

Does Study Design Influence Outcome?

The Effects of Placebo Control and Treatment Duration in Antidepressant Trials

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Key Words

Clinical trial · Methodology · Placebo · Comparator · Major depression · Duration, expectations

Abstract

Background: Clinicians and researchers synthesize data from randomized controlled trials (RCTs) of antidepressants to make conclusions about the efficacy of medications for depression. All treatments include nonspecific factors in addition to the specific effects of drugs, and study design may influence patient outcomes via nonspecific factors. This study investigated whether placebo control and treatment duration affect the outcome in antidepressant RCTs. **Methods:** Medline and the Cochrane Database were searched to identify RCTs of antidepressants for major depression approved by the Food and Drug Administration. Included studies enrolled outpatient participants aged 18–65, lasted 6–12 weeks, compared an antidepressant to placebo or another antidepressant and were published in English after 1985. Excluded trials enrolled inpatients, pregnant women and subjects with psychosis or mania. Mixed-effects logistic regression models including study type (placebo-controlled or comparator) and study duration (6, 8 or 12 weeks) as fixed effects determined whether these factors affected response and remission rates. **Results:** In the 90 trials analyzed, the odds of depression response (OR = 1.79, 95% CI = 1.45–2.17, $p < 0.001$) and remission (OR 1.53, 95% CI = 1.11–2.11, $p < 0.001$) were significantly higher in comparator relative to placebo-controlled trials. Trials lasting 8 (OR = 1.37, CI = 1.14–1.64, $p = 0.001$) and 12 (OR = 1.52, CI = 1.12–2.07, $p = 0.008$)

weeks had significantly greater response rates than 6-week trials without differing themselves. **Conclusions:** Response and remission rates to antidepressants are significantly affected by study type and duration. Clinicians and researchers must consider the study design when interpreting and designing RCTs of antidepressant medications.

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Introduction

When a psychiatrist prescribes an antidepressant, his or her patient may reasonably ask ‘what are the chances I will get better on this medication?’ and ‘how long will it take me to feel better?’ In answering these questions, a psychiatrist practicing evidence-based medicine is informed by research testing the proposed medication for depression [1]. However, there are many studies to choose between when gathering evidence about the anticipated effectiveness of antidepressants and the speed of treatment response.

For example, sources of information about the effectiveness of antidepressants include open studies, placebo-controlled randomized clinical trials (RCTs) and comparator (i.e., medication vs. medication) RCTs. Response rates are generally higher in open studies compared to placebo-controlled RCTs [2]. Similarly, information about the speed of antidepressant response may come from observing the time course of response within individual studies or comparing response rates across trials of different durations. Within a single 12-week RCT,

medication response rates are greater at the trial endpoint compared to 8 weeks [3], but similar response rates have been observed across trials of 6, 8 and 12 weeks duration [4, 5]. These discrepant results suggest that study design may affect treatment outcome, and they leave unclear which analyses constitute the best evidence to answer specific clinical questions.

Few previous investigators have directly addressed the questions of whether or how study design impacts treatment response [6]. In one of the few available reports, higher antidepressant response rates were found in placebo-controlled relative to comparator trials (58.1 and 50.6%, respectively) [7]. However, this analysis included unipolar as well as bipolar depression and examined RCTs dating to 1959, when methodological problems plagued many trials. Subsequent investigators found an average medication response rate of 49% in placebo-controlled versus 59% in comparator trials for late-life depression [4]. However, they did not conduct a formal literature search, provide inclusion and exclusion criteria for the studies they examined or test whether the observed difference was statistically significant.

Sneed et al. [8] recently examined antidepressant response rates in 9 placebo-controlled and 7 comparator trials for late-life depression. A 46% response rate to medication was found in placebo-controlled trials compared to 63% in comparator trials. The odds of medication response in comparator trials were nearly 2 times the odds in placebo-controlled trials (OR = 1.78, 95% CI = 1.10–2.90, $p < 0.001$). This study used rigorous trial selection criteria and statistical methods but was limited to subjects >60 years old, leaving unclear whether these results can be generalized to all adults.

