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Design Makes a Difference: A Meta-Analysis of Antidepressant Response Rates in Placebo-Controlled Versus Comparator Trials in Late-Life Depression

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Objective: *Qualitative reviews of late-life antidepressant clinical trials suggest that antidepressant response rates in comparator trials are higher than antidepressant response rates in placebo-controlled trials. No quantitative review has been conducted to test this hypothesis.* **Methods:** *A meta-analysis was conducted of all published articles in peer-reviewed journals from 1985 to the present to identify randomized clinical trials contrasting antidepressant pharmacotherapy to placebo or an active comparator in late-life depressed outpatients. Sixteen studies (nine comparator trials and seven placebo-controlled trials) were identified. Antidepressant response rates in both placebo-controlled and comparator trials were extracted and submitted for analysis using multilevel meta-analysis procedures.* **Results:** *The authors found significant variability in antidepressant response rates beyond chance. This variability decreased by 27% when the authors included study type in the model. As expected, antidepressant response rates in comparator trials were significantly higher (60%) than antidepressant response rates in placebo-controlled trials (46%).* **Conclusion:** *Antidepressant response rates are higher in comparator trials as compared to placebo-controlled trials. These findings have important implications for combined medication and psychotherapy trials that use placebo-controlled medication conditions because the response rates from these conditions are likely to be lower than those from unblinded conditions.* (Am J Geriatr Psychiatry 2007; 15:1–1)

Key Words: Randomized clinical trials, late-life depression, antidepressants, multilevel meta-analysis

Randomized clinical trials (RCTs) are the experimental gold standard for establishing evidence of treatment efficacy. Placebo-controlled trials are designed with the intention of determining whether

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or not a medication is effective in the treatment of an illness whereas comparator trials are designed with the intention of determining whether medication A is superior to medication B in the treatment of an illness. Although both designs accomplish their intended purposes, the designs of each may inadvertently affect patient expectations of whether or not they will improve.

Roose and Schatzberg[1] compared antidepressant response rates in five placebo controlled trials of late-life depression and compared them to antidepressant response in 10 comparator trials. They observed based on this selection of RCTs that antidepressant response rates in comparator trials are 20% to 30% higher than antidepressant response rates in placebo-controlled trials. However, they did not conduct a formal search of the literature, provide inclusion and exclusion criteria for the studies they examined, and they did not statically test their observation.

One reason for this is that the question of interest does not readily lend itself to conventional statistical methods. For example, a test of the difference between two proportions (antidepressant response in placebo-controlled trials versus antidepressant response in comparator trials) does not take into account the fact that subjects within a study are more similar than subjects between studies (this is commonly referred to as hierarchical or nested data). Traditional meta-analytic methods are also not easily adapted to answer the question. They are formulated to test whether antidepressant response rates are superior to placebo response rates not whether antidepressant response rates are different depending on the type of clinical trial.

If Roose and Schatzberg's[1] observation is correct, it stands out as an important hypothesis to be tested. One potential explanation for the observed difference in antidepressant response rates is that the two types of clinical trials have differential affects on patient expectations for therapeutic gain. Indeed, patients with high expectations regarding treatment outcome tend to improve more than those with more modest expectations.[2] In comparator trials, the patient *knows* they are going to receive a medication either proven or hoped to be effective for depression, while in placebo-controlled trials the patient *hopes* they will receive such a medication. Although hope for symptomatic improvement may lead to a placebo effect, the inverse of hope is doubt, which may lead to a suppressed response to antidepressants in placebo-controlled trials compared with comparator trials.

To test the possibility that clinical trial design affects antidepressant response rates, we conducted a meta-analysis of all articles published in peer-reviewed journals from 1985 to the present to identify RCTs contrasting antidepressant pharmacotherapy to placebo or an active comparator in late-life depressed outpatients. Using a hierarchical linear modeling (HLM) approach to meta-analysis (see Methods section), we hypothesized that: 1) response rates across studies would vary beyond chance, 2) study type would account for a significant proportion of this variability, and 3) antidepressant response rates in comparator trials would be higher than antidepressant response rates in placebo-controlled trials.

