A Systematic Review of Placebo Response in Studies of Bipolar Mania

Robyn Sysko, M.S., and B. Timothy Walsh, M.D.

Objective: In a previous review, we found that response to placebo in studies of major depression was increasing over time. The purpose of this study was to examine placebo response rates in trials of acute bipolar mania.

Data Sources: We searched MEDLINE for placebo-controlled trials in which patients with bipolar mania were randomly assigned to receive medication or placebo. Searches included combinations of the terms *acute bipolar mania*, *placebo-controlled*, *double-blind*, *randomized*, and common medication names (e.g., *lithium*, *risperidone*). In addition, reference lists from identified articles and any reviews of bipolar mania were examined. The search was limited to literature in English, published between January 1980 and November 2005.

Study Selection: The review identified 21 studies published between 1991 and 2005. Twenty studies used a response criterion of a 50% or greater decrease on the Young Mania Rating Scale (YMRS) or Mania Rating Scale (MRS), or a designation of much or very much improved on the Clinical Global Impressions-Improvement scale (CGI, score of 1 or 2).

Data Extraction: Data were extracted from the articles by one of the authors (R.S.) and all of the data used in the analyses were verified by the other author (B.T.W.).

Data Synthesis: Pearson correlation coefficients (2-tailed) and linear regression were used to examine the strength of the relationship between continuous variables. There was a significant association between the year of publication and placebo response rate in studies using the YMRS (N = 14) (r = 0.545, p = .04); however, when data from studies using the CGI and MRS were added, the association was no longer significant (r = 0.374, N = 20, p = .10).

Conclusions: The response rate to placebo in studies of bipolar mania (31.2%) was similar to the rate observed in major depression (29.7%). Over a limited number of years, there was some indication of a change in placebo response on the YMRS in studies of bipolar mania; however, the small number of studies available for analysis limits our ability to draw definitive conclusions.

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Received Oct. 10, 2006; accepted Dec. 18, 2006. *From the Department of Psychology, Rutgers University, Piscataway, N.J. (Ms. Sysko); and the Department of Psychiatry, College of Physicians and Surgeons of Columbia University, and New York State Psychiatric Institute, New York (Dr. Walsh). Ms. Sysko is now employed at the Psychology Service, Department of Veterans Affairs (VA) Connecticut Healthcare System, West Haven Campus, West Haven.*

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Corresponding author and reprints: B. Timothy Walsh, M.D., Unit 98, 1051 Riverside Dr., New York, NY 10032 (e-mail: btw1@columbia.edu).

Concerns have been raised regarding the use of placebo in randomized controlled trials for the treatment of mood disorders on both ethical and scientific grounds. Some who oppose the use of placebo argue that placebo groups are unethical and should be abandoned when research has already established the efficacy of a pharmacologic treatment for the condition to be examined.[1] Recently, the National Depressive and Manic-Depressive Association (NDMDA) published a consensus statement on placebo in trials for mood disorders[2] and concluded that the use of placebo in the short-term does not cause harm when the research involves appropriate monitoring for safety and the exclusion of high risk patients (e.g., suicidal patients, psychotic individuals, etc.). From a scientific standpoint, the absence of a placebo group complicates inferences about the efficacy of a medication for alleviating the symptoms of mood disorders.[3] The NDMDA statement echoed this conclusion by indicating that "mood disorder research is not at the point at which noninferiority trials can be considered scientifically valid designs."[2(p263)] In addition, as high rates of placebo response occur in pharmacologic trials for mood disorders, Charney[4] highlighted the importance of identifying patient and study characteristics associated with higher rates of placebo response. On the basis of such information, studies might be designed to minimize placebo response and thereby require a smaller number of patients with mood disorders to be assigned to placebo.[4]

The current report describes a literature review designed to examine placebo response rates reported in

pharmacologic trials of the treatment of acute bipolar mania. We were interested in determining whether the placebo response in studies of mania had increased in recent years, as described in a recent examination of placebo response in trials of major depression.[3,5]