To further explore the influence of RCT design on antidepressant treatment outcome, response and remission rates to antidepressant medications were compared across placebo-controlled and comparator trials enrolling outpatient participants aged 18–65. Analyses of antidepressant response and remission rates in trials of 6, 8 and 12 weeks duration were also performed. Response and remission were chosen as outcomes because they provide clinically meaningful measures denoting the significant decrease or absence of depressive symptoms and reduction in the risk of depression recurrence and adverse medical outcomes [9–11]. The primary hypotheses were that response and remission rates to medications in comparator trials would be significantly higher than those observed in placebo-controlled studies and that response and remission rates to medication in 6-, 8- and 12-week-duration trials would not be significantly different.

Method

Identification of Studies

A Medline search was conducted to identify RCTs contrasting antidepressants with placebo or active comparator in adults with depression. The index terms ‘depression – drug therapy’, ‘depressive disorder – drug therapy’, and ‘antidepressant agents’, in addition to the class and individual generic name of all antidepressants were combined using the ‘or’ operator. This returned 19,338 results, which were limited to (1) English language articles; (2) publication year from 1985 to 2006; (3) age group ≥ 18 (to be inclusive), and (4) publication types including clinical trials, controlled clinical trials, meta-analysis, multicenter study, RCT or review, which yielded 2,821 journal articles. The year 1985 was chosen to select trials utilizing more rigorous methods. The first author (B.R.R.) conducted a review of these titles to rule out those which were not clinical trials of antidepressants for depression, resulting in 564 titles.

Three judges (B.R.R., J.R.S. and S.P.R.) reviewed the 564 titles, sequentially proceeding from article title to abstract and finally full paper text, to determine whether they met inclusion or exclusion criteria (fig. 1). These evaluations were pooled, and any differences between judges were resolved by discussion. To further ensure all relevant papers were reviewed, the references of all meta-analyses and review articles published since 2000 among the 2,821 journal articles were searched for pertinent references. In addition, the Cochrane Database of Systematic Reviews was electronically searched using the topics depression, anxiety and neurosis. This yielded 24 protocols and completed reviews, each of whose references was reviewed to ensure they were among the reviewed trials.

Criteria for Including Studies

The inclusion criteria stipulated that articles report RCTs of an antidepressant medication for major depressive disorder in outpatient subjects aged 18–65 approved by the Food and Drug Administration (FDA). While meta-analyses were reviewed to identify studies, only data from individual RCTs were included in the analysis. Further criteria required trials to last between 6 and 12 weeks (inclusive), have comparison groups of placebo or another FDA-approved antidepressant medication, be written in English, published in 1985 or later and have response or remission rates specified using a standardized outcome measurement [e.g., Hamilton Rating Scale for Depression (HRSD) [12], Beck Depression Inventory [13], Montgomery-Asberg Depression Rating Scale (MADRS) [14], Clinical Global Impression (CGI) [15]]. Trials were excluded for enrolling inpatients, pregnant women, subjects who were psychotic or those defined to have treatment-resistant depression. Also excluded were antidepressant augmentation studies and trials requiring as inclusion criteria a specific subtype of major depression, a specific medical illness, or an axis I disorder other than depression.

Data Extraction

Publication information (year of publication, funding source, type of study, number of groups), demographic characteristics of the included subjects (sample size, age, gender, race, clinical characteristics), details of the treatment condition (medication name, mean dose) and outcome data (pre- and posttreatment means, standard deviations, response and remission rates) were extracted

