Correlation Between Different Levels of Placebo Response Rate and Clinical Trial Outcome in Major Depressive Disorder: A Meta-Analysis

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ABSTRACT

Objective: To investigate the relationship between specific levels of placebo response rates and the drug response rate and the relative risk of response to drug versus placebo in clinical trials of antidepressant monotherapy and adjunctive polypharmacy for MDD.

Data Sources: MEDLINE/PubMed databases were searched for studies published in the English language between January 1980 and March 2011 by using the search terms *depression*, *placebo*, *augmentation*, *adjunct*, *adjunctive*, and each of the antidepressant agents identified. The search was supplemented by manual bibliographic review and examination of relevant review articles.

Study Selection: The analysis included randomized, double-blind, placebo-controlled trials of antidepressants used as monotherapy for MDD, 4 weeks or longer, and of augmentation/combination treatments for antidepressant partial responders/nonresponders with MDD, 1 week or longer. 169 antidepressant monotherapy studies and 35 adjunctive polypharmacy studies were found eligible for inclusion in our analysis.

Data Extraction: Data extracted included number of patients enrolled, patient characteristics, drug dosages and scheme (fixed vs flexible dosing), duration of the trial, and response rates.

Results: In antidepressant monotherapy studies, a higher placebo response rate correlated with a lower risk ratio of responding to antidepressant versus placebo ($P < .001$) and correlated with higher antidepressant response rates ($P < .001$); the number needed to treat (NNT) for response was approximately 4, 6, and 9 in trials with placebo response rates < 30%, ≥ 30% and < 40%, and ≥ 40%, respectively. In adjunctive trials, a higher placebo response rate correlated with a lower risk ratio of responding to the adjunctive drug versus placebo ($P < .001$) and correlated with a trend toward statistical significance with higher response rates to the adjunctive drug ($P = .050$); the NNT was approximately 6, 7, 11, and 17 in trials with placebo response rates < 20%, ≥ 20% and < 30%, ≥ 30% and < 40%, and ≥ 40%, respectively.

Conclusions: These results suggest that the relative efficacy of the active drug compared to placebo in clinical trials for MDD is highly heterogeneous across studies with different placebo response rates, with a worse performance in showing a superiority of the drug versus placebo for studies with placebo response rates ≥ 30% and ≥ 40%, respectively, for monotherapy and adjunctive trials. It is important to maintain placebo response rates below this critical threshold, since this is one of the most challenging obstacles for new treatment development in MDD.

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Major depressive disorder (MDD) is a highly prevalent and potentially debilitating illness, associated with significant disability, morbidity, and mortality. Antidepressant medications have long been the mainstay of treatment for MDD, and their combination with other nonantidepressant agents or with antidepressants with a different pharmacologic profile (combination and augmentation therapies) is commonly used as a treatment strategy for patients who experience insufficient symptom response to a first-line monotherapy with antidepressants.

Double-blind, randomized, placebo-controlled clinical trials are considered the gold standard for the development of novel antidepressant therapies. Unfortunately, however, even for compounds that have repeatedly been proven to be efficacious in treating MDD, differences in efficacy versus placebo are not always apparent throughout all clinical trials. For instance, a recent meta-analysis,[1] which was conducted on the US Food and Drug Administration (FDA) database and included 74 randomized clinical trials of 12 drugs that, ultimately, received approval from the FDA, indicated that almost 50% of such clinical trials failed to show statistically significant differences in efficacy between drug and placebo. This high rate of failed or negative trials represents a major obstacle in the development of new treatments for MDD, resulting in significant delays in the time required to bring new treatments to the clinic and increasing the overall costs of drug development.[2] In light of estimates suggesting that as many as half of currently ongoing MDD trials will fail to demonstrate superior efficacy for drug versus placebo,[1] there is an urgent need to improve the efficiency of randomized controlled trials (RCTs) in MDD in order to reduce the frequency of failed and, especially, uninformative trials (equivocal or failed studies involving high placebo response rates).

One of the most challenging obstacles contributing to the failure of RCTs in MDD is the often substantial and highly variable placebo response rate.[3,4] In antidepressant trials, high response in the placebo arm may prevent the detection of a drug treatment signal of an agent that, in other experiments, has repeatedly been shown to be efficacious, thereby leading to an uninformative RCT.

