Guanfacine Trial in Children With ADHD and Tic Disorders Journal Article Review

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For children with attention deficit hyperactivity disorder (ADHD), stimulant medications such as methylphenidate (Ritalin) and dextroamphetamine (Adderall), are the most commonly prescribed medications for managing the disorder now (CDC, 2023) and at the time the following study was undertaken (Diller, 2000). Though drugs like Ritalin are shown to have the most success in treating the symptoms of ADHD (CDC, 2023; Greenhill & Pelham,1999), central nervous system stimulants are known to induce unwanted side effects, especially in children with coexisting tic disorders like Tourette's Syndrome (Scahill et al., 2001). To gain a more in-depth understanding of this study as it relates to the material I have learned in Statistics and Methods I, I will provide a review of *A Placebo-Controlled Study of Guanfacine in the Treatment of Children With Tic Disorders and Attention Deficit Hyperactivity Disorder* focusing on key elements of the statistical processes described within the article.

When the findings of this study were published, several non-stimulant medications for treating ADHD had been under review though the breadth of research was still limited. In medical trials that had already been completed, some findings were inconsistent and others raised concerns about the potential for severe side effects (Scahill et al.). Understanding that a safer, longer-acting non-stimulant medication was needed to treat ADHD in children who experience tics, a group of researchers at Yale University formed a hypothesis to test if guanfacine might satisfy medical treatment goals in subjects with both disorders.

The groundwork for the research of this study began twenty years prior when α_2 agonist clonidine was found to benefit patients with ADHD and tic disorders. Though some studies found clonidine to be useful, the duration of effectiveness was short and there was a known potential for serious side effects (Scahill et al.). While performing research on primates at Yale

University, associate professor of neurobiology Amy F.T. Arnsten along with a team of researchers, discovered guanfacine, another α_2 agonist, to be superior to clonidine in terms of effectiveness and safety. The research team determined guanfacine had fewer side effects than clonidine stating that it also improved functioning in the prefrontal cortex, a known area of neurological dysfunction in ADHD patients (Scahill et al.).

The aim of this study was to determine if the blood pressure lowering medication guanfacine would be useful in treating children with both ADHD and tic disorder. Prior findings in primate studies involving guanfacine led the researchers involved in this study to lean into the plausibility that the marked benefits seen within the samples of primates might also be observed in human subjects (Scahill et al.). While no hypotheses were explicitly stated, this beginning idea represented the research hypothesis or prediction that there is a relationship between the variables being studied (Howell, 2017).

With that research goal in mind, the authors of this article set up a medication trial involving a placebo-receiving control group and an experimental group to be medicated with guanfacine. As Howell explains, it is important for the scientific process to begin with a falsifiable idea, so researchers rarely begin a study with the alternative, or research hypothesis, which asserts a definite connection between variables exists, instead starting out with a null hypothesis as a base declaration that a relationship between variables does not exist (2017, p.159). The null hypothesis for this study was inexplicitly stated, but it was implied that there were no meaningful differences in scores measuring the improvement of ADHD symptoms or in the presentation of tics between the control or experimental groups. To test the hypotheses and establish a correlation between ADHD, tic disorders, and treatment outcomes with guanfacine a range of statistical tests discussed in the article were performed.

The methods section of this article provides details explaining the study's design including how the experiment was set up, how participants were selected, and how the data were collected and analyzed. The researchers set up a randomized, double-blind placebo-controlled trial of parallel groups. The subjects, children aged 7-14, were randomly assigned to separate groups with neither the subjects nor the attending clinicians having knowledge of which group was the treatment group. The mean age of the children was around 10.4 years with most others spread around that average being younger and older as indicated by (M=10.4, SD=2.0). Fifty children met the initial criteria for entrance into the study. After further screening and withdrawals, the total number of participants for the entire study was N=34. The subjects were split evenly into a control group (N=17) and a treatment group (N=17). *N* is the statistical notation representing the number of individual cases, observations, or subjects studied in a population (Howell).

Before the medical trial began, all subjects were rated on the severity of ADHD and tic symptoms with various instruments to set the baseline scores that were used for later comparisons. Behavioral symptoms of ADHD and tic severity were recorded with instruments using ordinal scales of measurement where scores are ranked along a continuum in a designated, but arbitrary order (Howell, p. 21). One of the more precise instruments used was the Continuous Performance Test. This tool was used to record response times and accuracy percentages on tests of visual attention and motor response inhibition (Scahill et al.). The scores from this test were also ranked, but because the scores were interval, the differences between scores were equal and meaningful (Howell, p. 21). The results from these tests along with others used either in the screening process or over the course of the experiment provided the information that was plotted and organized into charts displayed in the article.

