Does Inclusion of a Placebo Arm Influence Response to Active Antidepressant Treatment in Randomized Controlled Trials? Results From Pooled and Meta-Analyses

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Objective: To determine if the inclusion of a placebo arm and/or the number of active comparators in antidepressant trials influences the response rates of the active medication and/or placebo.

Data Sources: Searches of MEDLINE, PsycINFO, and pharmaceutical Web sites for published trials or trials conducted but unpublished between January 1996 and October 2007.

Study Selection: 2,275 citations were reviewed, 285 studies were retrieved, and 90 were included in the analysis. Trials reporting response and/or remission rates in adult subjects treated with an antidepressant monotherapy for unipolar major depression were included.

Data Extraction: The primary investigator recorded the number of responders and/or remitters in the intent-to-treat population of each study arm or computed these numbers using the quoted rates.

Data Synthesis: Poisson regression analyses demonstrated that mean response rate for the active medication was higher in studies comparing 2 or more active medications without a placebo arm than in studies comparing 2 or more active medications with a placebo arm (65.4% vs 57.7%, $P < .0001$) or in studies comparing only 1 active medication with placebo (65.4% vs 51.7%, $P = .0005$). Mean response rate for placebo was significantly lower in studies comparing 1 rather than 2 or more active medications (34.3% vs 44.6%, $P = .003$). Mean remission rates followed a similar pattern. Meta-analysis confirmed results from the pooled analysis.

Conclusions: These data suggest that antidepressant response rates in randomized control trials may be influenced by the presence of a placebo arm and by the number of treatment arms and that placebo response rates may be influenced by the number of active treatment arms in a study.

