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Does the increasing placebo response impact outcomes of adult and pediatric ADHD clinical trials? Data from the US Food and Drug Administration 2000–2009

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ABSTRACT

In a study of recent antidepressant clinical trial data, it was found placebo response had grown significantly over time and that contrary to expectations, trial outcome measures and success rate were not impacted. The aim of this paper was to evaluate if this trend of increasing placebo response and stable outcome measures could be seen in clinical trial data for Attention-Deficit Hyperactivity Disorder, a different psychiatric condition with susceptibility to placebo response. For this reason, we evaluated efficacy data reported in the FDA Medical and Statistical reviews for 10 ADHD medication programs (4917 patients, 17 trials, 29 treatment arms). Placebo and medication response were measured as percent symptom reduction and effect sizes and drug-placebo differences were calculated for each treatment arm and analyzed in relation to year of approval. We also investigated the potential role of age and medication class on trends and outcomes. Results showed a similar pattern to antidepressants wherein the placebo response is rising significantly over time ($r = 0.636$, $p = 0.006$) and effect size ($r < 0.0001$, $p = 1.0$), drug-placebo difference ($r = -0.238$, $p = 0.214$), and success rate (28/29 97%) have remained unaffected, likely due to a parallel, although not statistically significant increase in medication response ($r = 0.326$, $p = 0.085$). Age and medication class did not alter these observed time trends but pediatric trials and stimulants were found to have more robust treatment effects than adult trials and non-stimulants. The results of this study suggest that like antidepressants, the relationship between placebo response and the outcomes of ADHD clinical trials is weak at best.

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1. Introduction

The assumption that the poor outcomes and 50% failure rate of antidepressant clinical trials was related to the increasing magnitude of placebo response (Walsh et al., 2001) has come under scrutiny. This assumption does not appear to hold true. Despite a significant increase in the placebo response in depression trials over the last 30 years, the outcomes of effect size, antidepressant-placebo difference, and success rate in antidepressant clinical trials have remained unchanged (Khan et al., 2017). This stability in outcome measures is due to the fact that the drug response has also increased, maintaining essentially the same magnitude of superiority over placebo. In light of this finding, we questioned if this pattern is unique to antidepressant trials.

As a method of inquiry, we decided to evaluate if a similar pattern is seen among trials assessing efficacy for ADHD medications. We chose to evaluate ADHD medications because there are sufficient numbers of relatively homogenously-designed trials as in antidepressants, allowing for comparability. Additionally, like antidepressant trials many ADHD medication trials measure treatment response over a time period of several weeks. Also ADHD is a chronic illness with a measureable placebo response. Like in antidepressant clinical trials, this placebo response poses ongoing concern for pharmaceutical companies developing medications for ADHD.

On the other hand, unlike antidepressants which predominately seek approval indications for adults, ADHD medications are conventionally tested in pediatric populations with only some

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programs using adult populations for original approval. Also unique to ADHD medications is the fact that there are two major and divergent classes of drugs—stimulants and non-stimulants.

These differences in age of indicated population and classes of action mechanism may have an effect on outcomes of ADHD medications in clinical trials. In several large meta-analyses of published data (Faraone, 2009; Faraone et al., 2006), investigators have found that stimulants outperform non-stimulants in clinical trials. This difference appears to be augmented in meta-analysis of pediatric studies as compared to adult trials (Faraone and Glatt, 2010). Additionally, the indicated population for ADHD medications has historically consisted of pediatric patients. As more and more medications have been approved for treatment in adults, data suggest that treatment response may be less robust in adult populations than with pediatric patients (Antshel et al., 2011; Spencer et al., 1996).

Given this background, we evaluated the clinical trial data submitted for proof of efficacy and reviewed by the US FDA for the approval of 10 ADHD medications from 2000 to 2009. Our hypothesis was that the magnitude of placebo response in clinical trials of ADHD medications has increased over time without impacting the effect size, drug-placebo difference, or the success rate of these trials due to a compensatory increase in the magnitude of response in the ADHD treatment group. We also explored the roles of age group and class of medication in relation to placebo response and outcomes over time.

