Does the Presence of an Open-Label Antidepressant Treatment Period Influence Study Outcome in Clinical Trials Examining Augmentation/Combination Strategies in Treatment Partial Responders/Nonresponders With Major Depressive Disorder?

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ABSTRACT

Objective: The authors sought to determine study design factors that may influence clinical trial outcome in augmentation/combination trials for antidepressant partial responders/nonresponders with major depressive disorder (MDD) and to examine whether the use of a prospective treatment phase (lead-in) to assess antidepressant nonresponse may result in a better chance to detect a drug-placebo separation in such trials.

Data Sources: MEDLINE/PubMed publication databases were searched for randomized, double-blind, placebo-controlled trials of adjunctive pharmacologic strategies for antidepressant partial responders/nonresponders with MDD. The search term *depression* was successively cross-referenced with the terms *augmentation*, *adjunct*, and *adjunctive* to identify pertinent trials. (The search was limited to articles published between January 1980 and October 2010.)

Study Selection: Thirty-five articles involving 40 adjunctive drug versus placebo comparisons were pooled (n = 4,676). Final inclusion of articles was determined by consensus between the authors.

Data Extraction: Data extracted included whether there was a lead-in phase and, if so, the drugs, the doses, and the total duration of the lead-in phase. Additional data extracted included the number of patients enrolled, patient characteristics, methods used to define treatment resistance, drug dosages, duration of the adjunctive trial, response and remission rates, and rates of discontinuation for any reason and for adverse events.

Results: The risk ratio of responding to the adjunctive drug versus placebo was not influenced by any of the study design factors analyzed (probability of receiving placebo, year of publication, severity of depression at baseline). Meta-regression analysis yielded no significant difference in the risk ratio of responding and remitting to the adjunctive drug versus placebo between studies that did versus did not include an antidepressant lead-in phase. However, pooled response/remission rates for adjunctive drug and placebo were statistically significantly lower in trials that did versus did not include a lead-in phase (response rates: for adjunctive drug, 42.6% vs 47.4%, respectively, $P = .014$; for adjunctive placebo, 29.7% vs 36.2%, respectively, $P = .002$; remission rates: for adjunctive drug, 31.0% vs 37.3%, respectively, $P = .003$; and adjunctive placebo, 18.1% vs 24.7%, respectively, $P = .001$).

Conclusions: These results suggest that the choice to use historical data only to define treatment resistance prior to patient enrollment and randomization rather than requiring patients to first undergo a prospective lead-in phase can be a reasonable and evidence-supported approach to design effective clinical trials on augmentation/combination strategies for partial responders/nonresponders with MDD.

J Clin Psychiatry 2012;73(5):676–683

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Submitted: *March 1, 2011; accepted May 16, 2011.*
Online ahead of print: *April 3, 2012 (doi:10.4088/JCP.11r06978).*
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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, along with certain forms of psychotherapy, have long been the mainstay of treatment for MDD. However, despite the progressive increase in the number of available agents, it has become evident that the effectiveness of antidepressant monotherapy for MDD is much more modest than what was once believed.[1–3] As a consequence, several pharmacologic strategies have been developed to treat patients who have experienced insufficient symptom response to a first-line antidepressant.

One approach is combining the initial antidepressant with a second antidepressant with a different pharmacologic profile (combination pharmacotherapy) or augmenting the treatment regimen with a non-antidepressant agent (augmentation treatment). Augmentation strategies have a long history. The use of stimulants and triiodothyronine (T_3) to augment tricyclic antidepressants was first described as early as 4 decades ago.[4] Subsequently, the use of several other agents for augmentation has been described, including lithium, thyroid hormone, testosterone, lamotrigine, inositol, pindolol, omega-3 fatty acids, buspirone, and atypical antipsychotic agents.[5] When designing clinical trials of adjunctive treatments (augmentation and combination therapies) for treatment-resistant depression (TRD), one important issue regards the assessment of treatment resistance.[6–10] A broadly accepted definition of TRD is the failure to respond to at least 1 adequate trial of antidepressant therapy. However, antidepressant nonresponse may be determined either using a prospective trial (antidepressant lead-in phase) or relying on historical nonresponse. The decision whether to use a lead-in phase to assess treatment nonresponse prior to the randomization in the adjunctive trial may have a great impact on the design of the study, as using a lead-in phase requires a much larger number of patients to be recruited, as well as a longer duration of the overall trial. This reflects in significantly higher costs and might affect the feasibility of the trial, which, in turn, may delay the development of new effective treatments for TRD.