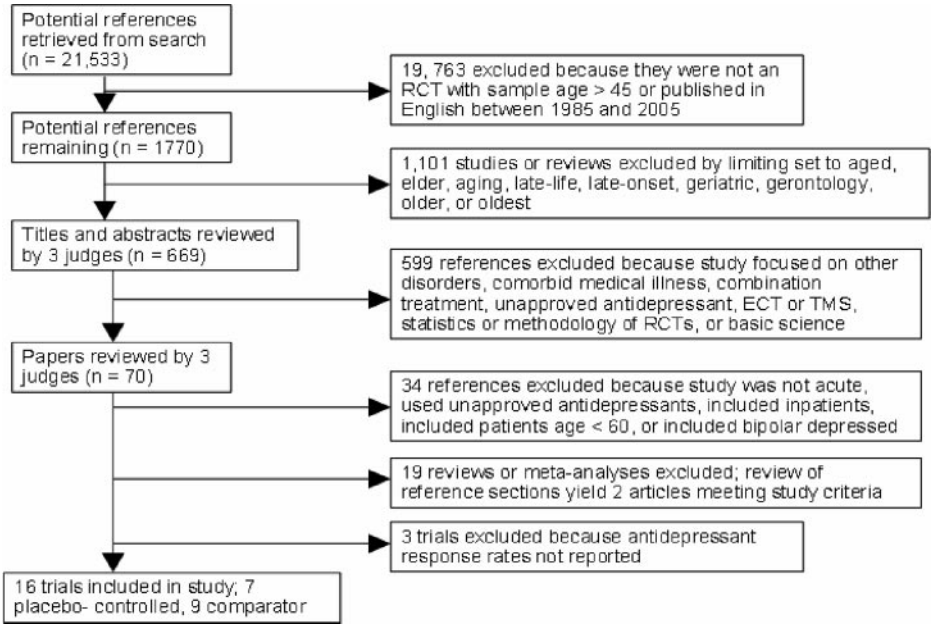
METHODS

Selection of Studies

To maximize the quality of the studies selected for the meta-analysis and to limit the magnitude of the meta-analytic undertaking, MEDLINE and the Cochrane Database of Systematic Reviews were searched from 1985 to 2005 for all RCTs and review articles published in peer-reviewed journals contrasting antidepressant pharmacotherapy to placebo or an active comparator in late-life depressed outpatients. We chose 1985 as the lower endpoint of our search period so that the database reflected modern pharmacotherapy practice with selective serotonin reuptake inhibitors being the most commonly prescribed antidepressant in late-life.[3]

Consistent with the Quality of Reporting of Meta-Analyses (QUOROM) conference guidelines,[4] Figure 1 depicts a flow diagram of the progress through the stages of study identification for inclusion in the meta-analysis. Of the 70 articles selected for detailed review by the three judges (JRS, BRR, and SPR), 51 were empirical reports and 19 were reviews or meta-analyses. Of the 51 empirical reports, 34 were excluded and 17 clinical trials met inclusion criteria for the study. The breakdown of the 34 excluded trials was as follows: 4 trials were not considered acute, 25 trials used either an unapproved antidepressant or

FIGURE 1. Flow Diagram Charting Progress Through the Stages of Study Identification for Inclusion in the Meta-Analysis



included inpatients, 2 trials did not meet the minimum age criteria, 1 trial used inpatients and was not acute, 1 included bipolar depressed patients, and 1 was an intermediate report at week 6 of an 8-week clinical trial. We examined the reference sections of the 19 nonempirical papers (17 qualitative reviews and 2 meta-analyses) to identify any other RCTs that were not identified in our previous search. This review resulted in an additional two references.[5,6] As a result, 19 double-blind RCTs met inclusion criteria for the present study. Of the 19 articles that met inclusion criteria, 3 comparator trials did not report response rates.[5–7] Therefore, the final sample consisted of 16 studies (7 placebo-controlled and 9 comparator trials) reporting antidepressant response rates for 29 distinct medication groups (Table 1).

