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General Information

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Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: PCORI
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-converted.pdf
https://yoda.yale.edu/system/files/yodabie.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. NCT00645099 - R076477SCH3020 - A Prospective Randomized Open-label 6-Month Head-To-Head Trial to Compare Metabolic Effects of Paliperidone ER and Olanzapine in Subjects With Schizophrenia
2. 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
3. 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

4. NCT00650793 - R076477-SCH-703 - A Randomized, DB, PC and AC, Parallel Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Dosages of Extended Release OROS Paliperidone (6, 9, 12 mg/Day) and Olanzapine (10 mg/Day), With Open-Label Extension, in the Treatment of Subjects With Schizophrenia - Open Label Phase
5. NCT00589914 - R092670PSY3006 - A Randomized, Double-Blind, Parallel-Group, Comparative Study of Flexible Doses of Paliperidone Palmitate and Flexible Doses of Risperidone Long-Acting Intramuscular Injection in Subjects With Schizophrenia
6. NCT00604279 - R092670PSY3008 - A Randomized, Open-Label, Parallel Group Comparative Study of Paliperidone Palmitate (50, 100, 150 mg eq) and Risperidone LAI (25, 37.5, or 50 mg) in Subjects with Schizophrenia
7. 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
8. 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
9. 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
10. 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
11. 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
12. 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
13. NCT00391222 - RISBMN3001 - A Randomized, Double Blind, Placebo and Active Controlled Parallel Group Study to Evaluate the Efficacy and Safety of Risperidone Long-acting Injectable (LAI) for the Prevention of Mood Episodes in the Treatment of Subjects With Bipolar I Disorder
14. NCT00132678 - RISBIM3003 - A Randomized, Double-blind, Placebo-controlled Study to Explore the Efficacy and Safety of Risperidone Long-acting Intramuscular Injectable in the Prevention of Mood Episodes in Bipolar 1 Disorder, With Open-label Extension
15. NCT00094926 - RIS-BIP-302 - A Prospective, Randomized, Double-blind, Placebo-controlled Study of the Effectiveness and Safety of RISPERDAL CONSTA Augmentation in Adult Patients With Frequently-relapsing Bipolar Disorder
16. NCT00237289 - CR002653 (CAPSS-168) - Topiramate Versus Placebo as add-on Treatment in Patients With Bipolar Disorder in the Outpatient Setting
17. NCT00240721 - CR002248 (TOPMAT-PDMD-005) - A Randomized, Double-Blind, Multicenter, Placebo-Controlled 12-Week Study Of The Safety And Efficacy Of Two Doses Of Topiramate For The Treatment Of Acute Manic Or Mixed Episodes In Subjects With Bipolar I Disorder With An Optional Open-Label Extension
18. NCT00037674 - TOPMAT-PDMD-004 - A Randomized, Double-Blind, Multicenter, Placebo-Controlled 12-Week Study of the Safety and Efficacy of Two Doses of Topiramate for the Treatment of Acute Manic or Mixed Episodes in Patients With Bipolar I Disorder With an Optional Open-Label Extension
19. NCT00035230 - TOPMAT-PDMD-008 - A Randomized, Double-Blind, Multicenter, Placebo-Controlled 12-Week Study of the Safety and Efficacy of Topiramate in Patients With Acute Manic or Mixed Episodes of Bipolar I Disorder With an Optional Open-Label Extension
20. NCT00249132 - RIS-INT-3 - A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients
21. NCT00253162 - RIS-INT-69 - The Efficacy And Safety Of Flexible Dose Ranges Of Risperidone Versus Placebo Or Haloperidol In The Treatment Of Manic Episodes Associated With Bipolar I Disorder
22. NCT00378092 - CR011992, RISSCH3024 - A Prospective Study of the Clinical Outcome Following Treatment Discontinuation After Remission in First-Episode Schizophrenia
23. NCT00299715 - R076477-BIM-3001 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response, Multicenter Study to Evaluate the Efficacy and Safety of Three Fixed Doses of Extended-