Placebo response represents the reduction in depressive symptoms experienced by patients during the course of a clinical trial that is not accounted for by the specific pharmacologic effects of the drug studied for patients randomized to drug therapy (ie, it can represent symptom improvement that is either due to study participation or simply due to course of illness). For patients who are

randomized to placebo therapy, *placebo response* is defined as the reduction of depressive symptoms that occurs from randomization to study end point. Several factors have been found to influence placebo response in antidepressant studies, including study duration,[3] the frequency of outcome assessments per study period,[5] the probability of receiving placebo during a trial,[3] illness severity,[3,6] study severity eligibility requirements,[7] the presence of anxious depression,[8] the study being conducted recently or not,[9] use or nonuse of a treatment lead-in phase,[10] and patient beliefs regarding the group to which they have been randomized.[11]

Previous research has shown that higher placebo response rates in RCTs are correlated with a lower probability to detect a statistically significant superiority of the drug compared to placebo.[12] However, no study so far has investigated in greater detail the relationship between gradations in placebo response rate and overall study outcome (ie, the relative risk or risk ratio of patients responding to an FDA- or a European Medicines Agency–approved drug versus placebo). Being able to understand how, quantitatively and qualitatively, study outcome in terms of risk ratio varies across different placebo response rates in already approved drugs can help interpret equivocal results from future clinical trials involving experimental therapies. Therefore, the aim of the present analysis is to investigate the relationship between specific levels of placebo response rates and the drug response rate and the relative risk of response to drug versus placebo in randomized, double-blind, placebo-controlled trials of antidepressants as monotherapy for MDD as well as for drugs used as adjunctive therapy for antidepressant partial responders/nonresponders with MDD. Since relatively fewer agents have been approved by the FDA for the latter indication versus MDD monotherapy, we broadened our analysis to include all drugs (not only aripiprazole, quetiapine, and olanzapine) in the case of adjunctive treatment studies.

Clinical Points

- The high and highly variable placebo response rate is a major obstacle contributing to the failure of randomized controlled trials in major depressive disorder.
- The relative efficacy of the active drug compared to placebo is highly heterogeneous across studies with different placebo response rates, with higher placebo response rates being correlated with a lower probability to detect a statistically significant superiority of the drug versus placebo.
- The response rate in the placebo group is an important aspect to take into account when interpreting results from a trial with an equivocal outcome.
- It is of primary importance to maintain placebo response rates below a critical threshold (30% and 40% for antidepressant monotherapy studies and augmentation/combination studies, respectively).

DATA SOURCES

We sought to identify double-blind, randomized, placebo-controlled trials of (1) antidepressants used as monotherapy for the treatment of MDD and (2) adjunctive pharmacologic strategies for antidepressant partial responders/nonresponders with MDD for possible inclusion in the meta-analysis. We defined *antidepressants* as pharmacologic agents that have or had, at one point, received a letter of approval from the US, Canadian, Japanese, Australian, or European Union drug regulatory agencies for the treatment of MDD. We defined *adjunctive pharmacologic strategies* as either the combination of 2 antidepressants (combination pharmacotherapy) or the combination of antidepressants with pharmacologic agents that are not approved for use as monotherapy in MDD but may boost or enhance the effect of antidepressants (augmentation treatment).

Eligible studies were first identified by using searches of PubMed/MEDLINE, by cross-referencing the search term *placebo* with each of the antidepressant agents as defined above, and then by cross-referencing the search term *depression* with the terms *augmentation*, *adjunct*, and *adjunctive*. In order to expand our database, we then reviewed the reference list of all studies identified, including reviews and meta-analyses. The PubMed/MEDLINE search was limited to articles published in the English language between January 1980 and March 2011 (inclusive). The year 1980 was used as a cutoff in order to decrease diagnostic variability, since the *DSM-III* was introduced in 1980. Final inclusion of articles was determined by consensus between the authors.