METHOD

Data Sources and Study Selection

We searched MEDLINE for peer-reviewed articles describing randomized, placebo-controlled trials of medication for individuals diagnosed with bipolar mania. Searches included combinations of the terms *acute bipolar mania*, *placebo-controlled*, *double-blind*, *randomized*, and common medication names (e.g., *lithium*, *risperidone*). In addition, reference lists from identified articles and any reviews of bipolar mania were examined. We identified 21 trials published between 1991 and 2005 for analysis. To be included in this review, articles were required to meet the following criteria: (1) reported in English; (2) published or e-published between January 1980 and November 2005; (3) primarily composed of patients with bipolar disorder, manic phase; (4) included at least 20 patients in the placebo group; (5) reported the total number of patients assigned to placebo and medication group(s); and (6) provided information about the number of patients who responded to medication or placebo by a reduction of at least 50% in their score on the Young Mania Rating Scale (YMRS) or the Mania Rating Scale (MRS) and/or by a Clinical Global Impressions-Improvement scale (CGI) rating of markedly or moderately improved (CGI score of 1 or 2) and/or by reporting the change in YMRS from pre- to post-treatment.

Twenty[6–25] of the studies met our criteria and reported response by the number of patients with at least a 50% reduction in either YMRS or MRS scores or with a CGI score of 1 or 2; some studies reported a combination of these response criteria. One study[26] reported outcome as the mean decrease on the YMRS score and was excluded from subsequent analysis. Six studies of adjunctive treatment were included,[13,16,17,19,24,25] in which patients were randomly assigned to receive either an additional medication or placebo with an active medication (e.g., olanzapine plus mood stabilizer). We chose to include these studies in the analyses because, at the time they entered the study, patients continued to exhibit manic symptoms (YMRS minimum scores between 12 and 20).

Data Extraction

Data were extracted from the articles by one of the authors (R.S.) and all of the data used in the analyses were verified by the other author (B.T.W.). For each study, the response rates for the placebo and medication group(s) were calculated by dividing the number of patients in each group (medication and placebo) who had responded according to the criteria by the number of patients assigned to the group. If response data were provided only on study "completers," it was assumed that noncompleters had not responded. Similar to our previous analysis,[3] for each study with more than 1 active medication group, the greatest response rate using YMRS, CGI, or MRS criteria in 1 medication group was designated the maximum medication response rate for that study and used in the analyses described below. In 3 studies[6,16,24] in which placebo response was reported for more than 1 measure (YMRS and CGI), we selected the measure with the maximum placebo response rate. Effect size was calculated as the difference between the arcsine-transformed response rate on active medication and the arcsine-transformed response rate on placebo.[27]

Statistical Methods

Means and standard deviations were calculated for the demographic characteristics (e.g., age, percentage of women included in the study), study characteristics (e.g., total number of patients enrolled in the study), and the percent response by placebo and medication. Pearson correlation coefficients (2-tailed) and linear regression were used to examine the strength of the relationship between continuous variables, and Spearman rank correlation (ρ) was used to examine the strength of the relationship between year of publication and dichotomous variables. Statistical calculations were performed using SPSS for Windows, version 10 (SPSS Inc., Chicago, Ill.).

RESULTS

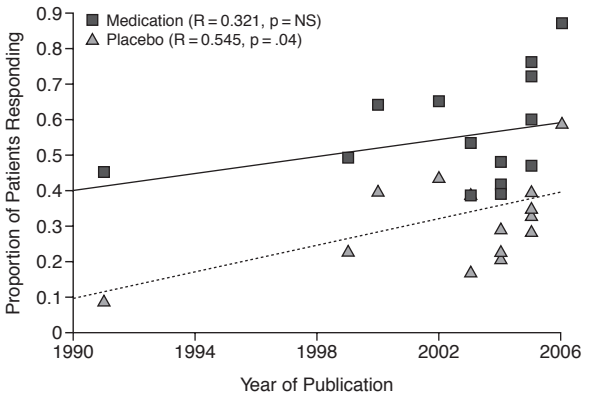
The mean ± SD age of patients enrolled in the 20 studies was 37.37 ± 6.10 years (range, 14 to 43 years), and the trials included a mean ± SD of 45.9% ± 6.82% women (range, 30.0% to 58.0%). The mean ± SD trial length was 31.50 ± 21.37 days (range, 21 to 84 days). The mean ± SD baseline YMRS scores were 28.87 ± 4.11 (range, 18.40 to 37.50) for the placebo group and 29.18 ± 3.79 (range, 18.80 to 37.10) for the medication group. The mean ± SD percent dropout from the placebo group was 46.4% ± 18.7% (range, 11.0% to 79.0%), and 35.9% ± 16.9% (range, 10.0% to 76.5%) of patients from the medication conditions terminated treatment prematurely. The total sample size was a mean ± SD of 200.65 ± 97.62 patients (range, 43 to 438), with a mean ± SD of 83.55 ± 38.17 patients (range, 22 to 145) randomly assigned to receive placebo and 93.68 ± 50.40 patients (range, 20 to 229) randomly assigned to receive medication. Five studies (25%) included 2 active medication groups (e.g., Sachs et al.[17] included risperidone and haloperidol). Six studies reported using a placebo washout, and 14 required some length of inpatient hospitalization.