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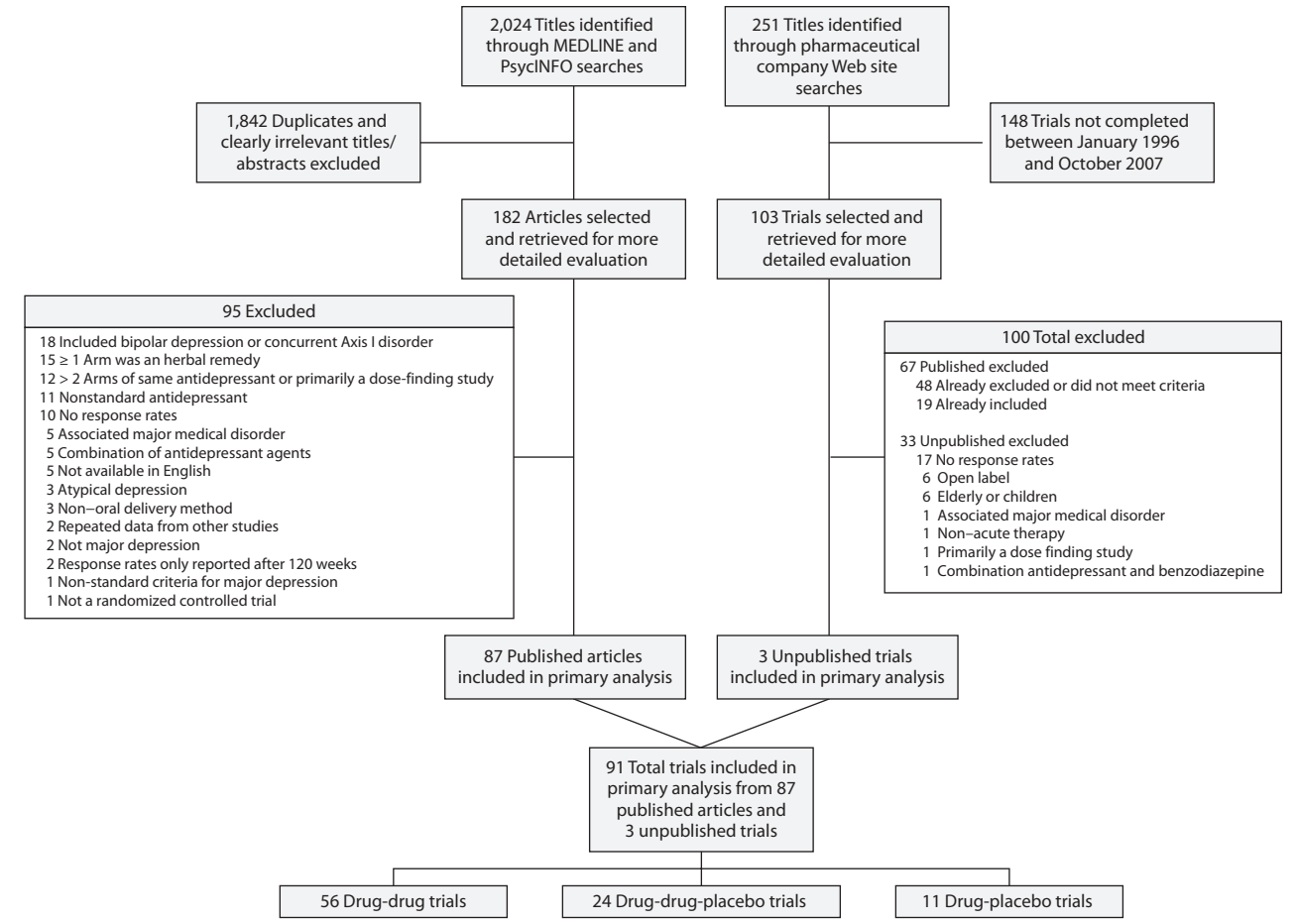
The placebo effect can be thought of as a complex interplay between biochemical reward mechanisms[1] and psychological factors such as expectation.[2] Expectations change throughout the course of placebo-controlled trials as patients wonder whether or not they are receiving placebo[3] and if they are "placebo responders." Some data suggest that higher pretreatment expectations of improvement may raise response rates to antidepressant treatment.[4] In a study focusing on the impact of placebo run-in on response rates to antidepressants, there was the suggestion that the presence of a postrandomization placebo arm might slightly lower the response rates to the active medication, though this result was not observed with most classes of antidepressants and was not statistically significant.[5] Recent work by Woods et al[6] demonstrated that the degree of improvement in subjects with schizophrenia treated with atypical antipsychotic medications in studies with active controls was nearly double that found in placebo-controlled trials. Thus, informing a randomized controlled trial (RCT) subject of the inclusion of a placebo group might change his or her expectations and, possibly, response to the active antidepressant treatment. Likewise, informing subjects that they have a higher chance of receiving an active treatment (ie that there are more active treatment arms in a study) might increase their response to placebo. Indeed, one recent study by Papakostas and Fava[7] showed that lower response rates to antidepressants were associated with increasing probability of receiving a placebo. However, no studies have tested the hypothesis that subject expectation may affect remission rates, where remission refers to the virtual absence of major depressive symptomatology rather than response, which is generally defined as a ≥ 50% improvement in symptoms, despite the fact it has been argued that remission is both more optimal and robust an outcome measure (ie, may be less affected by expectations) than response.[8] This argument arises because responders may still meet criteria for major depression and because failing to achieve remission significantly increases the risk of relapse.

The current study aims to probe the effect of the presence of a placebo group and of the number of active treatment arms on response and remission rates in antidepressant RCTs using both a pooled analysis and a meta-analysis. The

Figure 1. Flowchart of Included and Excluded Articles and Trials



primary hypotheses are that (1) subjects on active treatment will exhibit lower response and remission rates in studies that include a placebo arm than in studies that did not and that (2) subjects on placebo will exhibit higher response and remission rates in studies that had 2 or more active treatment arms than in studies comparing placebo to only 1 active treatment arm.

METHOD

Data Sources and Study Selection

Studies were derived from a literature search from January 1, 1996, to October 31, 2007, using MEDLINE and PsycINFO and the following search string: "*antidepressive agents* or *antidepressant drugs* or *agomelatine* or *amitriptyline* or *amoxapine* or *bupropion* or *citalopram* or *clomipramine* or *desipramine* or *doxepin* or *duloxetine* or *escitalopram* or *s-citalopram* or *fluoxetine* or *fluvoxamine* or *imipramine* or *lofepramine* or *maprotiline* or *milnacipran* or *mirtazapine* or *moclobemide* or *nefazodone* or *nk1 antagonist* or *nk2 antagonist* or *nortriptyline* or *paroxetine* or *reboxetine* or *sertraline* or *tianeptine* or *trazodone* or *trimipramine* or *venlafaxine* or *serotonin uptake inhibitors* or *antidepressive agents*, *tricyclic* or *serotonin norepinephrine reuptake inhibitors* or *dopamine uptake inhibitors* or *monoamine oxidase inhibitors* or *heterocyclic drugs* or *mixed re-uptake inhibitors* or *reversible monoamine oxidase inhibitors* or *placebo*" AND "*Depressive Disorder*" (MEDLINE)/"*Major Depression*" (PsycINFO) AND "*Double Blind*" (MEDLINE and PsycINFO) or "*Double-Blind Method*" (MEDLINE only). The search was limited to human subjects and to treatment outcome/randomized control trial.