STUDY SELECTION

We selected randomized, double-blind, placebo-controlled trials that also met the following criteria: the study (1) defined MDD according to the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition[13]; *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised[14]; *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition[15]; Research Diagnostic Criteria[16]; or Feighner et al[17] diagnostic criteria; (2) had a minimum duration of 4 weeks for antidepressant monotherapy trials and of 1 week for augmentation/combination trials; (3) focused on the use of antidepressants and adjunctive agents in their oral formulation; (4) presented entirely original (not previously published) data; (5) focused on adult patients; (6) did not exclusively focus on elderly patients, patients with comorbid alcohol or substance use disorders, patients with a specific comorbid medical illness, or patients with other depressive disorders, including bipolar disorder, depression with psychotic features, dysthymic disorder, neurotic depression, or minor depression; (7) involved the use of the Hamilton Depression Rating Scale (HDRS),[18] the Montgomery-Asberg Depression Rating Scale (MADRS),[19] or the Clinical Global Impressions-Improvement scale (CGI-I)[20] as one of its outcome measures; and (8) based

treatment nonresponse in the adjunctive trials on the failure of at least 1 antidepressant therapy in the current depressive episode. We included only trials that involved the following study design: antidepressant partial responders/nonresponders with MDD were randomized to continued treatment with the original antidepressant plus adjunctive pharmacotherapy or adjunctive placebo pill.

Our rationale for excluding studies exclusively focusing on patients with a specific Axis III comorbidity derives from a previous finding from our group,[21] demonstrating a trend for higher placebo response rates as well as statistically significantly higher antidepressant response rates in these trials versus traditional MDD trials that typically exclude patients with Axis III comorbidity. Given this difference, our concern was that this discrepancy may have biased our present work if those studies were also included in the present study. In addition, although we contemplated using the same duration criterion for augmentation/combination trials and monotherapy studies, we opted to utilize a shorter duration for potential inclusion in the polypharmacy studies (1 week) in order to retain in the dataset a number of older trials focusing on the use of lithium and triiodothyronine (T_3) primarily. Our rationale was that the inclusion of those studies would result in a dataset of greater statistical power and generalizability of findings to studies of shorter durations. Given that we did not seek to perform head-to-head comparisons of monotherapy and polypharmacy studies, we did not believe that the discrepancy in threshold of duration for inclusion of the respective studies in the dataset would serve to confound our findings.

DATA EXTRACTION

Data were extracted by one of the authors and checked for accuracy by the other. Data extracted included number of patients enrolled, patient characteristics, drug dosages and scheme (fixed versus flexible dosing), duration of the trial, and response rates. *Clinical response* was defined as a 50% or greater reduction in HDRS or MADRS scores from baseline to end point or a CGI-I < 3 at the final visit. For consistency, the HDRS was chosen over the MADRS or CGI-I when response rates from multiple scales were reported. For studies that reported only CGI-I–based response rates, the HDRS-based response rates were either obtained from the sponsor or imputed by using the method of Walsh et al.[5] For consistency, we used intent-to-treat (ITT)–based response rates. The sponsor was contacted to obtain ITT-based response rates whenever not available in the publication. For cases in which the sponsor could not retrieve ITT-based response rates, we utilized response rates based on completers. The probability of receiving placebo was computed from the number of treatment arms and the randomization schedule (ie, 1:1:1) of each trial. For example, a 2-arm trial with a 2:1 randomization favoring active treatment yields a 1 in 3 chance of receiving placebo. For the purposes of our analysis, *placebo response* will be defined as the response rates reported in the placebo group.

Quantitative Data Synthesis

Random-effects meta-analysis was utilized to estimate the pooled risk ratio of responding to antidepressants versus placebo in antidepressant monotherapy trials and to adjunctive drug versus adjunct placebo in adjunctive polypharmacy trials.

Meta-regressions were utilized to investigate the correlation between the placebo response rate and the risk ratio of responding to drug versus placebo, and multiple regressions were utilized to investigate the correlation between the placebo response rate and the drug response rate. Meta-regression is a weighted regression that gives studies with larger sample sizes more weight than smaller studies, since studies are weighted by the precision of their respective effect estimate, and is recommended in a meta-analytic context.

