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Magnitude and pattern of placebo response in clinical trials of antiepileptic medications: Data from the Food and Drug Administration 1996–2016

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ABSTRACT

This study aimed to replicate and extend the findings of previous investigations looking at treatment responses in antiepileptic clinical trials over time and to examine the effects of subject age and duration of treatment.

To address the potential biases of published literature, we examined the reported data from 14 investigational antiepileptic drugs (AEDs) (34 trials, 59 treatment arms, 10,783 patients) reviewed and approved by the US FDA (1996–2016). For each treatment arm, we recorded drug and placebo response (percent reduction in seizure frequency), calculated effect sizes, and examined these measures over time.

Regression analysis showed that placebo response has increased significantly over time (R^2 = 0.292, p = 0.001) from 5% to 20% reduction in seizure frequency in 20 years. Response to drug treatment appears to have increased in parallel but the trend was not statistically significant (p = 0.143). Effect sizes have remained stable over time (p = 0.084). Treatment duration was not related to treatment response or outcomes. Including younger patients in trials appeared to predict lower drug response (β = 1.44, p = 0.012) and effect size (β = 0.014, p = 0.047) but not placebo response (p = 0.141).

These FDA-reviewed and source-verified data support and extend prior findings from published literature that response to placebo treatment is noticeably increasing over time, nearly quadrupling in magnitude, while AED efficacy remains the same due to a parallel increase in drug response. The rise in placebo response appears to be an ongoing phenomenon rather than a mere historical artifact. Future design and interpretation of data from clinical trials of investigational antiepileptic drugs can be informed by these observations.

1. Introduction

The information gleaned from clinical trials of antiepileptic drugs (AEDs) guides effective treatment of epileptic seizures and understanding the variables that influence such trials is important [1]. One variable that has elicited investigator interest is the response to placebo treatment. Several meta-analyses have examined placebo response in clinical trials of antiepileptic medications. Defining placebo response as the percent of patients showing a ≥ 50% improvement in seizure frequency, these studies suggest that patient response to placebo is robust and that it is becoming increasingly more robust over time [2–4].

In a comprehensive meta-analysis of a large set of published antiepileptic trial data, Rheims et al. [3] found a significant trend in treatment response patterns over time (1987–2009), wherein both drug and placebo treatment groups showed an increase in response rate over time (increasing year of publication). Interestingly, the treatment effect (benefit of medication over placebo) was not significantly impacted, remaining fairly stable over time [3]. In this same analysis, duration of treatment was found to be associated with higher response to both placebo and antiepileptic treatment. In a separate analysis of published studies, Rheims et al. [5] found an age effect in clinical trials of antiepileptic drugs: placebo response was higher in children as compared to adults while drug response was statistically equivalent between the age groups. Therefore trials in pediatric populations yielded lower estimates of the drug-placebo difference for the investigational antiepileptic.

While these findings are intriguing, we consider the potential biases of reported clinical trial data in published literature. Publication biases may stem from unconventional statistical handling and overestimation of treatment effects, as seen in analyses of publication bias for other conditions [6,7]. In order to address some of the limitations of published trial data, we decided to replicate Rheims et al.'s prior analyses

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[3,5] in a dataset that might be less prone to publication bias. Additionally, since 2010 when Rheims et al. undertook their analysis [3], five new drugs have been approved to treat epileptic seizures. The addition of these new data allows us to examine if the trends observed by previous researchers have continued to present day.

To this end, we evaluated treatment response and outcomes in trials of investigational antiepileptic medications using systematically-evaluated antiepileptic clinical trial data presented in the original Medical and Statistical reviews submitted to the US FDA for approval (1996–2016). The benefit of this primary-sourced dataset is that trial data presented in these original documents have been verified by independent statistical reviewers and the data-handling and statistical operations used in these reviews are standardized to avoid either advantaging or disadvantaging the investigational medication.

The aim of this study was to replicate and extend the work of previous investigators [3,5] evaluating treatment response patterns and outcomes in trials of antiepileptic drugs over time. We hypothesized that we would observe the same pattern seen in published literature where placebo response is increasing with parallel growth in drug response and stable outcome measures over time. We also hypothesized that our inclusion of five more recently approved drugs not included in prior analysis would continue this trend, supporting the possibility that this phenomenon is ongoing. Exploratory analysis was used to examine patient age and duration of treatment in relation to placebo response and trial outcomes.

2. Methods

2.1. Source: FDA database

We chose to use the US FDA database (http://www.accessdata.fda.gov/) to collect antiepileptic medication efficacy trial data for the reason that the data presented in these New Drug Approval packets (NDAs) are potentially less prone to publication bias [6,7]. 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 oral antiepileptic investigational agents.

