HARVARD CATALYST

THE HARVARD CLINICAL AND TRANSLATIONAL SCIENCE CENTER

OPTICS: Open Translational Science in Schizophrenia

Funded Projects

This initiative of the Harvard Catalyst Reactor Program, which was a follow up to the ReSourcing Big Data Symposium, also offered by Harvard Catalyst's Reactor Program, enabled collaboration with the OPTICS Project. This opportunity allowed qualified investigators access to complete data from clinical trials in schizophrenia (Janssen Pharmaceuticals) and from related observational studies and trials in schizophrenia (NIH-dbGaP; NIMH-CATIE). Funding of up to $50,000 was available to support collaborative analysis of the open-source schizophrenia data sets. The goal of this opportunity was to support collaborations leading to insights about schizophrenia and 1) therapeutic safety and efficacy; 2) disease understanding including natural history, subtypes, etiologies, etc., and 3) statistical methods development.

This funding opportunity was only open to investigators who attended a training/educational event or met with Harvard Catalyst personnel.

Three pilot grants were awarded in amounts of up to $50,000 for each one-year project.

Funding decisions for the OPTICS: Open Translational Science in Schizophrenia pilot grants were announced in December 2015.

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

Principal Investigator: Karestan Koenen, PhD, Harvard School of Public Health

Co-Investigators: David Henderson, MD, Boston University School of Medicine
John Jackson, ScD, Harvard School of Public Health
Linda Valeri, PhD, McLean Hospital

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 has the potential to greatly aid the transparent reporting and analysis of randomized trials in schizophrenia.

Heterogeneous Causal Effects: Drug Exposure & Safety

Principal Investigator: Sharon-Lise Normand, PhD, Harvard Medical School

Understanding antipsychotic risks 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. Despite evidence on the association between second generation antipsychotics and metabolic risk, whether the risk is time-dependent and whether the time-dependency is drug-specific remain unknown. 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. Traditional intention-to-treat analyses of clinical trials provide valid inferences regarding average effectiveness but a regression of outcome on observed cumulative exposure is likely not causal. We exploit methodological advances in two related research fields, causal inference and network meta-analysis, to develop an approach to answer questions involving the relationship between duration of drug exposure and outcomes. We analyze the causal effect of cumulative exposure on a binary outcome for placebo controlled trials and active treatment trials. Using the randomization mechanism as an instrument, we estimate exposure-response curves for different exposure subsets. We then combine the treatment-exposure curves via network meta-analysis using individual participant data that (a) permit assessment of evidence compatibility from direct and indirect comparisons; (b) separate within from between-trial effects; and (c) bolster conclusions within subgroups. Our approach uses the placebo arms of no exposure as the outcome of zero exposure in the active treatment arms. The new methodology

can help reduce bias and uncertainty; and can do so in the presence of patient-level treatment heterogeneity.

Explaining Comparative Efficacy of Antipsychotic Medications for Treatment of Schizophrenia in Short-Term RCT and Comparative Effectiveness Trials: A Causal Mediation Approach

Principal Investigator: Linda Valeri, PhD, McLean Hospital

Co-Investigators: Franca Centorrino, MD, McLean Hospital
Garrett Fitzmaurice, PhD, McLean Hospital
John Jackson, ScD, Harvard School of Public Health

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. Mediation analysis is the study of the role of intermediate endpoints in explaining how a treatment affects the final outcome of interest. The goal of this proposal is to extend and apply causal mediation analysis approaches to quantify the joint effect, potentially synergistic or antagonistic, of intermediate factors that can explain differential efficacy among treatments for schizophrenia.

We plan to investigate mechanisms that could explain comparative efficacy in (a) 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 618 patients, and in (b) a comparative effectiveness trial of four atypical antipsychotics vs. perphenazine over 18 months in 1432 patients (Clinical Antipsychotic Trial of Intervention Effectiveness). 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. This work has the potential to produce important insights on the interplay of symptoms and side effects in explaining the efficacy of second generation antipsychotics from randomized trials in schizophrenia.