Principal Investigator

First Name: Karestan
Last Name: Koenen
Degree: PhD
Primary Affiliation: Harvard School of Public Health
E-mail: scz.methods.project@gmail.com
Phone number: 6174324622
Address: 677 Huntington Avenue

City: Boston
State or Province: MA
Zip or Postal Code: 02115
Country: USA

2015-0617

General Information

Key Personnel (in addition to PI): **First Name:** John
Last name: Jackson
Degree: ScD
Primary Affiliation: Harvard University

First Name: Linda
Last name: Valeri
Degree: PhD
Primary Affiliation: Partners Healthcare, Inc.

First Name: David
Last name: Henderson
Degree: MD
Primary Affiliation: Boston University Boston Medical Center

First Name: Erin
Last name: Schnellinger
Degree: BS
Primary Affiliation: Harvard School of Public Health

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 Reactor Program: Open Translational Science in Schizophrenia

coi_jackson_signed.pdf
coi_valeri.pdf
coi_koenen_signed.pdf

coi_henderson_signed_update.pdf
coi_schnellinger.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): 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

Diagnostics for Informative Censoring in Efficacy and Effectiveness Trials of Schizophrenia Therapy

Narrative Summary:
Randomized trials are usually analyzed under the intention-to-treat design where participants are treated as if they fully adhered to their assigned treatment group. Because of the high rate of study dropout in schizophrenia trials, which often exceeds 33%, it is often impossible to carry out an intention to treat analysis. In this study, we will develop statistical diagnostics that describe study dropout, its relation to assigned treatment and patient characteristics. They will be used to assess whether or not the study results are liable to bias, guide statistical decision-making to address study dropout, and assess how such methods perform.

Scientific Abstract:
The gold-standard for analyzing randomized trials is the intent-to-treat design. This is often unattainable in trials of schizophrenia therapy where study dropout often exceeds 33%. When dropout is related to poor efficacy (or emergent side-effects), it is often described as “informative” because it predicts treatment effectiveness (or safety). Moreover, if such dropout differs across treatment arms, then treatment effect estimates are liable to bias. We will develop and apply diagnostics for informative censoring in (i) a short-term placebo-controlled efficacy trial of 6 mg/day or 12 mg/day paliperidone vs. placebo in 361 schizoaffective patients over 6 weeks, and (ii) a long-term comparative effectiveness trial of four atypical antipsychotics vs. perphenazine over 18 months in 1432 patients (Clinical Antipsychotic Trial Intervention Effectiveness study). In both trials we will outline and apply three diagnostics: (1) how censoring relates to both assigned treatment and prior covariates that predict the outcome (2) whether covariates themselves are affected by assigned treatment—an indication that covariate adjustment is insufficient to remove bias (3) the performance of inverse probability weights for censoring to remove bias from study dropout. These metrics will be succinctly reported with intuitive plots that summarize the metrics over person-time. Software and documentation for the Statistical Analytic System (SAS) will be developed and made freely available. This work could greatly aid the transparent reporting and analysis of randomized trials in schizophrenia.

Brief Project Background and Statement of Project Significance:
Randomized trials are considered the gold standard for evaluating therapeutic effects because, on average, they produce comparator groups that are similar. An intent-to-treat analysis preserves the benefit of randomization, so that the crude difference in mean outcome between groups yields an unbiased estimate for the effect of assigned treatment.

It is often difficult to implement a true intent-to-treat analysis in schizophrenia trials because a third or more of patients drop out from studies.[1] Such patients often leave because the therapy did not improve their condition or because they experienced undesirable side-effects. Dropout for these reasons is called ‘informative censoring’ because it predicts outcomes (usually symptom reduction or adverse events). Informative censoring can bias estimates of symptom levels and adverse event rates.[2] Moreover, when it also varies across treatment arms,

informative censoring can bias estimates of treatment effects and also safety. When treatment and factors related to the outcome determine dropout, the treatment-outcome association among those who remain in the study does not reflect the treatment-outcome association for the original population. As a result, the estimated treatment effect will be biased.

