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

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Abstract

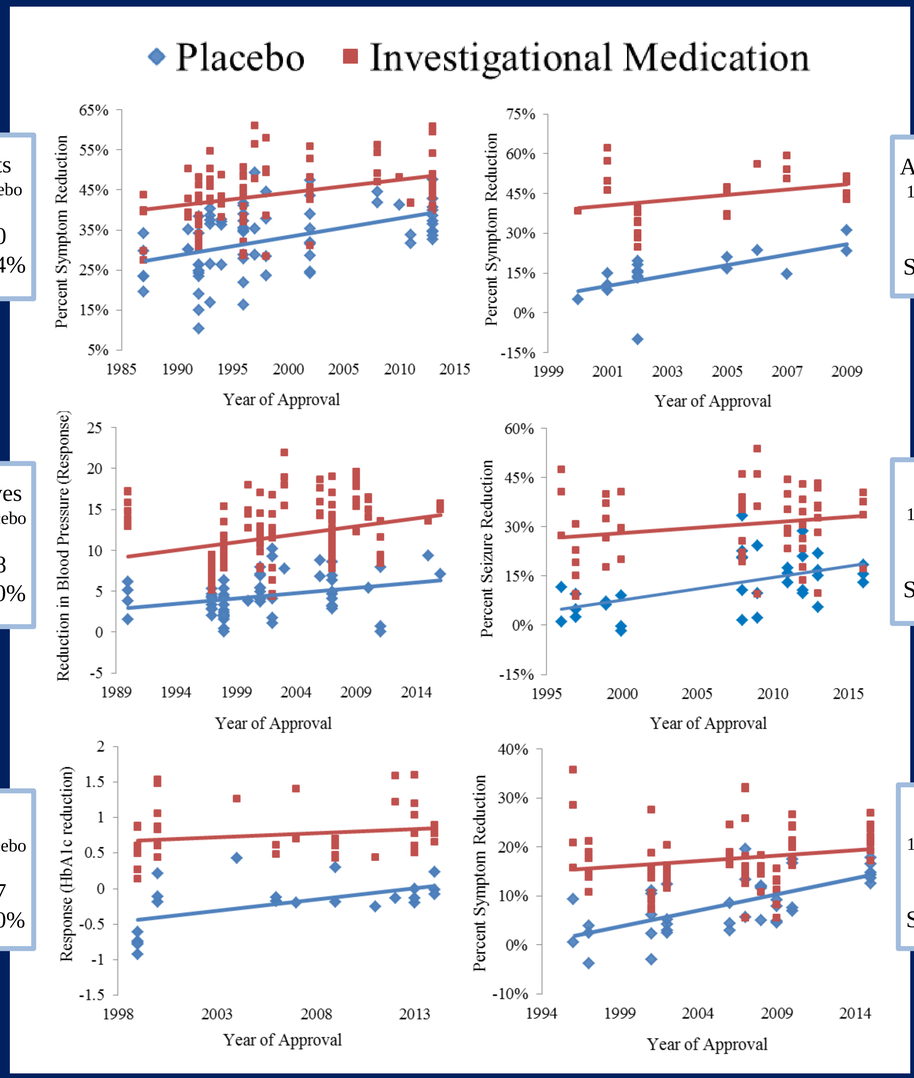
Introduction: Since the increasing placebo response in antidepressant trials was first discovered by Walsh et al (2001), the assumption has been that the historically high 50% failure rate of antidepressant trials was due to this phenomenon. However, data from more recent antidepressant clinical trials submitted for approval by the US FDA showed that although the placebo response has continued to increase since Walsh's discovery, 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 improvement in depression, 18% more in ADHD, 13% more in epilepsy, and 11% more in schizophrenia in more recent trials compared to earlier. Placebo-treatment reduced HbA1c by 0.5 points more in recent diabetes trials and decreased diastolic blood pressure by 3.3 points more in more recent hypertension trials compared to earlier. 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 under-powering. 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.

