Review

Meta-analysis of the placebo response in antidepressant trials

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Abstract

Improvements in placebo groups of antidepressant trials account for a major part of the expected drug effects. We aimed to determine overall effect sizes of placebo and drug effects in antidepressant trials, and to analyze whether the placebo effect in antidepressant trials also occurs for patient self-perception, general psychopathology, and quality of life.

Methods: Search terms covered different variants of pharmacotherapy for patients with depressive disorders from January 1980 to December 2005 in the databases Medline/Pubmed, PsychInfo and CENTRAL, a.o. We included RCTs with a placebo group and an antidepressant group in people with depression.

Results: We computed within group effect sizes for several outcome variables and integrated them using random-effect models. A total of 96 studies were included. Mean effect size in the placebo group for primary outcome variables was $d = 1.69$ (95% CI = 1.54–1.84) compared to 2.50 in the drug group (95% CI = 2.30–2.69). There was a major difference between placebo effect sizes assessed with observer ratings ($d = 1.85$, 95% CI = 1.69–2.01) versus patient self-perception ($d = 0.67$, 95% CI = 0.49–0.85). The effect sizes in placebo groups in 2005 were more than twice as great as those in 1980, but only for observer ratings, not for patient self-ratings. The result was partly due to increased homogeneity of samples of recently published trials.

Conclusions: The placebo effect accounted for 68% of the effect in the drug groups. Whereas clinical trials need to control the placebo effect, clinical practice should attempt to use its full power.

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1. Introduction

Placebo responses are general phenomena in medicine, and they seem to be particularly powerful in depression. However, the exact size of improvement in placebo groups compared to drug groups remains unclear because of serious shortcomings of existing reports (e.g., strong selection of included studies, poor methodology based on percentage scores, and inclusion of many studies with missing data). Moreover, it is unclear whether the improvements in placebo groups can only be found for primary outcome variables (e.g., depression), or whether they can also be found for other psychopathological variables and quality of life.

For the purpose of this paper, we will use the term “placebo response” to refer to improvements that occur in the placebo groups of clinical trials. Despite some critical evaluations (Hróbjartsson and Gøtzsche, 2001), the placebo response is still impressive in medicine and psychiatry. The most provoking examples of placebo effects in medicine come from sham surgery (Moseley et al., 2002; McKae et al., 2004), but the placebo effect is also impressive in relieving pain (Petrovic et al., 2002) and reducing hypertension (Preston et al., 2000).

The placebo response was also examined in antidepressant trials. Half of the drug group and 30% of the placebo group met the responder criterion of a 50%-reduction in depression scores from baseline (Rush, 1993; Walsh et al., 2002). The positive effects attained with selective serotonin reuptake inhibitors (SSRIs) that are explained by placebo are estimated to be as high as 82% depending on the study inclusion criteria and analysis methods used (Joffe et al., 1996; Kirsch and Sapirstein, 1998; Kahn et al., 2000; Kirsch et al., 2002). A recently published study shows an inverse relationship of placebo response and depression severity, with less placebo response in very seriously depressed patients (Kirsch et al., 2008). When antidepressants were compared not only to inert placebos, but also to active placebo conditions imitating the side effects of antidepressants, the differences in the efficacy of antidepressants and active placebos were much less pronounced (Moncrieff et al., 2004). However, this analysis was based on only a few, older studies.

When comparing different antidepressant trials, it became evident that there was tremendous variation in the size of the placebo response. An intriguing change of the placebo response with time was reported by Walsh and colleagues (Walsh et al., 2002) who analyzed 57 trials and found a correlation of r = 0.45 between the effect size in the placebo group and publication year. The reasons for this “publication year effect” are still poorly understood. In contrast, other studies show a decrease in effectiveness of the drugs with publication year (e.g., statins, Gehr et al., 2006).

