The Magnitude of Placebo Response Over Time in Clinical Trials for Psychiatric and Other Chronic Medical Conditions

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The Methodological Question Being Addressed: how does the magnitude of placebo response affect efficacy outcomes of clinical trials for chronic conditions?

Introduction: Since the increasing placebo response in antidepressant trials was first reported by Walsh et al (2001), the assumption has been that the historically high 50% failure rate of antidepressant trials was due to this phenomenon. However, data from more recent antidepressant clinical trials submitted for approval by the US FDA showed that although the placebo response has continued to increase since Walsh's report, treatment effect-sizes have remained consistent and success rates have actually increased to 68% (Khan et al, 2017). These findings prompted us to replicate our analysis in other chronic psychiatric and medical conditions to determine if this pattern of a rising placebo response and stable efficacy outcomes is unique to antidepressants or a more general trend.

Methods: We extracted efficacy data from New Drug Approval packets evaluating medications for five chronic conditions, in addition to depression. These conditions were ADHD, hypertension, epilepsy, diabetes mellitus type 2, and schizophrenia. For all FDA-reviewed efficacy trials, we recorded symptom reduction (response) for both placebo and drug-treatment groups. We also recorded the p-value from statistical comparison of each treatment arm and calculated Hedges' G (standardized effect-size). Using meta-regression of these data, we examined treatment response and efficacy outcomes over time (year of approval).

Results: We found that in each of the conditions we examined, the improvement with placebo had significantly increased over time. Specifically, placebo-treatment provided 12% more symptom reduction in depression, 18% more in ADHD, 13% more in epilepsy, and 11% more in schizophrenia in more recent trials compared to earlier trials. Placebo-treatment reduced HbA1c by 0.5 points more in recent diabetes trials and decreased diastolic blood pressure by 3.3 more in more recent hypertension trials compared to earlier trials. Effect-sizes and success rates remained consistent over time in all of the conditions except for schizophrenia, in which the effect-size decreased significantly. Maintenance of effect-size was related to the generally parallel increase in drug response across conditions.

Conclusions: The continuous increase in the magnitude of placebo response over time is not limited to depression or just psychiatric conditions. This pattern appears to be a general phenomenon occurring in clinical trials for various chronic conditions. With the exception of antipsychotic trials, parallel increase in drug response appears to have compensated for the rise in placebo, keeping efficacy outcomes the

same. Exploratory analysis revealed that the relationship of treatment arm sample size to the mean effect-size (adequacy of statistical power) may have a stronger role than the magnitude of placebo response in determining treatment arm success. In other words, the dependency of a trial's success on a low placebo response appears to be a statistical artifact of underpowering. Trials for conditions with more modest effect-sizes (depression, epilepsy, and schizophrenia) may be limited by their primary dependent measures, which may not be as reliable or precise. One possible explanation for the rise in placebo response across conditions may be related to increased expectations following the direct-to-consumer marketing paradigm shift.

References:

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