Several strategies exist for coping with missing data from study dropout. One practice called “Last Observation Carried Forward” (LOCF) simply imputes missing outcome data from the most recent recorded value. This method is widely used, and even recommended by the Food and Drug Administration, but leads to biased effect estimates.[3] Moreover, this bias is not guaranteed to be conservative for effects comparing two active treatments. Other strategies make assumptions about the dropout mechanism. One of these strategies uses all available data but conditions the analysis on time-varying covariates. Although this method is easy to implement it can bias effect estimates if the time-varying covariates are affected by assigned treatment. Other methods can yield unbiased effect estimates even in this setting, but they are more challenging to implement. Among them are “multiple imputation” and also incorporating “inverse probability of censoring weights” in analyses that use all available data.

Given that study dropout is common in randomized trials for schizophrenia therapy and is a major threat to validity, it is important to determine the nature of informative censoring. Doing so can inform of potential bias and whether advanced statistical methods are necessary to overcome this bias. This knowledge can also be used to evaluate how well statistical methods remove potential bias from informative censoring.

Specific Aims of the Project:
Develop and apply diagnostics for informative censoring in (aim 1) an efficacy trial of oral high and low-dose paliperidone extended release (ER) vs. placebo on symptoms after 6 weeks follow-up, and (aim 2) a long-term comparative effectiveness trial of oral olanzapine, risperidone, quetiapine, and clozapine vs. perphenazine on symptoms after 18 months of follow-up. Specifically, we will (i) describe whether censoring is associated with covariates that (a priori) predict the outcome (ii) assess whether time-varying covariates are affected by treatment assignment (iii) assess residual associations between censoring and prior covariates after re-weighting the data to adjust for informative censoring.

What is the purpose of the analysis being proposed? Please select all that apply. Preliminary research to be used as part of a grant proposal
Other

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
For aim 1 we will include all patients enrolled in the study NCT00397033. The inclusion criteria are: Diagnostic and Statistical Manual - Fourth Edition (DSM-IV) diagnosis of schizoaffective disorder; a total Positive and Negative Symptoms of Schizophrenia (PANSS) score of >= 60; a score of >= 16 on Young Mania Rating Scale (YMRS) or a score of >= 16 on the Hamilton Depression Rating Scale (HAM-D 21). The exclusion criteria are: a primary active mental illness diagnosis other than schizoaffective disorder; patients with first episode psychosis; active substance dependence within previous 6 months; treatment with clozapine within 6 months of randomization; a history of treatment resistance, defined by failure to respond to 2 adequate trials of antipsychotic medication; pregnancy, breast-feeding, or planning to become pregnant. For aim 2 we will include all patients enrolled in the first phase of the Clinical Antipsychotic Trials of Intervention Effectiveness study (CATIE), obtained separately from the National Institutes of Mental Health. We will apply the same inclusion/exclusion criteria as specified in Lieberman et al 2005 N Engl J Med;353:1209-23.[8]

Main Outcome Measure and how it will be categorized/defined for your study:
Our main outcome will be the primary outcome will be the mean difference in the Positive and Negative Syndrome Scale (PANSS) total score ?60 at the end of six-week follow-up (aim 1) or 18-month follow-up (aim 2). It will be categorized as a binary variable. Note that the terms "positive" and "negative" in the scale name refer to types of symptoms e.g. delusions (positive) or emotional withdrawal (negative) which are assessed in two separate subscales. There is also a subscale for general psychopathology. Following Lieberman et al 2005 N Engl J Med;353:1209-23,[8] the total PANSS score is the sum of these three subscales. The total PANSS score usually ranges from 30 to 210. We will dichotomize a patient's total PANSS score as "low" if it is less than 60, and as "high"