Treatment efficacy in psychiatry can be determined using 2 different methods, namely observer ratings and patient’s self-ratings. A special characteristic of antidepressant trials is the use of observer ratings to assess depression. Most drug trials focus on results of the Hamilton Depression Scale (HAMD) or the Montgomery Asberg Depression Rating Scale (MADRS). Some studies, however, use additional self-rating scales that allow investigators to examine improvement from the patient’s perspective. More information is needed to determine whether placebo effects in antidepressant trials are limited to observer ratings, or whether they also occur in patient self-ratings. Moreover, it is unclear whether the publication year effect can also be found for patient self-ratings.

The aim of this meta-analysis was to analyze the placebo effect when rated by patient self-report as compared to observer ratings. Moreover, the placebo response was not only computed for depression, but also for general psychopathology and quality of life. Special emphasis was given to possible moderating effects, such as publication year, diagnosis, drug groups, and others.

2. Method

The reporting of methods follows the QUORUM Checklist.

2.1. Searching

We searched Medline/Pubmed, PsychInfo, and the Cochrane Central Register of Controlled Trials (CENTRAL), using the following search procedures and key words: “pharmacotherapy or drug therapy or drug treatment or antidepressant ∗ or antidepressive” and “depression or affective disorder or depressive or depressed or dysthymia or dysthymic”. The publication language was limited to English or German, publication type = journal article. Results were restricted to hits including the search terms: “randomized or randomised”, and “placebo”, and “double blind or triple blind”. In the Cochrane database of systematic reviews, all reviews dealing with pharmacotherapy of depression were checked for further references.

2.2. Selection

Publication year was limited to January 1980 (introduction of DSM-III) until December 2005. Only studies addressing the treatment of adult patients with unipolar depressive disorder were considered. Studies were excluded if depression was
exclusively a comorbid disorder of a medical condition (e.g., post-stroke depression; depression after heart attacks). Concurrent medication was allowed if less than 20% of patients received it. The placebo groups had to have a minimum of 20 patients. In typical RCT designs with 2 groups (drug vs placebo) and 2 assessment times (pre vs post), this allows us to detect effect sizes of the interaction term group × time according to Cohen’s d of >0.33 (p < .05; power = .80); therefore, even moderate treatment effects were detectable in the included studies (Cohen, 1988). Additionally, the studies had to report sufficient data to compute pre–post-effect sizes (means, at least one standard deviation or pre–post-test statistics). The utilization of at least one instrument assessing depression was required.

2.3. Data abstraction

A structured coding plan was developed prior to the meta-analysis. The coding plan included a systematic definition of 43 items addressing general study characteristics (e.g., authors, publication year), study setting, study design (e.g., treatment duration, medication, randomization, blinding, assessment instruments), report of detailed results, and sample characteristics (e.g., diagnosis, comorbidity, drop-out).

2.4. Validity assessment

Because the frequently used JADAD-score (Jadad et al., 1996) does not cover all aspects of validity, we expanded it...
and coded additional aspects of internal validity (randomization, intent to treat analysis, report of means and standard deviations), construct validity (blinding, diagnosis, treatment adherence, assessment instruments), and external validity (report of selection of participants, participant characteristics, exclusion criteria, treatment duration). A random selection of 30 original studies was presented to two raters (SW, EW) and inter-rater reliability for study characteristics and validity characteristics were computed.

2.5. Data synthesis

We computed within group effect sizes for the drug and placebo groups. These effect sizes were defined as the mean difference from pre-to post-treatment divided by the pooled standard deviation (e.g., Hartmann et al., 1992). In cases of missing post-scores, we used Becker’s formula (Becker, 1988) which is based on the difference of the post-and pre-scores related to the standard deviation of the baseline. We used a study weighting procedure according to sample size (Hedges and Olkin, 1985). Homogeneity statistics using Q-statistics (DerSimonian and Laird, 1986) revealed significant deviation of the mean effect. Therefore, we applied random effect models for the integration of all effect sizes. Publication bias was controlled for by computing “safe-n rates”, stem-leaf-diagrams and funnel plots (Becker, 1988; Egger et al., 1997). Predefined subgroup analyses were performed to test whether the findings were sensitive to the type of antidepressants administered, the subtype of depression diagnosis, and the type of outcome variables. Furthermore, the potential influence of continuous moderator variables (such as publication year, study validity, treatment duration, mean age of patients) was analyzed in regression models.