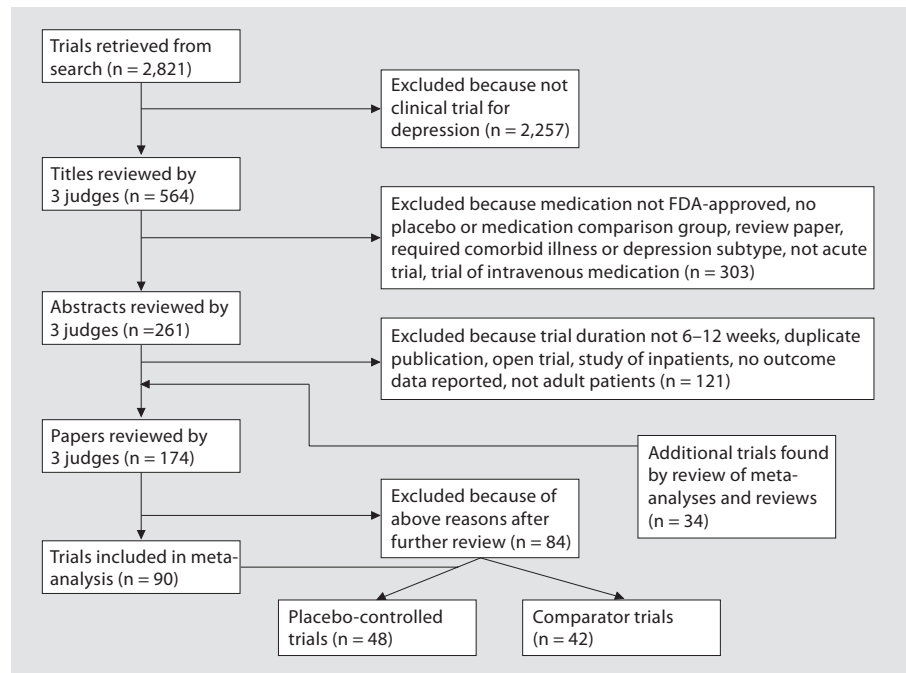


Fig. 1. Flow chart of included trials.

from each included RCT. The quality was also measured by determining whether studies reported critical methodological aspects such as (1) concealment of treatment allocation; (2) blinding of outcome assessment, and (3) use of intent-to-treat data analyses [16]. Three judges (B.R.R., J.R.S. and S.P.R.) extracted the data, and any differences were resolved by consensus.

Data Analyses

The data analyses followed those in a prior manuscript, where the procedures are described in greater detail [8]. Mixed-effects logistic regression models were used, similar to the approach taken by Bryk and Raudenbush [17], Hox [18] and Haddock et al. [19]. Response rates in all medication cells in the placebo-controlled and comparator trials were included, even when multiple cells comparing the same medication at different doses were present. Meta-analyses typically combine these cells to avoid making multiple contrasts with the same placebo comparison group, but since such contrasts were not of interest in this analysis, all medication cells were included separately.

The analyses proceeded in a stepwise fashion as follows. First, an unconditional model was fit to the data on antidepressant response rates to determine whether significant variability in response rates existed across studies. The unconditional model is described by a within- and a between-studies equation, which accommodate the nested structure of subjects within medication conditions within study. If the variability in antidepressant response rates was greater than that expected by chance alone, then the analysis proceeded with a conditional model adding study type (placebo-controlled or comparator) as a fixed effect in the between-studies equation. OR and estimated probabilities of response to antidepressant medication in the different study types were computed. For completeness, the estimated probability of response to placebo in placebo-controlled trials was also deter-

mined. Finally, a full interaction model was constructed by adding study duration to the conditional model of antidepressant response rates. In these analyses, 6- and 7-week duration trials were grouped together under the heading of 6-week trials, 8- and 9-week studies were grouped as 8-week trials, and 10- to 12-week investigations as 12-week trials.

This analysis of response rates was repeated in an identical fashion for the data on antidepressant remission rates. The regression models were estimated using HLM 6. Differences in participant characteristics between trials were investigated by 2-tailed independent-samples t tests for continuous variables and χ^2 tests for categorical variables (SPSS version 15).

Results

Characteristics of Included Trials and Subjects

Forty-eight placebo-controlled and 42 comparator trials met the study's inclusion and exclusion criteria [20–109]. Analysis of medication and placebo groups in individual RCTs is available from the authors upon request. As shown in table 1, there were 100 active treatment conditions enrolling 9,515 participants in the 48 placebo-controlled RCTs, since many of them compared more than 1 medication to placebo. Among the placebo-controlled analyses, 80% demonstrated significant differences in depression response rates between medication and placebo. There were 84 active treatment conditions enrolling 7,030 subjects in the 42 comparator RCTs. Among the compar-

Table 1. Selected characteristics of included studies**a** Trials

	Placebo-controlled trials	Comparator trials
Studies	48	42
Active treatment groups	100	84
Patients	9,515	7,030
Mean age \pm SD, years	40.4 \pm 2.6*	42.9 \pm 3.2
Mean pretreatment HRSD \pm SD	24.2 \pm 4.1	25.2 \pm 2.9
Mean dropout rate \pm SD	34.6 \pm 14.4*	22.0 \pm 9.7
Mean intent to treat \pm SD	95.2 \pm 47.5	83.7 \pm 48.4

