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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: NIH (R01GM111339)

Conflict of Interest

http://yoda.yale.edu/system/files/cois_signed_0.pdf
http://yoda.yale.edu/system/files/yoda_form_all_k_zelevinsky.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
Associated Trial(s):

1. Multiple NCT#s - OPTICS Trial Bundle

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

Research Proposal

Project Title

Heterogeneous Causal Effects: Drug Exposure & Safety

Narrative Summary:

People with schizophrenia are at higher risk for death from metabolic disease including obesity, dyslipidemia, hypertension, type 2 diabetes, and cardiovascular disease (CVD). Understanding the risks of antipsychotic medications is critical as these risks exacerbate the health burden of people with schizophrenia and add to the long-term economic burden borne by public payers. Currently, little evidence exists on the impact of the duration of drug exposure on the likelihood and size of the metabolic effects of antipsychotics; and whether sex modifies the effects. This project will use develop new statistical methods to address these gaps in knowledge.

Scientific Abstract:

Background: People with schizophrenia are at higher risk for metabolic morbidity including obesity, dyslipidemia, hypertension, type-2 diabetes, and cardiovascular disease. However, little evidence exists on the impact of exposure duration on the likelihood and size of the metabolic effects of antipsychotics; and whether sex modifies the effects. New methods are needed to address these gaps.
Objective: We propose an approach to analyze the causal effect of cumulative exposure on a binary outcome for placebo controlled and active treatment trials.
Study Design: We will exploit methodological advances in two related research fields, causal inference and network meta-analysis, to develop an inferential approach to answer questions involving the relationship between duration of drug exposure and outcomes.
Participants: We will utilize participant-specific information obtained from the CATIE trial (participants randomized to olanzapine, quetiapine, and risperidone arms only) and the 14 Janssen trials involving patients with schizophrenia or schizoaffective disorder.
Main Outcome Measure: Our metabolic endpoint is weight gain, which will be operationalized as a binary outcome.
Statistical Analysis: We exploit the randomization mechanism as an instrument to adhere to causal inference assumptions. We estimate exposure-response curves for different exposure subsets and then combine the treatment-exposure arms via network meta-analysis using individual patient data to study safety endpoints. Our approach uses the placebo arms of no exposure as the outcome of zero exposure.

Brief Project Background and Statement of Project Significance:

People with schizophrenia are at higher risk for metabolic morbidity including obesity, dyslipidemia, hypertension, type-2 diabetes, and cardiovascular disease (CVD). While a U.S. study conducted in the early 2000s found that patients with schizophrenia die approximately 25 years earlier than age- and sex-adjusted peers, an international review found that compared with the general population, this population has a two- to threefold increased risk of dying. Roughly 60% of the excess mortality is due to chronic medical conditions, with CVD accounting for over half of this excess risk. Treatment with antipsychotics, particularly some frequently used second-generation antipsychotics (SGAs), increases this risk. Current antipsychotic prescribing practices may pose a substantial long-term burden to patients and public payers. Little evidence exists on the impact of exposure duration on the likelihood and size of the metabolic effects of SGAs; and whether sex modifies the effects. Despite evidence from studies on the association between several SGAs and metabolic risk, little is known about the time-dependency of risk. The evidence on the dose-dependency is both limited and mixed. Men and women differ in how they experience disease and how they respond to treatment; yet little research on the influence of sex on efficacy and safety of antipsychotics exists. Studies conducting post-hoc analyses of RCT data aimed at describing response to SGAs among adults with schizophrenia found better outcomes for females with both early and chronic illness. A

naturalistic study of individuals with early psychosis found an advantage for males. Even less evidence exists on the modifying effect of sex on the metabolic risk of antipsychotics. Baseline analyses of subjects with chronic schizophrenia enrolled in the CATIE study reported that females were associated with higher rates of metabolic syndrome. The CATIE trial found no evidence of a modifying effect of sex on the association between specific antipsychotics and metabolic syndrome, results from the Comparison of Atypicals for First Episode (CAFE) trial suggest the opposite, reporting that females treated with quetiapine had the lowest mean weight gain and smallest mean increase in BMI. Placebo-controlled and active-controlled clinical trials provide different and valuable information for dose-response causal inferences. Traditional intention-to-treat analyses provide valid inferences of average effectiveness of therapy. While a simple regression of outcome on observed cumulative exposure is likely not causal, using the randomization assignment variable as an instrument can help identify causal dose-response relationships. Clinical trials are not powered to detect the effects of duration of exposure on risks nor the effects of modifiers. The numbers enrolled in RCTs are typically insufficient to determine subgroup effects or to reliably estimate dose-response relationships. While individual trials may not have sufficient power, network meta-analysis provides a quantitative method of integrating data from all available comparisons. Such analyses can be used to borrow information about effectiveness.

