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Requires Data Access? Yes

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?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/09/SV_57KskaKADT3U9Aq-R_8lCROU84v2m2VVf.pdf
https://yoda.yale.edu/wp-content/uploads/2024/10/mc.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 Per Day in Adults With Attention Deficit Hyperactivity Disorder
3. NCT00246220 - 42603ATT3002 - A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study To Evaluate the Safety And Efficacy Of Prolonged Release OROS Methylphenidate Hydrochloride (18, 36 and 72 mg/Day), With Open-Label Extension, In Adults With Attention Deficit/Hyperactivity Disorder
4. NCT00714688 - 42603ATT3013 - A Multicentre, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate Efficacy and Safety of Prolonged Release (PR) OROS Methylphenidate (54 and 72 mg/Day) in Adults With Attention Deficit/Hyperactivity Disorder

5. NCT00866996 - CR008329 (12-101) - A Multi-center Randomized Parallel Group Study Evaluating Treatment Outcomes of Concerta (Extended Release Methylphenidate) and Strattera (Atomoxetine) in Children With Attention-deficit/Hyperactivity Disorder
6. NCT00269815 - C98012 - Long-term Safety and Effectiveness of OROS (Methylphenidate HCl) in Children With ADHD
7. NCT00799409 - CONCERTA-ATT-4069 - The ABC Study: A Double-Blind, Randomized, Placebo-Controlled, Crossover Study Evaluating the Academic, Behavioral, and Cognitive Effects of CONCERTA on Older Children With ADHD
8. NCT00799487 - CONCERTA-ATT-4080 - Double-Blind, Randomized, Placebo-Controlled, Crossover Study Evaluating the Academic, Behavioral and Cognitive Effects of CONCERTA on Older Children With ADHD (The ABC Study)
9. NCT00937040 - CR015058 (CONCERTA-ATT-3014) - A Placebo Controlled Double-Blind, Parallel Group, Individualizing Dosing Study Optimizing Treatment of Adults With Attention Deficit Hyperactivity Disorder to an Effective Response With OROS Methylphenidate
10. NCT00326391 - 02-159/CR011560 - A Placebo-Controlled, Double-Blind, Parallel-Group, Dose-Titration Study to Evaluate the Efficacy and Safety of CONCERTA (Methylphenidate HCl) Extended-release Tablets in Adults With Attention Deficit Hyperactivity Disorder at Doses of 36 mg, 54 mg, 72 mg, 90 mg, or 108 mg Per Day
11. NCT01323192 - JNS001-JPN-A01 - A Double-blind, Placebo-controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of JNS001 in Adults With Attention-Deficit/Hyperactivity Disorder at Doses of 18 mg, 36 mg, 54 mg, or 72 mg Per Day

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

Research Proposal

Project Title

Predicting Methylphenidate Response in Adult-ADHD (A-ADHD) Using Machine Learning Approaches

Narrative Summary:

ADHD persists into adulthood with a 3.1% global prevalence, with common comorbidities that complicate its identification, potentially leading to underdiagnosis. While pharmacological treatment improves outcomes, one-third of adults with ADHD exhibit poor responses, necessitating personalized approaches. Existing studies lack strong predictors for treatment response, often relying on small samples and traditional methods. Recognizing this gap, the project explores potential ML techniques to predict treatment response in adults with ADHD gathered from existing clinical trials.

Scientific Abstract:

Background: Attention-deficit/hyperactivity disorder (ADHD) in adults (A-ADHD) affects approximately 3.1% of the global population and is often complicated by psychiatric comorbidities (1). These complexities can lead to challenges in diagnosis (2) and a significant portion of patients (about one-third) exhibit poor response to conventional treatments like methylphenidate (3), necessitating personalized treatment approaches.
Objective: The study aims to leverage machine learning (ML) to explore the variability of responses to methylphenidate among A-ADHD patients, identifying predictors of treatment effectiveness and clustering patients by their clinical profiles and responses.
Study Design: Post-hoc analysis of trials.
Participants: Subjects from these trials treated with methylphenidate.
Outcome Measures: Primary outcomes include treatment response measured by CAARS and CGI,

with secondary outcomes involving changes in SDS and Q-LES-Q scores.
Statistical Analysis: The research employs advanced ML techniques to predict treatment outcomes, involving steps like data preprocessing, feature selection using statistical methods, and model development with networks such as RNNs, LSTMs, and GNNs. Evaluation of these models is conducted through metrics like accuracy, precision, recall, F1-score, and ROC curves.

Brief Project Background and Statement of Project Significance:

A-ADHD affects about 3.1% of adults globally and is frequently accompanied by psychiatric comorbidities. Pharmacological treatment such as methylphenidate improves clinical and functional outcomes for most adults, while about one-third show poor response to treatment. In post-hoc analyses of trials, only the baseline severity of ADHD consistently emerged as a response predictor to methylphenidate (4). In this project, our aim is to address the lack of robust predictors of response to treatment by leveraging ML techniques on a big sample of patients by using data from clinical trials available at YODA. These results will be expected to provide information for effective and personalized treatment decisions and contribute to the advancement of reliable tools for clinicians in the treatment of adults with ADHD.

Specific Aims of the Project:

In this project, we aim to apply machine learning techniques (such as Recurrent Neural Networks, Long Short-Term Memory Networks and Graph Neural Networks) to a big sample of adults with ADHD from different clinical studies to validate a model to predict treatment response to methylphenidate. Baseline characteristics, such as gender, age, race, ADHD age diagnosis, ADHD subtype, psychiatric comorbidities, CAARS and CGI scores, etc. will be considered as predictor variables. The project will adhere to all relevant ethical guidelines, including ensuring patient confidentiality and data security. Models will also be evaluated for bias to prevent any discriminatory outcomes based on race, gender, or other demographic factors.
Moreover, to validate the generalizability of our findings, the techniques employed in this study will also be employed on an additional dataset, built with records from patients, collected at the outpatient service of the Psychiatry Unit 2 at Pisa University Hospital, between January 2018 and December 2023.

