for patients with more severe depressions and that CBT also may be of use as an adjunct to medications in the treatment of bipolar disorder, although the evidence in that regard is not so clear or extensive. With regard to enduring effects, CBT reduces relapse/recurrence rates, with a magnitude of effect that might be comparable to keeping patients on medications. Research regarding moderators of CBT efficacy found that patients who are married or show low levels of pretreatment dysfunctional attitudes seem to be more likely to respond to CBT than patients who are unmarried or show high levels of dysfunctional attitudes. Unemployment, more antecedent life events and previous antidepressant medication exposures, and the absence of Axis II comorbidity are prescriptive factors associated with better response to CBT than to medications. Research targeting mediation of CBT efficacy indicated that CBT seems to work through concrete cognitive therapy-specific strategies and may be mediated by changes in cognition as specified by theory, although it remains unclear whether it is necessary to deal directly with cognition to produce those changes.

Part III
A randomized clinical trial

The second half of this thesis consists of four chapters examining research questions with regard to the abovementioned issues C, D, and E in the context of a randomized clinical trial comparing the efficacy of short psychodynamic supportive psychotherapy (SPSP) and CBT in the outpatient treatment of depression. In **Chapter 6,** the protocol of this study is described. The aim of this study is, first, to compare SPSP and CBT in terms of acceptability, feasibility, and efficacy, and, second, to identify clinical predictors that distinguish patients that can benefit from either of these treatments in particular. In this study, adult outpatients, referred to one of three non-academic mental health clinics by their general practitioner that meet DSM-IV criteria for a major depressive episode and have moderate to severe depressive symptoms

(*Hamilton Depression Rating Scale* score ≥ 14) are randomly allocated to SPSP or CBT. Both treatments are individual psychotherapies consisting of 16 sessions within 22 weeks. Severely depressed patients (HDRS>24) received additional antidepressant medication according to protocol. Assessments take place at baseline (week 0), during the treatment period (week 5 and 10) and at treatment termination (week 22). In addition, a follow-up assessment takes place one year after treatment start (week 52). The main outcome measure is the number of patients with depressive symptoms in remission (HDRS<8) at the termination of psychotherapy at week 22.

In **Chapter 7**, the observer-rated and patient-rated outcomes of this study are presented, hypothesizing non-significant differences and noninferiority of SPSP to CBT (Issues C and D). In this chapter, outcome data of 341 participants were analyzed with generalized estimating equations and mixed model analyses using intention-to-treat samples. Noninferiority margins were pre-specified as odd's ratio (OR) of 0.49 for remission rates and Cohen's *d* of 0.30 for continuous outcome measures. Post-treatment remission rates were 24.3% for CBT and 21.1% for SPSP (OR=0.82; 0.45-1.50). No statistically significant treatment differences were found on any of the outcome measures. Noninferiority was shown for post-treatment mean depression scores, but could not be demonstrated for post-treatment remission rates and follow-up measures. These findings extend the evidence-base of STPP for depression, but also show that time-limited treatment is insufficient for a substantial number of patients encountered in non-academic routine outpatient clinics.

Therapist-rated outcome measures are then reported in **Chapter 8** (Issue D). Two therapist-rated outcome measures for symptom severity indicated a linear symptom decrease, while the one measure assessing improvement when compared to treatment start suggested an S-shaped curve indicating relative more improvement the first and last phases than in the middle phase of treatment. Again no significant post-treatment differences were found on any of the three therapist-rated outcome measures, adding to the evidence-base of STPP for depression.

Finally, **Chapter 9** describes efforts to identify factors associated with differential response to CBT or SPSP (Issue E). 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). If validated, these variables might be used to guide treatment selection, which might improve the efficacy of psychotherapy for depression.

Part IV
Conclusions

The thesis is concluded with a general discussion of the main findings, their limitations and implications in **Chapter 10**, which results in the following conclusions with regard to the five issues examined.

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.

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. Furthermore, they indicate that efficacy of psychotherapy for depression needs to be improved and high-quality research aimed at doing so should be stimulated and financially supported.