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Clinical Points

- The use of an antidepressant lead-in phase to assess treatment nonresponse does not enhance the ability to detect a statistically significant treatment effect in randomized controlled trials of augmentation/combination trials for treatment-resistant depression.
- The choice to rely on historical data only to assess treatment nonresponse and to allow patients with treatment-resistant depression to be randomized without having to go through a prospective lead-in phase is a reasonable and evidence-supported approach that results in lower cost of the trial and quicker time to completion.

However, to date, whether the use of a pre-randomization antidepressant lead-in phase in trials of adjunctive treatments for antidepressant partial responders/nonresponders with MDD has an impact on the clinical trial outcome (ie, higher chances of trial "success") has not been systematically studied. In fact, Nelson and Papakostas, in a meta-analysis of the efficacy of adjunctive atypical antipsychotic agents in MDD,[11] suggested that the relative probability of achieving response or remission with an atypical antipsychotic agent versus placebo augmentation was not influenced by the use of a lead-in phase to prospectively establish antidepressant resistance. They reached this conclusion in spite of the fact that the pooled response rates in trials requiring a failed prospective trial were considerably lower than response rates in trials using historical data, suggesting that patients who did not respond in prospective treatment were more treatment resistant. Identifying whether the presence of a pre-randomization lead-in phase, as well as other elements of study design, affects the clinical trial outcome of adjunctive treatments for antidepressant partial responders/nonresponders with MDD (ie, the likelihood to detect a drug-placebo separation) can lead to the design of more effective clinical trials for this patient population. Therefore, the purpose of the present work was (1) to examine whether elements of clinical trial design that have previously been found to predict clinical trial outcome in antidepressant monotherapy trials for MDD (eg, the probability of receiving placebo, the year of publication, and the severity of depression at baseline) also predict trial outcome in augmentation/combination strategies for TRD, and (2) to examine whether the use of a prospective lead-in phase to assess antidepressant nonresponse may result in a better chance to detect a drug-placebo separation in such trials.

METHOD

Data Sources and Search Strategy

We sought to identify double-blind, randomized, placebo-controlled trials of adjunctive pharmacologic strategies for antidepressant partial responders/nonresponders with MDD for possible inclusion in the meta-analysis. Specifically, we sought randomized, double-blind studies in which antidepressant partial responders and nonresponders with MDD were randomized to treatment with either (1) continued treatment with the original antidepressant plus adjunctive pharmacotherapy or (2) continued treatment with the original antidepressant plus adjunctive placebo pill. Adjunctive pharmacologic strategies were defined 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). Such augmenting agents include but are not limited to atypical antipsychotics, lithium, anticonvulsants, psychostimulants, T_3, estrogen, pindolol, buspirone, folate, *S*-adenosyl methionine, omega-3 fatty acids, and inositol. Eligible studies were first identified using searches of PubMed/MEDLINE, by successively cross-referencing the search term *depression* with the terms (1) *augmentation*, (2) *adjunct*, and (3) *adjunctive*. The PubMed/MEDLINE search was limited to articles that were published between January 1, 1980 and October 30, 2010 (inclusive); 1980, was used as a cutoff in our search in order to decrease diagnostic variability, since the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (*DSM-III*) was introduced in 1980. In order to expand our database, we then reviewed the reference list of all studies identified with PubMed/MEDLINE. Final inclusion of articles was determined by consensus between the authors.