Inclusion and Exclusion Criteria

To be included in the study, the trial must have been acute (no longer than 12 weeks) and patients must have been age 60 or older. We did not include antidepressant response rates from trials of longer than 12 weeks duration even if they reported antidepressant response rates in the acute (<12 weeks) phase because the expectations of a patient in a nonacute trial (e.g., 24-week trial) at week 12 are vastly different from the expectations of a patient in a 12 week trial at week 12.

We only considered studies that were reported in English, included a placebo or active medication comparison condition, and reported response rates for the intent-to-treat (ITT) sample based on either continuous outcome measures such as the Hamilton Rating Scale for Depression (HRSD) or Montgomery Asberg Depression Rating Scale (MADRS) or a measure of improvement such as the Clinical Global Improvement (CGI) scale. By ITT we mean all patients randomized to receive medication; therefore, this did not include studies only reporting response rates based on completer analyses. If studies reported more than one response rate, we used the following hierarchy to extract the data: 1) HRSD, 2) MADRS, and 3) CGI.

Only studies investigating treatment effects on unipolar major depression were considered in this quantitative review (i.e., studies of dysthymia or bipolar depression [depressed type] were not included). RCTs were excluded if they required comorbid medical illness as an inclusion criterion. RCTs were also excluded if either 1) dementia was in-

TABLE 1. Placebo-Controlled and Comparator Trials Included in the Meta-Analysis of Antidepressant Response Rates in Late-Life Depression Trials

Trials	Medication	Duration	Response Definition	Response Rate	ITT
Placebo-controlled					
Kasper et al.[8]	Escitalopram fluoxetine	8 weeks	50% MADRS reduction	0.46	173
				0.37	164
Rapaport et al.[9]	Paroxetine CR paroxetine IR	12 weeks	CGI = 1 or 2	0.72	104
				0.65	106
Roose et al.[10]	Citalopram	8 weeks	50% HRSD reduction	0.41	84
Schatzberg and Roose[11]	Venlafaxine fluoxetine	8 weeks	50% HRSD reduction	0.45	104
				0.39	100
Schneider et al.[12]	Sertraline	8 weeks	50% HRSD reduction	0.35	360
Schweizer et al.[13]	Imipramine buspirone	8 weeks	50% HRSD reduction	0.62	60
				0.52	54
Tollefson et al.[14]	Fluoxetine	6 weeks	50% HRSD reduction	0.37	335
Comparator					
Bondareff et al.[15]	Sertraline nortriptyline	12 weeks	50% HRSD reduction	0.52	105
				0.41	105
Feighner and Cohn[16]	Fluoxetine doxepin	6 weeks	CGI = 1 or 2	0.49	78
				0.48	79
Forlenza et al.[17]	Imipramine sertraline	8 weeks	50% MADRS reduction	0.61	28
				0.56	27
Guillibert et al.[18]	Paroxetine clomipramine	6 weeks	50% HRSD reduction	0.65	40
				0.72	39
Hutchinson et al.[19]	Paroxetine amitriptyline	6 weeks	50% HRSD reduction	0.60	58
				0.56	32
Nair et al.[20]	Trimipramine doxepin	5 weeks	CGI = 1 or 2	0.67	18
				0.53	19
Newhouse et al.[21]	Sertraline fluoxetine	12 weeks	50% HRSD reduction	0.73	117
				0.71	119
Schatzberg et al.[22]	Mirtazapine paroxetine	8 weeks	50% HRSD reduction	0.58	126
				0.50	120
Weihs et al.[23]	Buproprion paroxetine	6 weeks	50% HRSD reduction	0.71	48
				0.77	52

ITT, intent-to-treat sample size in each medication group.

cluded in the study inclusion criteria, or 2) dementia was not included in the study exclusion criteria. We considered all recognized antidepressant medications including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and others (bupropion, nefazodone, mirtazapine, and trazodone).

Data Extraction

All three judges extracted the data in a series of consensus conference meetings. A paper extraction form was generated for the purposes of the study and publication year, study design, methodological quality, sample size, medication type, and response rates were noted. Although methodological quality was assessed, there was no meaningful variation in quality across studies because rigorous inclusion and exclusion criteria were used. Consequently, methodological quality data are not presented. Any discrepancies among the judges in extracting the data were resolved by consensus.