Study Design:

Methodological research

What is the purpose of the analysis being proposed? Please select all that apply.

Confirm or validate previously conducted research on treatment effectiveness

Confirm or validate previously conducted research on treatment safety

Research on clinical prediction or risk prediction

Research Methods

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

None

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary Outcome Measures: Evaluation of the efficacy of treatment with changing from baseline to

trial completion of Conners' Adult ADHD Rating Scales (CAARS) total score and subscales and Clinical Global Impressions (CGI) score.
Secondary Outcome Measures: Evaluation of efficacy with other scales such as Sheehan Disability Scale (SDS) and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q); evaluation of safety of treatment.

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

As provided by each trial:
- Demographic attributes (gender, age, race). Gender will be categorized as male, female, and other (includes non-binary, genderqueer, etc.), based on self-reported gender identity. Age will be categorized into Children (6-12 years), Adolescents (13-18 years), Adults (19+ years). Race will be categorized according to standard classifications such as Caucasian, African American, Hispanic, Asian, Native American, and others or mixed race
- ADHD age diagnosis, categorized to age groups: Early childhood (before age 7), Late childhood (7-12 years), Adolescence (13-18 years), Adulthood (19+ years).
- ADHD subtype. Based on DSM-5, subtypes can be defined as: Predominantly Inattentive Presentation, Predominantly Hyperactive-Impulsive Presentation, Combined Presentation.
- psychiatric comorbidities, such as anxiety disorders, depression, bipolar disorder, etc.
- psychiatric medications other than methylphenidate, based on those available in the trials.
- substance use, based on those available in the trials.

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

N/A

Statistical Analysis Plan:

This research project aims to predict the response of adults with ADHD to Methylphenidate treatment by leveraging advanced machine learning techniques. The primary objective is to identify which baseline characteristics correlate with successful treatment outcomes and to develop a predictive model that can be utilized in clinical settings to personalize treatment plans. The project with follow four main steps:
1. Data Preprocessing. Data preprocessing will involve: Data Cleaning (Handling missing values, removing outliers, and correcting errors in the data); Normalization (scaling of numerical features to a standard range, important for neural network performance); Encoding (converting categorical variables into numerical formats using one-hot encoding or label encoding).
2. Feature Selection. Feature selection will be conducted to identify the most significant predictors of Methylphenidate response. This process will use techniques such as correlation matrices, recursive feature elimination, and possibly principal component analysis to reduce dimensionality while retaining important information.
3. Model Development. Treatment response prediction will be tackled by considering different classes of Machine Learning techniques. Specifically, Recurrent Neural Networks (RNNs) and Long Short-Term Memory Networks (LSTMs) are well-suited because they excel in processing sequential and time-series data, which is crucial when considering the progression of ADHD symptoms and treatment responses over time. They can effectively handle data where time-series insights, such as changes in CAARS and CGI scores, play a critical role in predicting outcomes. In addition, or in alternative, Graph Neural Networks (GNNs) might be utilized to explore the complex interdependencies and interactions between different symptoms and comorbidities. By representing symptoms and comorbid conditions as nodes in a graph, GNNs can capture the intricate patterns that might influence the treatment response.
4. Model Evaluation. Models will be evaluated based on their accuracy, precision, recall, and F1-score. A test dataset, separated from the training data, will be used for this purpose. Additionally, ROC curves and AUC metrics will be employed to assess the performance across various thresholds, which is particularly important for clinical decision-making processes.

Software Used:

Python

Project Timeline:

The project will span six months (denoted as M1-M6), to accomplish the four steps outlined in “research methods” section. Specifically, the initial phase (Data Preprocessing) will last for one month (M1). Subsequently, Feature Selection will also last for one month (M2). Model Development will happen over the course of three months (M3-M5). The final month (M6) will be devoted to Model Evaluation.

Dissemination Plan:

The target audience will be researchers and academia as well as clinician and healthcare professionals and patients. The resulting paper(s) will be submitted to relevant top-tier journals in psychiatry, pharmacology, and machine learning in medicine. Findings will be presented at conferences on the specific field. We also plan to work closely with clinicians to ensure their insights are considered and to facilitate knowledge exchange and collaborate with ADHD patient advocacy groups to ensure the project's accessibility to individuals. The source code of our analysis will be released in a public repository (e.g., GitHub), to facilitate the reproducibility of our methodology and results, and favour future advances in this area.

Bibliography:

1. Ayano G, Tsegay L, Gizachew Y, Necho M, Yohannes K, Abraha M, et al. Prevalence of attention deficit hyperactivity disorder in adults: Umbrella review of evidence generated across the globe. Psychiatry Res. 2023;328(August):115449.
2. Katzman MA, Bilkey TS, Chokka PR, Fallu A, Klassen LJ. Adult ADHD and comorbid disorders: clinical implications of a dimensional approach. BMC Psychiatry. 2017 Aug;17(1):302.
3. Edvinsson D, Ekselius L. Six-year outcome in subjects diagnosed with attention-deficit/hyperactivity disorder as adults. Eur Arch Psychiatry Clin Neurosci. 2018 Jun;268(4):337–47.
4. Bushe C, Sobanski E, Coghill D, Berggren L, De Bruyckere K, Leppämäki S. Post Hoc Analysis of Potential Predictors of Response to Atomoxetine for the Treatment of Adults with Attention-Deficit/Hyperactivity Disorder using an Integrated Database. CNS Drugs. 2016 Apr;30(4):317–34.