The search of MEDLINE resulted in 1,031 articles and the search of PsycINFO resulted in 993 articles, with a number of these representing duplicates. Of these articles, 87 (~5%) met criteria for inclusion in the pooled analysis (Figure 1). To be included, studies had to (1) report double-blind RCT data, (2) examine adult subjects given a diagnosis of either major depressive disorder (MDD) or of a major depressive episode (MDE), (3) be available in English, (4) include response rates and/or remission rates (or the raw number of responders and/or remitters) as well

as the number of subjects in the intent-to-treat population for 1 or more antidepressants, and (5) report response and/or remission rates within the first 120 days of treatment (ie acute treatment). A study was excluded if it examined subjects with bipolar or psychotic depression or if some or all subjects were pregnant or had a second primary psychiatric diagnosis, except anxiety disorders. A number of studies did not specifically declare that they excluded bipolar depression or psychosis or stated that they excluded only mood-incongruent psychosis. These studies were nonetheless included in the analysis. Studies focusing solely on elderly patients were excluded since response rates may be systematically lower in this population.[9] Studies of children or adolescents (≤ 16 years) were also excluded for similar reasons. Studies whose sole focus was atypical depression were excluded since these studies necessarily have very different definitions of response than in standard depression studies. For example, atypical depression is commonly associated with weight gain rather than weight loss. Standard depression rating scales, such as the Hamilton Depression Rating Scale (HDRS), do not include weight gain as a symptom and will actually score weight loss (symptom improvement in atypical depression) as though the subject is more depressed. Studies with subjects who were suffering or had recently suffered from a major medical condition such as a myocardial infarction were excluded as were studies examining combinations of antidepressant agents, nonstandard agents such as valproate, herbal remedies such as St John's wort or nonoral delivery methods such as the selegiline patch.

Unpublished antidepressant trials were also examined. Because publicly available US Food and Drug Administration reviews typically include mean change in depression scores and do not report response or remission rates (Erick H. Turner, MD, Oregon Health and Science University, e-mail communication, March 20, 2008), an online search of individual pharmaceutical company trial registries was performed.[10–16] This search resulted in 251 trials, of which 103 were completed/reported between January 1996 and October 2007. The majority (67 trials) were published and, of these, 19 met inclusion criteria and had already been identified in the previous searches and included in the analysis. Of the 36 unpublished trials identified, only 3 reported response and/or remission rates and met full inclusion criteria and were therefore included in the analysis.

In examining the published and unpublished studies, 3 different types of RCTs were identified: studies with (1) 2 or 3 active medications without a placebo arm (drug-drug)[17–72]; (2) 2 or 3 active medications and a placebo arm (drug-drug-placebo)[72–95]; and (3) a single active medication and a placebo arm (drug-placebo)[96–106] (Table 1).

In 2 studies, subjects were randomly assigned to 1 of 2 doses of duloxetine, both greater than standard clinically effective dosages, or placebo.[80,88] These studies were included and each dose was considered as an active comparator (drug-drug-placebo). Similarly, 1 study[83] examined the efficacy of controlled-release and immediate-release paroxetine as compared with placebo. This study was included in the drug-drug-placebo group. One study[55] did not describe specific diagnostic criteria to define MDD or an MDE; rather *major depression* was defined using a Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 20, a score consistent with mild to moderately severe depressive symptoms. This study was included in the analysis. One article[72] reported the results of 2 studies of reboxetine versus fluoxetine, 1 placebo controlled and 1 without a placebo group. Both studies were included separately as a drug-drug-placebo and drug-drug study respectively.

