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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?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/02/coi_form_NB.pdf
https://yoda.yale.edu/wp-content/uploads/2024/02/COI_Form_KarinKnudson.pdf
https://yoda.yale.edu/wp-content/uploads/2024/02/COI_YODA_TB.pdf
https://yoda.yale.edu/wp-content/uploads/2024/02/COI-form-CW.pdf
https://yoda.yale.edu/wp-content/uploads/2024/02/COI-form-AJ-updated.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. NCT00061802 - RIS-SCP-402 - A Randomized, Double Blind Study to Evaluate the Efficacy and Safety of Two Atypical Antipsychotics vs. Placebo in Patients With an Acute Exacerbation of Either Schizophrenia or Schizoaffective Disorder
2. NCT01193153 - R092670SCA3004 - A Randomized, Double-Blind, Placebo-Controlled, Parellel-Group Study of Paliperidone Palmitate Evaluating Time to Relapse in Subjects With Schizoaffective Disorder
3. NCT00412373 - R076477SCA3002 - A Randomized, Double-blind, Placebo-controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Flexible-dose Paliperidone ER in the Treatment of Patients With Schizoaffective Disorder
4. NCT00397033 - R076477SCA3001 - A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Two Dosages of Paliperidone ER in the Treatment of Patients With Schizoaffective Disorder
5. NCT00077714 - R076477-SCH-304 - A Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 2 Fixed Dosages of Paliperidone Extended Release Tablets and Olanzapine, With Open-label Extension, in the Treatment of Patients With Schizophrenia
6. NCT00590577 - R092670PSY3007 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia
7. NCT00210548 - R092670PSY3003 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (50 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia
8. NCT00101634 - R092670PSY3004 - A Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq, 50 mg eq, and 100 mg eq) of Paliperidone Palmitate in Patients With Schizophrenia
9. NCT00088075 - RIS-SCH-302/CR003370 - A Randomized, Double-Blind, Placebo-Controlled Clinical Study of the Efficacy and Safety of Risperidone for the Treatment of Schizophrenia in Adolescents
10. NCT00253136 - RIS-USA-121/CR006055 - Risperidone Depot (Microspheres) vs. Placebo in the Treatment of Subjects With Schizophrenia
11. NCT00524043 - R076477SCH4012 - A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of a Fixed Dosage of 1.5 mg/Day of Paliperidone Extended Release (ER) in the Treatment of Subjects With Schizophrenia
12. NCT00249132 - RIS-INT-3 - A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients
13. NCT00518323 - R076477PSZ3001 - A Randomized, Multicenter, Double-Blind, Weight-Based, Fixed-Dose, Parallel-Group, Placebo-Controlled Study of the Efficacy and Safety of Extended Release Paliperidone for the Treatment of Schizophrenia in Adolescent Subjects, 12 to 17 Years of Age
14. NCT00334126 - R076477SCH3015 - A Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Paliperidone ER Compared to Quetiapine in Subjects With an Acute Exacerbation of Schizophrenia
15. NCT00083668 - R076477-SCH-305 - A Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 3 Fixed Dosages of Paliperidone Extended Release (ER) Tablets and Olanzapine, With Open-label Extension, in the Treatment of Patients With Schizophrenia
16. NCT00078039 - R076477-SCH-303 - Trial Evaluating Three Fixed Dosages of Paliperidone

Extended-Release (ER) Tablets and Olanzapine in the Treatment of Patients With Schizophrenia
17. NCT00085748 - R076477-SCH-302 - A Randomized, 6-Week Double-Blind, Placebo-Controlled Study With an Optional 24-Week Open-Label Extension to Evaluate the Safety and Tolerability of Flexible Doses of Paliperidone Extended Release in the Treatment of Geriatric Patients With Schizophrenia
18. NCT00074477 - R092670-SCH-201 - A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of 50 and 100 Mg-eq of Paliperidone Palmitate in Patients With Schizophrenia
19. NCT01529515 - R092670PSY3012 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia
20. NCT00086320 - R076477-SCH-301 - A Randomized, Double-blind, Placebo-controlled, Parallel-group Study With an Open-label Extension Evaluating Paliperidone Extended Release Tablets in the Prevention of Recurrence in Subjects With Schizophrenia
21. 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

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

Research Proposal

Project Title

Individual-level and study-level predictors of placebo response and dropout in Schizophrenia Disorder clinical trials

Narrative Summary:

High levels of placebo effect can make more difficult the development of new therapeutics for schizophrenia, making it more challenging to distinguish between drug and placebo responses. Moreover, patient discontinuation in clinical trials make conducting trials for new treatments more difficult, costly, and time-consuming. Placebo response and dropout rates may vary based on patient characteristics, study design choices, regional variability, and the clinical outcome of interest. Understanding these factors associated with placebo response and dropout is therefore critical for optimally designing clinical trials to meet the outstanding need of patients with schizophrenia. That critical need motivates the proposed research, which will use tools from meta-regression, causal inference, and machine learning to explore individual and study-level predictors of placebo response and dropout in clinical trials for treatments of schizophrenia.

