Clinician-Administered Assessments and Impact on Placebo Response in Recent Major Depressive Disorder (MDD) Clinical Trials

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Methodological Issue Being Addressed Multiple clinical trial design factors are hypothesized to impact the magnitude of the placebo response in major depressive disorder (MDD) clinical trials. Here, data from MDD trials completed in the past 10 years that met our analysis criteria were investigated to identify associations between clinical trial design factors and magnitude of placebo change from baseline.

Introduction Participants in randomized, placebo-controlled MDD trials of antidepressants often show a robust response to placebo on clinical endpoints. Clinical trial design factors such as number of site visits, baseline symptom scores, and clinical assessments may contribute to the placebo response, increasing the challenge of demonstrating a treatment effect. The impact of these factors on placebo response in recently completed MDD trials has not been well studied.

Methods A systematic search of unique randomized, placebo-controlled trials with the following analysis inclusion criteria was conducted: Phase 2-4, industry-funded, conducted in adults with MDD, completed within the past 10 years, using the gold-standard primary endpoints of HAM-D or MADRS, with ≥100 total participants enrolled and ≥25 participants enrolled in the placebo arm. A total of 27 trials, 12 Phase 2 and 15 Phase 3, met the above criteria and had data available via public sources, including clinicaltrials.gov, publications, or company documents. 17 trials tested adjunctive treatments and overall, 8 of the 27 trials met their primary endpoint. Placebo response was measured by placebo group change from baseline score of the primary endpoint, either HAM-D or MADRS. To compare between trials that used different primary endpoint scales, we normalized to percent change from baseline score when baseline data was available.

Results Multiple linear regression analyses demonstrated that the frequency and total number of clinician-administered assessments conducted during these clinical trials were significantly associated with percent placebo group change, ($p<0.01$ and $p<0.0001$, respectively). Similar results were found for the frequency ($p<0.05$) and total number ($p<0.05$) of the primary endpoint assessment (HAM-D or MADRS), and the frequency ($p<0.01$) and total number ($p<0.001$) of other clinician-administered assessments during the study (e.g., HAM-A, CGI-I, CGI-S). When adjusting for placebo group size, the total number of all clinician-administered assessments remained significantly associated with percent placebo group change.

We also explored other factors that could impact placebo response, such as number of trial sites

and study duration. These two factors were not significantly associated with placebo change, but baseline HAM-D total scores were modestly associated with placebo response.

Conclusion Multiple regression analyses highlighted that the number and frequency of clinician-administered assessments were significantly associated with the magnitude of placebo change in MDD trials conducted over the past 10 years. Our findings suggest that reducing the number and frequency of clinician-administered assessments in MDD trials may reduce the placebo response and should be considered when designing such clinical trials.

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Keywords

Keywords
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Guidelines I have read and understand the Poster Guidelines

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