3. Results

3.1. Study characteristics

As shown in Fig. 1, 3322 different studies fulfilled the first level of inclusion criteria. After excluding studies based on information presented in study abstracts, 406 complete study reports were considered in more detail. The final sample consisted of 96 trials that reported sufficient data to compute effect sizes. The placebo groups of these studies comprised 9566 people. Approximately half of the studies were published after 1996, 68% were conducted in the United States, and the mean sample size was 86 participants. The mean discontinuation rate was 30.4%. Seventy-nine of the 96 studies addressed patients with major depression, 7 addressed patients with dysthymia, and 10 studies addressed patients with less specified or minor depressive disorders. In the active drug groups, the following medications were administered: SSRIs (36), tri-or tetra-cyclic antidepressants (18), MAO inhibitors (5), herbal remedies (10), and others (27).

Most studies (86 of 97; 89%) utilized the Hamilton Depression Scale (HAMD). Because various versions of the HAMD were used, we focused on the HAMD-17 version and estimated equivalent scores if a different version had been used. Equivalent scores were computed according to Walsh et al. (Walsh et al., 2002). Typical self-rating scales that were used in the studies included the Depression subscale of the Symptom Checklist SCL-90R (Derogatis, 1994) (10 studies), the Beck Depression Inventory BDI (Beck and Steer, 1987) (9 studies), and the Zung Depression Scale (Zung, 1965) (4 studies).

3.1.1. Validity ratings

In contrast to previous reviews on the placebo effect in antidepressant trials that reported substantially lower rates of complete data sets, we successfully detected relevant means and standard deviation scores for nearly three quarters of the trials (72 of 96 trials). The inter-rater reliability for the study quality characteristics was $r=0.95$ which can be considered excellent. The inter-rater reliability for other variables of the data selection process ranged from 0.85 (strategy of analysis) to 1.00 (study identification characteristics, publication year, etc.).

3.1.2. Overall effect size of the placebo effect

The overall effect size of the placebo effect was 1.69 (95% CI = 1.54–1.85), as compared to $d=2.50$ (95% CI = 2.30–2.69) in the drug group. The ratio of the effect sizes suggests that 67.6% of the improvements in the drug group were attributable to the placebo effect. There was a high correlation between the effect sizes in the placebo and drug groups ($r=0.69; p<.001$), indicating that reported improvements in placebo and drug groups were strongly interdependent. Stem-leaf diagrams revealed a normal distribution with most effect sizes lying in the area between 1.00 and 2.8, which indicates that publication bias does not explain the results. The effect sizes of the placebo response were not influenced by the category of drug that was investigated, with mean effect sizes ranging from 1.65 (SSRI-placebo) to 1.73 (other antidepressants). However, the placebo response was significantly greater in major depression ($d=1.83$; 95% CI = 1.67–1.99) than in dysthymia ($d=1.11$; 95% CI = 0.49–1.58). Interestingly, this diagnostic specificity remained even after controlling for depression severity (see below). The overall placebo effect was highest for the primary outcome variable (depression). However, substantial effect sizes also emerged for anxiety, general psychopathology and quality of life (see Table 1).

3.1.3. Self-rating versus observer rating

In the placebo groups, there was a substantial difference between effect sizes for improvements rated by observers ($d=1.85$; 95% CI = 1.69–2.01; 93 studies) compared to those rated by patients ($d=0.67$; 95% CI = 0.49–0.85; 28 studies). Pearson’s correlation between self-and observer ratings was $r=0.57$ for the 24 studies that reported both types of ratings. The difference between self-ratings and observer ratings was