Therefore, we performed the following analysis, separately in the antidepressant monotherapy trials and in the adjunctive trials:

(1) A meta-regression was conducted to assess the correlation between the placebo response rate and the risk ratio of responding to drug (antidepressant or adjunctive agent) versus placebo. Year of publication, severity at baseline, and the probability of being randomized to placebo were entered as covariates in the meta-regression of antidepressant monotherapy trials since they had previously been found to influence the risk ratio of response following antidepressant versus placebo therapy,[3] but they were not entered in the meta-regression of adjunctive trials, since the same variables did not affect the risk ratio of response following adjunctive drug versus adjunctive placebo.[15]

(2) A multiple regression was conducted to assess the correlation between the placebo response rate and the drug (antidepressant or adjunctive agent) response rate. The probability of being randomized to placebo and the dosing scheme (fixed versus flexible) were entered as covariates in addition to sample size when analyzing antidepressant monotherapy trials since they were found to correlate with antidepressant response rates in a previous meta-analysis.[3]

(3) We then divided the trials in 4 groups based on placebo response rates: (1) trials with a placebo response rate < 20%, (2) trials with a placebo response rate ≥ 20% and < 30%, (3) trials with a placebo response rate ≥ 30% and < 40%, and (4) trials with a placebo response rate ≥ 40%. We performed separate meta-regressions and multiple regressions for each group of trials in order to assess the relationship between the placebo response rate and the risk ratio of response to drug (antidepressant or adjunctive agent) versus placebo and the drug response rate.

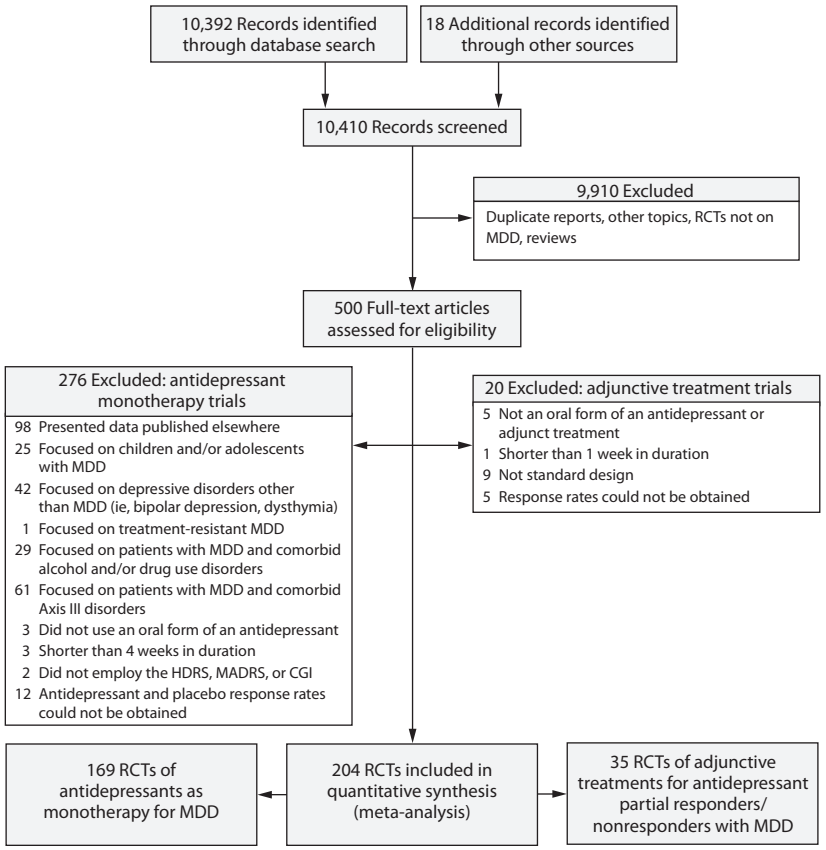
All tests conducted were 2-tailed, with α set at the .05 level.

RESULTS

Initially, 10,392 abstracts were identified in PubMed/MEDLINE. Of these, 9,910 were excluded (other topics, reviews, duplicate reports). Abstracts for the remaining 482 clinical trials (either trials of antidepressants in MDD or trials of adjunctive pharmacologic strategies for antidepressant partial responders/nonresponders with MDD) were obtained and reviewed. Eighteen additional articles were identified after reviewing the reference lists of the articles and 4 large reviews and meta-analyses. Of the 500 potential trials, 296 were excluded for the reasons listed in Figure 1.