Release Paliperidone in the Treatment of Subjects With Acute Manic and Mixed Episodes Associated With Bipolar I Disorder

24. NCT00309699 - R076477-BIM-3002 - A Randomized, Double-Blind, Active- and Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Flexibly-Dosed, Extended-Release Paliperidone Compared With Flexibly-Dosed Quetiapine and Placebo in the Treatment of Acute Manic and Mixed Episodes Associated With Bipolar I Disorder
25. NCT00309686 - R076477-BIM-3003 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Flexibly-Dosed Extended-Release Paliperidone as Adjunctive Therapy to Mood Stabilizers in the Treatment of Acute Manic and Mixed Episodes Associated With Bipolar I Disorder
26. NCT00752427 - R076477-SCH-702 - 24 week extension of NCT00085748: 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
27. 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
28. 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
29. 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
30. NCT00078039 - R076477-SCH-303 - Trial Evaluating Three Fixed Dosages of Paliperidone Extended-Release (ER) Tablets and Olanzapine in the Treatment of Patients With Schizophrenia

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

Research Proposal

Project Title

Causally interpretable meta-analysis with missing data: Generalizing evidence from bipolar disorder and schizophrenia trials to a target population

Narrative Summary:

Clinical trials are almost always conducted with a specific target population in mind, but data collected is rarely a random sample of that population. This project aims to develop new statistical methods that allow us to transport/generalize treatment effects from multiple clinical trials to the target population of interest. The methods will be evaluated using data from several bipolar disorder and schizophrenia randomized trials creating generalizable evidence about treatment efficacy.

Scientific Abstract:

Background: Many RCTs evaluate the effects of antipsychotic drugs on patients with schizophrenia or bipolar disorder. There is interest in synthesizing evidence across the different trials to improve precision of estimators of treatment efficacy. Furthermore, trial participants often differ from the underlying target population. This raises the question of how to combine information from multiple trials in a way that is interpretable in the context of the target population of interest. Such analysis are often complicated by data being systematically missing between trials (i.e., information on a certain variable is only collected in some trials).
Objective: We are going to develop and evaluate the performance of new statistical methods for handling systematic missing data in causally interpretable meta-analysis. A part of the evaluation will be done by applying the methods developed to the datasets requested in this data request.

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Study Design: We will conduct a causally interpretable meta-analysis using the datasets requested.
Participants: The analysis will be restricted to all participants that are 18 years or older with a DSM-IV diagnosis of schizophrenia or Bipolar I disorder.
Main Outcome Measure(s): For participants with schizophrenia we will focus on Positive and Negative Syndrome Scale total score and for participants with bipolar disorder we will focus on the Young Mania Rating Scale.
Statistical Analysis: The methods developed will be semi-parametric efficient and are extensions of our previously developed methods to the setting of missing data [1].

Brief Project Background and Statement of Project Significance:

Clinical trial results are commonly used to justify treatment options in different populations than the trial was conducted in (e.g., all participants who are eligible for a clinical trial rather than those that agreed to participate, a different geographic region, or a different clinical setting). Such justification requires generalization/transportation of clinical trial results to the target population for which the treatment is intended. A significant barrier to the practical utility of methods for generalizing/transporting treatment effects is the lack of methods for handling missing data. Data can be missing within trials or target and/or systematically missing where some covariates are not collected in some trials and/or the target. Within trial or target missing data has been extensively studied [2], but methods for addressing systematic missing data, a problem unique to the setting of having data from multiple data sources, have not yet been developed in the context of transporting treatment effects to a target population. We propose to develop and validate methods for handling systematic missing data when transporting treatment effects from one or more clinical trials to a target population, substantially improving the clinical utility of previously developed methods [1] for transportability of treatment effects from randomized controlled trials. The methods developed will be evaluated using the schizophrenia and bipolar disorder datasets requested and account for the differences in the populations underlying each trial. This will lead to results that are more generalizable to clinical practice and will provide understanding of the amount of treatment effect heterogeneity between different trials and how representative they are of more practical settings.

