Using Multiple Imputations And Dynamic Weighted Survival Modeling To Develop An Individualized Treatment Rule For The Choice Of An Antidepressant Drug

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Joint work with Dr. Erica E.M. Moodie and Dr. Susan M. Shortreed

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In previous work

In English data from the Clinical Practice Research Datalink (CPRD), we looked for important tailoring variables (i.e., effect modification) to:

- Maximize time to a severe depression-related outcome (Coulombe et al., 2021)
- Minimize "detrimental weight changes" (Coulombe et al., 2023)

We did not find any "good" tailoring variable for the choice of an antidepressant drug, or a class.

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- We focus on the choice between selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs)
- Information on **patient health questionnaires** (PHQ)

PHQ questionnaire (a validated tool)

- The DSM 5th version (Diagnostic and Statistical Manual) is a classification tool for common mental disorders
- The PHQ scores each of the 9 depression-related items from the DSM from 0 (not at all) to 3 (nearly every day)

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  - PHQ first 8 items (**PHQ-8**) ranging from 0 to 24, and
  - **PHQ-9i**, the 9th item, which focuses on suicidal ideation or self-harm, ranging from 0 to 3

(Kroenke et al., 2001)

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Notation:

- T_i the survival time for individual i and A_i a binary exposure,
- δ_i the indicator of experiencing the event before the end of study,
- $\mathbf{X}_i^{\psi}$ the potential effect modifiers,
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Suppose the accelerated failure time model:

$$\mathbb{E}[\log T_i | A_i, \mathbf{X}_i] = f\left\{\mathbf{X}_i^{\beta}; \boldsymbol{\beta}\right\} + A_i \boldsymbol{\psi}' \mathbf{X}_i^{\psi}$$

with the "treatment-free model" $f\left\{\mathbf{X}_i^{\beta}; \boldsymbol{\beta}\right\}$ and the "blip" $\boldsymbol{\psi}' \mathbf{X}_i^{\psi}$.

In the case of a one-stage treatment rule, it corresponds to solving the following equations:

$$U(\boldsymbol{\beta}, \boldsymbol{\psi}) = \sum_{i=1}^{n} \int_0^{\tau} w_i \begin{bmatrix} \frac{\partial f\left\{\mathbf{X}_i^{\beta}; \boldsymbol{\beta}\right\}}{\partial \boldsymbol{\beta}} \\ A_i(t)\mathbf{X}_i^{\psi} \end{bmatrix} \left[\log(T_i) - f\left\{\mathbf{X}_i^{\beta}; \boldsymbol{\beta}\right\} - A_i(t)\boldsymbol{\psi}'\mathbf{X}_i^{\psi}\right] \delta_i = 0.$$

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The weights w_i must satisfy a balancing condition (Theorem 1, Wallace and Moodie).

In Simoneau et al., they proposed the use of inverse probability of censoring weights to account for informative censoring multiplied by overlap weights (Li et al., 2018).

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Idea: to borrow information from previous months and baseline to impute future values.

Data

- We gathered a cohort of patients, 13 years or older, with a diagnosis for depression who initiated ADs between 2008-2018 (around 90K patients)
- We focused on the first year of follow-up (12 months). Creation of monthly variables: $PHQ8_m$, $PHQ9i_m$, weight_m, $m = 1, ..., 12$

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- We gathered a cohort of patients, 13 years or older, with a diagnosis for depression who initiated ADs between 2008-2018 (around 90K patients)
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- Other variables available:
  - demographics (age, sex, race and ethnicity, insurance type, etc.);
  - medication and treatment (psychotherapy, antipsychotics, etc.); and
  - outcomes (PHQ-8, PHQ-9i, suicide attempt, self-harm, weight, etc.).
- Other longitudinal variables can be transformed into monthly indicators (such as initiating psychotherapy during month j, $j = 1, ..., 12$)

Time-varying variables that were created:

- 1) Initiation and 2) continuation of SGA or FGA
- 1) Initiation and 2) continuation of psychotherapy
- End of the initiating treatment
- Adding a second medication during that month
- Ending the second medication
- Indicator of self-harm diagnosis, death, death by suicide, hospitalization for depression
- Psychiatric diagnoses: Autism spectrum disorder, anxiety, PTSD, schizophrenia, other psychosis, bipolar disorder, OCD, opioid use disorder, personality disorder, sedative use disorder that occurred anytime before
- Indicator of at least one psychiatric contact on a given month

Imputation

Sequential approach with multiple imputations with chained equations (MICE):

- Impute baseline variables first
- Impute month 1 data using the baseline information and time-varying variables measured at month 1
- Impute month j data ($j = 2, ..., 12$) using the baseline information + PHQ-8, PHQ-9i and weight imputed at month $j - 1$ and time-varying variables from month j

We created 25 such imputed datasets.