A total of 204 articles were found eligible for inclusion in our pooled analysis (169 articles focusing on antidepressant monotherapy and 35 articles focusing on adjunctive polypharmacy). All the articles on adjunctive polypharmacy and 164 of the 169 articles on antidepressant monotherapy reported the results of a single trial, while 5 reported results of several (a total of 12) trials. Therefore, we pooled a total of 305 antidepressant versus placebo comparisons from 176 antidepressant monotherapy trials (46,308 patients randomized to an antidepressant [n = 29,437] versus placebo [n = 16,871]) and 40 adjunctive drug versus adjunctive placebo comparisons from 35 adjunctive trials (4,676 patients randomized to treatment with an adjunctive drug [n = 2,543] versus adjunctive placebo [n = 2,133]). Specific description of the trials is reported in Table 1.

Figure 1. Flow Diagram: Trial Identification and Selection Process



Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, RCT = randomized controlled trial.

Trials of Antidepressants as Monotherapy for MDD

The result of the random-effects meta-analysis indicated that antidepressant therapy resulted in statistically significantly higher response rates than placebo (risk ratio = 1.392; 95% CI, 1.356–1.430; $P < .0001$), *with evidence for statistically significant heterogeneity across the trials* ($Q_{304} = 588.897$, $P < .001$).

Meta-regression and multiple regression analyses suggested that a higher placebo response rate correlated with a significantly lower risk ratio of responding to antidepressant versus placebo (coefficient = −1.517, $P < .001$) and correlated with higher antidepressant response rates (coefficient = 0.431, $P < .001$). The dosing scheme (fixed versus flexible) was the only cofactor entered in our model found to have a statistically significant correlation with the placebo response rate (coefficient = −0.0209, $P = .002$). Similar results were obtained when repeating the analyses for each of the 4 groups as previously defined (trials with a placebo response rate < 20%, ≥ 20% and < 30%, ≥ 30% and < 40%, and ≥ 40%) (Figure 2). The number needed to treat (NNT) in each of the 4 groups was 4.3, 4.0, 6.5, and 8.6, respectively (Figure 3A).

Trials of Adjunctive Treatments for Antidepressant Partial Responders/Nonresponders With MDD

The result of the random-effects meta-analysis indicated that adjunctive active therapy resulted in statistically significantly higher response rates than adjunctive placebo (risk ratio = 1.292; 95% CI, 1.191–1.402; $P < .0001$), and no evidence for statistically significant heterogeneity was shown across the studies ($Q_{39} = 33.814$, $P = .705$).

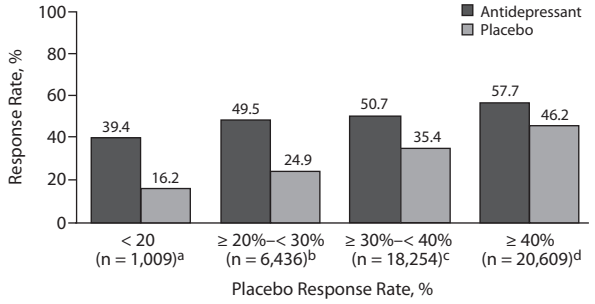
Meta-regression suggested that a higher response rate to the adjunctive placebo correlates with a significantly lower risk ratio of responding to the adjunctive drug versus placebo (coefficient = −1.182, $P < .001$). There was a trend toward statistical significance in the correlation between response rates to adjunctive placebo and adjunctive drug (coefficient = 0.393, $P = .050$). Figure 4 shows adjunctive drug and adjunctive placebo response rates and risk ratios to respond to adjunctive drug versus adjunctive placebo in the 4 groups of trials based on adjunctive placebo response rates. When we repeated the analyses in the 4 groups of trials based on

Table 1. Characteristics of the Trials in the 4 Placebo Response Rate Groups and in the Total Sample for Antidepressant Monotherapy Trials in MDD and for Adjunctive Polypharmacy Trials for Antidepressant Partial Responders/Nonresponders With MDD