<table>
<thead>
<tr>
<th>Variable</th>
<th>K/</th>
<th>/n</th>
<th>Mean $d$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>97/9,469</td>
<td>1.69</td>
<td>1.54–1.84</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>17/2,633</td>
<td>0.98</td>
<td>0.71–1.25</td>
<td></td>
</tr>
<tr>
<td>General Psychopathology</td>
<td>4/258</td>
<td>0.68</td>
<td>0.08–1.29</td>
<td></td>
</tr>
<tr>
<td>Quality of Life</td>
<td>12/1,214</td>
<td>1.00</td>
<td>0.57–1.43</td>
<td></td>
</tr>
</tbody>
</table>

$K=$ number of studies; $n=$ total sample size; mean $d=$ average effect size.
also found in the drug groups (self-rating $d = 1.12$ versus observer rating $d = 2.89$). Interestingly, the self-ratings and observer ratings of proportion of positive effects in the placebo group relative to the drug group were comparable (observer: 66.5%; self-rating: 66.6%).

3.1.4. Publication year effect

With our large sample size, we were able to replicate the strong linear association between publication year and effect sizes of the placebo group (see Fig. 2a). In fact, the mean effect sizes in the placebo groups of the studies published around 2005 were more than twice as great as those published before 1985. The correlation between effect size and publication year was 0.41 ($p < .001$; compared to 0.45 in the original study reporting this effect (Walsh et al., 2002)). However, this effect was not found when self-rating scales for depression were analyzed (see Fig. 2b). Patients’ perception of self-improvement in the placebo groups was not influenced by publication year ($r = −0.08$; NS). In the drug groups, the same tendency was found (see Fig. 2a, b; bottom), although due to more variance this effect was less clear and failed to reach significance.

3.1.5. Further moderators of the placebo response

Using bivariate regression models, we analyzed further correlates of the effect size of the placebo response. We could not confirm any significant influence for the average age of the sample ($β = −0.18$), percentage of female participants ($β = 0.17$), validity of the study ($β = 0.06$), or treatment duration in weeks ($β = 0.06$). However, there seemed to be a significant influence of diagnosis (major depression versus dysthymia; $β = 0.30$; $p < 0.003$), and severity of depression ($β = 0.26$; $p < 0.02$). Therefore, we entered publication year,

Fig. 2. a) Association of effect size with publication year (observer ratings; placebo groups at top, drug groups at the bottom). b) association of effect size with publication year (self-report; placebo groups at top, drug groups at the bottom).
diagnosis, and severity of depression in one regression analysis model. This analysis confirmed the major influence of publication year ($\beta = 0.48; p<0.001$) and diagnosis ($\beta = 0.29; p<0.003$), but failed to show an additional influence of depression severity ($\beta = 0.14; p = 0.07$).

3.1.6. Sensitivity analysis

A funnel plot confirmed that the greater the sample size, the closer the effect size was to the average effect size. This argues against a publication bias; if publication bias played a major role, large sample size trials would supposedly reveal lower effect sizes than small sample size trials (Egger et al., 1997). Fail-safe-rates were computed to determine how many unpublished studies would be needed to reduce the effect size to $d = 0.01$ thereby eliminating the positive effect in the placebo group. It was found that 16,300 unpublished studies reporting no positive placebo effects would be needed. To reduce the mean effect size of 1.69 to a low effect size of 0.21, a fail–safe-rate of 683 studies would be needed. Both rates confirm the stability of improvements in the placebo groups.

3.1.7. Sample homogeneity, inclusion criteria, and publication year

Effect sizes and significant findings for improvements can be increased if more homogeneous samples are included. Homogeneity of samples is reflected in the standard deviation of scores. The lower the standard deviation (e.g., at baseline), the higher the effect size if the average improvement is comparable. Therefore, we analyzed whether there was a linear association between publication year and standard deviation of depression scores at baseline. Fig. 3 shows that, in fact, a linear association between publication year and homogeneity of samples existed ($r = 0.30; p < .01$). However, the variation was less than 25% of the values from 1980; therefore, this reduction of heterogeneity can only partly account for the substantial changes of the effect sizes for improvements in the placebo groups. In the studies included in our analysis, we could not confirm significant associations between inclusion cut-off scores for depression and publication year ($r = 0.01; ns$) or mean baseline depression severity and publication year ($r = −.195; ns$). Therefore the association between depression standard deviation and publication year can be only attributed to increasing homogeneity.

