



Relationship between placebo response rate and clinical trial outcome in bipolar depression



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ABSTRACT

The aim of this work is to investigate the impact of placebo response rates on the relative risk of response to drug versus placebo in randomized, double-blind, placebo-controlled clinical trials of pharmacological therapy in Bipolar Depression (BPD).

Medline/PubMed publication databases were searched for randomized, double-blind, placebo-controlled trials of oral drugs used as monotherapy for the treatment of BPD. The search was limited to articles published between January 1980 and September 2015. Data extracted from 12 manuscripts and one poster with yet unpublished results, representing a total of 17 clinical trials were pooled ($n = 6578$). Pooled response rates for drug and placebo were 55.1% and 39.2%, corresponding to a risk ratio (RR) for responding to active treatment versus placebo of 1.29 ($p < 0.001$). Clinical response was defined as a 50% or greater reduction in depression scores, baseline to endpoint. A higher placebo response rate correlated with a significantly lower RR of responding to pharmacotherapy versus placebo ($p = 0.002$). The pooled drug and placebo response rates for studies with a placebo response rate $\leq 30\%$ were 50.5% versus 26.6%, while corresponding values from studies with a placebo response rate $> 30\%$ were 55.0% versus 41.6%.

These results suggest that the relative efficacy of the active drug compared to placebo in clinical trials for BPD is highly heterogeneous across studies with different placebo response rates, with a worse performance in showing a superiority of the drug versus placebo for studies with placebo response rates $> 30\%$. It is important to maintain placebo response rates below this critical threshold, since this is one of the most challenging obstacles for new treatment development in BPD.

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1. Introduction

Bipolar disorder, a prevalent debilitating illness, is distinguished by its defining feature of one or more episodes of abnormal mood elevation (i.e. mania or hypomania). However, depressive episodes are very common during the lifetime of patients with bipolar disorder and, in fact, are often associated with the majority of the burden on the patient's suffering, functional impairment, morbidity, and mortality (Judd et al., 2002, 2005; Kupka et al., 2007; Calabrese et al., 2003; Goldberg and Harrow, 2011). There has been a large amount of research that supports the treatment

efficacy of pharmacotherapies for mania and hypomania (Grunze et al., 2009, 2013; Cipriani et al., 2011; Yildiz et al., 2011; Kanba et al., 2014), however there are only a few adequately powered studies of rigorous design that examine the treatment efficacy of pharmacotherapies for bipolar depression (BPD) and that have gone on to be replicated (Vieta et al., 2010; Vieta and Valenti, 2013; Young et al., 2014). In a landmark meta-analysis, for instance, Vieta et al. (2010) found that of eight medications examined in randomized, double-blind trials, only quetiapine, olanzapine, and the combination of olanzapine and fluoxetine had demonstrated superior efficacy in treating BPD compared to placebo. More recently, lurasidone has also demonstrated higher remission rates versus placebo (Loebel et al., 2014a,b). In comparison, ziprasidone (Sachs et al., 2011), aripiprazole (Thase et al., 2008), and lamotrigine monotherapy (Geddes et al., 2009), in many but not all trials, failed to separate sufficiently from placebo for the treatment of BPD.

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Although double-blind, randomized, placebo-controlled clinical trials (RCTs) are considered the gold standard for testing the efficacy of proposed treatments for major depression (unipolar and bipolar), statistically significant differences in remission rates between drug and placebo are not always apparent. In major depressive disorder (MDD), for instance, Turner et al. (2008) conducted a meta-analysis of 74 RCTs of 12 FDA-approved drugs and found that approximately 50% of these RCTs failed to show statistically significant differences in efficacy between drug and placebo. Additionally, meta-analyses of placebo-controlled RCTs for MDD demonstrate that a large placebo response rate can mask a clinically significant effect of an antidepressant, thus making such trials uninformative (Iovieno and Papakostas, 2012). In fact, in MDD trials, it has been shown that treatment effect size is inversely proportional to placebo response rates, an important finding with implications both for clinical trials as well as clinical practice (Iovieno and Papakostas, 2012).

Unfortunately, to date, no study has examined in detail the relationship between placebo response rates and overall study outcome for pharmacological therapies in BPD. Therefore, the aim of the present analysis is to investigate the impact of placebo response rates on the relative risk of response to drug versus placebo in randomized, double-blind, placebo-controlled clinical trials of pharmacological therapy in BPD.