Data Extraction and Synthesis

For studies in which response/remission rates were quoted at several points in a particular trial, the rates closest to 8 weeks were used, since the majority of studies lasted for 6–9 weeks. In studies with multiple definitions of response, a standard definition of a ≥ 50% improvement in HDRS or MADRS scores was used. For instances in which both HDRS and MADRS response and/or remission rates were reported, rates based on the more widely used HDRS scale were used. Some studies had response/remission defined using the HDRS and/or the MADRS, but also included other rating scales such as the Clinical Global Impressions-Severity of Illness or -Improvement scales or the Inventory of Depressive Symptomatology in their definition of response and/or remission. These studies were included, even though the estimates of response/remission may have been slightly more conservative.

One of the authors (M.S.) performed all of the data extraction. Weighted mean response rates appearing in the results section were obtained by dividing the total number of responders across studies of a particular type by the total number of participants in those studies. Remission rates were obtained in the same way.

Descriptive statistics were calculated for all variables of interest. Response and remission data were summarized using counts and percentages. Statistics were calculated for response and remission rates by means of Poisson regression analyses, which weighted individual studies by the number of subjects in each. The Poisson regression analyses adjusted the standard errors of all estimates to account for the possibility of overdispersion (the case in which the variance exceeds the mean). These analyses were carried out using SAS version 9.1 (SAS Institute, Inc; Cary, North Carolina).

The comparison of rates between trial types, as opposed to drug-placebo differences, does not lend itself to a typical meta-analysis. However, meta-analytic techniques were employed to confirm Poisson regression findings while preserving trial heterogeneity. Results for each of the different trial designs were combined using the random-effects meta-analytic method of Cochran.[107,108] This method weighs studies by study variance and sample size. The

Table 1. Summary of the 91 Randomized Control Trials in the Pooled Analysis

	Definition of Response		Definition of Remission			
Type of Study	Definition Type	No. of Studies	Definition Type	No. of Studies	Treatments Studied (no. of studies)	
Drug-drug[17–72a]	≥ 50% ↓ in HDRS scores	40	HDRS score ≤ 7	21	Amineptine (1)	Milnacipran (1)
	≥ 50% ↓ in MADRS scores	9	MADRS score < 12	4	Amitriptyline (5)	Mirtazapine (8)
	≥ 50% ↓ in HDRS scores + CGI-I score of 1 or 2	2	HDRS score ≤ 8	3	Bupropion SR (1)	Moclobemide (1)
					Bupropion XL (1)	Nortriptyline (1)
	≥ 50% ↓ in HDRS scores or ≥ 50% ↓ in MADRS scores + CGI-I score of 1 or 2	2	HDRS score ≤ 7 + CGI-I score of 1 or 2	2	Citalopram (6)	Paroxetine (14)
					Clomipramine(3)	Reboxetine (4)
					Doxepin (1)	Sertraline (13)
	≥ 50% ↓ in HDRS scores or CGI-I score of 1 or 2	1			Duloxetine (3)	Tianeptine (1)
					Escitalopram (7)	Trazodone PR (2)
	≥ 50% ↓ in MADRS scores + MADRS score < 18	1			Fluoxetine (19)	Venlafaxine (10)
					Fluvoxamine (3)	Venlafaxine ER (1)
	≥ 50% ↓ in MADRS scores + CGI-S score 3 + CGI-I score of 1 or 2	1			Imipramine (2)	Venlafaxine XR (4)
					Maprotiline (1)	
Drug-drug-placebo[72–95a]	≥ 50% ↓ in HDRS scores	21	HDRS score ≤ 7	11	Amitriptyline (1)	Imipramine (2)
	≥ 50% ↓ in MADRS scores	4	MADRS score < 12	4	Bupropion SR (4)	Nefazodone (1)
					Bupropion XL (3)	Paroxetine (4)
					Citalopram (2)	Paroxetine CR (1)
					Duloxetine (3)	Reboxetine (2)
					Escitalopram (4)	Sertraline (4)
					Fluoxetine (9)	Venlafaxine (1)
					Fluvoxamine (1)	Venlafaxine XR (6)
Drug-placebo[96–106]	≥ 50% ↓ in HDRS scores	8	HDRS score ≤ 7	5	Agomelatine (1)	Nefazodone (1)
	≥ 50% ↓ in MADRS scores	1	HDRS score ≤ 6	1	Bupropion XL (1)	Pirlindole (1)
	≥ 50% ↓ in IDS-C-30 scores	1	IDS-C-30 score ≤ 13	1	Duloxetine (4)	Reboxetine (1)
					Escitalopram (1)	Venlafaxine XR (1)

