

Psychological treatment of depression compared with pharmacotherapy and combined treatment in primary care: A network meta-analysis

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Abstract (224 words)

Purpose. Most patients with depression are treated by general practitioners, and the majority of those patients prefer psychotherapy over pharmacotherapy. No network meta-analysis has yet examined the effects of psychotherapy compared with pharmacotherapy, combined treatment, care-as-usual and other control conditions in primary care patients.

Methods. We conducted systematic searches in bibliographic databases to identify randomized trials comparing psychotherapy with pharmacotherapy, combined treatment, care-as-usual, waitlist and pill placebo. Main outcome was treatment response (50% improvement of depressive symptoms between baseline and endpoint).

Results. A total of 58 studies with 9,301 patients were included. Both psychotherapy and pharmacotherapy were significantly more effective than care-as usual (Relative Risk [RR] for response: 1.60; 95% CI 1.40~1.83 and 1.65; 1.35 to 2.03, respectively), and waitlist control groups (RR: 2.35; 95% CI: 1.57~3.51 and 2.43; 1.57 to 3.74, respectively). We found no significant differences between psychotherapy and pharmacotherapy (RR: 1.03; 95% CI: 0.88~1.22). The effects were significantly larger for combined treatment compared with psychotherapy alone (RR: 1.35; 95% CI: 1.00~1.81). The difference between combined treatment and pharmacotherapy became significant when limited to studies with low risk of bias and studies limited to CBT.

Conclusions. Psychotherapies are probably effective in the treatment of depression when compared to care-as-usual and waitlist control groups. The effects are comparable to those of pharmacotherapies. Combined treatment may be better than either psychotherapy or pharmacotherapy alone.

Keywords: depression; major depression; primary care; psychotherapy; cognitive behavior therapy; network meta-analysis.

Introduction

Hundreds of randomized trials have examined the effects of pharmacological and psychological treatments of depression.^{1,2} However, only relatively few trials have focused on primary care, while the majority of depressed patients is treated in primary care.^{3,4} The results found for treatments across varying settings may, however, not be valid in primary care patients.

Antidepressant medication and psychotherapies have small, positive effects on depression. Both treatments have comparable effects in primary care.⁵ At the longer term psychotherapies may have better outcomes than pharmacotherapies.^{6,7} Many general practitioners (GPs) are inclined to mainly prescribe antidepressant medications,⁸ while 75% of patients prefer psychotherapies.⁹⁻¹¹

Conventional meta-analyses have shown that psychotherapies are effective in primary care patients.¹²⁻¹⁸ A network meta-analysis (NMA) of psychotherapies in primary care patients found few significant differences between types of therapy.¹² This is in line with meta-analyses across treatment settings consistently showing no relevant differences between therapies.^{19,20}

One previous NMA of treatments of depression in primary care was conducted, but focused mostly on clinical differences between types of trials in this field.²¹ To the best of knowledge, no NMA with a focus on outcomes has been conducted in which psychotherapies for primary care patients are compared to pharmacotherapy, combined treatment, and control conditions. NMAs can compare several alternative treatments in one analysis, are able to use direct and indirect evidence, and thus make optimal use of all available evidence.^{21,22}

We conducted a NMA comparing the effects of psychotherapy with pharmacotherapy, combined treatment and control conditions in depression. We include studies that focus on major depression, persistent mood disorders (dysthymia), or both, as well as studies that include patients scoring high on self-rating depression scales.

Methods

Identification and Selection of Studies

The protocol for this meta-analysis was registered at the Open Science Foundation.²³ Studies were identified through an existing database of randomized trials on psychotherapies for depression.²⁴ The database is continuously updated and every year in January searches for the previous year are conducted (from 1966 to January, 1st 2019). Four bibliographical databases (PubMed, PsycINFO, Embase, Cochrane Library) were searched by combining index and text words of depression and psychotherapies, with filters for randomized controlled trials (see Appendix A for full search string for PubMed). After importing the references in Endnote and removal of duplicates, two independent researchers (EK, PC) screened all records and full texts. Discrepancies were solved through discussion.

