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Review

The effects of blinding on the outcomes of psychotherapy and pharmacotherapy for adult depression: A meta-analysis

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ABSTRACT

Background: Randomized trials with antidepressants are often run under double blind placebo-controlled conditions, whereas those with psychotherapies are mostly unblinded. This can introduce bias in favor of psychotherapy when the treatments are directly compared. In this meta-analysis, we examine this potential source of bias.
Methods: We searched Pubmed, PsycInfo, Embase and the Cochrane database (1966 to January 2014) by combining terms indicative of psychological treatment and depression, and limited to randomized trials. We included 35 trials (with 3721 patients) in which psychotherapy and pharmacotherapy for adult depression were directly compared with each other. We calculated effect sizes for each study indicating the difference between psychotherapy and pharmacotherapy at post-test. Then, we examined the difference between studies with a placebo condition and those without in moderator analyses.
Results: We did not find a significant difference between the studies with and those without a placebo condition. The studies in which a placebo condition was included indicated no significant difference between psychotherapy and pharmacotherapy (g = −0.07; NNT = 25). Studies in which no placebo condition was included (and patients and clinicians in both conditions were not blinded), resulted in a small, but significant difference between psychotherapy and pharmacotherapy in favor of pharmacotherapy (g = −0.13; NNT = 14).
Conclusions: Studies comparing psychotherapy and pharmacotherapy in which both groups of patients (and therapists) are not blinded (no placebo condition is included) result in a very small, but significantly higher effect for pharmacotherapy.

1. Introduction

When assessing and comparing the outcomes of psychological and pharmacological antidepressant treatments, there is a fundamental problem regarding blinding of patients and therapists. In trials comparing psychotherapy to control conditions, patients randomized to psychotherapy typically know whether they have been randomized to the psychotherapeutic intervention or to the control condition, and the same is true for the treating therapists [26,28,54]. This may result in expectations of positive effects and hope in the psychological intervention in patients, therapists and researchers, and increases in frustration and despair (nocebo effects) [28] in the patients in the control condition, inflating the effect sizes of psychotherapy [26,59]. These biases are likely to be especially large in studies with waiting lists or care-as-usual control conditions. It is not surprising therefore that the effect sizes of psychotherapy studies are especially large when compared to waiting list controls [47,48].

In contrast, for treatment with antidepressants, blinding of both patients and therapists is possible in principle, and hope induction, activation and other unspecific factors influencing outcome can be controlled. As a consequence, the effect size of antidepressants may to be underestimated compared to those of psychotherapy because the fact that patients know about the risk to receive

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placebo will reduce the hope induced compared to an open treatment. However, it has also been questioned whether typical trials on antidepressants are blinded properly, because usually inert placebos are used instead of active placebos, resulting in many patients who know to which condition they have been assigned [22,35,49].

If this is true, the effects of hope induction and expectancies in patients, clinicians and researchers should be larger in placebo-controlled trials with two active treatments compared to that with one because the chance to get an active treatment is larger. This is supported by a meta-analysis which revealed that placebo response is higher in studies with two active treatments (44,8%) compared to those with one only (34,3%) [63]. The authors also report that the response rate to the antidepressants declined with increasing risk to get placebo only (66,5% with two active drugs without placebo, 55,7% with two active drugs and placebo, 51,7 with one active and one placebo arm). Similar results have been reported by another meta-analysis [64].

A consequence of the effects discussed above is that meta-analytic comparisons of efficacy between psychotherapy and pharmacotherapy may overestimate effects of psychotherapy and underestimate those of pharmacotherapy if a placebo-control group is included [1]. If no placebo control group is included, patients, therapists and researchers in both psychotherapy and pharmacotherapy are not blinded, and the advantage of psychotherapy over pharmacotherapy should not be expected here.

Our earlier meta-analyses of studies directly comparing psychotherapy and pharmacotherapy typically show that there are no significant differences between the two [13,14]. If blinding indeed affects outcome, one could expect a difference between studies with and without a placebo control condition. This question has not been examined in earlier meta-analyses of studies directly comparing psychotherapy and pharmacotherapy.