4. Discussion

We conducted a meta-analysis of improvements in placebo groups in 96 trials containing a total of 9,566 depressed patients. We found that the improvements in the placebo groups corresponded to 67% of the improvements in the active drug groups. We further confirmed that the reported placebo effect sizes increased tremendously from 1980 to 2005. However, this strong publication year effect was only found when the primary outcome variable was an observer rating of depression. Self-ratings of depression were less prone to publication year effects. Indeed, the placebo response in self-ratings was only of medium magnitude, but corresponded to other outcome measures (psychopathology, quality of life).

Our analysis confirms that the placebo effect can differ substantially depending on study design and outcome measures (Antonaci et al., 2007). The difference between self-ratings and observer ratings in evaluating clinical outcomes of depression trials is intriguing, and raises questions about which is the more valid assessment approach. Some scientists question whether people with depression can accurately detect small changes in mood, and therefore argue in favor of observer ratings. Others, however, including Fava and colleagues (Fava et al., 2003), believe that clinicians tend to overestimate changes in patients, and therefore endorse the use of additional assessment strategies.

The strong publication year effect found for observer ratings questions their validity. Following the view of Fava and others (Fava et al., 2003), this effect might indicate increasing overestimation of positive effects by clinicians. One possibility is that doctors became enthusiastic about the efficacy of the antidepressant drugs, and developed higher expectations for improvement. It is unlikely that the drug-and placebo effects actually increased more than 100% over the last 2 decades. Walsh et al. (Walsh et al., 2002) mention that the Hamilton cut-off score for study inclusion has also increased over the years, and that investigators might have tended to overestimate depression severity at baseline in order to include patients in studies. This might be associated with a substantial decrease in depression scores between the first and second assessments (Khan et al., 2007). While this effect might contribute in part to increasing effect sizes over time, it is unlikely that it explains the entire publication year effect. In most studies, the placebo response not only occurs between the first and second assessments, but rather, improvements increase continuously. Furthermore, we were able to show that increasing effect sizes for improvements in antidepressant trials were partly due to the decreasing heterogeneity of the samples. While this process might improve internal validity, samples of clinical trials differ more and more from clinical practice. However, the change of heterogeneity over the years is smaller than the increase of

![Fig. 3. Decreasing heterogeneity of depression with publication year ($r = 0.30; p < .01$). Abbreviation: SD = standard deviation.](image-url)
improvement effect sizes, therefore indicating that variations of heterogeneity can only partly explain the publication year effect.

Interestingly, we found differences in placebo responses depending on diagnosis. Patients with dysthymia reported lower placebo responses than patients with major depression. This is not only due to depression severity (which was controlled for in regression analyses), but depended on depression type. Dysthymia is chronic by definition, while major depression tends to follow a more cyclic course, thereby allowing more variability in placebo responses. Different placebo responses depending on diagnostic group have also been shown to exist in other areas of mental disorders (Huppert et al., 2004).

The question arises as to which mechanisms might be responsible for the placebo response. Rapaport and others (Rapaport et al., 2000) assume that placebo responders differ from drug responders, therefore indicating that the mechanisms of improvement under placebo might differ from the mechanisms of improvement under drug influence. However, other studies have found that many predictors and correlates of change are similar between placebo and antidepressant drug responders (Leuchter et al., 2002; Mayberg et al., 2002); this notion is confirmed by the high correlation of placebo group effect sizes and drug group effect sizes in our analysis ($r = 0.69$).

A positive placebo response depends on the activation of specific brain areas (Benedetti, 1996; Bingel et al., 2006). Classical conditioning might also explain the placebo response. Classical conditioning depends on prior experience. While prior experience might facilitate the placebo response, it has also been shown that the placebo response can be triggered by expectation alone (Benedetti et al., 2003; Levine et al., 2006).