Introduction:

- Walsh et al (2001) - placebo response found to be rising in antidepressant trials. assumed to be causing the 50% failure rate
- Khan et al (2017) - examined AD trials after Walsh's report and found that placebo response is still rising significantly, but unexpectedly efficacy outcomes not affected.
  - Effect size maintained and success rate increased.
- Unexpected findings prompted replication of analysis in other chronic psychiatric and medical conditions

Methods:

- Conditions: depression, hypertension, ADHD, epilepsy, diabetes type 2, schizophrenia.
- Extracted efficacy data from NDA reports of efficacy trials reviewed by FDA
- Inclusion criteria: placebo-controlled trials reviewed for efficacy by FDA, sufficient reporting of data to calculate measures, exclusive diagnosis of the target condition.
- Exclusion criteria: alternate/incomparable endpoints, trials with duration <2 weeks or >28 weeks, treatment arms using unapproved doses.
- Recorded symptom reduction (response) for drug and placebo on primary efficacy measure, p-values from endpoint analysis of treatment arms , and calculated Hedges' G effect-size.
- Weighted meta-regression of treatment response and efficacy outcomes by year of approval.



Results:

- Placebo response rising significantly ($p<0.05$) in all conditions (see individual conditions <left)
- Parallel growth in drug response keeping efficacy outcomes the same over time (except in schizophrenia, where ES decreased significantly)
- Magnitude of placebo response is only related to trial arm success when treatment arms are underpowered.

Table 1. The effect of median split of treatment arm sample size on the relationship between magnitude of placebo response and treatment arm success.

Depression	**<170 N**	**>170 N**
Mean PCBO Resp	29.9%	36.7%
Relationship of PCBO resp to success	R^2= 0.346 P<0.001	R^2= 0.043 p= 0.164
Success Rate	40%	68%

Even though placebo response is significantly ($p<0.001$) higher in the >170 N group (36.7%) than it is in the <170 N group (29.9%), the success rate is 28% higher.

Schizophrenia	**<202 N**	**≥202 N**
Mean PCBO resp	6.3%	10.1%
Relationship of PCBO resp to success	R^2= 0.377 p= 0.001	R^2= 0.067 p= 0.089
Success Rate	63%	77%

Even though placebo response is significantly ($p= 0.018$) higher in the >202 N group (10.1%) than it is in the <170 N group (6.3%), the success rate is 14% higher.

- Conditions with higher success rates were those with larger ESs (they were always more adequately powered for the size of the treatment effect).
- Previous associations of trial and patient characteristics (Khan et al 2004) and placebo response/efficacy outcomes were not replicated in more recent AD trials.

Conclusions

- Increase in magnitude of placebo response over time has occurred in 6 different chronic conditions- general phenomenon.
- Rise in placebo response did not increase trial failure or negative outcomes
- Achieving low placebo response only critical for success in underpowered treatment arms
- smaller ESs in depression, schizophrenia, and epilepsy may relate to their dependent measures (self-report, latently and indirectly measured).
  - heterogeneity in the course and presentation of the illness and the items being measured on the scales >> higher variance >> lower ESs >> requirement for larger sample sizes for adequate statistical power.
- increase in placebo may be related to increased expectations from direct to consumer marketing, complexity and number of visits in modern trials, and more lifestyle adjustments made by patients after enrolling in a trial.
- Increase in drug response may be related to the additivity theory

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Disclosure: This work was funded by Northwest Clinical Research Center. Arif Khan, M.D., principal investigator of over 503 clinical trials sponsored by over 80 pharmaceutical companies and 30 CROs, has done no compensated consulting or speaking on their behalf, nor does he own stock in any of these or other pharmaceutical companies and therefore declares no conflict of interest.. Kaysee Fahl Mar, M.A., Shirin Khan Schilling, M.D., Josh Schilling, M.D., and Walter A. Brown, M.D. declare no conflict of interest.