if it is 60 or above.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
For aim 1, the independent variable be random assignment to high dose paliperidone extended release (ER), low-dose paliperidone extended release (ER), or placebo. it will be coded as a categorical variable. For aim 2, the independent variable will be random assignment to oral olanzapine, risperidone, quetiapine, clozapine or perphenazine. It will also be coded as a categorical variable.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
For aim 1, we will use time-varying assessments at baseline and weeks 1, 2, 3, and 4. These will consist of PANSS, Clinical Global Impressions-Severity of Illness Scale for Schizoaffective Disorder (CGI-S-SCA), Clinical Global Impressions-Change Scale for Schizoaffective Disorder (CGI-I-SCA), Youth Mania Rating Scale (YRMS), 21-item Hamilton Depression Rating Scale, and number of adverse event reports (all coded as continuous variables). We will also use baseline covariates for age (continuous), sex (binary), race (categorical), weight (kg; continuous), prolactin (ng/mL; continuous), and fasting glucose (mg/dL; continuous). For aim 2, we will use time-varying assessments at baseline and months 1, 3, 6, 9, 12 and 15. These will consist of PANSS, CGI-S-SCA, Quality of Life Scale (QLS), Calgary Depression Rating Scale (CRDS), number of adverse event reports, weight-gain, past-month adherence, and recent hospitalization (all coded as continuous variables). Baseline covariates are age, years on prescription medication, BMI (all continuous), sex, race, marital status, education, employment status, hospitalization status at 3 months before baseline (all binary/categorical).

Statistical Analysis Plan:
In a preliminary step, we will first impute any missing data for uncensored persons (to focus this study on missing data from study dropout). As a first diagnostic, we will, for each study visit, (a) compare the risk of being censored between each paliperidone dose and placebo; (b) compare the mean of each prior time-varying covariate between the censored and uncensored, separately for each assigned treatment. As a second diagnostic, we will, for each study visit, compare the mean of each time-varying covariate among each paliperidone dose vs. placebo. As a third diagnostic, we will compare the weighted risk of being censored between each paliperidone dose and placebo; (b) compare the weighted mean of each prior time-varying covariate between the censored and uncensored, separately for each assigned treatment. These will be estimated using person-time data structures and unweighted (or weighted) generalized linear models for either the covariate or censoring, depending on the diagnostic. All results will be reported graphically as covariate balance plots. The weights will consist of stabilized cumulative inverse probability weights for censoring.[4] A similar analysis strategy will be used for aim 2, except comparisons between each second-generation antipsychotic and perhpenazine will replace the comparisons between paliperidone dose and placebo.

Project Timeline:
Estimated start date: March 1st, 2016. Estimated completion of software: September 1st, 2016. Estimated analysis completion date: November 1st, 2016. We plan to submit the results for publication around February 1st, 2017.

Dissemination Plan:
We will develop flexible SAS macros to implement the methods we will develop and implement in this work. These will be freely made available to the public. This study and the macro will be published in an open-access journal.

Bibliography:
1. Kemmler G, Hummer M, Widschwendter C, Fleischhacker WW. Dropout rates in placebo-controlled and active-control clinical trials of antipsychotic drugs: a meta-analysis. Arch Gen Psychiatry 2005;62(12):1305-12.
2. Daniel RM, Kenward MG, Cousens SN, De Stavola BL. Using causal diagrams to guide analysis in missing data problems. Stat Methods Med Res 2012;21(3):243-56.
3. Fitzmaurice G, Laird N, Ware J. Chapter 17. Missing Data and Dropout: Overview of Concepts and Methods. Applied Longitudinal Analysis, 2011;506-513.
4. Jackson JW. Diagnostics for confounding of time-varying and other joint exposures. Epidemiology 2016 (accepted).
5. Canuso CM, Lindenmayer JP, Kosik-Gonzalez C, Turkoz I, Carothers J, Bossie CA, Schooler NR. A randomized, double-blind, placebo-controlled study of 2 dose ranges of paliperidone extended-release in the treatment of subjects with schizoaffective disorder. J Clin Psychiatry 2010;71(5):587-98.
6. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N

Engl J Med 2005;353(12):1209-23.
7. Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychol Methods 2013;18(2):137-50.
8. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature 2014;511(7510):421-7.
9. Lieberman JA, Stroup TS, McEvoy JP et al. Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia. 2005;353(12):1209-23.