## Principal Investigator

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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:** Harvard Catalyst OPTICS Pilot Grant

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## 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):** 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

Mediation Analysis to explain comparative efficacy of antipsychotic medications for treatment of schizophrenia in short-term RCT

**Narrative Summary:**
Differences among antipsychotic medications for treatment of schizophrenia spanning from targeted mechanism of action, side effects and efficacy have been observed in randomized trial settings and in clinical practice. We will apply causal mediation analysis to study the interplay of symptoms and side effect in explaining how OPTICS trials treatments affect the final outcome of interest. We will compare drug and placebo (1) on a primary outcome, social functioning; (2) on secondary outcomes: (i) positive symptoms (ii) negative symptoms (iii) side effects; (3) quantify mediating and interactive role of the secondary outcomes. The work has the potential to guide clinical practice.

**Scientific Abstract:**
Background: Differences among antipsychotic medications for treatment of schizophrenia spanning from targeted mechanism of action, side effects and efficacy have been observed in randomized trial settings and in clinical practice. Explaining why differences in efficacy are observed is important to inform development of new drugs and to guide appropriate treatment strategies.
Goal & Main Outcomes: To quantify the joint effect, potentially synergistic or antagonistic, of intermediate factors that can explain differential efficacy among treatments for schizophrenia. We will (1) compare drug effects on a primary outcome, social functioning; (2) compare drug effects on secondary outcomes: (i) positive symptoms (ii) negative symptoms (iii) side effects; (3) quantify how much of the relative efficacy on social functioning is due to the mediating and interactive role of the secondary outcomes.
Study Design & Participants: We plan to investigate mechanisms that could explain treatment efficacy as a secondary analysis of a short-term randomized,
double blind, placebo and active controlled parallel group trial of 6, 9, 12mg/d dosage of paliperidone and olanzapine (10mg/d) in 630 patients.
Statistical Analysis: Mediation analysis is the study of the role of intermediate endpoints in explaining how a treatment affects the final outcome of interest. We will extend and apply mediation analysis approaches to longitudinal trial data in the presence of multiple, potentially interacting, mediators.

**Brief Project Background and Statement of Project Significance:**
Antipsychotic drugs are the cornerstone of treatment for schizophrenia. The first generation of antipsychotic medications were approved in the 1950's, while the second generation started with the approval of clozapine in the early 1990's. In the past 25 years a wealth of clinical trials and observational studies have evaluated relative efficacy, safety, and effectiveness of first and second generation medications. Such studies have shown that first and second generation antipsychotics differ significantly in (i) targeted mechanism of action (ii) side effects (iii) adherence to medication (iv) Positive and Negative Symptoms Scale (PANSS) scores improvement[1,2]. A consensus has not been reached on the relative efficacy and effectiveness of first and second generation antipsychotic drugs. This has induced an increasing trend in the administration of costly, and yet to be shown effective polytherapy and higher doses of antipsychotics[3]. Among psychotic patients, schizophrenia patients display the highest deficit in social functioning[4,5]. Social functioning has been recognized as an important contributor to overall quality of life and a determinant of treatment success. The ability of typical and atypical agents to improve social functioning has
not been fully explored[6]. Consensus has been reached on the impact of negative symptoms on social functioning[7]. Although first and second generation drugs target positive symptoms, several studies have shown the impact of second-generation drugs on negative symptoms through indirect mechanisms. It is of interest to investigate further the relative efficacy of first and second generation antipsychotics on social functioning and to assess the mechanisms that explain their relative efficacy. Clarity on the relative efficacy and effectiveness of typical and atypical antipsychotic drugs can be made only by accounting for the complex effects of antipsychotics. It is critical to investigate the interplay of symptoms and side effects that impact the overall well-being of the patient over the course of treatment. Secondary analyses of efficacy trials that explain treatment mechanism of action have

recently become popular in the field of psychiatry. Mediation analysis is an important approach for quantifying how much of the treatment effect on a primary outcome is through intermediate factors (also referred to as mediators) and how much is through pathways independent of the mediators. Recently, Dr. Valeri developed methods and software for mediation analysis[8]. We will apply this methodology to understand whether (i) positive symptoms (ii) negative symptoms (iii) side effects could act as mediators of the effect of antipsychotic medications for schizophrenia on social functioning. We will further allow the mediators to act synergistically or antagonistically. We will quantify how much of the effect of the antipsychotic medications on social functioning is either due to the effect through the mediators (indirect), the effect independent of the mediators (direct), and the effect due to drug-mediators and mediators-mediators interaction.