Table 1. Data on Individual Placebo Response Rates and Effect Sizes for Included Studies of Bipolar Mania (N = 20)

Study	Placebo Responders, %	Effect Size*
Pope et al (1991)[14]	9.0[a]	0.87[d]
Bowden et al (1994)[7]	26.0[c]	0.51[f]
Tohen et al (1999)[21]	23.0[a]	0.54[d]
Pande et al (2000)[13]	47.0[b]	–0.26[e]
Tohen et al (2000)[20]	40.0[a]	0.48[d]
Sachs et al (2002)[17]	27.0[b]	0.51[e]
Tohen et al (2002)[19]	44.0[a]	0.42[d]
Keck et al (2003)[10]	17.0[a]	0.46[d]
Keck et al (2003)[11]	33.0[c]	0.29[f]
Yatham et al (2003)[24]	39.0,[a] 41.0[b]	0.28,[d] 0.25[e]
Hirschfeld et al (2004)[9]	23.0[a]	0.39[d]
Sachs et al (2004)[16]	29.0,[a] 28.0[b]	0.40,[d] 0.36[e]
Weisler et al (2004)[23]	21.0[a]	0.38[d]
Bowden et al (2005)[6]	40.0,[a] 36.0[b]	0.73,[d] 0.75[e]
Delbello et al (2005)[8]	19.0[b]	0.22[e]
Khanna et al (2005)[12]	35.0[a]	0.75[d]
Potkin et al (2005)[15]	29.0[c]	0.34[f]
Smulevich et al (2005)[18]	33.0[a]	0.30[d]
Weisler et al (2005)[22]	28.0[a]	0.65[d]
Zhang et al (2005)[25]	59.0[a]	0.65[d]

*Effect size was calculated as the difference between the arcsine-transformed response rate on active medication and the arcsine-transformed response rate on placebo for YMRS,[d] CGI,[e] or MRS.[f]
[a]Percentage of participants responding by at least a 50% reduction in YMRS scores.
[b]Percentage of patients with a posttreatment CGI score of 1 or 2.
[c]Percentage of participants responding by at least a 50% reduction in MRS scores.
Abbreviations: CGI = Clinical Global Impressions-Improvement scale, MRS = Mania Rating Scale, YMRS = Young Mania Rating Scale.

Figure 1. Proportion of Patients Who Showed a 50% or Greater Improvement in Young Mania Rating Scale Score by Year of Publication



The correlation between year of publication and the total number of patients randomly assigned was statistically significant (r = 0.442, df = 19, p = .05), but the correlations between year of publication and the mean age of the samples (r = –0.224, df = 19, p = NS), the percentage of women included in the studies (r = 0.494, df = 18, p = NS), trial length (r = 0.425, df = 19, p = NS), the number of patients randomly assigned to receive placebo (r = 0.388, df = 19, p = NS), and the number of patients randomly assigned to receive medication were not significant (r = 0.406, df = 19, p = NS). In addition, none of the Spearman ρ correlations between year of publication and studies with and without adjunctive treatment (ρ = –0.087, df = 19, p = NS), a placebo washout period (ρ = 0.001, df = 19, p = NS), or required inpatient hospitalization (ρ = –0.029, df = 19, p = NS) were significant.