	Placebo Response Rate				
Characteristic, Mean ± SD	< 20%	≥ 20%–< 30%	≥ 30%–< 40%	> 40%	All Trials
Antidepressant monotherapy trials					
Year of publication	1988 ± 8.4 y	1992 ± 6.9 y	1997 ± 7.8 y	1998 ± 7.8 y	1996 ± 8.2 y
Sample size, n	50.4 ± 54.8	73.1 ± 73.1	99.2 ± 52.4	109 ± 52.9	96.3 ± 59.0
Duration, wk	5.9 ± 1.7	5.9 ± 1.4	7.1 ± 2.7	7.9 ± 3.5	7.1 ± 2.9
Age, y	50.9 ± 13.8	43.8 ± 8.6	43.4 ± 8.2	44.1 ± 8.7	43.9 ± 8.8
HDRS-17 score (severity at baseline)	24.7 ± 5.8	21.3 ± 4.2	22.2 ± 3.1	21.5 ± 3.9	21.9 ± 93.9
Probability placebo, %	35.4 ± 5.9	38.6 ± 10.4	34.8 ± 9.6	34.6 ± 7.8	35.5 ± 9.1
Women, %	55.0 ± 19.5	56.8 ± 12.9	62.2 ± 7.7	64.1 ± 9.7	61.7 ± 10.7
Adjunctive polypharmacy trials					
Year of publication	2000 ± 6.7 y	2003 ± 6.3 y	2001 ± 6.4 y	2003 ± 6.3 y	2002 ± 604 y
Sample size, n	37.4 ± 54.9	75.2 ± 77.6	43.2 ± 43.3	103 ± 49.9	60.9 ± 62.8
Duration, wk	3.9 ± 2.6	5.9 ± 2.9	5.5 ± 2.2	5.3 ± 0.8	5.2 ± 2.4
Age, y	44.3 ± 6.2	45.2 ± 2.2	44.5 ± 3.6	43.8 ± 2.8	44.7 ± 3.6
HDRS-17 score (severity at baseline)	20.6 ± 1.4	21.1 ± 2.3	20.9 ± 4.3	22.6 ± 2.1	21.3 ± 2.9
Probability placebo, %	46.3 ± 7.3	45.8 ± 9.0	46.7 ± 7.0	41.6 ± 9.1	45.5 ± 7.9
Women, %	66.3 ± 12.5	67.7 ± 11.9	71.1 ± 9.3	65.8 ± 7.4	66.7 ± 10.1

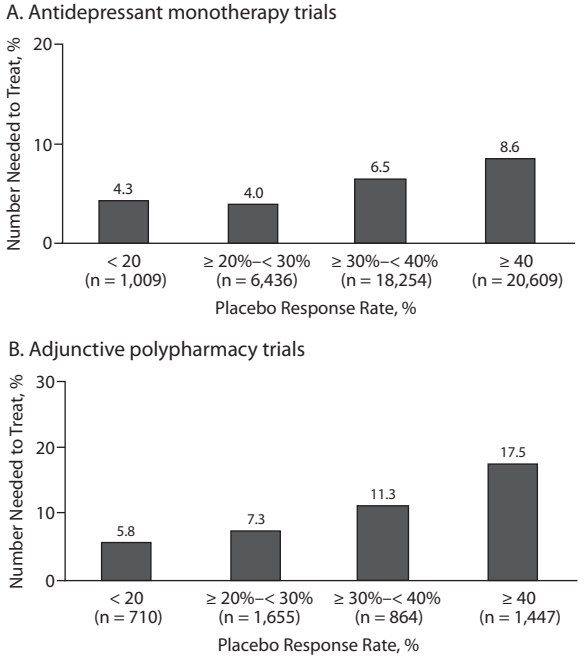
Abbreviations: HDRS-17 = 17-item Hamilton Depression Rating Scale, MDD = major depressive disorder.

Figure 2. Efficacy of Antidepressants Versus Placebo as a Function of Placebo Response Rates



[a]Risk ratio = 2.616; 95% CI, 1.873–3.654; $P < .001$ (12 drug-placebo comparisons).
[b]Risk ratio = 1.940; 95% CI, 1.819–2.068; $P \leq .001$ (52 drug-placebo comparisons).
[c]Risk ratio = 1.447; 95% CI, 1.394–1.503; $P \leq .001$ (120 drug-placebo comparisons).
[d]Risk ratio = 1.246; 95% CI, 1.213–1.279; $P \leq .001$ (121 drug-placebo comparisons).