[a]Massana[72] reported the results of 2 studies of reboxetine versus fluoxetine, 1 placebo controlled and 1 without a placebo group.
Symbol: ↓ = decrease.
Abbreviations: BQOL = Battelle Quality of Life Questionnaire, CGI-I = Clinical Global Impressions–Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, CR = controlled release, ER = extended release, HDRS = Hamilton Depression Rating Scale, IDS-C-30 = 30-item Inventory of Depressive Symptomatology-Clinician Rated, MADRS = Montgomery-Asberg Depression Rating Scale, PR = prolonged release, SR = sustained release, XL = extended release, XR = extended release.

random-effects model assumes that the treatment effects from the various studies in the meta-analysis form a distribution (ie, there is no fixed treatment effect) and this method is more robust when heterogeneity is present. Overall proportion of responders/remitters and 95% CI were calculated for each different trial design. Heterogeneity was estimated with Cochran Q, which is the weighted sum of squared differences between individual study effects and the pooled effect across studies.[107,108]

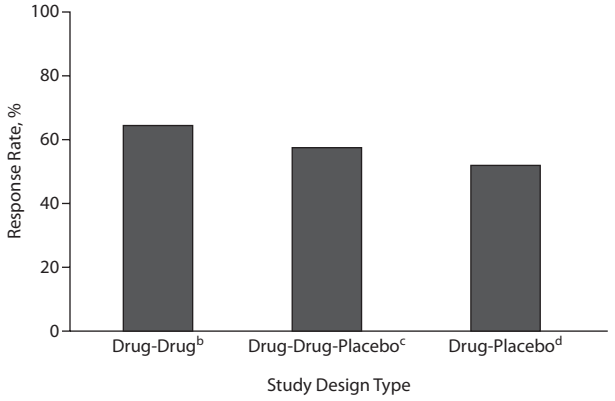
RESULTS

Figures 2 and 3 present overall weighted mean response rates for the pooled studies. The mean response rate for the active medication was highest (65.4% [n = 12,052]) when no placebo arm was present (drug-drug studies). This rate was significantly greater than the mean active medication response rate for either drug-drug-placebo studies (57.7% [n = 6,318], $P < .0001$) or drug-placebo studies (51.7% [n = 1,041], $P = .0005$). While response rate for active medication was numerically greater in drug-drug-placebo studies than in drug-placebo studies, this difference failed to achieve statistical significance in the pooled analysis (57.7% [n = 6,318] vs 51.7%, [n = 1,041], $P = .11$). Response rate for placebo was significantly higher in drug-drug-placebo studies than in drug-placebo studies (44.6% [n = 2,893] vs 34.3% [n = 1,066], $P = .003$).

The mean remission rate for active medication was significantly different between drug-drug and drug-placebo studies (46.7% [n = 6,235] vs 32.2% [n = 726], $P = .002$) and between drug-drug-placebo and drug-placebo studies (41.7% [n = 4,495] vs 32.2% [n = 726], $P = .018$) (Figure 4). Mean remission rate for active medication between drug-drug and drug-drug-placebo studies trended toward statistical significance (46.7% [n = 6,235] vs 41.7% [n = 4,495], $P = .05$). Remission rate to placebo was significantly higher in drug-drug-placebo studies than in drug-placebo studies (30.5% [n = 1,867] vs 19.1% [n = 742], $P = .013$) (Figure 5). When response and remission rates for both active medication and placebo, under the various study designs, were calculated using meta-analytic techniques, results were similar to those estimated with Poisson regression analyses (Table 2). Heterogeneity was present, supporting the use of a random-effects model to combine data.