Study Selection

We selected for randomized, double-blind, placebo-controlled trials of adjunctive pharmacologic strategies (combination and augmentation treatments) for antidepressant partial responders and nonresponders with MDD. Treatment nonresponse was based on the failure of at least 1 antidepressant therapy in the current depressive episode, determined either by history or by a prospective trial (lead-in phase) prior to the beginning of the adjunctive trial. We then selected for studies that also met all of the following criteria:

1. Defined MDD according to the *DSM-III*[12]; *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised[13]; *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [14]; Research Diagnostic Criteria [15]; or Feighner Diagnostic Criteria.[16]
2. Were of at least 1 week in duration.
3. Focused on the use of antidepressants and augmenting agents in their oral formulation.
4. Presented entirely original (not previously published) data.
5. Focused on the treatment of adult patients.
6. Did not exclusively focus on the treatment of patients with bipolar depressive disorder, depression

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with psychotic features, minor depression, or perinatal depression.
7. Did not exclusively focus on the treatment of MDD in patients with comorbid alcohol or substance use disorders or patients with a specific comorbid medical illness.
8. Involved the use of the Hamilton Depression Rating Scale (HDRS),[17] the Montgomery-Asberg Depression Rating Scale (MADRS),[18] or the Clinical Global Impressions-Improvement (CGI-I) scale[19] as one of their outcome measures.
9. Involved the following study design: antidepressant partial responders and nonresponders with MDD were randomized to treatment with either (a) continued treatment with the original antidepressant plus adjunctive pharmacotherapy or (b) continued treatment with the original antidepressant plus adjunctive placebo pill.

Data Extraction

Data were extracted by one of the authors and checked for accuracy by the other. Data extracted included whether there was a lead-in phase and, if so, the agents, the doses, and the total duration of the lead-in phase. Additional data extracted included the number of patients enrolled, patient characteristics, methods used to establish treatment resistance, drug dosages, duration of the adjunctive trial, response and remission rates, and rates of discontinuation for any reason and for adverse events.

Clinical response was defined as a 50% or greater reduction in HDRS or MADRS scores, baseline to endpoint, or a CGI-I score < 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 only reported CGI-based response rates, the HDRS-based response rates were either obtained from the sponsor or imputed using the method of Walsh et al.[20] (To compare the HDRS scores across studies using different versions of the HDRS, we prorated the HDRS score by dividing the score by the number of items in the HDRS version and multiplied by 17.) Remission rate and discontinuation rate were defined per each protocol. For consistency, we used intent-to-treat (ITT)–based response rates in the present analysis. Whenever ITT-based response rates were not available in the publication, the sponsor was contacted to obtain ITT-based response rates. In cases for which the sponsor could not retrieve ITT-based response rates, we utilized response rates based on completers. The probability of receiving adjunctive 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 adjunctive drug treatment yields a 1 in 3 chance of receiving adjunctive placebo.

Quantitative Data Synthesis

We first performed a meta-regression (first meta-regression) with the risk ratio of responding to the adjunctive drug versus placebo as a dependent variable and year of publication, severity at randomization, sample size, and the probability of being randomized to adjunctive placebo as the independent variables (multivariate, ie, entered simultaneously in a single meta-regression). Year of publication, severity at randomization, and the probability of being randomized to adjunctive placebo were entered as covariates since they had previously been found to influence the risk ratio of clinical response following antidepressant monotherapy versus placebo therapy in trials in MDD.[1] We then examined whether the risk ratio of response and remission differed in trials using history of drug failure rather than a prospective trial (lead-in phase) to establish treatment partial response/nonresponse. For this purpose, we performed 2 meta-regressions (second and third meta-regression) to compare the risk ratio of response and remission to the adjunctive drug versus placebo between trials that did versus did not include a lead-in phase. To control for possible confounding, variables found in the first meta-regression to influence the risk ratio of response and remission in a statistically significant manner were included as covariates along with the presence/absence of a lead-in in the second and third meta-regressions. The proportions of responders and remitters to the adjunctive drug and to the adjunctive placebo between the 2 clinical trials groups (ie, trials that did versus did not include a lead-in phase) were compared with the use of Fisher exact test. Finally, a fourth meta-regression was conducted in order to compare the risk ratio of discontinuing the adjunctive drug versus placebo between the 2 clinical trial groups (ie, trials that did versus did not include a lead-in phase). For this meta-regression, study duration was entered as covariate since it was found to influence the risk ratio of discontinuing antidepressants versus placebo in trials in MDD.[21] All tests conducted were 2-tailed, with α set at the .05 level.

