Meta-Regression Analysis of Placebo Response in Antipsychotic Trials, 1970–2010


The inclusion of placebo control groups has been standard practice, and often a regulatory requirement, in randomized psychopharmacology trials. An increasing placebo response in recent antipsychotic trials presents a major challenge in psychopharmacologic drug development, with studies reporting a trend toward diminished drug-placebo differences over time.

The purpose of this meta-regression analysis was to identify potential contributors to placebo response in randomized controlled trials of antipsychotic treatment in schizophrenia.

The authors extracted trial design and clinical variables from eligible randomized controlled trials (N=50) during the years 1960–2010. Standardized mean change (SMC) was used as the effect size measure for placebo response, based on change scores on the Brief Psychiatric Rating Scale or the Positive and Negative Syndrome Scale from baseline to endpoint (2 to 12 weeks).

The results suggest significant heterogeneities in the magnitude of placebo response and in study quality. There were significant heterogeneities in the magnitude of placebo response and study quality across studies. Both placebo response and study quality increased significantly overtime. Age, shorter duration of illness, greater baseline symptom severity, and shorter trial duration were significantly associated with greater placebo response, while country (United States compared with other countries) was not. More study sites, fewer university or Veterans Affairs treatment settings, and a lower percentage of patients assigned to receive placebo were associated with a greater placebo response, but these were not independent of publication year.

The influence of study publication year and related period effects (before or after 1993–1997) on placebo response and study quality were significant, possibly reflecting a shift in patient population, trial methodology, trial execution, or reporting of psychiatric trials over the years.

This meta-analysis identified a broader range of study design parameters as potential contributors to placebo response in clinical trials of antipsychotic drugs in schizophrenia, and perhaps in psychopharmacology trials in general. This meta-analysis findings argue for trials to be longer induration, with a minimum period of 6 weeks, as well as for caution when expanding the number of investigative sites beyond 40, especially in nonacademic settings or when incorporating unusually high baseline severity in study inclusion criteria (CGI severity score of more than 5).

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