We included studies in which a psychological treatment in adult patients (18 or older) with depression that were recruited from primary care was compared with antidepressant medication, combined treatment, care-as-usual (care usually delivered by GPs), waitlist, or pill placebo. Depression could be established with a diagnostic interview or a score above a cutoff point on a self-report measure. We included any type of psychotherapy.^{25,26} Therapies could be applied in individual, group, telephone-supported, or guided self-help (internet-based or not) format, because these formats have been found to have comparable effects across different settings.²⁷ Unguided interventions without human support were excluded, because these have been found to be less effective.²⁷ Co-morbid mental or somatic disorders were not excluded.²⁸ We included studies published in English, Spanish, Dutch and German.

When a study contained two or more arms to be included in the same node (for example when one study compared two types of psychotherapy with one pharmacotherapy condition), we considered them as separate comparisons. These were subdivided appropriately in order to avoid double counting.

Risk of Bias and Data Extraction

Risk of bias (RoB) was assessed using four criteria of the Cochrane tool:²⁹ adequate generation of allocation sequence; concealment of allocation to conditions; prevention of knowledge of the allocated intervention (masking of assessors); and dealing with incomplete outcome data (this was assessed as positive when intention-to-treat analyses

were conducted). Items were rated by two independent assessors (PC; EK) and disagreements were solved through discussion. Studies were judged as low RoB when all four items were rated positive.

Pharmacotherapy studies were assessed regarding the use of therapeutic dose and titration schedule (i.e. therapeutic dose achieved within three weeks). Pharmacotherapy was deemed adequate if both criteria were met. Psychotherapies were assessed on: 1) using a treatment manual, 2) specially trained therapists, and 3) verification of treatment integrity.^{30,31} We also coded participant and interventions characteristics (Appendix B).

Outcome measures

Treatment response (50% reduction in depressive symptomatology) was chosen as primary outcome. When not reported, we imputed response rate using a validated method, using the mean depression score at baseline and the means, standard deviation and number of patients at post-test.³² Patients randomized but not included in the analyses of responders were assumed to be non-responders and included in the analyses according to the intention-to-treat principle. The time-point for the primary outcome was the end of the psychotherapy. When multiple scales were used we selected one instrument using an algorithm, prioritizing clinician-rated instruments over to self-rated instruments and according to the frequency in which the instruments are used in depression trials (HAM-D; MADRS; another clinician rated instrument; BDI-I or II, another self-rated instrument).

Remission was defined as the number of patients with a depression score below a specific cut-off on a validated rating scale. The standardised mean difference (SMD) between each of the contrasts was based on the means, standard deviations and N of the conditions at post-test. Acceptability of the treatments was operationalized as study dropout for any reason.

Pairwise meta-analyses

We conducted pairwise meta-analyses for all comparisons, using a random effects model. To quantify heterogeneity, we calculated the I^2 -statistic, using the non-central chi-squared-based approach within the heterogi module for Stata.³³ We tested for small study effects with Egger's test.³⁴

Network meta-analyses

The comparative effectiveness was evaluated using NMA methodology. First, we summarized the geometry of the network of evidence using network plots for response.³⁵ Second, we conducted contrast-based NMA to assess comparative efficacy and acceptability.³⁶ Random effect models were used in all analyses.³⁷ Relative risks (RRs) and SMDs were reported with their 95% confidence intervals. The ranking of treatments was estimated with the “surface under the cumulative ranking” (SUCRA), based on the estimated multivariate random effects models.³⁵

The transitivity assumption was examined through a table of study characteristics. We verified if potential effect modifiers were similarly distributed across the comparisons in the network. We checked the consistency of the network using the local test inconsistency (with the loop-specific approach, which estimates in each triangular and quadrangular loop whether the direct and indirect effects are consistent)³⁸ and the global test of inconsistency (the design-by-treatment interaction test).³⁹ Potential influences of small study effects were examined with metaregression analyses adjusting the study-specific variance as a covariate.⁴⁰

Heterogeneity, meta-regression and sensitivity analyses

We evaluated the heterogeneity in the network with tau-squared in comparison with empirically derived values.^{41,42} To explore possible sources of heterogeneity, we conducted a multivariate meta-regression analysis with the characteristics that were also used to examine transitivity. We conducted sensitivity analyses (1) in which we limited the analyses to studies with low RoB; (2) to studies on CBT only; (3) studies with pill placebo excluded (in these studies patients receiving drugs are blinded, while patients in the therapy conditions are not).⁴³

The main analyses were conducted in Stata/SE 14.2 for Mac. The metaregression analyses examining small sample bias were conducted in OpenBUGS 3.2.3. In addition, the main analyses examining the effect sizes of all comparisons for response and acceptability were independently conducted by one of the authors with the Bayesian framework, using the gemtc package in R. The analyses were conducted in November 2019.