RESULTS

Initially 2,865 abstracts were identified in PubMed/MEDLINE. Of these, 2,791 were excluded for a number of reasons (other topics, reviews, duplicate reports), and 74 were screened. Of these, 52 abstracts described original clinical trials of adjunctive pharmacologic strategies for antidepressant partial responders and nonresponders with MDD. These 52 articles were obtained and reviewed thoroughly. Three additional articles were identified after reviewing the reference list of these articles as well as 2 large reviews and meta-analyses.

Nine articles were excluded because they did not involve a standard design as per inclusion criteria (specifically, in addition to adjunctive drug versus placebo, patients were also started on a new antidepressant during the adjunctive trial, ie, they underwent a single or double switch),[22–30] 5 were excluded because they did not involve the use of an oral form of adjunctive drug,[31–35] and 1 because it was less than 1 week in duration[36] (Figure 1).

Thus, a total of 40 articles were found eligible for inclusion in our pooled analysis.[37–76] We were able to obtain drug

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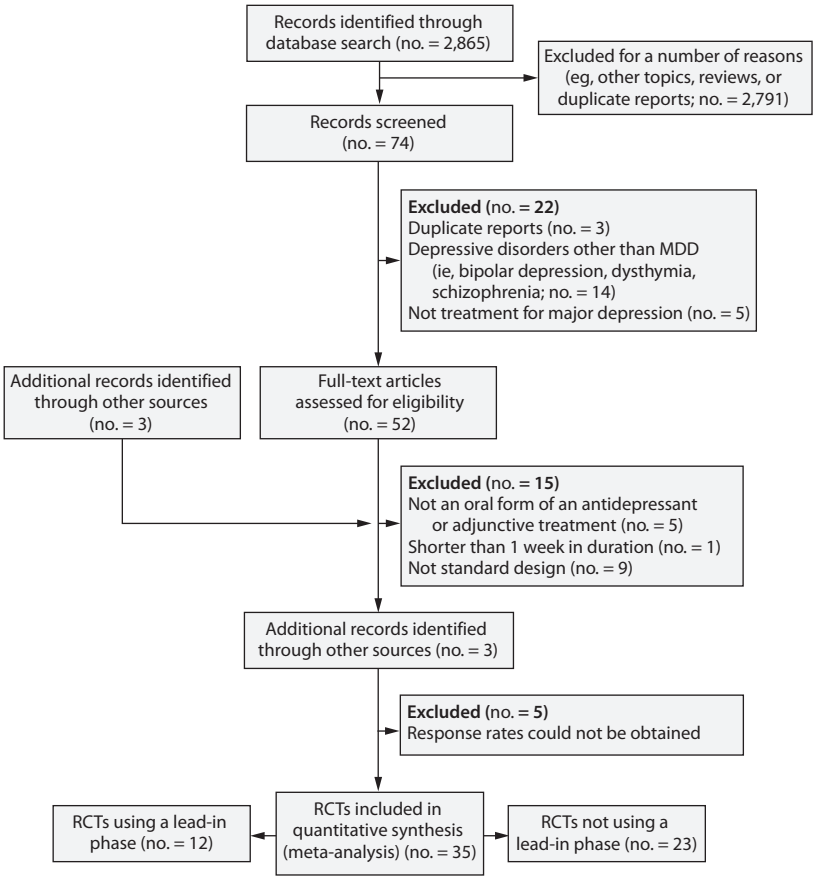
Figure 1. Flow Diagram: Trial Identification and Selection Process



Abbreviations: MDD = major depressive disorder, RCT = randomized clinical trial.