Figure 3. Number Needed to Treat for Response as a Function of Placebo Response Rates

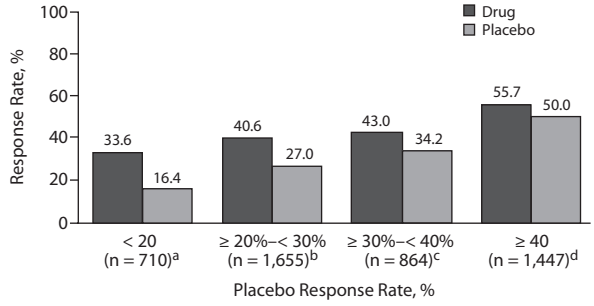


the response rates to adjunctive placebo, we found that only in the group of trials with placebo response rates ≥ 40% did a higher response rate to the adjunctive placebo correlate with a higher response rate to the adjunctive drug (coefficient = 0.601, $P = .028$) and correlate with a trend toward statistical significance a lower risk ratio of responding to the adjunctive drug versus placebo (coefficient = –0.868, $P = .058$). The NNT in each of the 4 groups with placebo response rates < 20%, ≥ 20% and < 30%, ≥ 30% and < 40%, and ≥ 40% was 5.8, 7.3, 11.3, and 17.5, respectively (Figure 3B).

DISCUSSION

This study is the first to systematically assess the correlation between different levels of placebo response rates and the drug response rates as well as the risk ratio of responding to drug versus placebo (drug-placebo "separation," a direct measure of the success of a clinical trial) in antidepressant monotherapy studies for MDD and in augmentation/combination studies for antidepressant partial responders/nonresponders with MDD. We found that higher placebo response rates correlated with higher drug response rates and with a lower risk ratio of response in both monotherapy and augmentation/combination trials. Specifically, when examining NNT for response among MDD monotherapy trials, numbers increased from as little as 4 among trials with a placebo response rate of 30% or less to as much as 8 among trials with a placebo response rate ≥ 40%. Similarly,

Figure 4. Response Rates to Adjunctive Drug Versus Adjunctive Placebo as a Function of Adjunctive Placebo Response Rates



[a]Risk ratio = 1.992; 95% CI,1.508–2.630; $P < .001$ (10 drug-placebo comparisons).
[b]Risk ratio = 1.512; 95% CI, 1.317–1.735; $P < .001$ (12 drug-placebo comparisons).
[c]Risk ratio = 1.253; 95% CI, 1.054–1.489; $P = .011$ (10 drug-placebo comparisons).
[d]Risk ratio = 1.130; 95% CI, 1.035–1.234; $P = .007$ (8 drug-placebo comparisons).

in augmentation studies, NNT for response increased from 5 to 7, to 11, and to 17 as adjunctive placebo response rates increased. Interestingly enough, in monotherapy studies, there was a consistent positive relationship between placebo response and antidepressant response, which was not as apparent in augmentation/combination studies. This may be due to the, overall, weaker placebo effects in the latter group of studies (given that patients are selected for treatment refractoriness) than in general MDD monotherapy studies (overall placebo response rates from this dataset were 38.0% for monotherapy studies and 32.9% for augmentation trials). This explanation is especially plausible given that the only polypharmacy group of studies to demonstrate a statistically significant positive correlation between active and control treatment arms was the one with the highest control response rates.