**Specific Aims of the Project:**
Study objective: Develop and apply causal mediation analysis approaches to explaining comparative efficacy in a trial of high, medium and low-dose oral paliperidone extended release (ER) vs. placebo/olanzapine on social functioning after 6 weeks follow-up.
AIM 1 Compare drug effects on the primary outcome, social functioning.
Hypothesis 1 Paliperidone will result in increased social functioning relative to placebo.
AIM 2 Compare drug effects on secondary outcomes, (i) PANSS Factor Scores for positive symptoms (ii) PANSS Factor Scores for negative symptoms (iii) side effects.
Hypothesis 2 Paliperidone will result in improved PANSS positive and negative symptoms and will increase the risk of side effects relative placebo.
AIM 3 Explaining comparative efficacy of treatment on the primary outcome, social functioning, via the mediating and interactive role of secondary outcomes.
Hypothesis 3 Secondary outcomes will be both mediators and modifiers of treatment effect on social functioning.

**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
New research question to examine treatment safety
Research that confirms or validates previously conducted research on treatment effectiveness
Research that confirms or validates previously conducted research on treatment safety
Preliminary research to be used as part of a grant proposal
Participant-level data meta-analysis will pool 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 use data from a 6-week randomized, double-blind, placebo- and active controlled, parallel group study (NCT00083668) of high dose (15 mg/d), medium dose (9 mg/d) and low dose (3 mg/d) paliperidone extendedrelease (ER) versus placebo/olanzapine (10 mg/day), in 617 patients with schizoaffective disorder. In our study we will consider the Social Performance Scale (SPS) measured at the last study visit as the primary endpoint.
Secondary endpoints are: (i) PANSS Factor Scores for positive symptoms (ii) PANSS Factor Scores for negative symptoms (iii) side effects, measured at the visit prior to the last study visit. We will estimate the mean difference in primary and secondary outcomes, comparing (a) patients randomly assigned to
paliperidone to those assigned to placebo, and (b) patients randomly assigned to paliperidone to those assigned to olanzapine. We will then proceed to evaluate the role of these secondary outcomes as mediators allowing for mediator-mediator and treatment-mediator interactions.

**Main Outcome Measure and how it will be categorized/defined for your study:**
We will consider the Social Performance Scale (SPS) measured at the last study visit as the primary endpoint.
Secondary endpoints are: (i) PANSS Factor Scores for positive symptoms (ii) PANSS Factor Scores for negative symptoms (iii) side effects, measured at the visit prior to the last study visit.
All outcome variables will be considered as continuous or count variables.

**Main Predictor/Independent Variable and how it will be categorized/defined for your study:**
In our analyses, assignment to paliperidone, placebo, or olanzapine is by definition assessed at baseline. The primary outcome, Social Performance Scale (SPS), will be derived from assessments at baseline and week 6, or last study visit. We will consider assessments of secondary outcomes at baseline and week 4, or visit prior to last

study visit. These will consist of PANSS Factor Scores for positive symptoms, PANSS Factor Scores for negative symptoms, and number of adverse event reports. Further, we will consider assessments of the Clinical Global Impressions-Severity of Illness Scale for Schizoaffective Disorder (CGI-S-SCA), the Clinical Global Impressions-Change Scale for Schizoaffective Disorder (CGI-S-SCA), Youth Mania Rating Scale (YRMS), 21-item Hamilton Depression Rating Scale, at baseline. These were chosen as a priori known predictors of the primary and secondary outcomes. In our models we will also consider baseline covariates for
age, sex, race, weight (kg), prolactin (ng/mL), and fasting glucose (mg/dL).