and placebo response rates for 35 (87.5%) of the 40 articles eligible for the meta-analysis.[37–71] Outcome in the remaining 5 trials was reported as a continuous measure only (change in depression severity scores), and response rates as required by our meta-analysis could not be obtained by contacting the study authors or sponsors. Twelve of the 35 trials involved an antidepressant lead-in phase.* While 31 articles reported the results of a single, head-to-head adjunctive drug-placebo analysis, 4 reported several (a total of 9) adjunctive, head-to-head drug-placebo analyses. Thus, a total of 40 adjunctive drug versus adjunctive placebo comparisons from 35 clinical trials were pooled (n = 4,676 patients randomized to treatment with an adjunctive drug [n = 2,543] versus adjunctive placebo [n = 2,133]), 12 of which were derived from clinical trials that involved an antidepressant lead-in phase (n = 2,218 patients randomized to treatment with an antidepressant [n = 1,128] versus placebo (n = 1,090]). A specific description of characteristics of these trials is reported in Table 1. A statistically significant difference was found between trials that did versus did not involve an antidepressant lead-in phase in mean ± SD age in years (42.9 ± 2.4 vs 45.7 ± 3.9, respectively, $P = .031$), mean proportion of women (60.5% vs 69.9%, respectively, $P = .007$), and mean ± SD sample size per treatment arm (90.8 ± 79.9 vs 45.3 ± 46.5, respectively, $P = .040$). There was no statistically significant difference between the 2 trial groups in mean ± SD baseline severity in terms of mean HDRS-17 scores at randomization (21.1 ± 2.3 vs 21.3 ± 3.2, respectively, $P = .834$), probability of receiving adjunctive placebo (44.4% ± 8.2% vs 46.0% ± 7.9%, respectively, $P = .584$), study duration in weeks (5.3 ± 2.1 vs 5.1 ± 2.6, respectively, $P = .799$), as well as mean year of publication (2002 ± 6.8 vs 2001 ± 6.3, respectively, $P = .716$). In the group of trials with a lead-in phase, 1 study (8.3%) required patients to have failed at least 2 antidepressant trials in the current depressive episode, 8 studies (66.7%) required patients to have failed at least 1 antidepressant trial, 3 studies (25%) did not require a history of failed trials before the prospective open-label antidepressant lead-in phase. In the group of trials without a lead-in phase, 1 study (4.3%) required at least 2 failed antidepressant trials in the current episode, and 22 studies (95.7%) required at least 1 failed antidepressant trial. There was no statistically significant difference in the proportion of studies with evidence-based augmentation/combination strategies (ie, strategies shown to be successful with at least 2 positive placebo-controlled trials) and with non–evidence-based strategies between the 2 groups (ie, studies that did versus did not include a lead-in phase) (0.75% vs 0.5%, respectively, $P = .575$).

Meta-Regression Results

Response rates for the adjunctive drug versus adjunctive placebo in all trials (ie, trials with and without a lead-in phase) were 45.3% (1,152 of 2,543) versus 32.9% (701 of 2,133), respectively (number needed to treat [NNT] ≈ 8). Meta-regression analysis suggested that none of the variables entered as covariates (year of publication, baseline severity, sample size, and the probability of being randomized to placebo) influenced the risk ratio of responding to the adjunctive drug versus adjunctive placebo in these trials. There was no statistically significant difference in the risk ratio of responding to the adjunctive drug versus placebo when studies that did versus did not include an antidepressant lead-in phase were compared (coefficient = −0.0685, $P = .122$). However, pooled response rates in trials requiring a failed prospective trial (ie, trials with a lead-in phase) were statistically significantly lower than response rates in trials using historical data (ie, trials without a lead-in phase), for either adjunctive drug (42.6% vs 47.4%, respectively, $P = .014$) or adjunctive placebo (29.7% vs 36.2%, respectively, $P = .002$), suggesting that patients randomized in trials

*References 39–41, 47, 49, 50, 52–54, 58, 67, 70.

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Table 1. Meta-Analysis of Augmentation/Combination Trials for Partial Responders and Nonresponders With Major Depressive Disorder (no. = 35 trials; 40 adjunctive drug vs placebo comparisons)

