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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/wp-content/uploads/2016/10/sv_6m4tqghhxq7w7uxe-r_2rkcpqza5kq7lkt.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
Research Proposal

Project Title

Early Prediction of Treatment Response to Antipsychotics for Irritability and Aggression in Autism Spectrum Disorder

Narrative Summary:

In this project, we will re-analyze existing data of randomized controlled trials with two antipsychotics, risperidone and aripiprazole, that are currently approved by the Food and Drug Administration for the treatment of irritability and aggression in individuals with autism spectrum disorder (ASD). The ultimate aim of this project is to clarify whether we can predict the ultimate treatment response to these medications based on early improvement in irritability and aggression symptoms.

Scientific Abstract:

Background: Risperidone and aripiprazole are two medications approved by the Food and Drug Administration for irritability and aggression (IA) in individuals with autism spectrum disorder (ASD). Despite the widespread use of these medications, prolonged treatment should be avoided if no adequate treatment response is expected given adverse effects of these medications, including weight gain and related metabolic abnormalities. However, there is a lack of scientific evidence on the early prediction of treatment response.

Objective: To examine the magnitude of the predictive power of early response to medications, measured by the reduction of IA symptoms, for ultimate treatment response at the study endpoint.

Study Design: individual participant data meta-analysis (IPD MA) of randomized controlled trials (RCTs). Data in the three RCTs with risperidone provided by YODA project will be combined with data in industry-sponsored RCTs with aripiprazole.

Participants: Individuals with ASD treated with risperidone or aripiprazole.

Main Outcome Measures: The Aberrant Behavior Checklist - Irritability subscale score and Clinical Global Impression-Improvement

Statistical Analysis: First, the proportion of response to antipsychotics at the study endpoint (6 or 8 weeks) given various levels of response at each assessment timepoint will be quantified. Second, a Bayesian analysis of conditional probabilities of response at the study endpoint weeks given various levels of response at the study assessment weeks will be analyzed with a chi-square test and graphically to identify trajectories of response based on the response at each week. Kaplan-Meier survival analysis will be used for the entire group and for subgroups on the basis of response levels at the first assessment week. Finally, subgroup analyses will be conducted to examine the effect of participants' characteristics on outcomes.
Irritability and aggression (IA) are highly prevalent in individuals with autism spectrum disorder (ASD) 1. Approximately 20% of people with ASD exhibit IA at moderate to severe levels, with >50% exhibiting significant emotion dysregulation. These problems lead to personal and social consequences, including greater functional impairment, increased family stress, and residential placement 2,3.

Along with behavioral interventions, medications are often considered for IA problems in this population especially when symptoms are severe. Currently, risperidone and aripiprazole, two atypical antipsychotics are the only medications approved by the FDA for the treatment of IA in people with ASD. Their efficacy has been supported by individual randomized controlled trials (RCTs) and a meta-analysis 4-7. RCTs using the above two drugs evaluated the efficacy of these drugs against placebo based on the improvement of IA symptoms at the study endpoint from the baseline. However, in real-world clinical practice, there remain several questions unaddressed: 1) by what time in weeks can we expect the efficacy of these psychotropic medications, 2) does early response to medications, measured by the reduction of IA symptoms, predict later-on treatment response at the study endpoint, and 3) does the maintenance of the treatment despite the failure to show early response to treatment still lead to ultimate treatment response in certain cases. Despite these two medications are widely used for irritability and aggression in this population, there are no clinical guidelines addressing the questions above.

There has been much debate about the timing of the onset of drug effects of antipsychotics. Although the delayed-onset of antipsychotic medication effects, which refers to the delay of two to three weeks between the start of medication administration and the onset of specific therapeutic benefits, was previously suggested in schizophrenia research 8, researchers have tested this hypothesis in individuals with schizophrenia and instead found that greater improvement in symptoms of psychosis starts by the two weeks of treatment and accumulates over time (early-onset hypothesis) 9. However, whether early treatment responses also occur in treatment for IA in individuals with ASD has never been examined. Additionally, in line with the growing trend of tailored medicine, there is an increasing interest in what factors determine the magnitude of patients’ response to treatment. In the treatment of depression, a meta-analysis of individual participant data has demonstrated baseline symptom severity and symptom profile (current suicidal ideation at the time of baseline assessment, for example) became significant modifiers of the efficacy of antidepressants over placebo 10,11. However, no such research has been conducted in autism research.

We believe our findings from this project will further our understanding of the predictive roles of early response to these antipsychotic medications in the treatment of IA and contribute to the development of evidence-based pharmacological approaches in ASD populations.

**Specific Aims of the Project:**

In this project, we will conduct a secondary analysis of RCTs with at least one arm of either risperidone or aripiprazole on individual participant data level to achieve the following aims.

**Aim 1:** To quantify the proportion of response to antipsychotics at the study endpoint (either 6 or 8 weeks) given various levels of response at each assessment time point and identify the time in study weeks we can expect the efficacy of these medications and the slope and trajectory of response.

**Aim 2:** To examine the magnitude of the predictive power of early response (and non-response) to medications, measured by the reduction of irritability and aggression symptoms at 2 weeks, for ultimate treatment response and non-response at the study endpoint.

**Aim 3:** To elucidate whether the maintenance of the treatment despite the failure to show early response led to the ultimate treatment response in certain cases (defined as late-responders) and whether the magnitude of the ultimate response to treatment is comparable between late-responders and early-responders.