A crucial question for the placebo response in antidepressant trials is whether the effect is simply a regression to the mean. It has been shown that the higher the depression score, the greater the “placebo response” ($r = 0.27$, Walsh et al., 2002). However, our results demonstrate that depression severity does not explain the major effects, and the results of Kirsch et al. (Kirsch et al., 2008) also contradict the assumption that a mere regression-to-the-mean effect explains placebo responses in depression. Moreover, regression to the mean cannot account for the observed publication year effect, the differences depending on diagnosis, or the differences depending on ascertainment strategy.

Another methodological shortcoming is the lack of activation of groups that show the natural course of the disorder. In fact, in a critical analysis of the placebo response, Hróbjartsson and Götzsche (Hróbjartsson and Götzsche, 2001) compared results of placebo groups to natural course groups and found substantially lower placebo effects than expected. Three years after assessment, remission rates for major depression can be up to 70% (Rhebergen et al., 2009); in contrast, other studies have described stable depression severity for samples with depression scores comparable to those in our included studies (Stoolmiller et al., 2005). Therefore only natural course control groups can elucidate the long-term influence of placebo reactions, but these groups are rarely included in depression trials due to ethical concerns.

Differences between the mechanisms acting in placebo groups compared to those acting in the drug groups have further implications for the rationale of placebo-controlled trials. It is highly questionable whether the nonspecific effects acting in placebo groups are the same as the nonspecific effects acting in active drug groups. If placebos are not completely inert, but instead mimic the side effects of the drug (“active placebos”), they are more effective. Therefore, it is not surprising that the difference between the improvements in drug groups compared to placebo groups diminish to insignificant levels if the effect of active placebos is compared to that of antidepressants (Moncrieff et al., 2004). In other words, if people experience side effects, they might experience more non-specific, “placebo” effects. However, in typical placebo controlled trials, this increase of nonspecific effects only occurs in the drug group, but not in the placebo group.

4.1. Limitations

A general limitation of meta-analyses is the quality of the included studies. However, we did not find any association between study quality and the reported results. The total sample size and the number of studies included in our meta-analysis were sufficiently high for the primary outcome variable. Publication bias is also a point of consideration in meta-analyses, and has been shown to influence systematically the report of positive effects for antidepressants (Turner et al., 2008). We controlled for publication bias computing fail-to-safe rates, and we were able to show that publication bias was unlikely to account for the substantial improvements in placebo groups. Although we had to exclude many studies because of insufficient data (Fig. 1), we still included more studies than other meta-analyses on antidepressants, and the reported fail-to-safe rates confirm that the results are robust. However, the results of self-rating scales in our analysis were based on only one-quarter of the studies included, which increases the risk of type-II-errors. Furthermore, different self-rating scales were investigated, while observer ratings were mainly based on the Hamilton scale. This might have contributed to a blunting of systematic influences such as the publication year effect in self-ratings. Further studies should directly compare self-and expert ratings using the same items (e.g., the MADRS versus MADRS self-report). Therefore, our meta-analysis leaves some questions unanswered. Although we can demonstrate a tremendous difference between the results of patient self-reports and observer ratings, we cannot completely explain this difference. The same is true for the publication year effect, which is only partly explained by ascertainment strategy and reduction of sample heterogeneity. Therefore, these effects should be analyzed further in future studies.

4.2. Implications for research and clinical practice

These results have several implications for research and clinical practice. As long as it remains unclear whether self-ratings or observer ratings are the more valid instrument, both types of instruments should be used in clinical trials. However, only one fourth of the studies included in this overview used self-rating scales for depression. For clinical practice, it should be kept in mind that the placebo response in the treatment of depression is substantial. Therefore, clinicians should attempt to retain and optimize the non-specific effects. Indeed, Benedetti (Benedetti et al., 2006)
demonstrated that the elimination of positive expectation effects made analgesic therapies less effective and that higher drug dosages were needed in those patients as compared to others with positive treatment expectations. Waber et al. were able to show that the analgesic placebo effect is higher if people expect the drug to be expensive and valuable (Waber et al., 2008). Therefore the systematic application of positive expectations can help to optimize medication use.

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References


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