Scientific Abstract:

Background: Both in the US and globally, schizophrenia has a large disease burden, and there is a significant need for new and better treatments [1]. However, participants in clinical trials for treatment of schizophrenia often show a significant placebo response, complicating the development of new therapeutics; the placebo effect in schizophrenia has also grown over time [2, 3]. High dropout rates additionally increase the difficulty of running clinical trials for schizophrenia, because recruiting enough participants to compensate for attrition requires additional time and expense. Identifying factors that are associated with (or predictive of) placebo response and/or dropout is therefore crucial in designing clinical trials that adequately assess the efficacy of new treatments to treat this often-debilitating disorder.

Objective: We seek to identify individual- and study-level features that relate to dropout, placebo response or the difference between drug and placebo response among participants in clinical trials of treatments for schizophrenia. We will further describe the directionality and strength of any identified associations, and their replicability across trials.

Study Design: We will perform both individual-level analyses and study-level meta-analyses to identify predictors of placebo response in PANSS total score and subscores, as well as trial discontinuation/dropout. The relationship between available individual-level features and PANSS placebo response will be tested using standard regression frameworks, multivariate predictive models, and causal inference approaches. The relationship between available individual-level features dropout will be tested using classification models for the binary outcome of dropping out, as well as survival analysis for the time-to-dropout.

Participants: We will include participants from clinical trials for treatments for schizophrenia or schizoaffective disorder.

Primary and Secondary Outcome Measure(s): The primary outcome will be placebo response on the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) total and subscores and Clinical Global Impressions Scale (CGI/CGI-S/CGI-SCA) and the time to drop out for those who dropped out. Secondary outcome measures will include placebo response on the Personal and Social Performance Scale (PSP) where available, as well as the YMRS and HAMD for schizoaffective disorder participants where available.

Statistical Analysis: We will use mixed-effect meta-regression to test the relationship between study-level features and placebo response [4]. Study-level features may include sample size, number of sites, year, number of arms, mean clinical severity scores, and enrollment criteria. For individual-level analyses, we will use multivariate regression, multivariate predictive models (e.g. regularized linear regression, ensemble methods like XGBoost and random forests, hierarchical Bayesian regression), as well as causal inference approaches (e.g. double machine learning, doubly robust learning, meta-learners, Bayesian causal inference) to assess the relationship between individual-level features and placebo response. Bayesian hierarchical modeling will be used to jointly model study-level effects and individual-level feature's effect on placebo response in schizophrenia. Lastly, we will use classification methods (e.g. logistic regression, random forests) to identify possible predictors of dropout and will use survival analysis (e.g. Cox proportional hazards regression) identify predictors of to time-to-dropout. We will assess generalizability of the predictive modeling component by holding out one or more trials during the training phase, and then testing the model predictions for placebo response, treatment effect, and/or dropout prediction on the held-out trial(s).

Brief Project Background and Statement of Project Significance:

Schizophrenia is a severe and complex mental illness, and current pharmacological treatments can have significant adverse effects [5]. The placebo response in schizophrenia is substantial and growing, which makes developing new therapeutics for this disease more challenging [2,3]. While several meta-analyses have sought to identify study-level predictors of placebo response, there is little understanding of patient-level predictors of placebo response [6,7,8]. Patients' individual characteristics may be particularly key to understanding placebo response in schizophrenia, given possible overlap between the cognitive basis of placebo response and psychosis, as both relate to the process and relative weighting that occurs when prior beliefs are updated with sensory information [8]. In addition to high placebo response, another hindrance to the success of trials for new treatments for schizophrenia is that trial attrition rates are high, especially within placebo-controlled designs [8]. The proposed research will use predictive and causal modeling explore individual-level and study-level predictors of placebo response and dropout in clinical trials for schizophrenia, creating an understanding of these factors that can support more successful development of therapeutics.

In addition to the need for a better understanding of placebo response in schizophrenia, there is also a need to better understand the generalizability of clinical trial models in schizophrenia more broadly. Recent work using YODA schizophrenia clinical trial data called into the question the

generalizability of predictive models across trials, but this work reported results with only a binary outcome (remission prediction) and did not make use of causal inference [9]. As part of our analysis, we will assess these specific recent generalizability findings using a causal modeling approach on the same data and making use of continuous outcome data.