2. Method

2.1. Source: FDA database

We used the New Drug Approval (NDA) packets published on the US FDA database (http://www.accessdata.fda.gov/) as our source for efficacy data for the reason that these data have been unbiasedly reviewed for approval by FDA medical and statistical staff as compared to data from published reports (Turner et al., 2008). Additionally, the statistical treatments and presentation of data in these reviews are of sufficient quality, completeness, and comparability such that we could analyze these efficacy data across different types of investigational agents.

2.2. Selection of programs

We selected programs for investigational ADHD medications with New Drug Approval applications accessible via the FDA Access Data website (http://www.accessdata.fda.gov/). We included trials submitted in support of efficacy claims for the indicated populations at the time of original approval. All of the programs included pediatric (<18 years old) efficacy trials and 2 programs included trials supporting efficacy in adults (18–65 year olds) at the time of the original submission for approval by the FDA. Patients had a primary diagnosis of ADHD (DSM-IV criteria in many cases), confirmed typically by use of clinician-administered diagnostic scale at screening and in some pediatric trials also verified by parent and school teacher rating. Programs used a variety of primary efficacy scales (listed in Table 1). New molecular formulations, such as extended-release versions of existing drugs, were included in the data if their approval was based on new data rather than re-evaluated data from trials submitted in a prior application.

The 10 programs that met criteria for this study were: OROS methylphenidate hydrochloride tablets (2000), mixed amphetamine salts XR (2001), dexmethylphenidate hydrochloride (2001), methylphenidate hydrochloride MR capsules (2001), atomoxetine hydrochloride (2002), methylphenidate hydrochloride LA (2002), dexmethylphenidate hydrochloride ER (2005), methylphenidate transdermal (2006), lisdexamfetamine dimesylate (2007), and guanfacine ER (2009).

We included all acute, placebo-controlled trials that were reviewed as proof of efficacy and that evaluated change scores after a period of at least one week of treatment compared to baseline. This left us with 10 NDA programs and 25 trials cited for efficacy. Following the exclusion criteria below, we excluded 8 of these trials for confounding differences in design or data analysis as explained: Trials with final measurement analysis only (not reporting change from baseline) (2 trials) or analysis of AUC (1 trial), hourly treatment effect studies (pre and post dose measurements taken within 24 h) (2 trials), and trials with confounding differences in design (ie withdrawal design) (3 trials) were excluded from this study in order to standardize the characteristics of the trials and evaluate comparable outcome measures. Although two programs, amphetamine XR (2015) and methylphenidate ER (2015), had reviews available on the FDA website, we did not include them in this analysis because they did not submit any proof of efficacy trials that were longer than one week in duration.

This process provided 17 trials with a total of 30 treatment arms for evaluation. We included treatment arms assigned to approved dose levels, thereby eliminating 1 treatment arm at a non-approved dose from our dataset and leaving a total of 29 treatment arms.

2.3. Trial arm outcome measures

Each treatment arm at different dose levels of the investigational medication is analyzed separately in the FDA review and the comparison of active treatment to placebo results in an individual p-value. Both successful and unsuccessful treatment arms from a single efficacy trial are considered for approval of the program. For this reason, we recorded and analyzed outcome measures from individual treatment arms rather than pooling the data.

Trial Arm Success: we recorded the p-values from the statistical evaluation of change scores for each treatment arm. Using the same threshold as the FDA, we counted treatment arm comparisons with p-value < 0.05 as successful and those with >0.05 as failed arms.

Baseline and Change Scores: Baseline scores were the mean score as reported in the reviews on the primary efficacy scale at the initiation of the treatment period. Change scores were the reported mean differences between baseline and end scores on the primary outcome measure.

Treatment Response/Percent Symptom Reduction: As a way to account for variability in baseline and the different ranges of primary efficacy scales, we calculated treatment response as a measure of percent symptom reduction. This was done by dividing the change score by the baseline score and multiplying by -100 to generate a magnitude of response for each treatment cell. This measure was positive if the treatment reduced symptoms.

Drug-Placebo Difference: As an estimate of the magnitude of separation between ADHD treatment and placebo response, we calculated the drug-placebo difference for each treatment arm by subtracting the placebo response from the drug response.

Effect Size: Hedges' g effect sizes were computed using reported mean change scores, standard deviation, and treatment arm sample size (n) taken from primary efficacy analysis tables.

2.4. Statistical measures

Statistical measures were generated with IBM Statistical Package for the Social Sciences (SPSS).

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