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- Post-processing and censoring

Tailoring variables (and confounders)

- Age, sex, race and ethnicity, weight at cohort entry, tobacco use, Charlson comorbidity index[1]
- Psychotherapy (previous year)
- Anxiety or generalized anxiety disorder (GAD)
- Indicator of other psychiatric diagnosis at cohort entry (autism spectrum, obsessive-compulsive, bipolar, personality, sedative use, or alcohol use disorders, schizophrenia, PTSD[2])
- Number of hospit. for mental health diagnosis or suicide attempt or self-harm (previous 6 months)
- Number of antidepressant drugs in previous 5 years
- Had a baseline PHQ score
- PHQ-8 and PHQ-9i at baseline

[1] categorizes comorbidities based on the risk of mortality

[2] post-traumatic stress disorder

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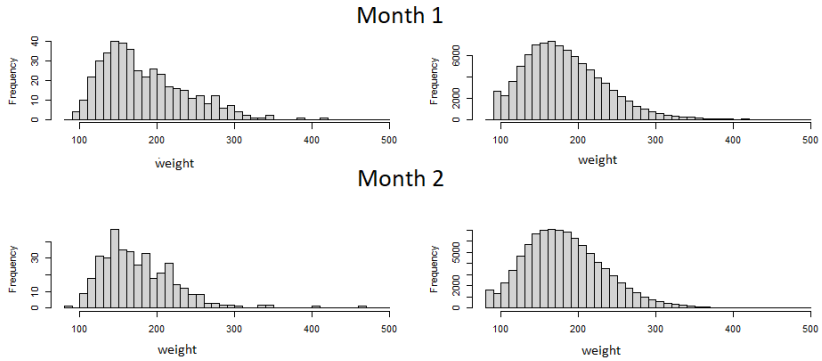
- Baseline covariates: Between 0% and 24% missing values
- PHQ-8 and PHQ-9i at baseline: 58 % missing
- PHQ: Between 86% and 99% missing between months 1 and 12 (roughly 3/4 of the patients have all PHQ missing from months 1 to 12)
- **However**, the correlation among PHQ scores across months was relatively high (e.g., 0.75 between months 2 and 3 when keeping complete cases)
- Naturally, months 4, 5, 7, 8, 10, and 11 not corresponding to the measurement schedule of PHQ-9 contained a lot of missing data.

Diagnostics

Imputation diagnostics, e.g.:



and causal inference - Before (left) and after imputation (right):

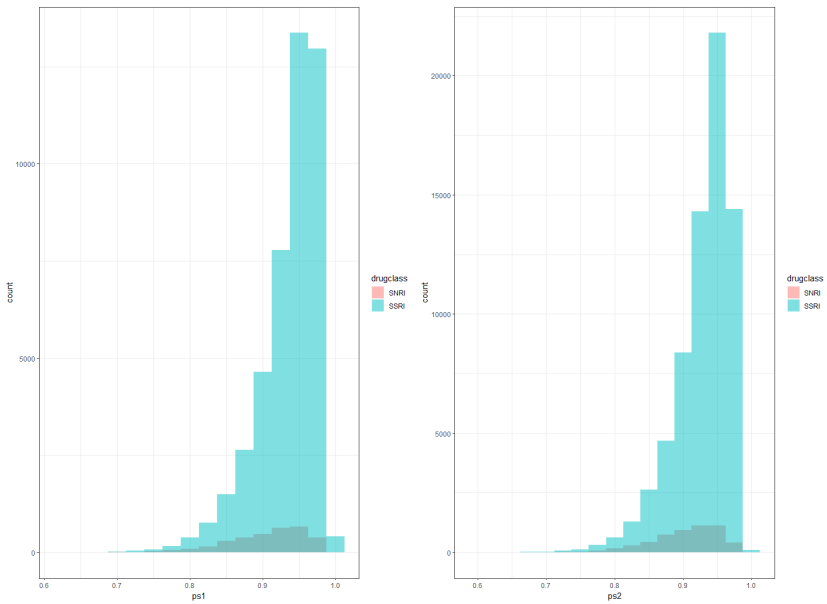


Figure 1: Overlap in the propensity score distributions. Blue: SSRI, Pink: SNRI

Time to 50% PHQ reduction - SSRI vs SNRI

Out of 25 imputed datasets:

- Sex (3)
- Anxiety or GAD (2)
- Diagnosis for a psychiatric diagnosis other than anxiety, GAD (2)
- No. of mental health inpatient stays in previous 6 months (2)
- No. mental health visits in previous 5 years (2)
- Had baseline PHQ (2)
- Psychotherapy (1)
- No. prior AD in previous 5 years (1)

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- Smoothness in the PHQ mean and investigation of interactions for future work (congeniality)
- Investigate the causal inference assumptions

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