Characteristics of the Pooled Study Population	
Age, mean ± SD, y	44.7 ± 3.6
Sex (female), mean ± SD, %	66.7 ± 10.1
Severity of depression (HDRS-17 score), mean ± SD	21.3 ± 2.9
Characteristics of the Trials	
Year of trial publication, mean ± SD	2002 ± 6.4
Duration of the trial, mean ± SD, wk	5.2 ± 2.4
Sample size per treatment arm, mean ± SD, n	60.9 ± 62.8
Probability of receiving placebo, mean ± SD, %	45.5 ± 7.9
Adjunctive drug (class), no.	
Trials without an antidepressant lead-in phase (no. = 28):	
Atypical antipsychotic[a]	5
Anticonvulsant[b]	1
Lithium	4
Psychostimulant[c]	4
Omega-3 fatty acids	5
S-Adenosyl methionine	1
Pindolol	2
Buspirone	2
Triiodothyronine	1
Antidepressant[d]	2
Inositol	1
Trials with an antidepressant lead-in phase (no. = 12):	
Atypical antipsychotic[e]	7
Lithium	3
Triiodothyronine	1
Antidepressant[f]	1

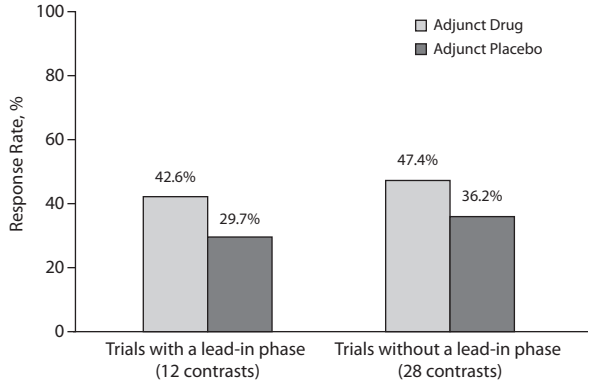
[a]Quetiapine. [b]Lamotrigine. [c]Methylphenidate (no. = 2), modafinil (no. = 2). [d]Mirtazapine, mianserin. [e]Olanzapine (no. = 2), aripiprazole (no. = 3), risperidone (no. = 2). [f]Mianserin.
Abbreviation: HDRS = Hamilton Depression Rating Scale.

with a prospective treatment were more treatment refractory (Figure 2).

Remission rates for adjunctive drug versus adjunctive placebo in all trials (ie, trials with and without a lead-in phase) were 34.1% (707 of 2,074) versus 20.8% (352 of 1,694), for adjunctive drug and adjunctive placebo, respectively (NNT ≈ 7). There was no statistically significant difference in the risk ratio for remission to adjunctive drug versus adjunctive placebo when studies that did versus did not include an antidepressant lead-in phase were compared (coefficient = −0.0651, $P = .211$). However, similarly to response rates, the pooled remission rates in trials requiring a failed prospective trial (ie, trials with a lead-in phase) were statistically lower than remission rates in trials using historical data (ie, trials without a lead-in phase), for the adjunctive drug (31.0% vs 37.3%, respectively, $P = .003$) and adjunctive placebo (18.1% vs 24.7%, respectively, $P = .001$), which, again, suggests that patients randomized in trials with a prospective treatment were more treatment refractory (Figure 3).

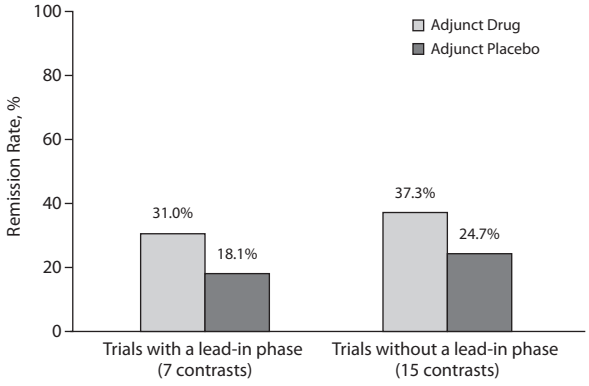
Finally, there was no statistically significant difference in the risk ratio of prematurely discontinuing the adjunctive drug versus placebo due to any reason (coefficient = −0.0696, $P = .335$) or due to adverse events (coefficient = −0.1724, $P = .287$) when comparing the 2 groups of clinical trials (ie, trials that did versus did not include lead-in phase), suggesting that the presence/absence of a lead-in phase does not influence adherence during the double-blind phase.