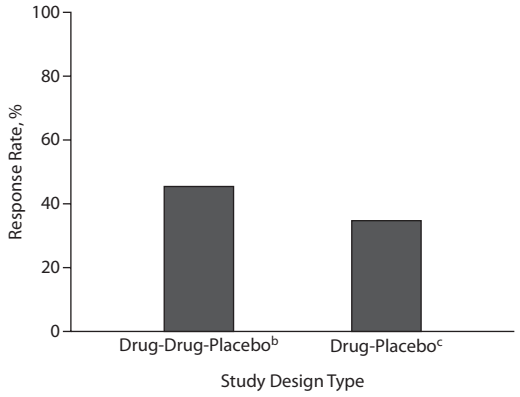
Poisson regression analyses also demonstrated that neither year of publication nor study duration had a significant impact on outcomes for subjects on either active medication or placebo.

Figure 2. Response Rates for Active Antidepressant Across Different Study Designs[a]



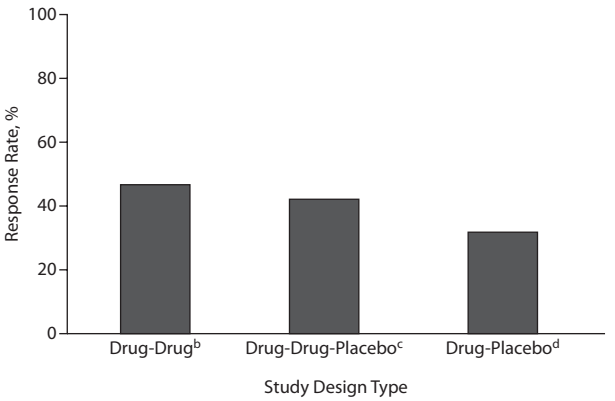
[a]Poisson regression was used for analysis of drug-drug studies vs drug-drug-placebo studies (IRR=1.13; 95% CI, 1.07–1.20; $P<.0001$), drug-drug studies vs drug-placebo studies (IRR=0.790; 95% CI, 0.694–0.899; $P=.0005$), and drug-drug-placebo studies vs drug-placebo studies (IRR=0.896; 95% CI, 0.783–1.02; $P=.11$).
[b]n = 12,052.
[c]n = 6,318.
[d]n = 1,041.
Abbreviation: IRR=incidence rate ratio.

Figure 3. Response Rates for Placebo Across Different Study Designs[a]



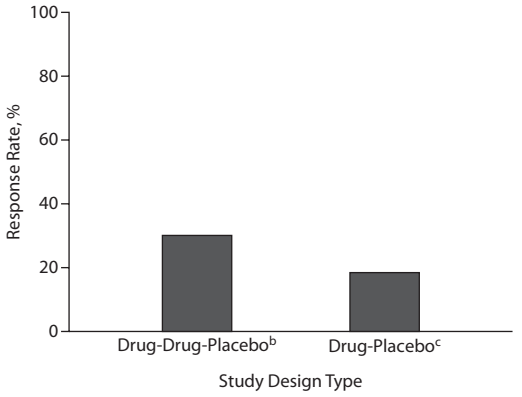
[a]Poisson regression was used for analysis of drug-drug-placebo studies vs drug-placebo studies (IRR=0.769; 95% CI, 0.648–0.913; $P=.003$).
[b]n = 2,893.
[c]n = 1,066.
Abbreviation: IRR: incidence rate ratio.

Figure 4. Remission Rates for Active Antidepressant Across Different Study Designs[a]



[a]Poisson regression was used for analysis of drug-drug studies vs drug-drug-placebo studies (IRR=1.12; 95% CI, 1.00–1.25; $P=.05$), drug-drug studies vs drug-placebo studies (IRR=0.630; 95% CI, 0.478–0.830; $P=.002$), and drug-drug-placebo studies vs drug-placebo studies (IRR=0.705; 95% CI, 0.532–0.934; $P=.018$).
[b]n = 6,235.
[c]n = 4,495.
[d]n = 726.
Abbreviation: IRR=incidence rate ratio.

Figure 5. Remission Rates for Placebo Across Different Study Designs[a]



[a]Poisson regression was used for analysis of drug-drug-placebo studies vs drug-placebo studies: (IRR=0.625; 95% CI, 0.434–0.899; $P=.013$).
[b]n = 1,867.
[c]n = 742.
Abbreviation: IRR=incidence rate ratio.

