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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/2024/05/Rubio_COI.pdf
https://yoda.yale.edu/wp-content/uploads/2024/05/Sadri_COI.pdf
https://yoda.yale.edu/wp-content/uploads/2024/05/Koki_COI_YODA.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. NCT03345342 - R092670PSY3015 - A Double-blind, Randomized, Active-controlled, Parallel-group Study of Paliperidone Palmitate 6-Month Formulation
2. NCT01559272 - R092670PSY1005 - A Single-Dose, Open-Label, Randomized, Parallel-Group Study to Assess the Pharmacokinetics, Safety, and Tolerability of a Paliperidone Palmitate 3-Month Formulation in Subjects With Schizophrenia
3. NCT02713282 - R092670SCH3015 - A 52-Week, Open-Label, Prospective, Multicenter,

International Study of a Transition to the Paliperidone Palmitate 3-Month Formulation In Patients With Schizophrenia Previously Stabilized on the Paliperidone Palmitate 1-Month Formulation

4. NCT01515423 - R092670PSY3011 - A Randomized, Multicenter, Double-Blind, Non-inferiority Study of Paliperidone Palmitate 3 Month and 1 Month Formulations for the Treatment of Subjects With Schizophrenia
5. NCT01157351 - R092670SCH3006 - A Fifteen-month, Prospective, Randomized, Active-controlled, Open-label, Flexible Dose Study of Paliperidone Palmitate Compared With Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults With Schizophrenia Who Have Been Incarcerated
6. NCT00111189 - R092670PSY3001 - A Randomized Double-blind Placebo-controlled Parallel Group Study Evaluating Paliperidone Palmitate in the Prevention of Recurrence in Patients With Schizophrenia. Placebo Consists of 20% Intralipid (200 mg/mL) Injectable Emulsion
7. NCT00210717 - R092670PSY3002 - A Randomized, Double-Blind, Parallel Group, Comparative Study of Flexibly Dosed Paliperidone Palmitate (25, 50, 75, or 100 mg eq.) Administered Every 4 Weeks and Flexibly Dosed RISPERDAL CONSTA (25, 37.5, or 50 mg) Administered Every 2 Weeks in Subjects With Schizophrenia
8. NCT00119756 - R092670PSY3005 - A Randomized, Crossover Study to Evaluate the Overall Safety and Tolerability of Paliperidone Palmitate Injected in the Deltoid or Gluteus Muscle in Patients With Schizophrenia
9. NCT01529515 - R092670PSY3012 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia
10. NCT01193153 - R092670SCA3004 - A Randomized, Double-Blind, Placebo-Controlled, Parellel-Group Study of Paliperidone Palmitate Evaluating Time to Relapse in Subjects With Schizoaffective Disorder
11. NCT01081769 - R092670SCH3005 - A 24-month, Prospective, Randomized, Active-Controlled, Open-Label, Rater-Blinded, Multicenter, International Study of the Prevention of Relapse Comparing Long-Acting Injectable Paliperidone Palmitate to Treatment as Usual With Oral Antipsychotic Monotherapy in Adults With Schizophrenia
12. NCT01051531 - R092670SCH3009 - Safety, Tolerability, and Treatment Response of Paliperidone Palmitate in Subjects With Schizophrenia When Switching From Oral Antipsychotics
13. NCT01258920 - PALM-JPN-5 - A Long-Term, Open-Label Study of Flexibly Dosed Paliperidone Palmitate Long-Acting Intramuscular Injection in Japanese Patients With Schizophrenia
14. NCT00216476 - RISSCH3001 - CONSTATRE: Risperdal® Consta® Trial of Relapse Prevention and Effectiveness
15. NCT00216671 - RISSCH4045 - Early Versus Late Initiation of Treatment With Risperdal Consta in Subjects With Schizophrenia After an Acute Episode
16. NCT00369239 - RISSCH4043 - Is Premorbid Functioning a Predictor of Outcome in Patients With Early Onset Psychosis Treated With Risperdal Consta?
17. NCT00216632 - RISSCH4026 - Treatment Success in Patients Requiring Treatment Change From Olanzapine to Risperidone Long Acting Injectable (TRESOR)
18. NCT00216528 - RIS-KOR-66 - A Prospective, Open-Label Study to Evaluate Symptomatic Remission in Schizophrenia With Long Acting Risperidone Microspheres (Risperdal Consta)
19. NCT00269919 - RIS-KOR-64 - Effect on Efficacy, Safety and Quality of Life by Long-Term Treatment of Long-Acting Risperidone Microspheres in Patients With Schizophrenia
20. NCT00992407 - RISSCH4178 - A Randomized, Open-label, Active-controlled Study to Evaluate Social Functioning of Long Acting Injectable Risperidone and Oral Risperidone in the Treatment of Subjects With Schizophrenia or Schizoaffective Disorder
21. NCT00236353 - RIS-USA-305 - An Open-label Study of the Efficacy and Safety of RISPERDAL Long-acting Microspheres (RISPERDAL CONSTA) Administered Once Monthly in Adults With Schizophrenia or Schizoaffective Disorder
22. NCT00495118 - RIS-INT-80 - Risperidone Depot (Microspheres) in the Treatment of Subjects With Schizophrenia or Schizoaffective Disorder - an Open-label Follow-up Trial of RIS-INT-62 and RIS-INT-85
23. NCT01855074 - RISSCH4186 - Evaluation of Efficacy and Safety of Risperidone in Long-acting Microspheres in Patients With Schizophrenia, Schizophreniform or Schizoaffective Disorders