**Statistical Analysis Plan:**
Analysis 1: Compare drug effects on the primary outcome, social functioning. We will compare SPS at last visit for each paliperidone dose to placebo or olanzapine. We will use a linear regression model for SPS given treatment status, baseline SPS, PANSS Factor Scores for positive symptoms and negative symptoms, and baseline covariates.
Analysis 2: Compare drug effects on secondary outcomes. The second analysis will compare each paliperidone dose to placebo or olanzapine in terms of: (i) PANSS Factor Scores for positive symptoms (ii) PANSS Factor Scores for negative symptoms (iii) number of side effects at previous to last visit. We will use a multivariate linear regression model for the, potentially correlated, secondary outcomes given treatment status, baseline SPS, PANSS Factor Scores for positive symptoms, PANSS Factor Scores for negative symptoms, and baseline covariates.
Analysis 3: Explaining comparative efficacy of treatment on the primary outcome, social functioning, via the mediating and interactive role of secondary outcomes. The third analysis will involve two steps. In the first step we will compare SPS at last visit between each paliperidone dose and placebo or olanzapine, while adjusting for the secondary outcomes at previous to last visit. We will use a linear regression model for the primary outcome given the secondary outcomes, treatment status, baseline SPS, and baseline covariates. The model will allow for treatment-mediator and mediator-mediator interaction. In the second step, we will estimate direct and indirect effects of treatment on SPS, potentially mediated by the secondary outcomes employing approaches developed by the PI.

**Project Timeline:**
Start date: February 15th 2016.
End date: February 15th 2017.
Analysis completion date: September 15th 2016
Manuscript drafted date: December 15th 2016
Manuscript submitted and results reported back to YODA: February 15th 2017

**Dissemination Plan:**
PAPER 1
Audience: Psychiatric community
Journal: American Journal of Psychiatry, Journal of Clinical Psychopharmacology, Schizophrenia Bulletin, Plos One,
Topic: Explaining the effect of second generation antipsychotics on social functioning via the mediating and interactive role of positive, negative symptoms and side effects.

PAPER 2
Audience: Psychiatric and Statistics community
Journal: Journal of Statistical Software
Topic: R package for longitudinal mediation analysis with multiple, potentially interactive, mediators.

**Bibliography:**
[1] Lieberman, J. A., Stroup, T. S., McEvoy, J. P., Swartz, M. S., Rosenheck, R. A., Perkins, D. O., ... & Hsiao, J. K. (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. New England Journal of Medicine, 353(12), 1209-1223.
[2] Centorrino, F., Masters, G. A., Talamo, A., Baldessarini, R. J., & Öngu?r, D. (2012). Metabolic syndrome in psychiatrically hospitalized patients treated with antipsychotics and other psychotropics. Human Psychopharmacology: Clinical and Experimental, 27(5), 521-526.
[3] Centorrino, F., Goren, J. L., Hennen, J., Salvatore, P., Kelleher, J. P., & Baldessarini, R. J. (2014). Multiple versus single antipsychotic agents for hospitalized psychiatric patients: case-control study of risks versus benefits. American Journal of Psychiatry.
[4] Nasrallah, H., Morosini, P., & Gagnon, D. D. (2008). Reliability, validity and ability to detect change of the Personal and Social Performance scale in patients with stable schizophrenia. Psychiatry research, 161(2),

213-224.
[5] Martin, E. A., Öngu?r, D., Cohen, B. M., & Lewandowski, K. E. (2015). Social functioning and age across affective and nonaffective psychoses. The Journal of nervous and mental disease, 203(1), 37-42.
[6] Burns, T., & Patrick, D. (2007). Social functioning as an outcome measure in schizophrenia studies. Acta Psychiatrica Scandinavica, 116(6), 403-418.
[7] Green, M. F., Olivier, B., Crawley, J. N., Penn, D. L., & Silverstein, S. (2005). Social cognition in schizophrenia: recommendations from the measurement and treatment research to improve cognition in schizophrenia new approaches conference. Schizophrenia Bulletin, 31(4), 882-887.
[8] Valeri, L., & VanderWeele, T. J. (2013). Mediation analysis allowing for exposure–mediator interactions and causal interpretation: Theoretical assumptions and implementation with SAS and SPSS macros. Psychological methods, 18(2), 137.