b Treatment groups

	Active treatment groups	Patients	Active treatment groups	Patients
Study duration, weeks				
6	51	3,960	44	2,898
7	0	0	2	98
8	35	4,348	24	3,110
9	2	249	0	0
12	9	958	8	924
Medications used				
SSRI	50	5,479	43	3,833
SNRI	22	1,892	11	1,211
TCA	16	1,096	13	777
Atypical	10	815	16	1,186
MAOI	2	233	1	23
Response definition				
HRSD \leq 50%	75	6,947	62	4,727
MADRS \leq 50%	11	1,534	10	1,241
CGI 1 or 2	12	740	10	1,023
Not reported	2	294	2	39
Remission definition				
HRSD \leq 7	20	2,256	22	2,140
HRSD \leq 10	5	720	10	528
HRSD \leq 12	0	0	2	303
MADRS \leq 8	0	0	4	393
MADRS \leq 12	3	502	6	882
Not reported	72	6,037	40	2,784

SSRI = Selective serotonin reuptake inhibitors; SNRI = selective norepinephrine reuptake inhibitors; TCA = tricyclic antidepressant; MAOI = monoamine oxidase inhibitor.

* $p < 0.05$: significant difference between groups.

ator trials, 10% demonstrated significant differences in depression response rates between medications.

Response rates to medication ranged from 25 to 74% (mean = 52.2 \pm 10.4) in the placebo-controlled and from 39 to 91% (mean = 65.2 \pm 11.9) in the comparator

trials, while remission rates varied between 22 and 62% (mean = 39.7 \pm 10.6) in the placebo-controlled and 27 and 70% (mean = 48.4 \pm 13.0) in the comparator trials. Response rates to placebo in the placebo-controlled trials were 13–53% (mean = 34.7 \pm 10.4), while remission rates ranged from 10 to 37% (mean = 24.5 \pm 8.0).

Placebo-controlled relative to comparator trials enrolled individuals who were significantly younger (40.4 \pm 2.6 vs. 42.9 \pm 3.2 years, $t = -3.86$, d.f. = 153, $p < 0.001$), of white ethnicity (Pearson $\chi^2 = 7.77$, d.f. = 1, $p = 0.041$) and had higher dropout rates (34.6 \pm 14.4 vs. 22.0 \pm 9.7, $t = 5.54$, d.f. = 145, $p < 0.001$). The 2 types of trial did not differ in subjects' pretreatment HRSD scores, mean number, sample size, medications used, gender, prior depressive episodes, response and remission outcome measures or quality ratings.

Unconditional Model of Antidepressant Response and Remission Rates

In the unconditional model of antidepressant response rates, variability between studies was >10 times that expected by chance alone (χ^2 /d.f. = 936.9/88 = 10.7). Therefore, the null hypothesis that antidepressant response rates are homogeneous across studies was rejected, and the analysis proceeded with the conditional model. The variability found in antidepressant remission rates across studies was >12 times that expected by chance alone (463.3/37 = 12.5), so this analysis likewise proceeded with the conditional model.

Conditional Model Including Study Type (Placebo-Controlled vs. Comparator)

In the conditional model of antidepressant response rates, study type accounted for 34% of the variability observed [table 2, (0.25–0.16)/0.25 = 0.34]. As shown in table 3, the odds of responding to medication in comparator trials were 1.79 times those in placebo-controlled studies (95% CI = 1.45–2.17, $p < 0.001$). The estimated response rate in placebo-controlled investigations was 52% compared to 65% in comparator trials. For the purposes of comparison, the estimated response rate to placebo in the placebo-controlled trials was 40%.

In the remission rate analysis, the study type accounted for 16% of the variability observed [table 2, (0.24–0.20)/0.24 = 0.16]. The odds of remitting to medication in comparator trials were 1.53 times those in placebo-controlled studies (95% CI = 1.11–2.11, $p < 0.001$), and the estimated remission rate in placebo-controlled trials was 38 versus 49% in comparator trials. The estimated remission rate to placebo in the placebo-controlled trials was 29%.

Table 2. Conditional model including study type in analyses of antidepressant response and remission rates

Fixed effect	Coefficient	SE	t ratio	p value
Response				
Intercept	-0.096	0.074	-1.30	0.198
Comparator	0.59	0.88	6.77	<0.001
Random effect intercept	VC = 0.136	d.f. = 85	$\chi^2 = 503.20$	<0.001
Remission				
Intercept	-0.959	0.266	-3.610	0.001
Comparator	0.710	0.302	2.348	0.025
Random effect intercept	VC = 0.180	d.f. = 32	$\chi^2 = 277.831$	<0.001

VC = Variance component. Comparator = Dummy variable coded 1 for comparator and 0 for placebo-controlled trials. Intercept reflects the reference category of placebo-controlled trials.