Specific Aims of the Project:

We will exploit methodological advances in two related research fields, causal inference and network meta-analysis, to develop an inferential approach to answer questions involving the relationship between duration of drug exposure and outcomes. Two specific aims guide our work:
Aim 1: To estimate the average causal effect of treatments on binary outcomes and ordered exposure in network meta-analysis of individual participant data. We will exploit the randomized assignment mechanisms, treatment arms, and placebo arms to estimate exposure-outcome curves in different exposure subsets.
Aim 2: To extend Aim 1 to estimate the heterogeneous (conditional) average treatment effects. We will modify methodology to include a binary-valued moderator to estimate the exposure-outcome curves within groups defined by a moderator and different exposure subsets.

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 populationsNew research question to examine treatment safetyParticipant-level data meta-analysisParticipant-level data meta-analysis pooling data from YODA Project with other additional data sources

Research Methods

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

We will utilize participant-specific information obtained from the CATIE trial (participants randomized to the olanzapine, quetiapine, and risperidone arms only) and the 14 Janssen trials involving patients with schizophrenia or schizoaffective disorder (Table 1). We will obtain these study data from YODA, assess for completeness and comparability to reported study summaries, and organize into SAS as well as R datasets. We will focus on the trial-specific end-point of weight (rather than intermediate within-trial outcomes) and the cumulative duration of exposure at end-point for each trial participant.

[Attached research proposal document contains Table 1]

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

Our metabolic endpoint is weight gain which will be operationalized as a binary outcome assuming a value of 1 if the subject experienced a weight increase of at least 7% of baseline weight at the trial endpoint and 0 otherwise.

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

Our main predictor is cumulative exposure to treatment. The set of all treatments,?, we consider include {paliperidone, olanzapine, quetiapine, risperidone, and placebo}. The data include j = 1,…,N_i participants in trial i who have been randomized to treatment R_ij=k_ij. For participant j in trial i on treatment k_ij, a treatment cumulative exposure level, e_ij^k, at trial termination (Table 1), and an observed outcome, Y_ij^k=1, if the outcome occurred and 0 otherwise, are available. Finally, we will use G+1 ordered (cumulative) exposure levels, {g = 0,1,2,…,G}. For instance, G = 5 in Table 1 based on our preliminary review of the published trial data.

[Attached research proposal document contains formatted mathematical notation]

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

We are interested in identifying the modifying effects of patient characteristics such as sex. We let x_ij generically denote a vector of participant-level baseline covariates. For Aim 2, we create a dummy variable denoting female, the treatment modifier, ?female?_ij = 1 if participant j in trial i is female and 0 otherwise. Unless otherwise specified, ?female?_ij?x_ij.

[Attached research proposal document contains formatted mathematical notation]

Statistical Analysis Plan:

We will adopt two different approaches to estimation. Approach 1: we will employ a two-step procedure: in Step 1 we will estimate an instrumental variable-based (structural) marginal model within each trial. This step yields a contingency table that describes a dose-response curve for participants at their selected cumulative exposure level. The rows of the table denote cumulative drug exposure while the columns reflect outcomes for the specific cumulative exposure. In Step 2 using the estimated parameters characterizing the contingency table, we will conduct a network-meta analysis of the estimates. Because of the advantages exploiting the individual participant data (such as separating within-trial effects from across-trial effects), in Approach 2 we will simultaneously model the contingency table across all the trials, including study-specific relative random effects when modeling participant-specific information. Our methodology relies on the availability of individual participant data that permit separation of within-study effects from across-study effects, the randomized assignment indicators and placebo arms that permit identification of outcomes under zero exposure for treatment arms, and the existence of multiple different studies that permit assessment of evidence compatibility from direct and indirect comparisons. We will illustrate our new methodology to characterize the causal effect of drug duration on weight gain for (a) all patients, and (b) males and females separately. We describe the proposed data sources, our key assumptions, and our approach to the development of new the statistical methodology.

Project Timeline:

Year 1
• OPTICS Data applications: YODA & NIMH (CATIE)
• IRB application & approval
• Develop R function that will include code to estimate dose-response curves in the presence of a binary outcome, G exposure levels, and K treatments for a single trial as well as options for models
• Analyze the causal effect of cumulative exposure on a binary outcome for placebo-controlled and active-treatment trials
• Estimate exposure-response curves for different exposure subsets
• Combine the treatment-exposure curves via network meta-analysis using individual participant data to
o assess evidence compatibility from direct and indirect comparisons;
o separate within from between-trial effects; and
o bolster conclusions within subgroups
• Manuscript 1: describe new methodology, assess operating performance characteristics of the estimation procedures, and illustrate the approach using the data from the 15 clinical trials

Year 2
• Apply for methodology R01 to NIMH or National Institute of General Medical Sciences using preliminary results
• Develop methodology to handle time-dependent confounders and censoring using Marginal Structural Cox models
• Develop methodology using flexible approaches to model cumulative exposure effects
• Manuscript 2

Dissemination Plan:

We will develop an R function that will be made freely available (loaded onto the Comprehensive R Archive Network). The function will include code to estimate dose-response curves in the presence of a binary outcome, G

exposure levels, and K treatments for a single trial. The code will include options for models (including a multivariate Dale model). During the one-year time-frame we anticipate completing one manuscript that describes the new methodology, assesses the operating performance characteristics of the estimation procedures, and illustrates the approach using the antipsychotic drug data from the 15 clinical trials.

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Supplementary Material:

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