Results

Selection and inclusion of studies

We examined 21,976 abstracts (16,701 after removal of duplicates). 2,553 full-text papers were retrieved. The PRISMA flowchart describing the inclusion process,⁴⁴ is presented in Appendix C. Fifty-eight studies met inclusion criteria (9,301 patients). Selected characteristics of included studies are given in Appendix B, and references in Appendix D. In four studies two types of psychotherapy were examined as separate arms (including one in which the treatment was either provided by a nurse or by the GP). In total, 62 comparisons were available for the NMA (psychotherapy: 56; pharmacotherapy: 19; combined: 5; CAU: 39; waitlist: 6; pill placebo: 3).

Characteristics of included studies

The aggregated characteristics of the included studies are presented in Table 1. In 19 trials patients were recruited through systematic screening. Twelve trials were aimed at specific target groups, 32 used CBT as therapy, 39 used an individual treatment format, and the therapy was adequate in 28. An SSRI was applied in 7 of the 15 studies examining pharmacotherapy, and in 9 of these the pharmacotherapy was adequate.

44 studies reported an adequate sequence generation, 44 reported allocation to conditions by an independent party, 25 reported masking of outcome assessors and 30 only used self-report outcomes. In 44 studies intention-to-treat analyses were conducted. Twenty-eight studies met all four RoB criteria, 14 met three criteria, 20 met two criteria or less.

Pairwise meta-analyses

Appendix E shows the results of the pairwise meta-analyses. The forest plots for the response rates with ≥ 5 comparisons are given in Appendices F to I. Heterogeneity was low to moderate in most comparisons. In the comparisons on response only heterogeneity of combined treatment versus pharmacotherapy was high (84%). Egger's

test was only significant for psychotherapy versus care-as-usual ($p=0.01$) and for psychotherapy versus waitlist ($p=0.01$).

Network plot

The network for response is graphically presented in Figure 1. The number of studies for each comparison can be seen in Appendix E. The most examined nodes were pharmacotherapy, psychotherapy, and care-as-usual. Only a small number of comparisons included combined treatment, pill placebo and waitlist. Several nodes were not well connected to the network. Waitlist only had a small connection to psychotherapy, but not to any other node. The control conditions were not connected to each other, and combined treatment was not connected to any of the control conditions. The contribution plot, giving the percentage of contributions from the direct comparisons separately for the mixed and indirect estimates, is presented in Appendix J.

Network meta-analysis

The main results of the NMA for response, acceptability, remission and the SMD are presented in Table 2. The outcomes are graphically presented in Figure 2. No significant difference was found between psychotherapy and pharmacotherapy for response (RR 1.03; 95% CI: 0.88~1.22). Combined treatment was significantly more effective than psychotherapy (RR 1.35; 95% CI: 1.00~1.81), but not than pharmacotherapy (RR 1.30; 95% CI: 0.98~1.73), although this may be caused by low power. Psychotherapy, pharmacotherapy and combined treatment were all more effective than care-as-usual and waiting list (RRs: 1.60, 1.65, 2.15). The number of studies including pill placebo was too small to result in meaningful outcomes.

The outcomes for remission were comparable to those for response, except that the combined treatment was not significantly different from psychotherapy. The SMDs for care-as-usual ranged from 0.70 (95% CI: 0.35~1.05) for combined treatment, to 0.44 (95% CI: 0.31~0.57) for psychotherapy, and 0.41 (95% CI: 0.18~0.64) for pharmacotherapy. None of the outcomes for acceptability was significant.

The distribution of potential effect modifiers for the four comparisons with 5 or more studies are presented in Table 1. Visual inspection of the distribution across comparisons indicated that the potential effect modifiers were similarly distributed

across the comparisons. This suggested no significant evidence against the transitivity assumption. This must be considered with caution, however, because of small sample sizes in some cells.

