Comparative Effectiveness of Disease Modifying Therapies in Multiple Sclerosis using Electronic Health Record Data

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## Abstract

**Background**: Disease-modifying treatments (DMT) reduce relapse rates in multiple sclerosis (MS).

**Objective**: To compare the effectiveness of different DMTs in reducing the risk of relapse in people with MS.

**Design, Setting, and Participants**: We analyzed an EHR cohort of MS patients from Partners Healthcare Systems, a subset of which also belongs to the Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women’s Hospital (CLIMB) registry.

**Main Outcomes and Measures**: We performed estimation of the average treatment effects of two different pairs of DMTs on the one- and two-year risk of relapse using a doubly robust estimator in the semi-supervised setting.

**Results**:

**Conclusion and Relevance**:

**Trial Registration**: N/A

**Funding**:

## Introduction

Multiple sclerosis (MS) is a chronic neurological disease with a high socioeconomic burden [@noteworthy2000medical;@compston2008multiple;@asche2010all;@hartung2015cost]. Since the approval of the first disease-modifying therapy (DMT) in 1993, MS treatment has shifted from primarily managing acute relapses to reducing disease activity and delaying disability as DMTs have become the standard of care for people with MS[@hartung2015cost]. The current approach to MS management emphasizes early DMT initiation to mitigate disease activity and to prevent or postpone long-term disability. However, with over 15 DMTs currently approved by national and international regulatory agencies, each with distinct mechanisms of action, risk profiles, and monitoring requirements, it becomes crucial to perform studies comparing the effectiveness of different DMTs in the treatment of MS.

In this study, we compare the effectiveness of two pairs of DMTs in reducing the two-year relapse rate since DMT initiation among MS patients. We previously integrated research data from the Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women’s Hospital (CLIMB) cohort with electronic health records (EHR) data to develop models of MS outcomes using EHR data (Source). Since EHR data contain evidence of disease activity as well as records of electronic prescriptions, we can harness such information for treatment outcome comparison with the appropriate analytical methods.

### Justification for Drug Comparison

For this study, we compared two pairs of DMTs: (1) rituximab vs. natalizumab, and (2) dimethyl fumarate vs. fingolimod. We chose pairs of drugs that were roughly similar to each other to ensure most equal probability of treatment assignment, given baseline covariates. We justify these two pairs of drugs using the following: (1) rituximab and natalizumab are both infusion drugs and considered “high-efficacy”; (2) dimethyl fumarate and fingolimod are both oral drugs and considered “standard-efficacy.”

## Methods

### Study Population

In this study, we obtained electronic health record data of over 5000 patients from Partners Healthcare Systems with at least one MS-related International Classification of Disease 9th/10th edition (ICD-9/10) code (340, 323, or 341). A subset of the patients also belongs to the Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women’s Hospital (CLIMB) registry, containing additional adjudicated outcomes of 2380 patients including relapse status over time.

### Treatment Assignment and Baseline Covariates

For both CLIMB and non-CLIMB patients, we defined treatment group and date of treatment initiation to be the drug and encounter date, respectively, corresponding to the first codified RxNorm prescription appearance of either drug within a pair in the EHR. We then compiled demographic information (i.e., race and sex), other clinical variables (i.e., age at first MS ICD code, follow-up duration, duration of prior DMT treatment), and occurrence counts of MS-related codified variables derived from diagnostic billing codes (ICD-9/10), procedural codes (Current Procedural Terminology, CPT), and concept unique identifiers (CUI) as a measure of healthcare utilization (i.e., total number of ICD codes during entire follow-up duration, total number of ICD codes in the 3 months prior to treatment initiation, adjusted frequency of ICD code and CUI for MS in the 3 months prior to DMT start). Follow-up duration was defined as the time period between date of occurrence of first of any ICD code in EHR and time of treatment initiation.

\*\*We also included derivatives of billing codes (e.g., annualized ICD-9 code for MS) - edit this

### Statistical Analysis

To estimate average causal treatment effect, we utilized the doubly-robust, semi-supervised estimator outlined in Cheng et al. (2018). To do this, we fit a propensity score model, to model the probability of treatment, and a regression model, to model the two-year relapse probability, both including the baseline covariates outlined above. For patients not included in the CLIMB cohort, we imputed their two-year relapse probabilities using the LASSO-Hidden Markov logistic regression model built \*\*via previous research in our group, which takes ICD codes, CPT codes, and CUIs as covariates.

## Results

### Demographics

## Discussion

## Acknowledgments

## Funding

## [1] "LASSO done"  
## [1] "HMM done"

## Results

### Estimation of Average Treatment Effects

## [1] "Estimate using only CLIMB:"

## [1] 0.07383178

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## [1] "95% confidence interval"

## 2.5% 97.5%   
## -0.01613858 0.17177270

## [1] "Significance"

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## FALSE

## [1] "Empirical distribution summary"

## Min. 1st Qu. Median Mean 3rd Qu. Max.   
## -0.59340 0.04604 0.07821 0.07831 0.11061 0.60860

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## [1] "95% confidence interval"

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## [1] "Significance"

## 2.5%   
## FALSE

## [1] "Empirical distribution summary"

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