Overcoming Temporal Confounding in the Assessment of Therapeutic Equivalence of Brand and Generic Drugs

Lamar Hunt, Irene B. Murimi, Daniel Scharfstein, Ramin Mojtabai, Ravi Varadhan, Jodi Segal

Target Conference: International Society for Pharmacoepidemiology

Background: Generic drugs are required to be bioequivalent to their brand counterparts; yet, the generic approval process does not require demonstration of therapeutic equivalence. The FDA considers that if a generic meets its therapeutic equivalence criteria it can be substituted for its brand counterpart with the full expectation that it will have the same clinical effect and safety profile. While most generics are considered to be therapeutically equivalent to their brand counterpart this is not routinely assessed with a formal statistical evaluation. Methods are needed to assess therapeutic equivalence in situations where questions arise. A primary difficulty is that dates of initiation for brand and generic users largely do not overlap. This positivity violation makes it difficult to adjust for temporal confounding due to secular trends in health outcomes.

Objective: We aimed to develop a method to obtain causal estimates of the effectiveness of a generic compared to a brand product that accounts for temporal confounding in the presence of a positivity violation.

Methods: Using venlafaxine as a case study, we identified new users of brand and generic products within OptumLabs™ Commercial Claims Data from 1994-2016. The primary outcome is treatment failure defined as a switch to a new antidepressant, use of electroconclusive therapy, a psychiatric hospitalization or emergency department visit, a suicide-related encounter or death within the first 9 months of use. We apply regression discontinuity to survival curves with a discontinuity in the probability of initiation to generic at the date when generic becomes available. The survival curves are estimated using G-computation to adjust for time-varying confounding. We also adjust for baseline variables like age, sex, and race.

Results: The method provides a comparison between the survival curves under adherent use of brand and generic, conditional on initiating treatment on the date of generic market entry.

Conclusions: Usual methods for estimating survival curves under adherence to a treatment regime do not result in meaningful comparisons of treatment groups when there is temporal confounding. Our approach builds on these using regression discontinuity to allow for meaningful comparisons. Because brand and generic initiation times often do not overlap, this method is useful for assessing differences in the effectiveness of brand and generic drugs.