Table 3. Summary of findings for effect of study type and duration on antidepressant response and remission

Design parameter		Response			Remission		
		patients	OR	estimated rate	patients	OR	estimated rate
Study type	placebo	9,221		52	3,478		38
	comparator	7,030	1.79 ^a	65	4,246	1.53	49
Study duration	6 weeks	6,956		48	2,080		28
	8 weeks	7,413	1.37 ^b	55	4,390	1.80	41
	12 weeks	1,882	1.52 ^b	58	1,254	1.81	41

^a p < 0.05 for comparison with placebo trials.

^b p < 0.05 for comparison with 6-week duration trials.

Table 4. Conditional model including study duration in analyses of antidepressant response and remission rates

Fixed effect	Coefficient	SE	t ratio	p value
Response				
Intercept	-0.096	0.074	-1.30	0.198
Comparator	0.59	0.88	6.77	<0.001
Eight weeks	0.31	0.092	3.38	0.001
Twelve weeks	0.42	0.15	2.72	0.008
Random effect intercept	VC = 0.136	d.f. = 85	$\chi^2 = 503.20$	<0.001
Remission				
Intercept	-0.959	0.266	-3.610	0.001
Comparator	0.710	0.302	2.348	0.025
Eight weeks	0.590	0.296	1.989	0.055
Twelve weeks	0.594	0.510	1.163	0.254
Random effect intercept	VC = 0.180	d.f. = 32	$\chi^2 = 277.831$	<0.001

VC = Variance component. Comparator = Dummy variable coded 1 for comparator trials and 0 for placebo-controlled trials. Eight weeks = dummy variable coded 1 for 8-week duration trials and 0 for all others. Twelve weeks = dummy variable coded 1 for 12-week duration trials and 0 for all others.

Full Model Including Study Duration (6, 8 and 12 Weeks)

Study duration accounted for 17% of the variability in antidepressant response rates once study design was taken into account [table 4, $(0.16-0.14)/0.16 = 0.17$]. The odds of medication response were significantly greater in 8-week (OR = 1.37, CI = 1.14–1.64, $p = 0.001$) and 12-week (OR = 1.52, CI = 1.12–2.07, $p = 0.008$) compared to 6-week duration clinical trials. However, there was no difference between 8- and 12-week analyses (OR = 1.11, 95% CI = 0.81–1.5, $p = 0.497$). No significant interactions between study duration and study type were found for medication response rates.

Duration accounted for 11% of the variability in antidepressant remission rates once the study design was taken into account [table 4, $(0.20-0.18)/0.20 = 0.11$]. There was a trend toward higher remission rates to medication in 8- versus 6-week duration clinical trials (OR = 1.803, CI = 0.987–3.295, $p = 0.055$), but no significant differences were observed between remission rates in 12- and 6-week clinical trials (OR = 1.810, CI = 0.641–5.111, $p = 0.254$) or 8- and 12-week trials (OR = 1.003, 95% CI = 0.398–2.532, $p = 0.993$). No significant interactions between study duration and study type were found for medication remission rates.

Discussion

Study design explained a significant amount of the variability observed in medication response and remission rates in this sample of antidepressant RCTs. Consistent with the primary hypotheses, response and remission rates to antidepressants were significantly higher in comparator relative to placebo-controlled trials. In contrast to the stated hypotheses, antidepressant treatment outcome also depended on the study duration to some extent. The odds of treatment response were higher in 8- and 12-week duration trials compared to those lasting 6 weeks, while there were no significant differences between 8- and 12-week RCTs. No significant differences in remission rates to medication were found between 6-, 8- and 12-week duration RCTs.

One explanation of the large discrepancies observed in antidepressant response and remission rates between placebo-controlled and comparator trials are patient expectations [110]. These trials differ in that subjects in comparator trials know they are receiving medications demonstrated to be effective for depression, while participants in placebo-controlled trials may be taking pla-

cebo. This raises the possibility that higher expectations of improvement among subjects in comparator trials may account for the observed differences in treatment outcome [6, 111].