Most of the data recorded for this study were analyzed using repeated measures analysis of variance (ANOVA) (Scahill et al.). Using this statistical technique, tests were repeated multiple times under differing conditions to measure the mean changes in scores within and between groups. The means of the baseline and endpoint scores for each assessment and group were evaluated using a *t*-test to determine if there were a significant difference in means between the two groups of data. A chi-square test was used to compare the frequency of side effects to the proportion of positive effects in each group (Scahill et al.). To compare differences in the variances of scores between and within the groups another statistical test similar to the *t*-test, the F-test, was used. Since the researchers were interested all possible deviations of scores falling either above or below the mean of the sampling distribution, a two-tailed significance test was used with the alpha set at 0.05 (α=.05) (Scahill et al.). The scores that fell beyond the critical value set by the alpha at the extreme ends of the distributions were viewed as significant.

Testing procedures for this study were carried out over a period of 8 weeks. The placebo group (N=17) and the control group (N=17) were both given medications to take three times daily. Dosing for the treatment group increased gradually over 4 weeks. Each subject was evaluated by physicians, parents, and teachers and retested with the same tools of measurement used to set the baseline scores for midpoint and endpoint comparisons. After statistical analysis of the scores, the data showed there was a correlation between guanfacine and the improvement of ADHD symptoms and tic disorder severity (Scahill et al.).

A two-factor ANOVA found a significant relationship between guanfacine treatment and ratings of hyperactivity/impulsivity and inattention ($F=7.83$, $df=2, 64$, $p=0.001$) (Scahill et al.). Included in this statistic are the degrees of freedom (*df*), individual scores that can vary without restraint that are used to determine the shape of the *t*-distribution, and *p*, the probability that the

results would be obtained if the null hypothesis were true (Howell, 2017). It was also determined that a significant relationship existed between guanfacine treatment and tic severity ($F=4.04$, $df=2,30$, $p=0.05$). Overall, the group that received guanfacine showed a 37% improvement in ADHD Rating scores compared to only 8% in the placebo group ($t=3.61$, $df=32$, $p=0.001$) and a 27% improvement in tic severity compared to none in the control group ($p=0.001$). Another significant find that showed guanfacine to be of benefit was seen in the Continuous Performance Test response and accuracy times where results of a *t*-test indicated guanfacine led to around a 20% improvement overall while performance in the placebo group declined. When comparing the groups for side effects and cardiovascular changes there were no significant results (Scahill et al.).

After looking over this study it appears the study could have benefited from more participants. The sample size was small (N=34) then split leaving only 17 subjects in the treatment group. The chances of failing to reject the null hypothesis, a Type II error, occurs more frequently when sample sizes are not larger enough (Howell). In this case, the null hypothesis was rejected but there was little room for variability among the scores and for sampling errors. Besides the sample being too small, the participants were selected from a single specialty clinic and were subject to criteria that excluded potential subjects for common mental health issues like depression and anxiety which likely reduced the chances that the subjects included were representative of the larger population they were chosen to represent. The study was interested in the relationship between guanfacine and tic disorders but did not test on any subjects with tics that were more severe. A large percentage of the scoring came from parental ratings, and while the input from parents was entirely useful, it was open to bias and

inaccuracies. The researchers did admit future studies with larger samples including children who have ADHD with and without tics were needed (Scahill et al.).

Dissecting this study gives a clearer understanding of the medical trial process and the statistical methods used to collect, analyze, and present the data recorded. This study included many variables, continuous and categorical, gathered from the observation, screening, and testing of multiple subjects in multiple settings with many different people repeated over and again. From start to finish many of the statistical techniques were repeated as well. The most basic operations of this study, still somewhat complicated to learn though, involved averaging scores to determine a mean (M), calculating the standard deviations (SD), finding the variances (σ^2), performing *t*-tests, F-tests, or Chi-square tests to examine effect size to determine if any results returned were proof that this medication would do what the researchers suspected (Scahill et al.). The authors of this article described their entire research process which exemplified most of the concepts we have gone over in class providing a real-life example that was procured independently which has helped give a better understanding of the scientific process and how statistical procedures are applied in real research projects.

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