2. Material and methods

2.1. Data source and search strategy

Our aim was to identify randomized, double-blind, placebo-controlled trials of oral medications used as monotherapy for the treatment of BPD for inclusion in the analysis. Potentially eligible trials were first identified with a systematic search of several literature databases (PubMed, PsychInfo, EMBASE, and ClinicalTrials.gov) using the search terms “bipolar” and “placebo”. The search was limited to papers published between January 1st, 1980 (since the DSM-III was introduced in 1980 (20)) and September 30th, 2015. In order to expand our database, we then reviewed the reference list of all studies identified, including reviews and meta-analyses (Sidor and Macqueen, 2011). Abstracts of initially identified papers were screened for possible relevance and evaluated for meeting eligibility criteria by independent review of full texts by 2 investigators. Final inclusion of articles was determined by author consensus.

2.2. Trial selection

We selected for randomized, double-blind, placebo-controlled studies that also met the following criteria:

- 1) Defined BPD according to the Diagnostic and Statistical Manual of Mental Disorder, Third Edition (American Psychiatric Association, 1980), Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised (American Psychiatric Association, 1987), Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 1994), Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013), Research diagnostic criteria (Spitzer et al., 1978), or Feighner's Diagnostic Criteria (Feighner et al., 1972).
- 2) Had a minimum duration of four weeks of treatment.
- 3) Focused on the use of oral medications.
- 4) Presented entirely original data.
- 5) Focused on the treatment of adults.

- 6) Did not exclusively focus on the treatment of patients with comorbid alcohol or substance use disorders, patients with a specific comorbid medical illness, or patients with other affective disorders, including major depressive disorder (MDD), MDD with psychotic features, dysthymic disorder, neurotic depression, minor depression, hypomania, mania or mixed states.
- 7) Involved the use of either the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), or the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) as an outcome measure.

2.3. Data extraction

Data were extracted by one of the authors and checked for accuracy by a second. Data included year of publication, number of patients randomized, dosing scheme (fixed versus variable), probability of receiving placebo, trial duration, clinical response rates, completion rates, and abnormal mood switch rates. Clinical response was defined as a 50% or greater reduction in depression scores, baseline to endpoint. For consistency, the HDRS was chosen over the MADRS when response rates from both scales were available, utilizing the modified intent-to-treat based response rates reported in the manuscripts (“efficacy sample”). When baseline severity of illness was only reported for the MADRS, these scores were converted to HDRS-equivalent scores by multiplying with a factor of 0.7524. This factor was calculated based on data from the study by Carmody et al. (2006), which reports both MADRS and HDRS scores for more than 1200 patients with MDD. When plotting MADRS versus HDRS total scores in the linear proportion of the dataset (from MADRS 0–52 and HDRS 0–40), the resulting linear regression defines the conversion as follows: $\text{HDRS} = 0.7524 \times \text{MADRS}$. Consequently, MADRS baseline scores were multiplied by a factor of 0.7524 to estimate the baseline HDRS scores. The probability of receiving placebo was computed based on the number of treatment arms and the randomization schedule of each trial. For example, a two-arm trial with a 1:2 randomization favoring “active” treatment yields a 1 in 3 chance of receiving “placebo”. For this analysis, placebo response will be defined as the response rates reported in the placebo group.

2.4. Quantitative data synthesis

Random-effects meta-analysis was used to estimate the pooled risk ratio (RR) of responding to medication versus placebo in drug monotherapy trials for BPD. Meta-regression was then utilized to investigate the correlation between placebo response rates and the RR of responding to drug versus placebo. We then divided the trials in 2 groups based on placebo response rates:

- 1) trials with a placebo response rate $\leq 30\%$,
 - 2) trials with a placebo response rate $> 30\%$.
- We estimated pooled drug and placebo response rates and number needed to treat (NNT) for the two groups of trials. All tests conducted were two-tailed, at the $\alpha = 0.05$ level of significance.

3. Results

A total of 1658 abstracts were identified in the PubMed search (Fig. 1). Of these, 1633 were excluded for various reasons (other topics, reviews, duplicate reports, non-monotherapy (adjunctive) trials). Abstracts for the remaining 25 manuscripts (describing trials of medications as monotherapy for BPD) were collected and reviewed. No further manuscripts were identified after reviewing the reference list. Of these 25 papers, 5 were excluded for the reasons listed in Fig. 1. Thus, a total of 15 manuscripts (Calabrese

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