The examination of consistency with the loop-specific approach (Appendix K) indicated that no loop was found to be significantly inconsistent. This cannot be considered as evidence for the absence of inconsistency, however, because of the small or zero number of comparisons in several loops. The design-by-treatment interaction model did not indicate global inconsistency in the network ($\chi^2=8.02$; $df=5$; p for the null hypothesis of consistency in the network: 0.16).

Ranking of treatments

The results for the SUCRA are given in Table 3. Combined treatment ranked clearly best for response, remission and SMD. There were no big differences between psychotherapy and pharmacotherapy for response, remission and SMD. No clear directions were found for acceptability.

Heterogeneity and metaregression

The common tau-squared estimates were 0.06 for response, 0.12 for remission, 0.10 for SMD and 0.09 for acceptability. Compared to the empirically predicted distribution for semi-objective outcomes in drug vs placebo comparisons (median 0.049; 95% range 0.001–1.83),⁴² the heterogeneity variance estimates would be moderate.

The results of the multivariate meta-regression analysis, that was conducted to examine possible sources of heterogeneity, are reported in Appendix L. For several comparisons a considerable number of outcomes were not available, because there were not enough studies in the comparisons or because of collinearity. Only one predictor (screening versus other recruitment of patients) was found to be significant in the comparison between psychotherapy and care-as-usual ($p=0.03$).

Sensitivity analyses and follow-up

The results of the sensitivity analyses in which we included only studies with low RoB (Appendix M) resulted in comparable outcomes as the main analyses. The only exception was that the difference between psychotherapy and combined treatment, as

well as the difference between pharmacotherapy and combined treatment was now significant. In the analyses in which we included only trials on CBT (Appendix N), we also found that combined treatment was significantly more effective than either CBT or pharmacotherapy alone. The results of the other sensitivity analyses that were conducted are reported in Appendix O to S. Overall these analyses supported the main findings of the study.

Twenty-seven studies reported outcomes at 6 months follow-up or longer, but the follow-up periods differed considerably and because of the small number of studies for each of the different follow-up periods, we decided not to analyze these data.

Discussion

In this NMA we found that combined treatment, psychotherapies and pharmacotherapies are clearly more effective than care-as-usual and waitlist conditions. No significant differences between psychotherapies and pharmacotherapies were found. The magnitude of the effect was larger for combined treatment compared with psychotherapy and pharmacotherapy alone, although that was not significant in all analyses. We found no difference for acceptability between any of the conditions. This meta-analysis was the first to show these results in primary care, based on the best evidence currently available.

These results are broadly in line with a broader previous meta-analysis of trials across different settings.⁴⁵ In this study the effects of combined treatment were found to be superior to psychotherapy or pharmacotherapy alone, while those of psychotherapy and pharmacotherapy were comparable.⁴⁵ However, in this meta-analysis combined treatment was not superior in all analyses. This may be related to the smaller number of trials and statistical power, or to differences in the primary care population. In the broader meta-analysis it was also found that the acceptability of psychotherapy and combined treatment was higher than in pharmacotherapy. The fact that this was not supported in the current study may again be related to lower power or to differences in the populations. However, although the findings are not unique to primary care, they do

indicate that combined treatment has the best effects, and that pharmacotherapy and psychotherapy have comparable effects.

Several included studies were focused on patients with moderate to severe depression, while patients in primary care usually suffer from mild to moderate depression. It is also assumed that antidepressants typically work better in more severe depression.⁴⁶ These studies may therefore have resulted in an overestimation of the effects of pharmacotherapy in this study.

This study has several limitations. First, RoB was considerable in many studies and publication bias was suspected for some comparisons. Second, waitlist was compared to psychotherapies only and did not form any closed loop, so that only indirect evidence was available. Furthermore, insufficient studies were available on long-term effects. In addition, most studies included mixed populations of patients with major depression and dysthymia, while the outcomes may differ for these populations. Finally, previous research has indicated that there may be some differences in efficacy and acceptability of specific types of drugs,¹ while we merged all antidepressants in one node.

Despite these limitations we can conclude that both psychotherapies and pharmacotherapies seem similarly effective in the treatment of depression when compared to care-as-usual or waitlist and that the effects of combined treatment may be superior to either psychotherapy or pharmacotherapy alone. Treatments in primary care must be so organized to be able to accommodate any of these treatments in response to patients' preferences and values.

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