Multilevel Meta-Analysis

As previously indicated, meta-analytic data are hierarchically structured, such that subjects are nested within studies. Such data can yield multiple outcomes per study such as antidepressant response rates for two medications within a single three arm placebo-controlled RCT. Because conditions within studies are more alike than conditions between studies, such data are nonindependent. If the researcher hopes to accurately estimate the standard errors of the parameter estimates and correctly assess the significance of explanatory variables, nested, nonindependent data must be correctly modeled. As is true

for other types of nested data (e.g., longitudinal data), such nesting can be correctly modeled by distinguishing between two levels of equations: a within-studies equation (level 1) and between-studies equations (level 2). In fact, meta-analysis using HLM can be considered a special case of multilevel regression (in this case, logistic regression).

The focus of HLM models is on the variability in the outcome (in this case, response rates), which is assumed to come from two sources: sampling variation and real, between-study differences. Random effects models are used to estimate the variability in the outcome, and when this variance is significantly greater than zero, this indicates that the outcomes are heterogeneous and unexplained variance exists. (Note: In the absence of statistically significant variability, any variability in the outcome simply reflects sampling variation and the random effects model reduces to a fixed effects model.) In the presence of variation that is beyond chance, moderator analyses are conducted to account for systematic variance between studies. For a further discussion of the multilevel modeling approach to meta-analysis, see Bryk and Raudenbush,[8] Hox,[9] and Haddock, Rindskopf, and Shadish.[10]

The initial step in the present study is to determine whether there is significant variability in antidepressant response rates across studies. To do this, we fit an unconditional random effects model in which the within-studies equation is:

$$\mathrm{In}\left(\frac{p}{1-p}\right)_{ij} = \pi_{0j}$$

where $\mathrm{In}\left(\frac{p}{1-p}\right)_{ij}$ is the log odds of antidepressant response rate *i* for study *j* and π_{0j} is the corresponding parameter value that is assumed initially to be the same for all groups within a study. At the between-studies level, the equation is:

$$\pi_{0j} = \beta_{00} + \mu_{0j}$$

which describes the true antidepressant response rate as varying around a grand mean (β_{00}) with error (μ_{0j}). Thus, the unconditional model provides estimates of the overall antidepressant response rate (β_{00}) and its variability (the variance of μ_{0j}). If this variability is greater than is expected on the basis of sampling error alone, then we reject the null hypothesis that antidepressant response rates are homogeneous across studies. We use the Birge ratio $\left(R_B = \frac{x^2}{df}\right)$ to test this hypothesis,[10] where values of 1 are indicative of chance variation and values greater than one indicative of heterogeneity beyond what would be expected on the basis of chance alone.

Given significant variability in antidepressant response rates across studies (i.e., nontrivial variation in μ_{0j}), we retain the random effects model and include study type as a study level characteristic in the between-studies equation (the within-studies equation does not change). Because response rates vary depending on duration of trial, we also include trial duration as a study characteristic in the between studies equation. The between studies equation becomes:

$$\pi_{0j} = \beta_{00} + \beta_{01}\,\mathrm{Comparator}_j + \beta_{02}\,\mathrm{Duration} + \mu_{0j}$$

Comparator is a dummy variable coded 0 for placebo-controlled trials and 1 for comparator trials. Duration (mean centered) indicates the length of the trial. Thus, when comparator equals zero, the intercept (β_{00})refers to the average log odds of antidepressant response in placebo-controlled trials for a trial of average duration, and when comparator equals one, β_{01} expresses the difference in the log odds of antidepressant response between comparator trials and placebo-controlled trials for a trial of average duration. We estimated all statistical models using HLM 6. All parameters were tested for statistical significance at the 5% level.

RESULTS

Table 2 reports the fixed and random effects estimates for the unconditional model for the meta-analysis of antidepressant response rates in randomized controlled clinical trials of late-life depression. As can be seen in this table, the variance across studies is significantly different from zero ($\chi^2(15) = 201.54$, $p < 0.001$, $R_B = 201.54/15 = 13.44$), indicating that true variability in antidepressant response rates.

