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General Information

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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019.docx.pdf
https://yoda.yale.edu/system/files/yodacoi.suhr_.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT00307684 - 42603ATT3004 - An Open International Multicentre Long-Term Follow Up Study to Evaluate Safety of Prolonged Release OROS Methlyphenidate in Adults With Attention Deficit Hyperactivity Disorder
2. NCT00326300 - 12-304 - An Open-Label, Dose-Titration, Long-Term Safety Study to Evaluate CONCERTA (Methylphenidate HCL) Extended-release Tablets at Doses of 36 mg, 54 mg, 72 mg, 90 mg, and 108 mg

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Expectancy Effects as a Confounding Factor in ADHD Treatment Research

Narrative Summary:

My aim is to pilot a novel method of data analysis for randomized controlled trials that mimics that of balanced placebo design studies. I am seeking data from an RCT in ADHD treatment in which the participants reported what group they believed they had been assigned to: placebo or active treatment. I will then analyze the data to determine whether group assignment belief (expectancy) had an effect on any of the outcome variables. I believe this is a possibility because similar expectancy effects have been identified in analgesics, antidepressants, and treatments for Parkinson's disease. Clarifying the role that expectancies play in ADHD treatment could guide future treatment standards.

Scientific Abstract:

Background: Expectancy effects, the effects of the belief that one has taken an effective drug, make up a significant portion of several common treatments for neuropsychological conditions. Some, including those for depression and Parkinson's disease, are associated with the same brain areas as Attention Deficit/Hyperactivity Disorder (ADHD). Thus, clinical trials for drugs for ADHD should assess expectancy effect size. The balanced placebo design (BPD) allows researchers to identify expectancy effect size more easily than a randomized controlled trial (RCT) does.
Objective: I will pilot a BPD-style analysis for RCTs with data on group assignment belief to determine the expectancy effect size.
Study Design: RCTs often have single or double blind designs. The degree to which the participants were blind to group assignment is typically assessed by asking them to guess their treatment condition. Blinding is typically

reported in the research, so this variable, also called stimulus expectancy, must be coded into the data. I will use stimulus expectancy to assess the hypothesized interaction between perceived treatment condition and actual treatment condition using a BPD.

Participants: The participants must have ADHD.

Main Outcome Measure: I will use the same treatment efficacy measures as the RCT, including self report, behavioral or cognitive measures, neuroimaging, etc.

Statistical Analysis: Using a pseudo-BPD analysis, I will determine effect sizes for the drug and drug expectancy. I will determine the impact of other covariates on these effects when appropriate.

Brief Project Background and Statement of Project Significance:

Expectancy effects have been shown to play a significant role in the outcomes of treatments for several neuropsychological conditions (1-4, 11-15). These include depression (5) and Parkinson's disease (6), both of which involve similar systems to those implicated in ADHD (7,8).

9.4% of children in the USA have been diagnosed with ADHD, and about 62% of those take medication for their symptoms (9). Symptoms can continue into adulthood; 4.4% of adults in the USA have a current diagnosis of ADHD (10). These symptoms can cause problems in many areas of life, including social relationships and school and work performance. Because of the prevalence of ADHD, we must understand the mechanism of the drugs used to treat it, including the proportion of symptom improvement attributable to the drug itself and the proportion attributable to non-drug effects like expectancies.

RCTs do not necessarily isolate the drug effect. Expectancy effects only make up a part of the improvements seen in the placebo arm of a study. Other effects that are unrelated to the participant's beliefs about what they took, including spontaneous remission, patient/observer bias, etc, can influence the outcomes of placebo groups in RCTs. As seen in research on pain (1, 11-14) and other phenomena (2-4, 15) with large expectancy effects, expectancies can differentially affect the different arms of a study. Part of the difference seen between the placebo and drug arms of a study may be due to differences in expectancies.

Expectancy effects have been identified for interventions often used in ADHD, including neurofeedback (16, 17) and psychostimulants (18, 19). Placebo effects in ADHD clinical trials have increased over time (20). However, expectancy effects are not always acknowledged in ADHD drug efficacy studies.

Studies using a BPD isolate expectancy effects more effectively because outcomes are analyzed using both treatment condition (placebo or drug) and group assignment belief. This allows researchers to identify expectancy effect size by comparing participants who believed they took the drug to participants who believed they took placebo, both overall and within treatment condition groups. To determine the approximate expectancy effect size in existing research, we need a way to break RCT data into pseudo-BPD groups that take group assignment belief into account.

Specific Aims of the Project:

My study objectives are to use a pseudo-BPD analysis to determine the size of the expectancy effect in ADHD treatment. This will have implications for understanding the efficacy of interventions in ADHD. My hypothesis is that a pseudo-BPD style analysis of existing RCT data will reveal expectancy effects that are not already revealed by the placebo arm of the RCT. I will pilot this style of analysis and compare the effect size of expectancies to the effect sizes found for the drug group and placebo group of the RCT.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
Other

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

The data that I use must come from a study that is available in English, uses a double-blind, placebo-controlled, randomized study design (parallel or crossover), was published since 2000 in a scientific journal of good standing, encodes some measure of expectancy into the data (such as a measure to assess the success of blinding), and must assess the effect of some pharmacological treatment on ADHD symptoms in participants with ADHD.

Main Outcome Measure and how it will be categorized/defined for your study:

I will use the same outcome variables as defined in the data that are shared with me, including self report, behavioral or cognitive measures, etc. I will define them in the same way the original researchers defined them.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The main predictor variables will be actual group assignment and group assignment belief. Studies may measure group assignment belief in different ways, including the Early Impressions Questionnaire (21). I am particularly interested in the interaction between group assignment belief and actual group assignment. Group assignment belief will be defined as the guess each research participant makes as to whether they were in the placebo group or active treatment group.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

If the study has other outcomes not related to treatment efficacy, such as safety, these will be secondary outcomes in my study. I will define them the same way that the original researchers defined them.

Statistical Analysis Plan:

The analysis will differ depending on the nature of the data, as studies vary in the number of group assignments possible, crossover vs parallel design, continuous vs discrete outcome variables, etc. Regardless of the dataset, I will be stratifying the data based on the participants' group assignment belief as well as actual group assignment and performing a similar statistical analysis to that of the original study. I will then examine whether actual group assignment interacts with group assignment belief in predicting study outcomes.
Software Used:
R
Project Timeline:

I hope to start the project as soon as the DUA is signed, around January 2021. The project will be completed by April 21, 2021. I will report the results to YODA by summer of 2021. The manuscript will be first submitted for publication in summer 2021.

Dissemination Plan:

This project is for fulfillment of an undergraduate senior thesis. The intended audience is ADHD researchers, expectancy researchers, and biological sciences faculty at the undergraduate institution. Initial dissemination will be at the local/university level but will also include conference presentations. The manuscript may be edited and submitted to journals appropriate for work on expectancy effects, depending on the results. Potentially suitable journals include Journal of Attention Disorders, Journal of Clinical Psychopharmacology, and Journal of Psychopharmacology.

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