Diagnosed According to the DSM-IV Criteria, After Switching Treatment With Any Antipsychotic Therapy With Long-acting Microspheres of Risperidone
24. NCT00236457 - RIS-INT-62 - Randomized, Multi-center, Open Label Trial Comparing Risperidone Depot (Microspheres) and Olanzapine Tablets in Patients With Schizophrenia or Schizoaffective Disorder
25. NCT00236587 - RIS-USA-265 - An Open Label, Long Term Trial of Risperidone Long Acting Microspheres in the Treatment of Patients Diagnosed With Schizophrenia
26. NCT00297388 - RIS-SCH-401 - A 52-wk Prospective, Randomized, Double-blind, Multicenter Study of Relapse Following Transition From Oral Antipsychotic Medication to 2 Different Doses (25 or 50 mg Every 2 Wks) of Risperidone Long-acting Microspheres (RISPERDAL CONSTA) in Adults With Schizophrenia or Schizoaffective Disorder
27. NCT00299702 - RISSCH4060 - A 2-year, Prospective, Blinded-rater, Open-label, Active-controlled, Multicenter, Randomized Study of Long-term Efficacy and Effectiveness Comparing Risperdal® Consta® and Abilify® (Aripiprazole) in Adults With Schizophrenia
28. NCT00526877 - RISSCH4119 (RISC-TWN-MA10) - Evaluation of Efficacy and Safety of Long-acting Risperidone Microspheres in Patients With Schizophrenia or Schizoaffective Disorders, Who is Receiving Psychiatric Home-care Treatment, When Switching From Typical Depot or Oral Antipsychotics to Long-acting Risperidone Microspheres

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

Research Proposal

Project Title

Heterogeneity of treatment effects during guaranteed antipsychotic maintenance treatment in schizophrenia as a window into the mechanisms of treatment

Narrative Summary:

In many cases, schizophrenia is associated with a deteriorating course of illness. Such poor prognosis may be related to either insufficient symptom improvement when antipsychotic drugs are reintroduced following a relapse for non-adherence, or to worsening of symptoms despite ongoing antipsychotic treatment. In this proposal, we will test the hypothesis that there are individuals for whom there is a statistically significant progressive deterioration of symptoms despite guaranteed treatment. To do this, we will apply effect score analysis to the symptom trajectories in individuals with schizophrenia or schizoaffective disorder treated with a long acting injectable. We will develop a machine

Scientific Abstract:

Background: Individuals with schizophrenia may have a deteriorating course of illness over the long-term. This could be related to dwindling efficacy of antipsychotic drugs over time.
Objective: To test whether there are individuals for whom there is a statistically significant worsening symptom trajectory during guaranteed antipsychotic delivery based on their baseline clinical and demographic characteristics.
Study Design: We will select individuals with schizophrenia treated in a clinical trial with long acting injectable antipsychotic for relapse prevention. After data preprocessing, we will apply an effect score analysis framework. To this end, we will develop and test several machine learning models to predict symptom trajectory and chose the model with best performance in leave one site out cross-validation. Using the test sets, we will apply the model to calculate individual scores predictive of symptom trajectory. Those scores will be used to stratify individuals in 3-5 strata. We will study the effect of strata on the trajectory of symptoms observed for each participant. Furthermore, we will

examine the variables driving the stratification.
Participants: We will use data from 25 clinical trials of long-acting injectable antipsychotic used for relapse-prevention in schizophrenia for >6 months.
Primary and Secondary Outcome Measure(s): PANSS Total and component scores over time on treatment.
Statistical Analysis: To compare the effects between strata, we will conduct an interaction test of strata on symptoms ~ time in a linear model.

Brief Project Background and Statement of Project Significance:

Individuals with schizophrenia may experience a deteriorating course of illness over the long term. As a group, epidemiological studies show that overall function, positive, and total symptoms may worsen over time1. Part of this undesired outcome may be related to a decreasing efficacy of antipsychotic drugs, the cornerstone of treatment, in addressing symptoms. For instance, it is generally accepted that individuals in the early phase of treatment respond to a lower dose of antipsychotic medication2,3, and that overall response rates are larger than for individuals who have been ill for longer periods of time4. Similarly, it is estimated that while most individuals with treatment resistance are so from the first treatment episode, in ~20% of the cases treatment resistance occurs after having been responsive to medications previously 5,6. There are data showing that the response to antipsychotic treatment is of decreased magnitude and delayed in the second compared to the first treatment episode, suggesting that some individuals may lose part of the benefits of drugs after each relapse7. Similarly, data from the Finnish national registry show that after each relapse, the doses used to treat psychotic symptoms escalates without evidence of greater effectiveness, again pointing at the possibility that after each relapse there might be an irreversible loss in the effects of antipsychotic drugs in managing symptoms in schizophrenia8. Recently, we also showed that relapse in schizophrenia may occur even while antipsychotic treatment is guaranteed by a long-acting injectable (LAI) antipsychotic9. We found that among 5130 individuals treated in 19 cohorts with a LAI antipsychotic for relapse prevention, there was an incidence of 22·97 study defined relapses per 100 participant-years. At the group level, we found that residual psychosis, substance use, and tardive dyskinesia were associated with time to study defined relapse. These results have been further validated in at least 2 other datasets in which we found comparable results10,11. Overall, this literature points out that part of the worsening outcomes over the course of illness in schizophrenia might be related to a decreasing efficacy of antipsychotic drugs.
The dwindling effects of antipsychotic drugs could then be related to irreversible loss in acute efficacy when these drugs are reintroduced following a relapse, and/or to their inability to sustain relapse-prevention effects over time. Understanding these processes could be helpful in various ways to improve long-term outcomes of those living with schizophrenia. For instance, identifying mechanisms associated in the inability to sustain relapse-preventing effects could be used to develop therapeutics that mitigate such effect for currently existing antipsychotics or to develop novel treatments with mechanisms of action that are less vulnerable to losing such effect. The advent of antipsychotic drugs with novel mechanisms of action that bypass dopaminergic receptor blockade12 could be promising on this regard. Also, understanding the features that increase the risk of a given individual to show decreased treatment response upon treatment

Specific Aims of the Project:

1. Develop and validate an individual score predictive of trajectory of the positive, negative, general, and total symptom domains during guaranteed maintenance antipsychotic treatment in individuals with schizophrenia.
2. Test the hypothesis of heterogeneity of treatment effects in the trajectory of the positive, negative, general, and total symptom domains during guaranteed maintenance antipsychotic treatment in individuals with schizophrenia.
3. Identify features predictive of the trajectory of the positive, negative, general, and total symptom domains during guaranteed maintenance antipsychotic treatment in individuals with schizophrenia.