Studies that have specifically investigated patient expectations in clinical trials suggest they do influence the depression outcome [112]. In the Treatment of Depression Collaborative Study, which enrolled 239 outpatients with major depressive disorder, higher patient expectations of improvement predicted greater likelihood of depression response and lower final depression scores across treatment conditions [113]. In a single-blind trial of reboxetine for 25 subjects with major depressive disorder, 90% of patients with a higher pretreatment expectation of medication effectiveness responded, compared to 33% of those with lower expectations [114]. Therefore, patient expectations may be an important variable influencing the response to antidepressant medication, and the study design may affect the outcome by modifying expectations.

That patient expectations strongly influence the antidepressant response may not be surprising, given that expectations are hypothesized to be a major mechanism of the placebo effect [115, 116], which is a key component of the medication response observed in antidepressant trials. A meta-analysis of 75 placebo-controlled antidepressant RCTs published between 1981 and 2000 found a mean medication response rate of 50%, compared to a mean placebo response rate of 30% [117]. More recently, Kirsch et al. [118] analyzed data from 47 RCTs of antidepressants submitted to the FDA for marketing approval, finding a mean improvement of 9.60 points on the HRSD in the drug group compared to 7.80 in the placebo groups. The response to placebo therefore duplicated >80% of the change found in the drug groups, and the difference between drug and placebo response did not meet standard criteria for determining clinical significance.

These data indicate that the specific effect of medication accounts for a minority of the change observed in clinical trials. Optimizing patient expectations may offer a safe and effective way of enhancing the clinical response to antidepressant medications. Despite a greater than fourfold increase in the rate of antidepressant drug treatment between the early 1990s and early 2000s [119], many patients will not experience sustained remission of their depression [120]. Among those who achieve remission of their depression on antidepressant medication, >60% will experience relapse of depression within 2 years despite continued medication use [121].

A number of limitations should be considered when interpreting the results of this study. First, publication bias

may have affected which studies were included in these analyses. Examination of the FDA clinical trial database has revealed that 48% of the trials involving an investigational antidepressant and 64% those concerning established agents demonstrate a significant difference between drug and placebo [122]. These values are lower than the 80% of the placebo-controlled trials considered in this study that report a significant difference between drug and placebo, which indicates the presence of publication bias among the included studies. However, the implications of publication bias for the results reported here are unclear, since it is not the efficacy of drugs compared to placebo that is being investigated. In fact, the inclusion of unpublished RCTs not demonstrating a difference between medication and placebo seems likely to strengthen the observed results, since lower antidepressant response rates in placebo-controlled RCTs would increase their relative differences with respect to the rates in comparator trials.

Second, a recent meta-analysis of medication and placebo response rates in antidepressant RCTs found placebo response was correlated with year of publication [117]. While medication response was not significantly associated with year of publication in this meta-analysis once covariates were taken into account, it remains possible that differences in publication year between comparator and placebo-controlled trials in this study may have affected the observed pattern of response and remission rates.

Third, because this analysis combines subjects across different trials, the results may be due to variation among participants enrolled in the different study types and durations rather than the study design itself. This possibility was investigated by comparing subjects in placebo-

controlled and comparator trials on a number of demographic and clinical characteristics, which revealed higher dropout rates among participants in placebo-controlled trials. If subjects in placebo-controlled trials dropped out when they had higher depression symptom scores, this could result in decreased response and remission rates compared to those in comparator trials, who more often completed the study. Interestingly, the dropout rates may also be influenced by anticipation, since greater expectations may lead subjects to form stronger therapeutic alliances, continue treatment during periods of clinical worsening or increased side effects, and report less severe symptoms. This potential limitation also illustrates how retrospective analyses alone can never definitively answer the question of whether the study design influences the treatment outcome. It is essential to randomize a single sample to different study types or durations and prospectively assess their treatment outcomes. Such a prospective trial is now underway by the current authors.

Acknowledgements

The authors thank David Rindskopf, PhD at the Graduate Center of the City University of New York for his assistance in planning the data analyses. This study was supported by grants from the National Institute of Mental Health. B.R.R. receives funding under T32 – MH151414 ‘Research Fellowship Training: Affective and Related Disorders’ and Dr. J.R.S. under K23 – MH70056 ‘Vascular Depression: A Distinct Diagnostic Entity?’ S.P.R. reports receiving research grants from Forest Laboratories and Novartis Pharmaceuticals as well as consultant fees from Forest Laboratories, Organon, Wyeth Pharmaceuticals and Eli Lilly & Company.

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