Specific Aims of the Project:

AIM 1: Develop methods for handling systematic missing data when transporting treatment effects from a single or multiple trials to a target population. This involves: a) developing conditions under which treatment effects can be transported from one or more clinical trials to a target population in the presence of systematic missing data; and b) deriving and developing properties of estimators for transporting treatment effects from one or more clinical trials to a target population in the presence of systematic missing data.
AIM 2: Apply and empirically evaluate the methods developed in Aim 1 using the schizophrenia and bipolar disorder trials requested as a part of this proposal.

What is the purpose of the analysis being proposed? Please select all that apply.
Confirm or validate previously conducted research on treatment effectiveness
Participant-level data meta-analysis
Participant-level data meta-analysis using only data from YODA Project
Develop or refine statistical methods
Research on clinical trial methods

Research Methods

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

In the analysis we will include all randomized trials that evaluate the effect of antipsychotic treatments on schizophrenia and bipolar disorder. To implement the analysis we need individual level data on all participants. This includes outcome information, treatment information, and individual level characteristics that allow us to account for differences in the underlying populations (e.g., demographic information, family history, severity of mental illness at baseline etc.). The analysis will include participants who are older than 18 and are diagnosed with schizophrenia or bipolar I disorder using the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnosis of schizophrenia or bipolar I disorder. We are requesting individual level data from all trials that involve paliperidone, paliperidone palmitate and/or risperidone (identified through the trial search on the YODA website).

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

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For participants with schizophrenia we will focus on Positive and Negative Syndrome Scale total score and for participants with bipolar disorder we will focus on the Young Mania Rating Scale. For the analysis we will focus on the difference in these measures from baseline to end of study.

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

We are requesting information on all covariates collected in the studies. This includes demographic variables (age, race, ethnicity, etc.), clinical information (BMI, drug abuse, alcohol abuse etc.), and severity of symptoms at baseline. These variables will be used to account for differences in the covariate distributions underlying the studies and will allow us to generalize the treatment efficacy to different populations.

Statistical Analysis Plan:

For Aim 1 we will use semi-parametric efficiency theory developed in the context of missing data and causal inference to develop methods for generalizing/transporting treatment effects from multiple clinical trials to a target population in the presence of systematic missing data. This involves extending the groups prior work to handling systematic missing data. This also involves identifying conditions under which such transportability analysis can be done and using falsification test of these assumptions to decide which datasets to include in the analysis. For Aim 2 we will use the methods developed in Aim 1 on the trials requested in this application.
Software Used:
R
Project Timeline:

These analysis are a part of a PCORI funded proposal with a funding period from 1/1/21-1/1/23. In year 1 we expect to develop the methods described in Aim 1 of the proposal and clean and harmonize the datasets. In year 2 we expect to analyze the data using the methods developed in Aim 1.

Dissemination Plan:

The results from this project will be journal publications and presentations at research meetings. The target audience will be statisticians, clinical trialists, and psychiatrists and the publication and presentation venues will focus on these groups (e.g, submit to more methodological work in biostatistics journal and more applied work in psychiatry journals).

Bibliography:

[1] Dahabreh, I. J., Petito, L. C., Robertson, S. E., Hernán, M. A., & Steingrimsson, J. A. (2020). Toward Causally Interpretable Meta-analysis: Transporting Inferences from Multiple Randomized Trials to a New Target Population. Epidemiology, 31(3), 334-344.

[2] Little, Roderick J., Ralph D'Agostino, Michael L. Cohen, Kay Dickersin, Scott S. Emerson, John T. Farrar, Constantine Frangakis et al. "The prevention and treatment of missing data in clinical trials." New England Journal of Medicine 367, no. 14 (2012): 1355-1360.