Specific Aims of the Project:

This project aims to 1) identify individual-level causal factors underlying elevated placebo effect in clinical trials for treatments of schizophrenia 2) identify study-level factors underlying elevated placebo effect in clinical trials for treatments of schizophrenia 3) assess generalizability of the causal models of placebo and drug response across separate trials, and 4) identify predictors of discontinuation/dropout and their generalizability across trials.

Study Design:

Individual trial analysis

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

Participant-level data meta-analysis

Meta-analysis using only data from the YODA Project

Research on comparison group

Research Methods

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

We will analyze clinical trials of treatments for schizophrenia and schizoaffective disorder that are double-blind and include a placebo arm. Requested trials are:

NCT00061802 (RIS-SCP-402)
NCT01193153 (R092670SCA3004)
NCT00412373 (R076477SCA3002)
NCT00397033 (R076477SCA3001)
NCT00077714 (R076477-SCH-304)
NCT00590577 (R092670PSY3007)
NCT00210548 (R092670PSY3003)
NCT00101634 (R092670PSY3004)
NCT00088075 (RIS-SCH-302/CR003370)
NCT00253136 (RIS-USA-121/CR006055
NCT00524043 (R076477SCH4012)
NCT00249132 (RIS-INT-3)
NCT00518323 (R076477PSZ3001)
NCT00334126 (R076477SCH3015)
NCT00083668 (R076477-SCH-305)
NCT00078039 (R076477-SCH-303)
NCT00085748 (R076477-SCH-302)
NCT00074477 (R092670-SCH-201)
NCT01529515
NCT00086320 (R076477-SCH-301)
NCT00111189 (R092670PSY3001)

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

The primary outcome measures will be the total, item-level and factor subscales of the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impressions Scale (CGI) and time-to-dropout for participants who discontinued the trial. Secondary outcomes include time-to-relapse, measure of functioning such as the Personal and Social Performance scales where available, and for participants with schizoaffective disorder, the YMRS/HAMD.

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

The main predictor is treatment arm under an intent-to-treat framework (eg randomization label).

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

Additional predictors to be analyzed will include patient demographic and clinical characteristics. Demographics will include:
- Age
- Sex
- Race/ethnicity
- Country/region
- Study site

Clinical characteristics include:
- Baseline severity -- PANSS total, item-level PANSS, and PANSS factor subscales
- Baseline PSP
- Time since disease onset
- Diagnosis (schizophrenia or schizoaffective disorder)
- Mood disorder scales where present (YMRS, HAMD)
- Psychiatric history and comorbidities
- Baseline CGI
- Vital signs
- Inpatient setting
- Concomitant medications

Meta-analytic analyses will include study level characteristics such as:
- Study year
- Trial length
- Number of study sites
- Size of placebo arm
- Trial design (number of arms, run-in/stabilization period)
- Percent male/female
- Mean age
- Enrollment criteria
- Mean PANSS severity

The precise independent variables to be used may change somewhat based on analysis of their availability in requested clinical trial data.

Statistical Analysis Plan:

We will use mixed-effect meta-regression to test the relationship between study-level features and placebo response [4]. Study-level features may include sample size, number of sites, year, number of arms, mean clinical severity scores, and enrollment criteria. For individual-level analyses, we will use multivariate regression, multivariate predictive models (e.g. regularized linear regression,

ensemble methods like XGBoost and random forests, hierarchical Bayesian regression), as well as causal inference approaches (e.g. double machine learning, doubly robust learning, meta-learners, Bayesian causal inference) to assess the relationship between individual-level features and placebo response. Bayesian hierarchical modeling will be used to jointly model study-level effects and individual-level feature's effect on placebo response in schizophrenia. Lastly, we will use classification methods (e.g. logistic regression, random forests) to identify possible predictors of dropout and will use survival analysis (e.g. Cox proportional hazards regression) identify predictors of to time-to-dropout. We will assess generalizability of the predictive modeling component by holding out one or more trials during the training phase, and then testing the model predictions for placebo response, treatment effect, and/or dropout prediction on the held-out trial(s). We will explicitly compare results to a recent publication in cross-study predictions [10].

Software Used:

Python

Project Timeline:

Anticipated Project Start Date: April 2024
Meta Analyses Completion Date: July 2024
Individual Analyses Completion Date: December 2024
Manuscript Drafted: March 2025
Manuscript Submitted and Results Reported back to YODA: April 2025

Dissemination Plan:

This work will be submitted for publication in a peer-reviewed academic journal if our analyses yield results that merit publication. Possible journals include JAMA Psychiatry, Schizophrenia Bulletin and/or Schizophrenia Research.

Bibliography:

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