Next, we test the possibility that study type (placebo-controlled or comparator trial) explains a significant proportion of this variability when added to the unconditional model while at the same time adjusting for trial duration. We hypothesized that

TABLE 2. Unconditional Model for the Meta-Analysis of Antidepressant Response Rates in RCTs of Late-Life Depression

Effect	Estimate (SE)	Variance Component	t Ratio	χ^2	df	p Value
Fixed						
Intercept	0.15 (0.14)		1.12		15	0.28
Random						
Intercept		0.26		201.54	15	0.001

study would explain significant variability in the outcome and that comparator trials would yield higher antidepressant rates as compared to placebo-controlled trials. Table 3 reports the fixed and random effects estimates for this conditional model. As can be seen, the variability in the random intercept term has been reduced from 0.26 to 0.19 and study type accounted for 27% of the original, unexplained variability in antidepressant response rates [(0.26 – 0.19)/0.26 = 0.27]. The difference between comparator and placebo-controlled clinical trials was accurately different from zero ($t(13) = 2.52$, $p < 0.026$). As expected, antidepressant response rates were higher in the comparator trials as compared to the placebo-controlled trials. The odds of being classified as a responder were 1.82 times higher in comparator trials as compared to placebo-controlled trials ($e^{0.58} = 1.82$, 95% CI: 1.09, 3.04). The estimated probability of antidepressant response in placebo-controlled trials was $e^{-0.18}/(1 + e^{-0.18}) = 0.46$ (95% CI: 0.38, 0.54) as compared to $e^{0.42}/(1 + e^{0.42}) = 0.60$ (95% CI: 0.53, 0.67) in comparator trials.

DISCUSSION

Our findings provide support for the hypothesis that clinical trial design affects antidepressant response rates in studies of late-life outpatient depression. As expected, we detected significant variability in response rates beyond what would be expected by chance and explained 27% of this variation by including study type in the model. The estimated antidepressant response rate in comparator trials was 60% as compared to 46% in placebo-controlled trials.

One possible explanation for the overall difference in antidepressant response rates between placebo-controlled and comparator trials is patient expectation. As previously discussed, the patient knows they are going to receive an active medication in a comparator trial, whereas in placebo-controlled trials the patient hopes they will receive an active medication but there is some doubt on the part of the patient (as well as doctor) as to whether they receive an active agent. Although hope for symptomatic improvement may lead to a placebo effect, the inverse of hope is doubt, which may lead to a suppressed response to antidepressants in placebo-controlled trials as compared to comparator trials. Support for the importance of expectation comes from its critical role in mediating the placebo effect.[11,12] For example, when people with chronic pain, anxiety, and Parkinson disease are completely unaware that a treatment is being administered, the treatment is less effective than when they are aware the treatment is being administered.[13] Expectation has also been shown to affects response to drugs of abuse such as methylphenidate in both drug abusers[14] and nondrug abus-

TABLE 3. Conditional Model for the Meta-Analysis of Antidepressant Response Rates in RCTs of Late-Life Depression Adjusting for Trial Duration

Effect	Estimate (SE)	Variance Component	t Ratio	χ^2	df	p Value
Fixed						
Intercept	−0.18 (0.17)		−1.037		13	0.32
Comparator	0.60 (0.24)		2.52		13	0.026
Study duration	0.054 (0.055)		0.97		13	0.35
Random						
Intercept		0.19		115.43	13	0.001

Notes: Comparator is a dummy-coded variable with 1 indicating comparator trial and 0 indicating placebo-controlled trial.

ers.[15] Taken together, these findings support the idea that knowledge of treatment condition affects outcome.

Conceptually, a strong case can be made for the central role of expectation in moderating the response rates of placebo-controlled and comparator trials; however, other possibilities exist. For example, study doctors and raters may have different sets of expectations regarding patient improvement in placebo-controlled versus comparator trials. Another possibility is that there may be important differences in the make-up of the samples between placebo-controlled and comparator studies that might contribute to the observed differences in response rates. For example, patients who agree to enter placebo-controlled trials may have more severe or recurrent depression as compared to patients who agree to enter comparator trials who may have less severe depression or a preponderance of single episodes. Therefore, response rates in placebo-controlled trials might be expected to be lower than response rates in comparator trials. There may also be differences in studies conducted in North America versus studies conducted in Europe. Future research that aims to sort out these different potential contributions is required.