Figure 2. Efficacy of Adjunct Drug Versus Placebo in Combination/Augmentation Trials for Antidepressant Partial Responders and Nonresponders With MDD: Response Rates[a,b,c]



[a]$P = .122$ comparing the risk ratio of response of adjunctive drug vs placebo in trials that did (no. = 2,218) and did not (no. = 2,548) include a lead-in phase.
[b]$P = .014$ comparing the response rate to the adjunctive drug in trials that did and did not include a lead-in phase.
[c]$P = .002$ comparing the response rate to the adjunctive placebo in trials that did and did not include a lead-in phase.
Abbreviation: MDD = major depressive disorder.

Figure 3. Efficacy of Adjunct Drug Versus Placebo in Combination/Augmentation Trials for Antidepressant Partial Responders and Nonresponders With MDD: Remission Rates[a,b,c]



[a]$P = .211$ comparing the risk ratio of remission of adjunctive drug vs placebo in trials that did (no. = 2,061) and did not (no. = 1,707) include a lead-in phase.
[b]$P = .003$ comparing the remission rate to the adjunctive drug in trials that did and did not include a lead-in phase.
[c]$P = .001$ comparing the remission rate to the adjunctive placebo in trials that did and did not include a lead-in phase.
Abbreviation: MDD = major depressive disorder.

DISCUSSION

The present study is the first to systematically assess study design factors that may influence the chances of "success" of clinical trials for augmentation/combination strategies in antidepressant partial responders/nonresponders with MDD. In the present work, we found that the likelihood to detect a statistically significant drug-placebo separation in augmentation/combination trials (ie, a direct measure of the success of the clinical trial) was not influenced by any of

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the study design factors that have already been identified as predictive of antidepressant-placebo separation in antidepressant monotherapy trials for MDD (ie, the probability of receiving placebo, the year of publication, and the severity of depression at baseline).[1] Most importantly, however, we also found that the difference in efficacy (response and remission rates) between adjunctive drug versus placebo in clinical trials for treatment-resistant MDD did not differ between studies that did versus did not employ a lead-in prospective antidepressant treatment trial in order to define antidepressant partial response/nonresponse. However, pooled response/remission rates in trials requiring a failed prospective trial (ie, trials with a lead-in phase) were statistically significantly lower than response rates in trials using only historical data (ie, trials without a lead-in phase), for either adjunctive drug or adjunctive placebo, suggesting that patients randomized in trials with a lead-in phase were more treatment refractory.

Several theoretical and practical implications stem from these findings. From a study design point of view, since the use of an antidepressant lead-in phase to assess treatment partial response/nonresponse did not appear to enhance the ability to detect a statistically significant treatment effect in randomized augmentation/combination trials for TRD, the choice to rely on historical data of nonresponse appears to be a reasonable and more feasible approach. Specifically, allowing TRD patients to be randomized without having to go through a lead-in phase would result in lower cost and quicker time to completion, since fewer subjects would be required and a lengthy lead-in period would not be required. For example, US Food and Drug Administration (FDA) registrational studies for quetiapine[38,44] involved, on average, 308 patients treated for 6 weeks, versus an average of 731 patients treated for up to 14 weeks in registrational studies for aripiprazole[41,54] and olanzapine,[70] which did involve the use of a lead-in phase. All things being equal, achieving the desired goal (FDA approval of a drug as adjunctive therapy in MDD) with less than half the total sample (308/731 = 42.1%) could result in the enhanced feasibility of a phase 3 clinical trial program (fewer patients treated for less time, resulting in fewer sites required, and shorter time from the enrollment of the first subject to study completion, both resulting in reduced cost).

Moreover, the finding that adjunctive drug/placebo response/remission rates in clinical trials requiring patients to have failed a prospective treatment trial prior to randomization were statistically significantly lower than those relying only on historical data suggests that, on average, findings from agents that are established with the use of trials involving a lead-in phase are generalizable to more refractory populations than those stemming from trials that allowed TRD patients to be directly randomized to adjunctive drug/placebo. Since most studies involving the use of a prospective lead-in derived from the atypical antipsychotic and lithium augmentation literature (10/12 = 83.3%), it could be argued that, perhaps, these treatments should be preferred over others for more highly refractory patients. However, it is important to point out that clinical trials conclusively demonstrating the superiority of one versus another polypharmacy strategy for TRD have not been published to date.