2.2. Limitations of original NDAs

While the new drug approval packets comprising the dataset for this analysis are standardized and source-verified, they have several weaknesses and limitations related to FDA regulations for trial conduct and the methods chosen by reviewers. In particular, although many efficacy endpoints may be measured within a trial, the statistical reviewer will report the primary efficacy measure which was predetermined at the outset of the trial and which may be different than what is reported in published literature. In addition, statistical reviews of these data typically utilize last observation carried forward (LOCF) data-handling techniques and so these data may be biased by this procedure. Lastly, non-approved antiepileptic drug programs are not included in this dataset and so this analysis represents only a successful subset of the medications that have been used in trials of epilepsy.

Furthermore, because these are summary data and we do not have access to individual patient data, we could not perform adequate analyses of patient-level characteristics such as gender differences or differences in response based on duration of epilepsy before the start of the trial. While factors like severity of seizure frequency at baseline may be of interest, because of the heterogeneity in baseline measurements (i.e. observation timeframe or included seizure types) it was not possible to standardize the baseline measure to examine this variable. Importantly, the year of approval serves as our measure of time because it is not possible to determine in what timeframe the data for these trials were collected. These limitations represent just some of the biases that may be present in this dataset.

2.3. Selection of programs

We selected programs for investigational antiepileptic medications if corresponding original Medical and Statistical Reviews were available on the FDA Access Data website (see aforementioned) and if they were indicated for treatment of adults, adolescents, or children with all forms of partial epileptic seizures. All medications were oral antiepileptic agents intended to lower the frequency of seizures over several months of treatment. Extended release formulations of previously approved drugs were included if they presented data that had not been previously used for approval of the prior submission.

There were 14 oral antiepileptic agents (year of approval) that met inclusion for this study: topiramate (1996), tiagabine hydrochloride (1997), levetiracetam (1999), zonisamide (2000), lacosamide (2008), levetiracetam XR (2008), rufinamide (2008), lamotrigine XR (2009), vigabatrin (2009), ezogabine (2011), oxcarbazepine XR (2012), perampanel (2012), eslicarbazepine (2013), and brivaracetam (2016).

Two programs, lamotrigine ODT (2009) and topiramate XR (2013), could not be included in this analysis due to absence of FDA reviewed efficacy data in the New Drug Approval packet published on the FDA Access Data website. An additional two programs, lamotrigine CD (1998) and clobazam (2011), were excluded because their efficacy trials were conducted in a population with Lennox-Gastaut Syndrome and trials evaluating efficacy with this population may present a risk to comparability due to the significantly younger age range and natural course of this form of epilepsy. Two programs, carbamazepine (1997) and oxcarbazepine (2000), could not be included because the trials cited for efficacy evaluation in these programs had “time to first seizure” as the reported primary outcome measure, making the data incomparable to the standard seizure frequency outcome measure used by the majority of the trials.

2.4. Selection of trials/treatment arms

After inclusion of all programs meeting requirements, we tabulated all acute, placebo-controlled trials using approved doses of the investigational oral antiepileptic medications that were cited as pivotal trials and considered in the integrated review of efficacy for approval. All trials of investigational oral antiepileptic agents were designed as adjunctive placebo-controlled trials, meaning that placebo or investigational medication was added on top of a background control medication. There were no trials using a monotherapy design.

Out of the 42 placebo-controlled efficacy trials cited in the 14 programs, we excluded three trials for only evaluating unapproved doses of the medication, two trials for reporting and evaluating endpoint scores rather than change from baseline, two trials for not reporting any statistical results, and one trial for being conducted on a population with Lennox-Gastaut Syndrome. This left a total of 34 unique efficacy trials for evaluation.

Out of 69 treatment arms from these 34 trials, we eliminated 10 treatment arms at unapproved doses leaving a total of 59 treatment arms for analysis. It is important to note that sub-therapeutic doses are intentionally included in dose-finding studies in order to demonstrate the lowest effective dose. We excluded such treatment arms using unapproved doses of the active medication because these treatment arms are intended to demonstrate the efficacy threshold rather than included with the intention of gaining approval for that dose.

2.5. Treatment arm response measure

FDA reviewers conduct independent statistical analysis of efficacy for each treatment arm at different dose levels within a trial. For this reason, we decided to examine treatment arms independently of the trials they were in. Efficacy endpoint analysis compares symptom reduction between antiepileptic-treated and placebo control groups on the pre-specified primary outcome measure (seizure frequency in trials