The mean ± SD percent response to placebo was 31.6% ± 12.8% for YMRS (N = 14), 33.1% ± 10.4% for CGI (N = 6), and 29.1% ± 3.6% for MRS (N = 3), and 31.2% ± 11.7% when using any measure (YMRS, CGI, or MRS, N = 20). For medication, the maximum mean ± SD percent responses were 55.9% ± 15.0% for YMRS, 47.5% ± 15.8% for CGI, and 47.4% ± 2.5% for MRS. Over the course of treatment, YMRS scores decreased a mean ± SD of 7.64 ± 2.43 points among patients receiving placebo and 14.06 ± 6.46 points among patients receiving medication. The mean ± SD effect size for the response rate by YMRS was 0.52 ± 0.18 (range, 0.28 to 0.87), 0.30 ± 0.34 for the response rate by CGI (range, –0.26 to 0.75), and 0.38 ± 0.11 (range, 0.29 to 0.51) for the response rate by MRS. Data on the placebo response rates and effect sizes for each of the 20 individual included studies are provided in Table 1.

We observed a significant correlation (r = 0.545, N = 14, p = .04) between year of publication and the percentage of patients receiving placebo who demonstrated a 50% or greater reduction in YMRS scores (Figure 1); however, when all data from 3 response criteria (YMRS, CGI, and MRS) were combined, the association between response and year of publication was no longer significant (r = 0.374, N = 20, p = .10). No significant correlations were observed between year of publication and effect sizes for response by YMRS (r = –0.365, N = 14, p = NS), CGI (r = 0.690, N = 6, p = NS), MRS (r = –0.932, N = 3, p = NS), or the maximum effect size from any measure (r = –0.168, N = 20, p = NS).

DISCUSSION

This study found a positive correlation between placebo response on the YMRS and year of publication in studies of bipolar mania published between 1991 and 2005. Among the 20 studies included in this review, the mean response rate for placebo as measured by YMRS was 31.6%, and the mean response rate for medication by YMRS was 55.9%. The results resemble those of an earlier study of placebo response in major depression, which indicated that placebo response rates were substantial (29.7%) and increasing over time.[3] In addition, the findings are consistent with a previous meta-analysis of controlled studies in bipolar mania and depression, which found a moderate effect size for placebo[28] (effect

size = 0.40). The authors of that study concluded that the moderate placebo response in bipolar mania could be attributed to a number of different factors related to study design, including the use of additional rescue medications, severity of illness, or trial duration.[28]

The current study did not find any statistically significant relationships between year of publication and most study variables, including mean age of the samples, the percentage of women included in the studies, trial length, the number of patients randomly assigned to placebo, the number of patients randomly assigned to receive medication, the number of studies using adjunctive treatment, the number of studies using a placebo washout period, or the number of studies requiring patients to be hospitalized. The relationship between year of publication and the total number of patients randomly assigned in the studies was significant, suggesting that the sample size for studies included in this review have increased from 1991 to 2005. None of the correlations between year of publication and effect size (YMRS, CGI, MRS, or combined across scales) were significant, and we therefore did not find evidence for a more general trend in overall responsivity for placebo and medication over time across study designs.

Although the similarities among the results of the prior review for major depression,[3] the meta-analysis of Keck and colleagues,[28] and the current review are reassuring, there are significant limitations to the findings of the current review. The number of studies available for review was small, the publication years were limited in range (15 years), and the relationship observed between placebo response and year of publication was influenced by outliers (see Figure 1). Finally, there were significant variations across studies with regard to the length of the trials, the mean baseline YMRS scores, and the rate of dropout from placebo or medication groups. Thus, while the data suggest that the rate of response to placebo in bipolar mania (as measured by YMRS) has increased, the relatively small number of studies and substantial differences in study design limit confidence in this conclusion.

In summary, the limited information available suggests that placebo response may be changing over time in controlled studies of bipolar mania. This observation lends support to the conclusion of the National Depressive and Manic-Depressive Association that placebo control groups are still needed in pharmacologic trials for mood disorders to provide a scientifically rigorous test of psychiatric medications.[2] While these designs pose some risk for patients receiving placebo, with appropriate safeguards, such risks can be minimized, and the inclusion of a placebo group provides substantial, and possibly essential, scientific benefit.

Drug name: olanzapine (Zyprexa).

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