Several theoretical and practical implications stem from these findings. First, the high variability of the NNT across studies depending on their placebo response rate, the proportional relationship between placebo response rate and NNT for response, and the statistically significant heterogeneity present across studies suggest that the evidence in support of the efficacy of antidepressants and augmentation/combination therapies in MDD derives primarily from a subset of well-designed and executed trials that demonstrate low placebo response rates, with studies demonstrating high placebo response rates predominantly obscuring treatment effects. On the basis of these findings, it is worth questioning whether results from previous meta-analyses that pool together all studies (with different placebo response rates and heterogeneous risk ratio of response to active drug versus placebo) may not reflect the true drug effect, but rather considerably underestimate it. On the contrary, had our finding shown no heterogeneity across studies in terms of outcome and no statistically significant relationship between placebo response rate and NNT, one would feel more confident in assuming that pooled effects across all studies are representative of the true treatment effect. From a practical standpoint, given the greatly reduced risk ratio for response to drug versus placebo for studies with a control group response rate ≥ 40% and ≥ 30% in monotherapy and adjunctive polypharmacy studies, respectively, we might suggest that, in the case of future clinical trials with an equivocal outcome (efficacy of drug is no different than placebo), the conclusion that the drug is not efficacious in MDD can be reached with much less confidence in cases where the response rate in the control group is above this threshold than if it were much lower (ie, lower than the cutoff observed in our analysis). Taking this consideration a step further, it would be of great advantage to be able to perform an interim analysis at a reasonably early stage of a trial, with the purpose of assessing the placebo response rate alone and deciding whether or not to continue the trial based on these thresholds. In fact, the discontinuation of a clinical trial with an unfavorable, high placebo response rate would reduce unnecessary costs, both in terms of financial cost and ethical concerns, since additional patients would avoid being randomized to an, ultimately, uninformative study.

Several limitations should be taken into account when interpreting our findings. Specifically, 1 limitation pertains to the identification of studies to be included in meta-analyses. For example, it is quite possible that either publication bias or the file drawer phenomenon, whereby unpublished studies are more likely to be equivocal than published trials, may have distorted our findings or inflated our results (since our study focused on published clinical trials only). Moreover, the clinical trials included in our study usually included a number of exclusion criteria, and our findings may not be generalized to the excluded patients (ie, patients with bipolar depression or psychotic MDD, patients actively abusing alcohol or drugs, patients with specific medical comorbidities, or patients with serious suicidal ideation). Additionally, there are several limitations regarding the existing clinical literature on augmentation/combination strategies for treatment-resistant depression. Definitions of treatment resistance are still evolving, and no standard exists for studies such as these; therefore, the methods used to define treatment resistance may vary across the studies included in the analysis. Finally, we assume that placebo response rates are uniform throughout the lifetime of a clinical trial, although there are no studies so far that have demonstrated this. Whether time of enrollment during the course of the trial can be a variable affecting placebo response rates, indeed, is an interesting aspect that deserves further investigation in future research, since it may lead to modified enrollment approaches that could further reduce placebo response rates.

In conclusion, the results of the present analysis suggest that the relative efficacy of the active drug compared to placebo in antidepressant monotherapy trials for MDD and in augmentation/combination trials for antidepressant partial responders/nonresponders with MDD is highly heterogeneous across studies with different placebo response rates, with a worse performance in showing a superiority of

the drug versus placebo for studies with placebo response rates greater than 30% and 40%, for monotherapy and augmentation/combination trials, respectively. This finding underlines the importance to maintain response rates below this critical threshold, since excessive placebo responses rates in clinical trials represent one of the most challenging obstacles for new treatment development in MDD.

Drug names: aripiprazole (Abilify), lithium (Lithobid and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others).
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Potential conflicts of interests: **Dr Papakostas** has served as a consultant to Abbott, AstraZeneca, Brainsway, Bristol-Myers Squibb, Cephalon, Dey Pharma, Eli Lilly, GlaxoSmithKline, Evotec AG, Inflabloc, Jazz, Otsuka, PAMLAB, Pfizer, Pierre Fabre, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Shire, Theracos, and Wyeth; has received honoraria from Abbott, Astra Zeneca, Bristol-Myers Squibb, Brainsway, Cephalon, Dey Pharma, Eli Lilly, Evotec AG, GlaxoSmithKline, Inflabloc, Jazz, Lundbeck, Otsuka, PAMLAB, Pfizer, Pierre Fabre, Ridge Diagnostics, Shire, Theracos, Titan, and Wyeth; has received research support from AstraZeneca, Bristol-Myers Squibb, Forest, the National Institute of Mental Health, PAMLAB, Pfizer, and Ridge Diagnostics; and has served (not currently) on the speaker's bureau for Bristol Myers Squibb and Pfizer. **Dr Iovieno** reports no competing interests.
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