DISCUSSION

The Lessebo Effect

The most significant finding of the present study is that response rates to the active antidepressant medication are lower in studies that include a placebo arm. This confirms previous speculation by Trivedi and Rush[5] and demonstrates the same effect for antidepressants in depression that was shown by Woods et al for antipsychotics in schizophrenia.[6] The literature is replete with articles on the placebo effect and the nocebo effect, which respectively describe positive and negative effects of an inactive treatment itself. However, there has been little discussion of how including a placebo arm affects the response of subjects to active treatment. An important component of the placebo effect is that a patient taking an inert or innocuous substance derives a benefit as

Table 2. Meta-Analysis of Outcomes Across Different Study Designs

Study Design	n	Meta Success Rate (95% CI)	Homogeneity (df)	*P* Value
Response on active medication				
Drug vs drug	12,052	0.65 (0.62–0.68)	593.15 (55)	<.0001
Drug vs drug vs placebo	6,318	0.58 (0.55–0.60)	121.33 (23)	<.0001
Drug vs placebo	1,041	0.54 (0.49–0.59)	25.10 (10)	.0052
Remission on active medication				
Drug vs drug	6,235	0.46 (0.42–0.50)	301.91 (29)	<.0001
Drug vs drug vs placebo	4,495	0.41 (0.37–0.45)	82.71 (13)	<.0001
Drug vs placebo	726	0.35 (0.25–0.45)	52.99 (6)	<.0001
Response on placebo				
Drug vs drug vs placebo	2,893	0.44 (0.41–0.46)	59.63 (23)	<.0001
Drug vs placebo	1,066	0.32 (0.28–0.36)	19.69 (10)	.032
Remission on placebo				
Drug vs drug vs placebo	1,867	0.29 (0.25–0.33)	51.38 (12)	<.0001
Drug vs placebo	742	0.18 (0.15–0.22)	9.14 (6)	.1658

a result of a belief that he or she may be receiving an active therapy. The current findings suggest that the inclusion of a placebo arm might lead to a reduction in the beneficial effect of an active compound because the patient is uncertain as to whether his or her randomly assigned compound is truly active or not. For purposes of brevity we will refer to this as the "lessebo effect." Trivedi and Rush[5] speculated that the expectations of subjects might influence their response to active antidepressant therapy, but concluded that there was insufficient evidence to make this assertion. The present research demonstrates that the lessebo effect does have a significant impact on response and remission rates in antidepressant RCTs. This lessebo effect appears, generally, to be affected by the perceived odds of receiving active treatment, supporting the notion that it is the result of rational skepticism on the part of subjects. The current analysis has shown that the pooled response rate to active medication in the treatment group was 65.4% in drug-drug studies as compared with 51.7% in drug-placebo studies. When 2 medications were tested against placebo (drug-drug-placebo), that is, when there was only a ~33% chance of receiving placebo, the response rate was an intermediate 57.7%. Furthermore, the magnitude of the lessebo effect, in the published RCTs evaluated here, appears to be on the order of 6%–14% depending on the study designs being compared.

The corollary of this effect is seen in the placebo response rate. When only 1 medication is studied against placebo (drug-placebo), placebo group response rates are 34.3%. However, when subjects are told that they have a 2 in 3 chance of being placed in a treatment group (drug-drug-placebo), the placebo response rate is significantly higher (up to 44.6%). This corollary effect, whose magnitude is on the order of 10%, further supports the notion that rational skepticism/optimism has a significant impact on response rates in placebo-controlled antidepressant RCTs.

Of course, there are many variables that influence subjects' response rates to active medications including demographic factors,[109–111] severity of illness,[112] number of follow-up visits,[113] their expectations[4] as well as the expectations of the raters in each study.[114] One might also question whether other components of the therapeutic interaction might induce a lessebo effect; for example, the attitude of the treatment team or preexisting negative evaluation by subjects of the study medication or of medications in general. Indeed, it is possible that rater bias accounts for some or all of the present findings. For example, in double-blind RCTs that have a drug-drug-placebo design, raters may also come to the conclusion that there is a 67% chance that subjects will be receiving the active treatment and this may unconsciously affect their judgment regarding how many people "ought" to respond and therefore potentially elevate the ratings of recovery across all subjects and treatment conditions.

Remission rates to active medication also decreased with the inclusion of a placebo arm and increased with the addition of multiple active comparators. As with response, placebo remission rates were significantly higher in drug-drug-placebo studies than in drug-placebo studies ($P = .013$). Therefore, it appears that the lessebo effect impacts remission rates in much the same way as it does response rates. So, despite the fact that remission may be a more optimal and robust outcome than response, it seems to have little or no advantage in terms of mitigating the lessebo effect.