Study Design:

Meta-analysis (analysis of multiple trials together)

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

Participant-level data meta-analysis

Meta-analysis using only data from the YODA Project

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:

We will apply the following inclusion criteria for the selection of trials:
- Patient population: Schizophrenia or schizoaffective disorder.
- Intervention: At least one arm with long-acting injectable antipsychotic for relapse prevention.
- Duration of treatment: at least 6 months
We will apply the following inclusion criteria for individuals within selected trials:
- Symptom stability has been achieved as defined by trial.
- Participants are allocated to a long-acting injectable antipsychotic treatment with a duration longer than 6 months.
Other than not meeting inclusion criteria, there are no exclusion criteria

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

Primary outcome will be:
- Individual random slope derived from “Total PANSS ~ visit_day + (1 + visit_day | id)"
Secondary outcomes will be:
- Individual random slope derived from “PANSS Positive ~ visit_day + (1 + visit_day | id)"
- Individual random slope derived from “PANSS Negative ~ visit_day + (1 + visit_day | id)”
- Individual random slope derived from “PANSS General ~ visit_day + (1 + visit_day | id)"

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

We will include all variables in AIMS, BARS, CGI, CHEM, DEMOG, HEMAT, PSYHIST, SARS, URINE, VITALS. Any additional baseline characteristics provided by each trial will be included as features in the machine learning model.

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

Any additional baseline characteristics provided by each trial will be included as features in the machine learning model.

Statistical Analysis Plan:

We will preprocess the selected clinical trials adapting scripts from17 to wrangle data to workable formats, visualize distributions, handle categorical attributes, clean the data for missing values and scale (within sample) if necessary and map out available features per trial. After this initial step, we will proceed to the effect score analysis, as generally described in Wang et al16. The main steps in these analyses will be the following:
1. Creation of effect score model: We will use the above-described independent variables as

predictive features for an array of machine learning (ML) to predict the trajectory of Total, Positive, Negative, and General PANSS scores over time. To this effect, we will apply ML models that are appropriate to address our research question based on the nature of the problem, the size of the data, interpretability, and performance metrics. The models will be developed and tested iteratively in leave one site out cross validation. We will select the model with greatest performance for the rest of the analyses. Our choice of models and justification will be the following:
a. Linear Mixed Effects Models (LMMs): LMMs are commonly used for longitudinal data analysis, allowing for the modeling of individual trajectories over time while accounting for correlations between repeated measures within individuals. Baseline variables can be incorporated as fixed effects, allowing the model to account for individual differences at baseline. Leave-one-site-out cross-validation can be performed to assess the model's predictive performance by comparing predicted symptom trajectories with observed trajectories.
b. Random Forest Regression: Random forests are versatile ensemble learning methods that can handle high-dimensional data and nonlinear relationships. Baseline variables can be used as input features to predict symptom trajectories. Each tree in the forest can provide individual predictions, allowing for the generation of individual effect scores. Leave-one-site-out cross-validation can be used to assess the generalization performance of the random forest model.
c. Elastic Net Regression: Elastic Net is a regularization technique that combines the penalties of Lasso and Ridge regression, allowing for feature selection and handling multicollinearity. It can be applied to model the relationship between baseline variables and symptom trajectories. Leave-one-site-out cross-validation can be performed to tune the hyperparameters of the Elastic Net model and assess its predictive performance.
2. Stratification by individual scores in test dataset: After having selected the best performing model through leave one site out cross validation, we will use the individual scores calculated in the test set (i.e., the trial not used to train the model) to stratify the trial participants in groups by their individual scores. We will test stratification schemes of 3, 4 and 5 strata.
3. Estimation of treatment effects by strata: We will examine the distribution of individual symptom trajectories calculated through a LMM by the different strata and proceed to statistical testing by examining interaction effects. Specifically, the null hypothesis is that there are no difference symptom trajectories by strata whereas the alternative hypothesis is that there is an interaction effect of the strata on the effect of time on PANSS scores.
4. Description of feature importance: For the selected model, we will develop feature importance plots to identify the baseline characteristics that are most informative towards the stratification, and which are most relevant to identify individuals with a worsening symptom trajectory despite guaranteed treatment delivery and which may be most informative about a deteriorating course of illness.

Software Used:

R

Project Timeline:

We will need for the analyses both R (through RStudio) and Python (through Jupyter Lab or Jupyter Notebook)

We plan to start as soon as we are granted access to the data. We anticipate 3 months for data preprocessing, 6 for analyses, and 3 for manuscript preparation and submission.

Dissemination Plan:

We are planning to publish these results in a similar way as what we have done with previous YODA projects. We believe that this will be of interest to high impact journals given the significance of results and large data access.

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