Several limitations should be taken into account when interpreting our findings. Specifically, one limitation pertains to the identification of studies to be included in pooled analyses or 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). It would be interesting to examine whether the inclusion of unpublished studies strengthens or weakens our findings. Moreover, the clinical trials included in the present study usually included a number of exclusion criteria, and the findings of this study may not be generalized to the excluded (ie, patients with bipolar depression, psychotic MDD, patients actively abusing alcohol or drugs, patients with specific medical comorbidities, or patients with serious suicidal ideation). In addition, while the total number of patients included in the trial with a lead-in phase (n = 2,218) is fairly large, the number of trials on which this trial-level data analysis is based is limited (12 trials versus 23 trials without a lead-in phase). Therefore, it may be difficult to rule out more subtle differences in the risk ratio for response or remission with adjunctive drug versus placebo between the 2 types of trials. However, even if more subtle differences were found to be statistically significant in future larger meta-analyses, it would be questionable whether the magnitude of the advantage in terms of higher risk ratio for lead-in versus non–lead-in studies would be justified by the higher cost and poorer feasibility of the lead-in type study design. An additional limitation has to do with the quality of the retrospective assessment of treatment history, which varies across trials (with many trials not administering a specific tool designed to minimize the risk of retrospective treatment assessment error/omission). In addition, it should be pointed out that, when comparing 2 different patient (in the cases of a clinical trial) or study (in the case of meta-analysis) groups, while it is assumed that the 2 groups are identical in all ways except for group assignment (ie, drug versus placebo in the case of a clinical trial or lead-in versus non–lead-in design in the case of this meta-analysis), this assumption can never be made with absolute certainty. For example, while the 2 trial populations in our meta-analysis were of equivalent severity, they may have differed in terms of various clinical, genetic, or biologic markers that do impact treatment outcome. A study that prospectively measures for the presence of such surrogate markers (clinical, demographic, and biologic) would be more definitive. Finally, there are several limitations regarding the existing clinical literature on augmentation/combination strategies for TRD. Definitions of treatment resistance are still evolving, and there is no standard for studies such as these; therefore, the methods used to define treatment resistance may vary across the studies included in the analysis.

In conclusion, the results of the present analysis suggest that the relative efficacy of the drug compared with adjunctive

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placebo in augmentation/combination trials for antidepressant partial responders/nonresponders is not influenced by whether treatment resistance is determined using a prospective trial (antidepressant lead-in phase) or historical data only. Therefore, in light of optimizing the feasibility of a clinical trial and a phase 3 clinical trial program, the choice to use historical only data in order to define treatment resistance prior to patient enrollment and randomization, rather than requiring patients to first undergo a prospective lead-in phase, can be a reasonable and evidence-supported approach to designing effective clinical trials of adjunctive pharmacologic strategies for partial responders/nonresponders with MDD.

Drug names: aripiprazole (Abilify), lamotrigine (Lamictal and others), lithium (Lithobid and others), methylphenidate (Focalin, Daytrana, and others), mirtazapine (Remeron and others), modafinil (Provigil), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), triiodothyronine (Cytomel, Triostat, and others).

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Potential conflicts of interests: **Dr Papakostas** has served as a consultant for Abbott, AstraZeneca, Brainsway, Bristol-Myers Squibb, Cephalon, Eli Lilly, GlaxoSmithKline, Evotec, Inflabloc, Jazz, Otsuka, Pamlab, Pfizer, Pierre Fabre, Ridge Diagnostics, Shire, and Wyeth; has received honoraria from Abbott, Astra Zeneca, Bristol-Myers Squibb, Brainsway, Cephalon, Eli Lilly, Evotec, GlaxoSmithKline, Inflabloc, Jazz, Lundbeck, Otsuka, Pamlab, Pfizer, Pierre Fabre, Ridge Diagnostics, Shire, and Wyeth; has received grant/research support from Bristol-Myers Squibb, Forest, the National Institute of Mental Health, Pamlab, Pfizer, and Ridge Diagnostics; and has served (in the past but not currently) on the speakers bureaus for Bristol-Myers Squibb and Pfizer. **Dr Iovieno** reports no competing interests.

Funding/support: None reported.

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