It is interesting to contrast the results presented here with those of Khan et al[115] who looked at the correlation between the number of active antidepressant treatment arms and the relative "success" of trials (where more "successful" trials were defined as having greater antidepressant-placebo differences). They found that a greater number of treatment arms was associated with trials that were not as successful/had smaller antidepressant-placebo differences. Though trial success was not the focus of the current study, a similar pattern can be inferred from the data presented here. That is, active antidepressant response rates were 6.0% greater (57.7% vs 51.7%) in drug-drug-placebo studies than in drug-placebo studies, whereas placebo response rates were 10.3% greater (44.6% vs 34.3%). Therefore, the relative magnitude of the lessebo effect on placebo response may be greater than its impact on the active medication response,

making it harder to show superiority in studies with more active treatment arms.

Apart from research by Trivedi and Rush[5] as well as Papakostas and Fava[7] in depression and Woods et al[6] in schizophrenia, the effect of a placebo arm on treatment response has not been investigated in other mental health conditions. While this work has focused on antidepressants, it is reasonable to speculate that the lessebo effect is relevant to other kinds of treatment for a variety of other psychiatric and medical conditions.

Limitations

The main limitation of this study is that it is a pooled analysis of a large number of studies that did not have identical experimental protocols. Participants necessarily differed between these studies, introducing the possibility that participant characteristics might influence the differences between the 3 study types. However, for patient characteristics to systematically affect these results, it would be necessary to hypothesize that specific subject groups are attracted or recruited for specific types of studies. For example, a systematic bias would be introduced if patients with the highest chance of response, or the greatest expectation to respond, were recruited specifically to drug-drug trial as compared with drug-drug-placebo trials. It is unlikely that for all 90 studies (91 trials) conducted across multiple sites that this kind of systematic bias would exist and influence the results: nonetheless, it is important to consider this factor in interpreting these results. Furthermore, quantitative information was extracted from studies meeting inclusion criteria without any assessment or statistical weighting based on the quality of the individual study design so that, as in a meta-analysis, sources of bias between studies were not controlled for. Again, for this to affect the conclusions of the present analyses, one would have to hypothesize that certain study types are systematically biased toward having designs of greater or lesser quality, which is unlikely. It is also important to note that these results may apply only to adults with unipolar, nonpsychotic major depression.

The current work relied on the definitions and conclusions calculated from raw data by each group of investigators. We did not have access to the raw HDRS scores for these manuscripts. In all cases, however, this research focused on response and/or remission rates which, it has been argued, may be a more clinically meaningful measure of efficacy than change in absolute depression rating scale scores.[75] Finally, the vast majority of studies examined and reported in this analysis were published trials; it is likely that there are other unpublished trials that could not be accessed and therefore, the current findings may not be representative of all RCTs of antidepressants. Indeed, unpublished studies tend to be failed studies, that is, with no appreciable difference between active drugs and placebo. Inclusion of more unpublished studies may have diminished or even rendered insignificant the effects that were observed. In light of recent work by Turner et al[116] demonstrating that there has been selective publication of placebo-controlled antidepressant trials over the past 2 decades, further investigation of unpublished studies would be a worthwhile endeavor in the future to determine how robust the lessebo effect is in antidepressant RCTs. Nonetheless, we did search and include as many unpublished datasets as were available.

CONCLUSIONS

This pooled analysis of 88 published and 3 unpublished antidepressant trials found that the inclusion of a placebo arm influences response and remission rates in antidepressant treatment trials of adults with nonpsychotic, unipolar major depression. This important finding may have significant implications for interpretation of past and future antidepressant trials and should be taken into account when comparing response rates for antidepressants derived from RCTs that have different designs. The investigators propose that this effect (the lessebo effect) should be further investigated. Other factors, such as the number of assessments, the duration of the trial and the class of antidepressants tested could be examined to determine if they have any added contribution to the lessebo effect.

Drug names: bupropion (Aplenzin, Wellbutrin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Zonalon and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), milnacipran (Savella), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), trimipramine (Surmontil and others), venlafaxine (Effexor and others).

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