The findings from this study have important implications for the design of RCTs, particularly combined psychotherapy and medication trials, because the medication condition in these trials is typically placebo-controlled. For example, the typical combined psychotherapy and medication study includes the following conditions: psychotherapy alone, medication alone, combined psychotherapy and medication, and pill placebo. This type of design compares the effect of unblinded conditions (psychotherapy and psychotherapy plus medication) to placebo-controlled medication treatment but does not include an open medication treatment cell. Since on the basis of the present findings we can expect different antidepressant response rates to medication depending on whether it is given in an open or blinded fashion, such comparisons are potentially flawed.

There are a number of limitations that should be noted. Our study examined only published data. Because the comparison of interest in traditional meta-analysis is medication response versus placebo response, meta-analyses of published data are more likely to identify and include studies with positive outcomes such as higher medication response rates compared to placebo. This is especially true given that most pharmacotherapy studies are supported by the pharmaceutical industry. As a result, a number of statistical methods have been devised to account for publication bias.[16] However, because we were not interested in a drug-placebo comparison, it is unlikely that this bias affected the results of the present study. If anything, the file drawer phenomena made detecting an effect of study type in the present study more difficult because published studies are likely to have the highest medication response rates resulting in positive medication to placebo condition comparisons. If negative studies were included, this would only make the difference observed in this study greater.

There were several other limitations. The rigorous inclusion criteria resulted in a small number of studies, which limited the number and type of moderator analyses that could be conducted. We also restricted ourselves to articles published in English since 1985. It is unclear whether the findings from the present study would generalize to non-English articles or to articles published prior to 1985, when there would be a greater preponderance of RCTs of tricyclic antidepressants and monoamine oxidase inhibitors selected for review. We also restricted ourselves to the analysis of response rates because response rates are the most commonly available outcome reported in the literature. It is unclear whether the findings would generalize beyond response rates to remission rates or mean change in depression severity over time.

These limitations are balanced by the unique methodological strengths of the study. First, by restricting ourselves to rigorous, double-blind RCTs of outpatient geriatric depression, we conducted a best evidence synthesis of available research.[17] Such an approach recognizes randomized controlled trials as the gold standard in clinical trials research and that the results based on these studies are more reliable and valid as compared to studies based on lower methodological rigor. Thus, a synthesis of best available evidence gives us greater confidence in the findings regarding medication response rates.

This study also highlights the benefits of a multilevel approach to meta-analysis. First, it offers a comprehensive approach to research synthesis because it allows for the analysis of statistically nonindepen-

dent (nested) data and tests for heterogeneity in outcomes within a single statistical model.[18] Second, it is quite simple to add moderators and their interactions to the multilevel model in order to account for unexplained (systematic) variation in the outcome. In contrast, traditional meta-analysis disaggregates the outcome of interest into smaller and smaller categories, which can become impractical especially as the number of predictors gets large.[10] Third, by using iterative Maximum Likelihood estimation, multilevel meta-analysis produces more precise parameter estimates, allowing the researcher to more accurately test the statistical significance of explanatory (moderator) variables.[9] Finally, multilevel meta-analysis is easy to implement because it is based on a relatively common statistical framework (multilevel regression) and can be conducted using readily available multilevel modeling software.

This study improves on previous efforts to understand the impact of trial design on medication response rates.[1] It represents the first systematic examination of the impact of trial design on antidepressant response rates in late-life depression in which search criteria are explicitly stated (along with inclusion and exclusion criteria) and differences in antidepressant response rates tested using appropriate statistical methods. While not definitive, our findings suggest that clinical trial design strongly affects antidepressant response rates with comparator trials yielding higher rates than placebo-controlled trials. It should also be pointed out that although meta-analyses of antidepressant medication response in late-life depression have been conducted,[19–21] these studies were not designed to determine whether antidepressant response rates differ depending on trial design. Thus, the present study makes unique contributions to the geriatric psychiatry literature.

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