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

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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.