We therefore decided to perform a new meta-analysis of studies directly comparing psychotherapy and pharmacotherapy for adult depression, and to examine whether studies that also included a placebo condition (blinded pharmacotherapy) differed significantly from the studies in which no placebo condition was included (unblinded pharmacotherapy).

2. Methods

2.1. Identification and selection of studies

This meta-analysis was conducted according to the PRISMA guidelines [39]. We used a database of papers on the psychological treatment of depression that has been described in detail elsewhere [12], and that has been used in a series of earlier published meta-analyses (http://www.evidencebasedpsychotherapies.org). This database has been continuously updated through comprehensive literature searches (covering studies published between 1966 to January 2014). In these searches, we examined 14,902 abstracts from Pubmed, PsycInfo, Embase and the Cochrane Register of Trials. These abstracts were identified by combining terms indicative of psychological treatment and depression (both MeSH terms and text words). The searches were usually conducted by two independent researchers, but some of the yearly updates were done by only one researcher. Thus, a biased study selection cannot be completely excluded. For this database, we also checked the primary studies from earlier meta-analyses of psychological treatment for depression to ensure that no published studies were missed (http://www.evidencebasedpsychotherapies.org). From the 14,902 abstracts, we retrieved 1613 full-text papers for possible inclusion in the database.

We included (a) randomized trials (b) in which the effects of a psychological treatment (c) was directly compared with the effects of antidepressant medication (d) in adults (e) with a depressive disorder. We included studies with and without a pill placebo condition, but in order to keep the comparison between blinded and not-blinded studies as clear as possible, we excluded studies in which another type of control condition was used (such as care-as-usual or relaxation).

Only studies in which subjects met diagnostic criteria for the disorder according to a structured diagnostic interview (such as the SCID, CIDI, or MINI) were included. Comorbid mental or somatic disorders were not used as an exclusion criterion. Studies on inpatients, adolescents and children (below 18 years of age) were also excluded. We further excluded maintenance studies, aimed at people who had already recovered or partly recovered after an earlier treatment. Language was not used as an exclusion criterion.

2.2. Quality assessment and data extraction

We assessed the validity of included studies using four criteria of the "Risk of bias" assessment tool, developed by the Cochrane Collaboration [29]. This tool assesses possible sources of bias in randomized trials, including the adequate generation of allocation sequence; the concealment of allocation to conditions; the 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, meaning that all randomized patients were included in the analyses).

We also coded additional aspects of the included studies, including participant characteristics (recruitment method: community, from clinical samples, or other; target group: adults in general, or more specific target groups such as older adults), intervention characteristics (format: individual, group, or guided self-help; number of sessions; type of psychotherapy: cognitive behavior therapy, interpersonal psychotherapy, or other type; type of medication: SSRI, TCA, or other); and study characteristics (country: United States or other).

2.3. Meta-analyses

For each comparison between a psychotherapy and a pharmacotherapy condition, the effect size indicating the difference between the two groups at post-test was calculated (Hedges's g). Effect sizes were calculated by subtracting (at post-test) the average score of the psychotherapy group from the average score of the pharmacotherapy group, and dividing the result by the pooled standard deviation. Because some studies had relatively small sample sizes, we corrected the effect size for small sample bias [25].

In the calculations of effect sizes, we used only those instruments that explicitly measured symptoms of depression. If means and standard deviations were not reported, we used the procedures of the Comprehensive Meta-analysis software (see below) to calculate the effect size using dichotomous outcomes; and if these were not available either, we used other statistics (such as *t*-value or *P*-value) to calculate the effect size. To calculate pooled mean effect sizes, we used the computer program Comprehensive Meta-Analysis (version 2.2.021; CMA).

We tested whether the effect sizes of the studies with a placebo condition differed from the effect sizes of the studies without placebo with a mixed effects model. In this mixed effects model, studies within subgroups were pooled with the random effects model, while tests for significant differences between subgroups were conducted with the fixed effects model