**Aim 4:** To examine what factors influence the accuracy of prediction of the early treatment response and non-response for the ultimate treatment response and non-response.
Research Methods

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

Inclusion criteria:
? Individuals diagnosed with DSM autism spectrum disorder, pervasive developmental disorder (PDD), autistic disorder, Asperger disorder, PDD-not otherwise specified
? Ages 5 to 18
? Participants had to be clinically stable upon randomization however defined by the study
? Randomized controlled clinical trials with at least one arm of aripiprazole or risperidone
? Data is available for our primary or secondary outcome measures
? Data is available for dates of administration of the medication
? Trial duration of at least 6 weeks

The source of data will be IPD provided by the YODA project for RCT on risperidone. We plan to combine these with the IPD of industry-sponsored RCTs on aripiprazole meeting the same inclusion criteria, which will be provided directly to us by the companies.

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

For the main outcome measure, the ultimate treatment responders will be defined based on the following criteria: 1) equal or greater than 25% reduction in the irritability subscale score of the Aberrant Behavior Checklist (ABC) from baseline to study endpoint and 2) Clinical Global Impression-Improvement (CGI-I) score of 1 [very much improved] or 2 [much improved] at the endpoint.

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

The main predictor for the present study will be the status of early treatment responders and non-responders at week 2 based on the CGI-I score and the ABC-irritability subscale score.

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

ABC irritability subscale score and CGI-severity score at baseline
ABC irritability subscale score and CGI-Improvement score at each assessment
Dose of risperidone at each assessment point
Participants? sex
Participants? Race
Participants? Age
Participants? IQ (verbal, non-verbal, and full-scale)
Adaptive functioning scale (Vineland)
The Autism Diagnostic Interview-Revised
DSM and/or ICD diagnosis
Psychiatric comorbidities
Medical comorbidities
Medications used concomitantly during a trial
Previous psychotropics use
Age when diagnosed with autism spectrum disorder
Household income
Single parent or not (family structure)
Parental education level
Weight at baseline and at each visit
Neurologic side effects at each visit
Other adverse effects at each visit

Statistical Analysis Plan:
To address the above-mentioned project aims, in this proposal, we will conduct a secondary data analysis combining individual participant data (IPD) from the industry-sponsored three RCTs on risperidone provided by the YODA project, along with IPD of the industry-sponsored RCTs for aripiprazole provided to us directly by the companies. All the IPD data from sources other than YODA will be uploaded to the secure platform, where the analyses will be conducted using STATA and R. Responders at the study endpoint will be defined as those whose decrease in the Aberrant Behavior Checklist-Irritability (ABC-I) subscale score from baseline was 25% or greater and whose Clinical Global Impression-Improvement (CGI-I) score was either 1 (very much improved) or 2 (much improved) at the study endpoint (either week 6 or week 8). To define categories of response at week 2, those whose CGI-I score is either 1 or 2 will defined as early responders and those whose CGI-I score is 3 (minimally improved) or greater (i.e. no change or worse) will be defined as non-responders.

Initially, we will quantify the proportion of response to antipsychotics at the study endpoint (6 or 8 weeks) given various levels of response at each assessment timepoint (weeks 1, 2, 3, 4, 5, and 6). Responders at the study endpoint are defined as those whose decrease in the ABC-I irritability subscale score from baseline was 25% or greater and whose CGI-I score was either 1 (very much improved) or 2 (much improved). We will then determine the proportion of patients who responded by the study endpoint and examined the relationship between improvement at weeks 1, 2, 3, 4, 5, and 6 and ultimate responder status. To define categories of response at each assessment time point, we used the CGI-I score of 1 (very much improved), 2 (much improved), 3 (minimally improved), and 4 or greater (non-responders).

Next, a Bayesian analysis of conditional probabilities of response at the study endpoint week given various levels of response at weeks 1, 2, 3, 4, 5, and 6 will be analyzed with a chi-square test and graphically to identify trajectories of response based on the response at each week. Kaplan-Meier survival analysis will be used for the entire group and for subgroups on the basis of response levels at the first assessment week.

Finally, we will also conduct subgroup analyses to examine the effect of participants' characteristics (sex, race, IQ, baseline ABC-I subscale severity, study design: fixed-dose vs. flexible-dose, medication type (risperidone vs. aripiprazole)) on the outcomes. For covariates and subgroups shown to be important, a Cox proportional hazard model will be fit. Post hoc sensitivity analyses will examine the influence of specific studies on the outcome and quality assessment of the original studies. Quality assessment of the studies will use Cochrane's tool for assessing risk of bias 12.

This study will follow the PRISMA-IPD guidelines for reporting systematic reviews and meta-analyses of IPD 13.

Project Timeline:

Project Start: by April/May 2022
Analysis Completion: by December 2022
Manuscript Draft: by February 2023
Manuscript Submission: by April 2023
Report to Yoda Project: by June 2023

Dissemination Plan:

The manuscript will be submitted to peer-review academic journals whose target audiences will include psychiatrists, pediatricians, advanced nurse practitioners, pharmacists, and allied professionals in child and adolescent psychiatry and mental health. In addition to publication in peer reviewed journals, we expect to be able to present the findings of this study in various research forums, (international scientific meetings in the areas of child and adolescent psychiatry and psychopharmacology).

Bibliography:


