TARGETED LEARNING IN OBSERVATIONAL STUDIES WITH MULTI-LEVEL TREATMENTS: AN EVALUATION OF ANTIPSYCHOTIC DRUG TREATMENT SAFETY FOR PATIENTS WITH SERIOUS MENTAL ILLNESSES

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We investigate estimation of causal effects of multiple competing (multi-valued) treatments in the absence of randomization. Our work is motivated by an intention-to-treat study of the relative metabolic risk of assignment to one of six commonly prescribed antipsychotic drugs in a cohort of adults with serious mental illness. Doubly-robust estimators of multi-level treatment effects with observational data, such as targeted minimum loss-based estimation (TMLE), require that either the treatment model or outcome model is correctly specified to ensure consistent estimation. However, common TMLE implementations estimate treatment probabilities using multiple binomial regressions rather than a single multinomial regression. We implement a TMLE estimator that uses multinomial treatment assignment and ensemble machine learning to estimate average treatment effects. Our implementation achieves superior coverage probability relative to the binomial implementation in simulation experiments with varying treatment propensity overlap and event rates. An evaluation of the causal effects of six antipsychotic drugs on the risk of diabetes or death illustrates our approach. We find a relative safety benefit of moving from a second-generation antipsychotic thought to have more favorable metabolic risk profile relative to other second-generation drugs to a less commonly prescribed first-generation antipsychotic known for having a low rate of metabolic disturbance.

1. Introduction. Methods for and applications of causal inference in the setting of multiple competing (multi-valued) treatments are relatively limited compared to those for binary treatments. Multi-valued therapies to treat a single condition are often available in usual care settings because as new treatments enter the market, only a few exit. This is particularly common for prescription drug treatments because of competition among branded drugs, patent expirations leading to generic equivalents, and minor reformulation changes.

Several estimators have been proposed for estimating causal effects in observational data settings with multi-valued treatments, although applications of these estimators have been limited to a small number of treatment levels and a focus on continuous outcomes. The propensity score, the probability of receiving a treatment given the observed covariates (Rosenbaum and Rubin, 1983), has played a central role in causal inference. For instance, inverse probability weighted estimators, which weight outcomes by the inverse of the propensity score to units in each treatment group with the goal of matching the covariate distribution

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†See Linden et al. (2016) and Lopez and Gutman (2017) for comprehensive reviews.
of a target population, is a common strategy for binary treatments (Hirano and Imbens, 2001; Frölich, 2004; Li and Greene, 2013; McCaffrey, Lockwood and Setodji, 2013; Austin and Stuart, 2015). Two decades ago, Imbens (2000) and Imai and van Dyk (2004) generalized the propensity score framework from the binary treatment setting to the setting of multi-valued treatments. Yang et al. (2016) proposed subclassification or matching on the generalized propensity score to estimate pairwise average causal effects, and Li and Li (2019) introduce generalized overlap weights for pairwise comparisons that focus on the target population with the most covariate overlap across multiple levels of treatment. Similar to other propensity score methods, these generalized approaches depend on the correct specification of the treatment model and do not eliminate bias from unmeasured confounding. A different approach proposed by Bennett, Vielma and Zubizarreta (2020) does not require estimation of a generalized propensity score. Rather, the authors directly match on the covariates using mixed integer programming methods to balance each treatment group to a representative sample drawn from the target population. This approach has the advantage of directly balancing covariates without the need to specify a statistical model but is difficult to implement when adjusting for a large number of confounders as is frequently necessary.

Doubly-robust estimators require that either the treatment model or outcome model is correctly specified to ensure consistent estimation (Bang and Robins, 2005; Kang and Schafer, 2007; Rose and Normand, 2019). Targeted minimum loss-based estimation (TMLE) is a widely-used doubly-robust estimator that permits data-adaptive estimation strategies to improve specification of models for causal inference (van der Laan and Rubin, 2006; van der Laan and Rose, 2011; van der Laan and Gruber, 2012; Muñoz and van der Laan, 2012; Balzer et al., 2016; Schuler and Rose, 2017; Benkeser et al., 2017). The TMLE, which is doubly robust for both consistency and asymptotic linearity, reweights an initial estimator with a function of the estimated generalized propensity score. The use of nonparametric methods helps avoid model misspecification which is likely to occur in high-dimensions (Lee, Lessler and Stuart, 2010; Austin, 2012; Pirracchio, Petersen and van Der Laan, 2015). An additional attractive feature of TMLE is its simple extension to longitudinal data by iteratively (at each time point) fitting the outcome and treatment models (Decker et al., 2014; Schnitzer et al., 2014; Petersen et al., 2014; Kreif et al., 2017; van der Laan and Rose, 2018; Tran et al., 2019; Sofrygin et al., 2019; Schomaker et al., 2019; Díaz et al., 2021) and its use for for a variety of outcome types (e.g, see Stitelman, De Gruttola and van der Laan (2012)). Despite these advantages, few researchers have used TMLE for causal inference in multi-level treatments settings. An exception is Cattaneo (2010) who focuses on TMLE for inferences in the multi-valued treatment setting using a generalized method of moments approach that is also doubly-robust and semiparametrically efficient. In this paper, we combine TMLE with a machine learning ensemble to estimate the causal effects of multi-valued treatments. Our study is the first to our knowledge to evaluate TMLE in the multi-level treatment setting in simulations, and the first to provide doubly-robust estimates of relative safety of antipsychotic drugs.

Our paper is motivated by an intention-to-treat study of the relative metabolic risk of assignment to one of six commonly prescribed antipsychotic drugs in a cohort of adults with severe mental illnesses: schizophrenia, major depressive disorder, or bipolar disorder. The number of potential treatments complicates inferences along several dimensions. First, meeting the weak unconfoundedness assumption that treatment assignment is independent of the potential outcomes conditional on covariates requires the availability of a large number of covariates to differentiate among the treatment choices, which becomes challenging as the number of treatments increase. Second, there are a number of options for defining a target population. We focus on the population of individuals eligible for any of the six drugs. Finding individuals from all treatment groups in subsets determined by the covariate space becomes increasingly difficult as the number of treatment choices increases. Regression, many
machine-learning algorithms, propensity-score based approaches, and matching methods often extrapolate over areas of the covariate space with no common support (referred to as areas of "non-overlap"). To circumvent non-overlap, a common strategy discards units with estimated propensity scores near the boundaries (Crump et al., 2009; Yoshida et al., 2019). However, these “trimming” methods are sensitive to the choice of cut-off value and often discard a large proportion of the sample, potentially introducing bias to the estimator of the treatment effect. An alternative approach that maintains the sample size winsorizes extreme estimated treatment probabilities by setting probabilities exceeding a specified threshold to the threshold (Cole and Hernán, 2008; Lee, Lessler and Stuart, 2011). Third, in the observational setting, it is common for the probability of assignment to vary considerably across treatment arms which will impact the precision of estimates, and with more treatment levels, the observed number of individuals in any treatment arm may be small. Fourth and related, as in any study, if the outcome rate is low, finding differences among treatments is challenging, and this difficulty is increased as the number of treatments is expanded.

Our paper contributes to the causal inference literature along several dimensions. First, we add to the sparse literature on inference for multi-valued treatments with a focus on implementation. We review the assumptions required to make causal inference in the multi-valued treatment setting, define several key causal parameters, and describe approaches for assessing the validity of the common support assumption. Second, we develop and implement a TMLE estimator that uses multinomial treatment assignment. Surprisingly, all peer-reviewed implementations of TMLE for multi-level treatments use a series of binomial treatment assignments. McCaffrey, Lockwood and Setodji (2013) suggest a binomial assignment approach, noting that while the sum of the estimated probabilities across all treatment levels may not equal one as it would if using a multinomial model, this poses no problem for weighted estimators because only the estimated probability of the treatment actually received for each individual is used. However, this approach will result in a loss in efficiency because the wrong treatment model is estimated and complicates the assessment of common support because estimates for all treatment levels for each unit are required. Third, we evaluate the comparative performance of the current implementations and our approach of TMLE through numerical studies. While theory dictates that TMLE estimators will be unbiased if only one model is misspecified, efficiency will suffer. Our study of the operating characteristics of the doubly-robust estimator using data-adaptive techniques in the multi-value setting provides insights into the robustness of inferences. We vary the number of treatment levels, sample size, areas of common support, and treatment effect sizes. Simulations demonstrate that our implementation achieves comparable bias and superior coverage compared to the existing implementations. Fourth, our numerical studies never correctly specify the outcome models and sometimes misspecify both outcome and treatment models; rather, we adopt machine learning approaches for each model. Prior numerical studies (Yang et al., 2016; Li and Li, 2019) have focused on parametric treatment models. Our strategy is in line with what researchers are likely to do when faced with many treatments and many covariates. Fifth, we apply the estimators to the antipsychotic drug data to determine the safety of each drug and assess heterogeneity of safety in subgroups defined by diagnosis. The sample sizes and covariates in our application are common in health services research, thus reflecting the type of observational data likely encountered by other researchers.

2. Doubly-robust Estimators for Multi-valued Treatments.

\footnote{Inferences are made conditional on the study population. Thus, we do not assume that our population is a sample from a larger population.}
2.1. Notation and Setup. We observe a sample of size \( n \) in which each subject has been assigned to one of \( J \) treatment levels. For each subject \( i \), \( y_i \) is the observed outcome, \( x_i \) is a \( p \times 1 \) vector of covariates measured prior to treatment initiation with \( x \in \mathbb{X} \), and \( a_i \in A \) is the observed treatment level for subject \( i \), with \( a \) the length-\( n \) vector of treatment assignments, and \( A = \{ j = 1, 2, \ldots, J \} \) the collection of possible treatment levels. The sample size for each treatment level \( j \) is denoted \( n_j \), with \( \sum_{j=1}^{J} n_j = n \). For each subject we observe \( o_i = (y_i, a_i, x_i) \) arising from some probability distribution \( P \).

Let the binary treatment indicator \( d_i(j) = 1 \) if \( a_i = j \) and 0 otherwise. The potential outcomes under treatment level \( j \) is \( y_i(j) \) so the observed outcome is \( y_i = \sum_{j=1}^{J} d_i(j)y_i(j) \). We denote the conditional probability subject \( i \) is assigned treatment level \( j \), \( \Pr(a = j \mid x_i) \), by

\[
p_j(x_i) \text{ such that } \sum_{j=1}^{J} p_j(x_i) = 1.
\]

For causal inference in the multi-valued treatment setting, Imbens (2000) refers to \( p_j(x_i) \) as the generalized propensity score. We let \( \mu_j = \mathbb{E}\{y(j)\} \) denote the marginal mean outcome and \( e_j(x_i, \mu_j) = \mathbb{E}(y(j) \mid x) \) denote the conditional mean outcome. We make the following assumptions, the first two explicitly made in Imbens (2000).

**Assumption 1.** Weak Unconfoundedness. The distribution of the potential outcome is independent of treatment assignment, conditional on the observed covariates, for each level of treatment \( j \).

\[
y(j) \perp\!\!\!\!\perp d(j) \mid x.
\]

The unconfoundedness assumption is weak because the conditional independence is assumed at each level of treatment rather than joint independence of all the potential outcomes. This assumption is not testable and typically justified on substantive grounds. Bolstering its validity requires conditioning on many covariates, making the dimensionality of \( x \) large. The weak unconfoundedness assumption leads to

\[
e_j(x_i, \mu_j) = \mathbb{E}(y(j) \mid x) = \mathbb{E}(y_i \mid x).
\]

In the antipsychotic data, six-month medical history information prior to the index antipsychotic fill is available, including all drugs filled by the subject and billable medical services utilized. Demographic information that also includes place of residence is known. All subjects have the same health insurer, although how the benefits are managed may differ across states. Nonetheless, treatment preferences, results of diagnostic tests, and some information known only to physicians, such as the subjects’ body mass index, are unknown.

**Assumption 2.** Positivity. For all possible \( x \), there is a positive probability that someone with the covariate pattern could be assigned to each \( j \).

\[
\Pr(a = j \mid x) > 0, \quad \forall \ x \in \mathbb{X} \text{ and } a \in A.
\]

The positivity assumption is required to avoid extrapolating treatment effects for covariate patterns where there are no observations for some treatments. Structural violations occur if subjects with specific covariate patterns cannot receive one of the treatment levels, due to, in our case, absolute contraindications. However, practical violations of the positivity assumption could occur due to finite sample sizes. While the positivity assumption is testable in high dimensions, detecting violations is challenging (Petersen et al., 2012).

**Assumption 3.** Stable unit treatment value assumption (SUTVA). (i.) The potential outcome for any subject does not vary with treatment assignments to other subjects; and (ii.), a single version of each treatment level exists:

\[
y_i(a_1, a_2, \ldots, a_n) = y_i(a_i).
\]
This assumption asserts that the potential outcomes for a subject is caused only by the treatment the subject receives and not by treatments received by other subjects; e.g., no spill-over effects. The no interference assumption is plausible for the treatment examined in this paper — a subject’s diabetes status cannot be caused by another subject’s antipsychotic treatment assignment. The second part of SUTVA, which ensures that a single version of each treatment level exists, may be violated if treatment levels are loosely defined. In our example, we include both oral and injectable versions of the same drug, and some may argue that these two versions are different. However, biologically there is no difference and it is only adherence to the drug that varies. The SUTVA implies the following assumption

**Assumption 4. Consistency.** The potential outcome for a subject under the subject’s observed treatment is their observed outcome.

If $a_i = j$ then $y_i(j) = y_i$.

The consistency assumption is not testable.

2.2. **Causal Parameters.** Our primary inferential goal is estimation of the difference in the average outcome if everyone was treated with any other treatment $j^*$ and the average outcome if everyone was treated with a reference treatment $j$. Thus, the causal parameter is

**Definition 1.** Average Treatment Effect (ATE). The average effect caused by any other treatment $j^*$ over the reference treatment $j$ in the sample.

\[
ATE_{j, j^*} = E(y(j^*) - y(j)) = \mu_{j^*} - \mu_j; \quad j^* \neq j.
\]

In our study, we are interested in understanding how patients treated with any antipsychotic other than the reference drug ($j^*$) would fare if they were instead treated with a reference drug ($j$) with a more favorable metabolic risk profile. Evidence suggests that switching to potentially safer drugs has the potential to improve some metabolic indices without causing significant psychiatric deterioration (Mukundan et al., 2010).

Frequently, researchers are interested in understanding whether treatment effects vary among specific patient subgroups. In this setting, the causal parameter is conditional average treatment effect,

**Definition 2.** Conditional Average Treatment Effect (CATE). Letting $C$ denote a subset of the covariate space, the CATE is the average effect in the sample, treating $x \in C$ as fixed.

\[
CATE_{j, j^*, x \in C} = E(y(j^*) - y(j) \mid x \in C) = \mu_{j^*}(x) - \mu_j(x); \quad j^* \neq j.
\]

The CATE is often examined in randomized trials as an exploratory tool for determining the homogeneity of treatment effects across subgroups. In our study, those diagnosed with schizophrenia are of particular interest given that there are no effective treatment alternatives and most individuals with this illness require antipsychotic drugs throughout their entire lives.

2.3. **The Targeted Minimum-Loss Based Estimator.** The TMLE is an estimator that updates an initial estimate of a parameter with a correction determined by optimizing the bias-variance trade-off using a loss function for the causal parameter. The estimator is asymptotically linear with influence curve equal to the canonical gradient.
2.3.1. Average Treatment Effect. We focus on estimation of the marginal mean outcome for each treatment level $j$, $\mu_j$, and collect estimators into a vector. This strategy is useful for making joint inferences between and across the multiple treatment levels as demonstrated by Cattaneo (2010). When Assumptions (1) – (4) are met, van der Laan and Rubin (2006) demonstrate that the efficient influence curve for $\mu_j$ is

$$IC_j(a_i) = \frac{d(j)}{p_j(x)} (y - e_j(x, \mu_j)) + e_j(x, \mu_j) - \mu_j,$$

leading to a doubly-robust asymptotically efficient estimator for the marginal mean

$$\hat{\mu}_j = \frac{1}{n} \sum_{i=1}^n \hat{e}^1(x_i, \mu_j) = \frac{1}{n} \sum_{i=1}^n h^{-1} \left( h(\hat{e}^0(x_i, \mu_j)) + \hat{e}_j d_i(j) \right).$$

In equation (2), $\hat{e}^1(\cdot)$ and $\hat{e}^0(\cdot)$ are final and initial estimates of $\mathbb{E}(y(j) \mid x)$, respectively, $h$ is a link function, and $(\hat{e}_j d_i(j)) / p_j(x)$ is a correction that targets the unknown parameter $\mu_j$. Parametric or nonparametric estimators for $e_j(x, \mu_j)$ and $p_j(x)$ are substituted into Equation (2). The term $\hat{e}_j$ is obtained by estimating a parametric regression model

$$h (\mathbb{E}(y_i = 1 \mid a_i, x_i, \epsilon)) = h (\hat{e}^0(x_i, \mu_{a_i})) + \sum_{j=1}^J \epsilon_j \frac{d_i(j)}{p_j(x_i)},$$

and fixing the coefficient of $h (\hat{e}^0(x_i, \mu_{a_i}))$ at one. The correction is determined using a log-likelihood loss function to minimize the bias of $\hat{\mu}_j$. The estimator for the variance of $\hat{\mu}_j$, $V(\hat{\mu}_j)$, is

$$\frac{1}{n} \sum_{i=1}^n \hat{IC}_j^2(a_i) = \frac{1}{n} \sum_{i=1}^n \left\{ \frac{d_i(j)}{p_j(x_i)} (y_i - \hat{e}^1(x_i, \mu_j)) + \hat{e}^1_j(x_i, \mu_j) - \hat{\mu}_j \right\}^2.$$

Letting $\mu = \{\mu_1, \mu_2, \ldots, \mu_J\}^T$ denote the $J \times 1$ vector of marginal mean outcomes, then inference is made using $\sqrt{n}(\hat{\mu} - \mu) \rightarrow N_J(0, V)$. Each marginal mean outcome can be estimated separately yielding $\hat{\mu}$ with variance,

$$\hat{V}(\mu) = \frac{1}{n} \sum_{i=1}^n \left( \hat{IC}_1, \hat{IC}_2, \ldots, \hat{IC}_J \right)^T \left( \hat{IC}_1, \hat{IC}_2, \ldots, \hat{IC}_J \right).$$

The ATE can be estimated using linear contrasts. For example, if interest centers on the ATE of treatments 1 and 2, then let $c = (1, -1, 0, 0, \ldots, 0)$ denote a $1 \times J$ contrast vector. The estimated ATE is then $c\hat{\mu}$ having estimated variance $c\hat{V}(\mu)c^T$. In the software implementation of TMLE (Gruber and van der Laan, 2012), each $p_j(x_i)$ is modelled separately as a Bernoulli random variable, estimating the probability of receiving treatment level $j$ relative to all other treatment levels. Thus, equation (3) is replaced by

$$h (\mathbb{E}(y_i = 1 \mid a_i, x_i, \epsilon)) = h (\hat{e}^0(x_i, \mu_{a_i})) + \epsilon_j \frac{d_i(j)}{p_j(x_i)} + \epsilon_{-j} \frac{d_i(-j)}{p_{-j}(x_i)}$$

where the subscript $-j$ refers to all treatments except $j$. In this strategy, there is no guarantee that $\sum_j p_j(x_i) = 1$ and the estimates of $\epsilon_j$ may differ from those obtained using Equation (3).

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3 A practical reason for this modeling decision is that the implementation of the super learner in van der Laan, Polley and Hubbard (2007) does not support multinomial outcomes.
2.3.2. Conditional Average Treatment Effect. The TMLE estimator of the conditional mean under treatment level $j$, for those with $x \in C$ is

$$
\hat{\mu}_{j,x} \in C = \frac{1}{n_x} \sum_{i: x \in C} \hat{e}^1(x_i, \mu_j),
$$

that is, the average among those having $x \in C$, for a sample of size $n_x$. This estimator characterizes the average outcome among individuals characterized by observed covariates, treating the covariates as fixed. The estimator for the variance of $\hat{\mu}_{j,x} \in C$ is

$$
\frac{1}{n_x} \sum_{i=1}^{n_x} \left\{ \frac{d_i(j)}{\hat{p}_j(x_i)} \left( y_i - \hat{e}^1_j(x_i, \mu_j) \right) + \hat{e}^1_j(x_i, \mu_j) - \hat{\mu}_{j,x} \in C \right\}^2.
$$

3. Implementation. We employ the super learner (van der Laan, Polley and Hubbard, 2007; Polley and van der Laan, 2010; Polley, Rose and van der Laan, 2011) for estimating the outcome and treatment models in order to minimize the bias resulting from model misspecification. The super learner is an ensemble method that uses cross-validation to select the optimal weighted average of estimators obtained from a pre-selected library of classification algorithms. Optimality is defined in terms of a pre-specified loss function (Kreif et al., 2015). We rely on the sl3 package in R for constructing the treatment and outcome model ensembles, as it supports multinomial classification algorithms and a multinomial loss function for the super learner (Coyle et al., 2021). When estimating a multinomial treatment model, the super learner combines the predictions from multiple classification algorithms by multinomial linear regression. For binomial treatment or outcome models, the super learner combines algorithmic predictions by binomial logistic regression. The super learner weights are optimized by minimizing a negative log-likelihood loss function that is cross-validated with $V$ folds each consisting of a validation set and a training set. The routine for optimizing the super learner weights, given the loss function and combination function, is nonlinear optimization using Lagrange multipliers (Ghalanos and Theussl, 2012).

We use a variety of flexible and nonparametric classification algorithms for the treatment and outcome model ensembles. These algorithms include gradient boosting (Chen et al., 2015); random forests with varying forest sizes (Wright and Ziegler, 2017); $\ell_1$-penalized lasso regression; $\ell_2$-penalized ridge regression; and elastic net regressions weighting the $\ell_1$ penalty at $\alpha \in \{0.25, 0.50, 0.75\}$ and the $\ell_2$ penalty at $1 - \alpha$ (Friedman et al., 2021). The penalized regressions internally perform $V$-fold cross validation to select the optimal regularization strength. Table C1 in Supplement C provides further information on the classification algorithms and their hyperparameters.

3.1. Positivity and Common Support. The assessment of the positivity assumption in the setting of multi-valued treatments is challenging due to the dimensionality of the treatment variable. One suggested diagnostic measure is the effective sample size associated with each treatment level.

**Definition 3. Effective Sample Size (ESS).** The $ESS$ is a measure of the weighted sample size for treatment level $j$ defined as

$$
ESS_j = \frac{\left( \sum_i^n d_i(j) w_j(x_i) \right)^2}{\sum_i^n d_i(j) w_j(x_i)^2}, \quad \text{with} \quad \sum_j \hat{p}_{ij}(x_i) = 1, \quad \text{and} \quad w_j(x_i) = 1/\hat{p}_{ij}(x_i).
$$

Following the guidelines of Phillips et al. (2022) on the choice of $V$ depending on the sample size, we use $V = 2$ folds in the numerical studies for computational feasibility and $V = 5$ in the empirical application.
Small values of the ratio of $ESS_j/n_j$ indicate weak overlap among the treatment groups (McCaffrey et al., 2013). Comparison of this metric among different estimators provides a rough measure of the amount of information in the sample used to estimate the marginal mean outcome.

4. Numerical Studies. We conduct extensive numerical studies to assess operating characteristics of the various estimators in the finite sample-size setting. We follow closely the simulation design of Yang et al. (2016), who examined multi-valued treatments but focused on continuous outcomes. This particular design has also been used in the simulation study of Li and Li (2019) to assess the comparative performance of matching, weighting, and subclassification estimators using generalized propensity scores.

We generate potential outcomes under each of $J = 6$ treatments assigned to $n = 6000$ individuals and estimate ATEs for each of the 15 pairwise comparisons, which we denote $\lambda_{j,j^*}$. We iterate this process $H = 1000$ times, and calculate three performance metrics for each simulation run $h$: absolute bias, coverage probability of 95% confidence intervals, and confidence interval widths. Because estimators are compared on the same generated dataset in each simulation run, differences between estimators reflect meaningful differences in performance rather than variability in the data generation.

We evaluate three different TMLE implementations for the treatment model: (i.) TMLE using multinomial treatment probabilities estimated with super learner; (ii.) TMLE using multinomial treatment probabilities estimated using a parametric multinomial regression model, which we denote GLM; and (iii.) TMLE using binomial treatment probabilities estimated with super learner. The outcome model is always estimated with TMLE using binomial outcome probabilities estimated with super learner for implementations (i.) and (iii.) or a GLM for implementation (ii.). Implementation (i.) is the approach we use in the application because it reflects the multinomial stochastic structure of the treatment probabilities and has the advantage of nonparametric estimation via super learner. We include implementation (ii.) because the true model used to simulate treatment probabilities uses a multinomial regression model. Implementation (iii.) closely aligns with the software implementation of TMLE, which incorrectly assumes binomial treatment probabilities. In all of the implementations, we winsorize extreme estimated treatment probabilities to the threshold of $(0.001, 0.999)$.

4.1. Treatment Assignment. We assign treatments according to six covariates: $x_{1i}$, $x_{2i}$, and $x_{3i}$ are generated from a multivariate normal distribution with means zero, variances of $(2,1,1)$ and covariances of $(1, -1, -0.5)$. The latter three covariates are generated as follows: $x_{4i} \sim \text{Uniform} [-3,3]$, $x_{5i} \sim \chi^2_1$, and $x_{6i} \sim \text{Ber}(0.5)$, with the covariate vector $x_i^T = (x_{1i}, x_{2i}, \ldots, x_{6i})$. The treatment model follows the multinomial logistic model:

\begin{equation}
(d_i(1), \ldots, d_i(J)) \mid x_i \sim \text{Multinom} (p_1(x_i), \ldots, p_J(x_i)),
\end{equation}

with $p_j(x_i) = \frac{\exp(x_i^T \beta_j)}{\sum_k \exp(x_i^T \beta_k)}$ where

$\beta_1^T = (0, 0, 0, 0, 0, 0, 0)$,

$\beta_2^T = \kappa_2 \times (0, 1, 1, 2, 1, 1, 1)$,

$\beta_3^T = \kappa_3 \times (0, 1, 1, 1, 1, -5)$.

\footnote{In Supplement A, we describe the data generating process for the case of $J = 3$ treatments, which is the focus of the simulation studies of the aforementioned papers.}
Different values of the $\kappa$ values are selected to to vary the amount of overlap, or similarity in the distributions of the propensity scores across treatment levels, and thus produce three treatment model settings. Following Li and Li, we use $(\kappa_2, \ldots, \kappa_6) = (0.1, 0.15, 0.2, 0.25, 0.3)$ to simulate experiments with “adequate overlap”; i.e., similarity in the distributions of propensity scores across treatment groups. In a different setting, we set $(\kappa_2, \ldots, \kappa_6) = (0.4, 0.6, 0.8, 1.0, 1.2)$, which are the same values used in Yang et al., to simulate an “inadequate overlap” scenario with strong propensity tails (i.e., some treatment propensities are close to zero). We examine a third setting that is reflective of a randomized control trial (RCT). In the RCT setting, $(\kappa_2, \ldots, \kappa_6) = (0, 0, 0, 0, 0)$ so that the covariates have no influence in assignment treatment.

Figure A1 in Supplement A provides box and whisker plots of the observed treatment probabilities across 1000 simulation runs in each of the three treatment model settings. In the adequate overlap setting, the treatment probabilities are typically within 0.1 and 0.25; in the inadequate overlap setting, the probabilities of the first three treatment levels are close to zero; and in the RCT setting, there is a probability of $1/6$ for each treatment level.

4.2. Outcome Generation. In each simulation run, we generate ground-truth potential outcomes using the Bernoulli model

$y_i(j) \sim Bern \left( \frac{\exp (x_i^T \gamma_j)}{1 + \exp (x_i^T \gamma_j)} \right)$.

We simulate three different settings to vary the outcome event rate. We are especially interested in low probability outcomes under treatment in order to mimic the relatively low event rates in our application. In a “low event rate” setting, we generate outcome event rates using

$\gamma_1^T = (-4, 1, -2, -1, 1, 1, 1)$,
$\gamma_2^T = (-6, 1, -2, -1, 1, 1, 1)$,
$\gamma_3^T = (-2, 1, -1, -1, -1, -1, -4)$,
$\gamma_4^T = (1, 2, 1, 2, -1, -1, -3)$,
$\gamma_5^T = (-2, 2, -1, -1, -2, -1, -3)$, and
$\gamma_6^T = (-3, 3, -1, 1, -2, -1, -2)$.

This setting generates event rates that range from 0.1 to 0.4, on average. In a “moderate event rate” setting, we use the same $\gamma_j$ values in Yang et al.:

$\gamma_1^T = (-1.5, 1, 1, 1, 1, 1, 1)$,
$\gamma_2^T = (-3, 2, 3, 1, 2, 2, 2)$,
$\gamma_3^T = (3, 3, 1, 2, -1, -1, -4)$,
$\gamma_4^T = (2.5, 4, 1, 2, -1, -1, -3)$,
$\gamma_5^T = (2.5, 1, 2, -1, -1, -2)$, and
$\gamma_6^T = (1.5, 6, 1, 2, -1, -1, -1)$.
On average, outcomes generated using these parameters range from 0.2 to 0.9. Lastly, to study a setting where there is no treatment effect, we specify \( \gamma_1^\top, \ldots, \gamma_6^\top = (0, 0, 0, 0, 0, 0) \). In this setting, the outcome model does not use covariate information so the outcome probability is a coin flip. Figure A2 provides box and whisker plots for the event rate under each treatment level for each simulation setting.

4.3. Performance metrics. We consider three metrics to evaluate the ability of each TMLE implementation to recover the true ATE. The first metric focuses on bias.

**Definition 4.** Mean absolute bias. The mean absolute difference between the true ATE and the estimated ATE when comparing reference \( j \) to \( j^* \), averaged over \( H \) simulations.

\[
\text{Absolute bias} = \frac{1}{H} \sum_{h=1}^{H} \left\{ \left| \hat{\text{ATE}}_{j,j^*}^{(h)} - \text{ATE}_{j,j^*}^{(h)} \right| \right\}
\]

\[
= \frac{1}{H} \sum_{h=1}^{H} \left\{ \left| \left( \hat{\mu}_{j^*}^{(h)} - \mu_{j^*}^{(h)} \right) - \left( \mu_{j^*}^{(h)} - \mu_{j}^{(h)} \right) \right| \right\}; \ j^* \neq j,
\]

where \( \mu_{j^*}^{(h)} \) and \( \mu_{j}^{(h)} \) are the averages of the true potential outcomes under treatment and reference, respectively, generated according to the outcome model (10).

The second metric assesses the performance of the influence function (4) in terms of coverage of 95% confidence intervals for the estimated ATE, \( \hat{\text{CI}}_{j,j^*}^{(h)} = \hat{\text{ATE}}_{j,j^*}^{(h)} \pm 1.96 \hat{\sigma}^{(h)} \), where \( \hat{\sigma}^{(h)} \) is the standard deviation for the ATE in simulation \( h \).

**Definition 5.** Coverage probability. The proportion of the estimated 95% confidence intervals in the \( H \) simulations that contain the true ATE.

\[
\text{Coverage probability} = \frac{1}{H} \sum_{h=1}^{H} 1 \left\{ \text{ATE}_{j,j^*}^{(h)} \in \hat{\text{CI}}_{j,j^*}^{(h)} \right\}; \ j^* \neq j.
\]

We also average the coverage probability and absolute bias metrics over all pairwise comparisons to provide a more concise summary of the implementations’ performance. We provide these summary plots in Figures 1 and 3, respectively. The third performance metric is confidence interval width, which provides a measure of the variability of estimated ATE.

**Definition 6.** Average confidence interval width. The difference between the upper and lower bounds of the estimated 95% confidence intervals over the \( H \) simulations.

\[
\text{Confidence interval width} = \frac{1}{H} \sum_{h=1}^{H} \left\{ 2 \times 1.96 \hat{\sigma}_n^{(h)} \right\}; \ j^* \neq j.
\]

4.4. Results. We expect the performance improvement of using the correct multinomial distribution to estimate the treatment model to be in terms of efficiency, rather than consistency. If the outcome model distribution is correctly specified but the distribution of the treatment model is not, in general, the doubly-robust TMLE estimator should remain unbiased; however, the standard errors will underestimate the true variability of the estimator so that the confidence intervals will be too narrow and coverage will be less than nominal.
Figure 1, which plots the coverage probability averaged over all 15 pairwise comparisons in each of the nine simulation settings, shows that the TMLE-multinomial implementations (propensity scores using a multinomial probability of treatment model) achieve superior coverage compared to the TMLE-binomial implementation. The one exception involves the simulation setting in which treatment is randomly assigned (RCT) and there is no treatment effect (the ninth simulation setting): all three estimators achieve the nominal coverage of 95% represented by the dotted horizontal line. In contrast, when there is adequate treatment overlap and no treatment effect (the third simulation setting), the multinomial implementations achieve nominal coverage while the binomial implementation undercovers. The multinomial GLM implementation achieves nominal coverage in all simulation settings except in those with inadequate overlap. This parametric implementation is a useful benchmark in the simulations because it uses the correct parametric treatment model, except in the RCT treatment assignment setting, where covariates have no role in the treatment model. However, in real-world applications, researchers may be reluctant to use a parametric function of the observed covariates. All three estimators struggle in the inadequate overlap settings, which features treatment probabilities that are close to zero. Our preferred implementation, the TMLE-multinomial uses the correct probability distribution for the treatment model and estimates both outcome and treatment models using super learner, has an average coverage rate of between 54% and 95%.

The coverage performance advantage of the multinomial implementations over the binomial implementation follows from the binomial implementations having too small confidence interval widths. Figure 2 is a box and whiskers plot of the interval widths for all 15 pairwise comparisons, summarizing the median, the first and third quartiles, and outlying points of the distribution of interval widths across the 1000 simulation runs. In the inadequate overlap settings, the multinomial implementations have appropriately wide confidence intervals, reflecting the variability of the treatment model estimator, while the binomial implementation underestimates the true variability yielding intervals that are much too narrow.

The estimated propensity scores and final outcome estimates play an important role in the influence curve (4), and consequently, for the confidence intervals for the estimated ATE. Supplement A provides insight into how well the implementations estimate the initial outcome and treatment probabilities. Figure A4, which plots the absolute difference between the estimated and true treatment probabilities, shows that the multinomial implementation estimated via super learner produces no detectable bias in the estimated treatment probabilities across treatment model settings. The binomial implementation generally exhibits more bias and greater variability in terms of the estimated treatment probabilities, and slightly underestimates the true treatment probabilities, which is detectable in the plots of the estimated treatment probabilities in Figure A3. Interestingly, the parametric multinomial implementation struggles to make accurate treatment model predictions in the settings with no treatment effect and either adequate or inadequate overlap. In the RCT setting, the parametric multinomial treatment model is incorrect and performs poorly in a low event rate setting. Likewise, in several settings the parametric multinomial implementations exhibit bias when estimating the initial outcome model (Figure A5). The difficulty of this implementation in correctly predicting the outcome or treatment, even when it is correctly specified, underscores the advantage of the super learner.

Misspecification of only the treatment model is expected to impact efficiency rather than consistency. Therefore, it is not unexpected that the performance of the TMLE-multinomial implementations in terms of bias is mixed. Figure 3, which averages bias across all 15 pairwise comparisons, shows that the TMLE-multinomial implementations demonstrate lower or equivalent average bias compared to the TMLE-binomial implementation in only four of the nine settings. In the “RCT” settings, average bias is comparable across the three estimators. Figure A6, which looks at the bias for each pairwise comparison, reveals that the
FIG 1. Simulation: average coverage probability for the ATE over all 15 pairwise comparisons ($J = 6$ and $n = 6000$).

TMLE-binomial implementation struggles with comparisons involving treatments with low assignment probabilities; i.e., treatments 1, 2, and 3, in the inadequate overlap setting (middle row).

Figure A7 show that when we increase the sample size from 600 to 10000, the average bias across all pairwise comparisons converges more quickly as $n$ increases for the TMLE-multinomial implementations compared to TMLE-binomial in certain settings. For example, the average bias for the three implementations are about the same when $n = 600$ when there is adequate overlap and a low event rate; when $n = 1000$, the TMLE-multinomial implementations have noticeably lower bias than the binomial implementation in the same simulation setting.

Supplement B details the data generation process and simulation results for the case of $J = 3$ treatments. Compared to the case of $J = 6$, the observed treatment probabilities (Figure B1) and event rates under each treatment level (Figure B2) are more similar across treat-
FIG 2. Simulations: widths of estimated confidence intervals for the ATE, for each of the 15 pairwise comparisons ($J = 6$ and $n = 6000$).

ment levels in the case of $J = 3$. Similar to the case of $J = 6$, the TMLE-multinomial implementations have comparable average bias (Figure B3), while typically having better average coverage probability across the three pairwise comparisons compared to the TMLE-binomial implementation (Figure B4) due to larger confidence interval widths (Figure B5).

5. Safety Effects of Antipsychotic Drug Treatments. Antipsychotic drugs effectively control some of the most disturbing symptoms of schizophrenia and no other treatments have comparable effectiveness (Keepers et al., 2020). These drug are also valuable for the treatment of bipolar I disorder (Carvalho, Firth and Vieta, 2020) and treatment-resistant major depressive disorder (MDD) (Zhou et al., 2015). Although more than 20 antipsychotic drugs are available in the U.S., the most widely used are the subset of second generation antipsychotics (SGAs). However, some some frequently used SGAs carry a higher risk for cardiometabolic
morbidity (e.g., dyslipidemia, hypertension, diabetes, and cardiovascular disease) and mortality relative to the older first generation antipsychotics (FGAs) (Solmi et al., 2017; Correll et al., 2015; Tiihonen et al., 2019; Clark, 2004; Meyer et al., 2008). Despite a U.S. Food and Drug Administration class warning on the metabolic risks of SGAs, SGAs with evidence of adverse cardiometabolic effects remain popular (Donohue et al., 2014).

Much of the existing observational evidence on the safety of antipsychotics compare recent initiators of antipsychotic drugs to a control group not receiving an antipsychotic drug (Gianfrancesco, Wang and Nasrallah, 2006; Bobo et al., 2013), compare the group receiving FGAs to the group of SGAs (Guo et al., 2007), or compare groups receiving specific SGAs to a group receiving any SGA (Yood et al., 2009). These studies cannot draw conclusions on the comparative safety of commonly used antipsychotic drugs based on one-to-one comparisons because they do not balance covariates across the drug groups. An exception is the study of

**FIG 3.** Simulation results: average bias for the ATE over all 15 pairwise comparisons ($J = 6$ and $n = 6000$).
Gianfrancesco, Wang and Nasrallah (2006), which fits a single outcome model in the form of a single logistic regression controlling for patient characteristics.

5.1. Medicaid and Medicare data. We utilize patient-level health insurance billing claims data collected by the Centers for Medicare & Medicaid Services (CMS) from seven states: California, Georgia, Iowa, Mississippi, Oklahoma, South Dakota, and West Virginia. These states are selected for their racial diversity and lower rates of managed care penetration. Our sample includes adults aged 18-64 years of age enrolled in one or both programs diagnosed with serious mental illness between 2008 and 2010, and who are relatively new monotherapy antipsychotic users of one of six antipsychotics. The latter requirement restricts the sample to patients who have not used any antipsychotic drugs within the six months prior to treatment assignment.

We focus on four commonly-used SGAs, denoted drugs “B”, “C”, “D”, and “E”, a Reference SGA thought to have lower metabolic risk relative to the other SGAs, and a FGA known for having low cardiometabolic risk (denoted drug “A”). The study design is intention-to-treat: patients are assigned to the first drug filled regardless of initial dose or duration, except we consider only patients who remain on the assigned drug for the first three months (for those who are alive during this period). Further restricting the sample to patients who are followed for three years (or died before the three-year follow-up) yields a sample size of \( n = 38762 \).

Table 1 summarizes the observed three-year safety outcomes by antipsychotic drug. There is a wide range of treatment assignment probabilities, with drug A initiated in only 6% of the sample and drug C initiated in 26.5%. The Reference drug was initiated in less than 1 in 5 patients. Across all treatment arms, incident diabetes is 9.3% and all-cause death 5%. While the Reference drug is associated with the lowest risk of mortality (3.4%), drug B is associated with the lowest unadjusted risk of diabetes (6.7%).

| Antipsychotic | Patients | Diabetes or death | Diabetes | Death |
|---------------|----------|-------------------|----------|-------|
| Reference     | 6686 (17.2) | 891 (13.3) | 679 (10.2) | 225 (3.4) |
| A             | 2328 (6.0)  | 309 (13.3) | 217 (9.3) | 103 (4.4) |
| B             | 6301 (16.2) | 714 (11.3) | 421 (6.7) | 313 (5.0) |
| C             | 10309 (26.5) | 1602 (15.5) | 989 (9.6) | 662 (6.4) |
| D             | 9897 (25.5) | 1360 (13.7) | 941 (9.5) | 470 (4.8) |
| E             | 3241 (8.3)  | 508 (15.7) | 357 (11.0) | 166 (5.1) |
| All           | 38762 (100) | 5384 (13.9) | 3604 (9.3) | 1939 (5.0) |

The CMS data include person-level demographic, diagnostic, and pharmacy, behavioral health, physical health, laboratory tests, and other service use information measured six months prior to drug initiation. Tables 3 and 4 in the Appendix summarize the baseline binary and continuous baseline covariates, respectively, by treatment drug. Selection is apparent with 42.8% of Reference drug initiators having schizophrenia compared to 87% of drug A initiators, and 11.6% of drug A initiators having a psychiatric comorbidity compared to 21.9% of drug C initiators.

5.2. Results. As in our simulation studies, the outcome and treatment models are both estimated by super learner, following the estimation procedure described in Section 3. Each model relies on the same set of baseline covariates, which includes binary indicators for state,
race and ethnicity, and health status (Table 3), and count variables of health service utilization such as ER visits (Table 4) that are centered and scaled when fitting the models. Table C1 provides a summary of the cross-validated super learner ensemble weights assigned to each classification algorithm for the TMLE-multinomial implementation. In the super learner ensemble for the multinomial treatment model, random forests implemented with 500 trees is heavily favored, while lasso regression, random forests implemented with 50 trees, and elastic net regression with the mixing parameter set at $\alpha = 0.75$ receive low weights. In the outcome model ensemble, the gradient boosting classifier is favored, while random forests, elastic net regression, and lasso regression also receive positive weights.

As expected, TMLE-multinomial does better in terms of overlap, ensuring the treatment probabilities sum to one. Table 2 summarizes the estimated treatment probabilities for the multinomial and binomial implementations estimated with super learner, along with the ESS and the ratio $ESS_j/n_j$ for each drug. Overall, the predicted probabilities of the TMLE-binomial implementation take on more extreme values and are more variable compared to the TMLE-multinomial implementation. Moreover, the TMLE-binomial implementation produces zero-probability predictions for drug A — and are thus winsorized to the value of 0.001 — whereas the TMLE-multinomial implementation avoids winsorization. The estimated values of the ratio $ESS_j/n_j$ are all above 0.9, except for the TMLE-binomial estimated ratio with respect to drug A, which is initiated in only 6% of the sample and tends to be initiated with patients with a schizophrenia diagnosis at baseline. Values of the ratio close to one indicate a similarity in estimated propensity scores and adequate overlap among drug groups. We demonstrate a substantial performance benefit of using super learner to estimate the multinomial treatment model, rather than GLM. Table C2 shows that the ratio $ESS_j/n_j$ of estimated multinomial probabilities using GLM are all under 0.9, indicating a lack of overlap of estimated propensity scores among drug groups. For drugs A and B, the multinomial treatment model estimated by GLM produces zero-probability predictions and are thus winsorized to 0.001. The superiority of the super learner estimated propensity scores vis-à-vis the GLM estimates in terms of overlap underscores the importance of using nonparametric algorithms to avoid model misspecification, which is likely to occur in high-dimensions. Note that GLM estimation of the multinomial treatment model performs comparatively well in the simulation results presented in Section 4.4 since it mimics the true treatment model.

| Antipsychotic | Min. | Mean | Max. | S.d. | $ESS_j$ | $ESS_j/n_j$ | Min. | Mean | Max. | S.d. | $ESS_j$ | $ESS_j/n_j$ |
|---------------|------|------|------|------|---------|------------|------|------|------|------|---------|------------|
| Reference     | 0.010| 0.173| 0.646| 0.114| 6296    | 0.04       | 0.005| 0.172| 0.739| 0.148| 6404    | 0.95       |
| A             | 0.001| 0.060| 0.756| 0.076| 2105    | 0.90       | 0.000| 0.056| 0.818| 0.080| 2041    | 0.87       |
| B             | 0.013| 0.013| 0.825| 0.140| 5713    | 0.90       | 0.005| 0.160| 0.864| 0.157| 5857    | 0.92       |
| C             | 0.014| 0.265| 0.765| 0.160| 9490    | 0.92       | 0.016| 0.263| 0.884| 0.178| 9505    | 0.92       |
| D             | 0.006| 0.255| 0.817| 0.178| 9225    | 0.93       | 0.002| 0.257| 0.861| 0.228| 9582    | 0.96       |
| E             | 0.006| 0.084| 0.558| 0.080| 2980    | 0.91       | 0.002| 0.080| 0.637| 0.093| 3033    | 0.93       |

Figure 4 presents the estimated ATEs for each treatment drug relative to the Reference on the combined outcome of diabetes diagnosis or death within 36 months, or each outcome separately. According to our preferred TMLE-multinomial implementation, moving patients from the Reference drug to drug A yields a 0.8% [0.4%, 1.2%] reduction in the probability of diabetes diagnosis or death, a small clinical difference. For the remaining four pairwise comparisons, the confidence intervals cover zero. The ATEs estimated using the TMLE-binomial implementation are similar in magnitude compared to those from the TMLE-multinomial
implementation, and are associated with smaller confidence intervals due to the estimated treatment probabilities being larger and more variable when estimated using binomial treatment assignment probabilities. The interpretation of the result generally does not depend on the treatment model distribution; however, the TMLE-binomial implementation estimates a 0.4% [0.05%, 0.8%] increase in the risk of death or diabetes by initiating drug E rather than Reference. When using GLM rather than super learner as the estimator for the multinomial treatment model and the binomial outcome model, the confidence intervals are much wider due to the estimated treatment probabilities being smaller and less variable (Table C2), and cover zero for each pairwise comparison. The estimated coefficients extracted from the GLM models appear reasonable: the largest coefficient in the outcome model for the combined outcome is associated with the use of antidiabetic drugs in the pretreatment period and in the treatment model, the largest coefficient is associated with a pretreatment diagnosis of schizophrenia for predicting assignment to drug A, which is commonly initiated by patients with schizophrenia (Table C3).

The treatment effect on the combined outcome is driven by a reduction in diabetes risk rather than mortality: moving patients from the Reference to drug A confers a 1.3% [1.0%, 1.7%] reduction in diabetes risk. There is a significant, albeit much smaller treatment effect favoring drug B over the Reference drug, 0.5% [0.1%, 0.9%]. The Reference drug is generally the safest in terms of mortality risk: moving patients from the Reference to drugs C, D, or E would increase the risk of death, although the point estimates are very small (under 0.4%). There is no safety benefit of the Reference drug relative to drugs A or B in terms of mortality risk.

Figure C1 presents the average effects on the combined outcome for patients with schizophrenia. There is no change in the interpretation of the results when the average causal effect is taken over patients with schizophrenia, rather than the whole sample.

6. Discussion. Extensive simulation studies demonstrate that when estimating pairwise ATEs with multi-valued treatments, our TMLE implementation using a multinomial treatment assignment yields better coverage than the binomial implementation. This finding is in line with the theoretical properties of doubly-robust estimators, such as TMLE, and is not just a finite sample size finding. If the outcome regression model is correctly specified but the treatment model is not, in general, the doubly robust estimator should remain unbiased but the standard errors will underestimate the true variability of the estimator, so that the confidence intervals will be too narrow and coverage will be less than nominal. These results underscore the importance of using a correct probability distribution for the treatment model. The average coverage probabilities of 95% confidence intervals are uniformly poorest for the TMLE-binomial estimator except when treatments are assigned randomly with equal probabilities and there was no treatment effect. Our experiments focused on using nonparametric data-adaptive strategies for both treatment and outcome model estimation. The super learner yielded remarkably precise estimated treatment probabilities, even better than using the correct model in some settings.

While not presented, we compared the ESS for each treatment level and estimator across experiments. Because the denominator in the ESS involves the sum of squared terms of one divided by the inverse propensity score, sample sizes for treatments with small estimated assignment probabilities are impacted more than sample sizes for treatments with probabilities away from the boundaries. Probabilities estimated from binomial models tended to be slightly larger than those estimated from multinomial models, so that the ESS used in the TMLE-binomial estimates are (incorrectly) larger than those for the TMLE-multinomial implementation.

The paper presents, to the best of our knowledge, the first doubly-robust estimates of the relative safety of antipsychotic drugs using observational data. We find a small reduction
(A) Diabetes diagnosis or death within 36 months.  (B) Diabetes diagnosis within 36 months.

(c) Death within 36 months.

FIG 4. ATE estimates for each pairwise comparison (relative to Reference drug). Horizontal ranges are 95% confidence intervals calculated using standard errors estimated from the influence function. TMLE: ●, Multinomial (super learner); ○, Multinomial (GLM); ◦, Binomial (super learner).

in metabolic risk of a first-generation antipsychotic known to have a low rate of metabolic disturbance (drug A) relative to a more popular second generation antipsychotic (Reference drug) thought to have a more favorable metabolic profile relative to other second generation drugs. The estimated effect size of 0.8% [0.4%, 1.2%] on reducing the risk of death or diabetes by initiating drug A rather than Reference is small compared to the observed combined
event rate in the sample, 13.9%. Similarly, the effect size on reducing diabetes risk, 1.3% [1.0%, 1.7%], is small relative to the observed rate of diabetes in the sample, 9.3%. Given the observational nature of our data, these small differences may be due to unmeasured confounding.

APPENDIX: DESCRIPTIVE SUMMARIES FOR ANTIPSYCHOTIC DATA APPLICATION

Data corresponding to 38,762 adults aged 18 - 64 diagnosed with schizophrenia, major depressive disorder, or diabetes. Individuals are insured by U.S. government under its Medicaid program. Covariates are measured during the six-month period prior to their index antipsychotic fill.

TABLE 4. Summary statistics of continuous baseline covariates included in the outcome and treatment models, by assigned antipsychotic drug.

| Variable                     | Drug       | n_j | Min. | Mean  | Max.  | S.d. |
|------------------------------|------------|-----|------|-------|-------|------|
| Age                          | Reference  | 6686| 19.9 | 43.7  | 64.0  | 10.2 |
|                              | A          | 2328| 20.8 | 45.4  | 63.7  | 10.0 |
|                              | B          | 6301| 20.2 | 44.9  | 64.2  | 10.1 |
|                              | C          | 10309| 20.1| 45.0  | 64.1  | 9.9  |
|                              | D          | 9897| 20.0 | 44.2  | 64.5  | 10.4 |
|                              | E          | 3241| 20.0 | 43.6  | 64.1  | 10.1 |
|                              | All        | 38762| 19.9| 44.5  | 64.5  | 10.2 |
| Antipsychotic drug use (days)| Reference  | 6686| 0.0  | 96.0  | 183.0 | 71.2 |
|                              | A          | 2328| 0.0  | 105.4 | 183.0 | 68.0 |
|                              | B          | 6301| 0.0  | 124.6 | 183.0 | 65.2 |
|                              | C          | 10309| 0.0 | 102.2 | 183.0 | 70.8 |
|                              | D          | 9897| 0.0  | 114.7 | 183.0 | 68.7 |
|                              | E          | 3241| 0.0  | 115.7 | 183.0 | 68.2 |
|                              | All        | 38762| 0.0 | 109.3 | 183.0 | 69.7 |
| Drug B-equivalent dose       | Reference  | 6686| 0.0  | 1217.3| 10380.0| 1245.9|
|                              | A          | 2328| 0.0  | 1902.5| 17648.5| 2070.7|
|                              | B          | 6301| 0.0  | 2318.5| 13160.0| 1867.9|
|                              | C          | 10309| 0.0 | 1085.6| 12675.0| 1233.1|
|                              | D          | 9897| 0.0  | 1013.0| 7757.9 | 928.4 |
|                              | E          | 3241| 0.0  | 2035.6| 8760.0 | 1602.2|
|                              | All        | 38762| 0.0 | 1418.7| 17648.5| 1478.9|
| Psychiatric ER visits        | Reference  | 6686| 0.0  | 0.1   | 9.0   | 0.5  |
|                              | A          | 2328| 0.0  | 0.2   | 10.0  | 0.6  |
|                              | B          | 6301| 0.0  | 0.1   | 16.0  | 0.6  |
|                              | C          | 10309| 0.0 | 0.2   | 13.0  | 0.6  |
|                              | D          | 9897| 0.0  | 0.1   | 33.0  | 0.7  |
|                              | E          | 3241| 0.0  | 0.1   | 8.0   | 0.5  |
|                              | All        | 38762| 0.0 | 0.1   | 33.0  | 0.6  |
| Non-psychiatric ER visits   | Reference  | 6686| 0.0  | 0.4   | 25.0  | 1.2  |
|                              | A          | 2328| 0.0  | 0.3   | 31.0  | 1.3  |
|                              | B          | 6301| 0.0  | 0.3   | 24.0  | 1.1  |
|                              | C          | 10309| 0.0 | 0.6   | 35.0  | 1.4  |
|                         | Reference | A     | B     | C     | D     | E     | All    |
|-------------------------|-----------|-------|-------|-------|-------|-------|--------|
| **Injury-related ER visits** | 6686      | 2328  | 6301  | 10309 | 9897  | 3241  | 38762  |
|                         | 0.0       | 0.0   | 0.0   | 0.0   | 0.0   | 0.0   | 0.0    |
|                         | 0.1       | 0.0   | 0.0   | 0.1   | 0.0   | 0.1   | 0.1    |
|                         | 14.0      | 6.0   | 8.0   | 15.0  | 5.0   | 4.0   | 15.0   |
|                         | 0.3       | 0.3   | 0.3   | 0.4   | 0.2   | 0.3   | 0.3    |
| **Psychiatric outpatient visits** | 6686      | 2328  | 6301  | 10309 | 9897  | 3241  | 38762  |
|                         | 0.0       | 0.0   | 0.0   | 0.0   | 0.0   | 0.0   | 0.0    |
|                         | 0.0       | 0.0   | 0.0   | 0.0   | 0.0   | 0.0   | 0.0    |
|                         | 6.4       | 6.7   | 6.1   | 5.3   | 7.1   | 6.2   | 6.3    |
|                         | 172.0     | 183.0 | 183.0 | 183.0 | 183.0 | 180.0 | 183.0  |
|                         | 12.2      | 15.5  | 13.8  | 10.0  | 16.5  | 12.5  | 13.4   |
| **Non-psychiatric outpatient visits** | 6686      | 2328  | 6301  | 10309 | 9897  | 3241  | 38762  |
|                         | 0.0       | 0.0   | 0.0   | 0.0   | 0.0   | 0.0   | 0.0    |
|                         | 0.0       | 0.0   | 0.0   | 0.0   | 0.1   | 0.0   | 0.1    |
|                         | 1.4       | 1.4   | 2.0   | 3.2   | 2.0   | 2.7   | 2.5    |
|                         | 97.0      | 97.0  | 119.0 | 123.0 | 106.0 | 117.0 | 123.0  |
|                         | 3.5       | 3.5   | 4.1   | 4.3   | 3.9   | 4.1   | 4.2    |
| **Injury-related outpatient visits** | 6686      | 2328  | 6301  | 10309 | 9897  | 3241  | 38762  |
|                         | 0.0       | 0.0   | 0.0   | 0.0   | 0.0   | 0.0   | 0.0    |
|                         | 0.0       | 0.0   | 0.0   | 0.0   | 0.1   | 0.0   | 0.1    |
|                         | 0.1       | 0.0   | 0.0   | 0.1   | 0.1   | 0.1   | 0.1    |
|                         | 9.0       | 5.0   | 6.0   | 53.0  | 20.0  | 8.0   | 53.0   |
|                         | 0.4       | 0.3   | 0.3   | 0.7   | 0.4   | 0.5   | 0.5    |
| **Psychiatric inpatient (days)** | 6686      | 2328  | 6301  | 10309 | 9897  | 3241  | 38762  |
|                         | 0.0       | 0.0   | 0.0   | 0.0   | 0.0   | 0.0   | 0.0    |
|                         | 0.0       | 0.0   | 0.0   | 0.0   | 0.1   | 0.0   | 0.1    |
|                         | 1.4       | 2.7   | 2.0   | 1.9   | 2.3   | 1.7   | 2.0    |
|                         | 183.0     | 106.0 | 183.0 | 183.0 | 183.0 | 165.0 | 183.0  |
|                         | 7.8       | 9.6   | 8.9   | 7.8   | 9.4   | 8.1   | 8.6    |
| **Non-psychiatric inpatient (days)** | 6686      | 2328  | 6301  | 10309 | 9897  | 3241  | 38762  |
|                         | 0.0       | 0.0   | 0.0   | 0.0   | 0.0   | 0.0   | 0.0    |
|                         | 0.0       | 0.0   | 0.0   | 0.0   | 0.5   | 0.5   | 0.6    |
|                         | 0.5       | 0.5   | 0.5   | 0.9   | 0.5   | 0.5   | 0.6    |
|                         | 94.0      | 183.0 | 109.0 | 183.0 | 183.0 | 100.0 | 183.0  |
|                         | 3.1       | 4.7   | 3.7   | 5.3   | 4.1   | 3.6   | 4.3    |
| **Injury-related inpatient (days)** | 6686      | 2328  | 6301  | 10309 | 9897  | 3241  | 38762  |
|                         | 0.0       | 0.0   | 0.0   | 0.0   | 0.0   | 0.0   | 0.0    |
|                         | 0.0       | 0.0   | 0.1   | 0.1   | 0.1   | 0.1   | 0.1    |
|                         | 26.0      | 22.0  | 79.0  | 42.0  | 20.0  | 42.0  | 26.0   |
|                         | 0.7       | 0.5   | 1.3   | 1.1   | 0.7   | 1.1   | 0.7    |
|     |     |   |   |   |   |
|-----|-----|---|---|---|---|
| D   | 9897| 0.0| 0.1| 83.0| 1.6|
| E   | 3241| 0.0| 0.1| 29.0| 1.1|
| All | 38762| 0.0| 0.1| 83.0| 1.2|
TABLE 3. Summary statistics of binary baseline covariates included in the outcome and treatment models, by assigned antipsychotic drug.

| Variable                                      | Reference | All | B | C | D | E | All |
|-----------------------------------------------|-----------|-----|---|---|---|---|-----|
| General State: California                     | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| General State: Georgia                        | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| General State: Iowa                           | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| General State: Mississippi                    | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| General State: Oklahoma                       | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| General State: West Virginia                  | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| Race/ethnicity: black                         | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| Race/ethnicity: latino                        | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| Race/ethnicity: white                         | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| Primary diag.: MDD                           | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| Primary diag.: schiz                          | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| Sex: female                                   | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| Payer: Medicare                               | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| Index year: 2008                              | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| Index year: 2009                              | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| Index year: 2010                              | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| Health status: Psychiatric comorbidity        | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| Health status: Metabolic risk                 | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| Health status: Other chronic condition        | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| Health status: Other (CM) disorders           | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |
| Health status: Other (CM effects)             | 1998      | 191 | 181 | 191 | 181 | 191 | 191 |

**Notes:** 2010 indicates summary statistics for the index years of 2010 and 2011. MDD is major depressive disorder; and CM is cardiometabolic syndrome.
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SUPPLEMENTARY MATERIAL

Supplement A: Numerical studies descriptive plots and results for \( J = 6 \) treatment levels
We provide descriptive plots of the data generating process for the case of \( J = 6 \) treatments, as well as additional simulation results.

Supplement B: Numerical studies for \( J = 3 \) treatment levels
We describe and provide descriptive plots of the data generation process for the case of \( J = 3 \) treatment levels, and provide simulation results.

Supplement C: Additional results from empirical application
We provide a summary of the cross-validated super learner ensemble weights; additional summary statistics of treatment probabilities and ESS estimates; and CATE estimates for patients with schizophrenia.
Supplement A: Numerical studies descriptive plots and results for $J = 6$ treatment levels.

![Observed treatment probabilities (J=6, n=6000)](image)

**FIG A1.** Simulations: observed treatment probabilities.
Observed outcomes under each treatment level ($J=6$, $n=6000$)

| Outcome setting                  | Low event rate | Moderate event rate | No treatment effect |
|----------------------------------|----------------|--------------------|---------------------|

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**Fig A2.** Simulations: observed outcomes.
Figure A3. Simulations: estimated treatment probabilities.
FIG A4. Simulations: accuracy of treatment estimation in terms of the absolute difference between the observed and estimated treatment probabilities.
FIG A5. Simulations: accuracy of outcome estimation in terms of the absolute differences between the observed and estimated initial outcomes.
FIG A6. Simulations: absolute bias for the ATE for each of the 15 pairwise comparisons.
FIG A7. Simulations: average bias for the ATE across over all 15 pairwise comparisons, with varying sample size $n$. 
**Supplement B: Numerical studies for \( J = 3 \) treatment levels.** In the simulation design with \( J = 3 \), the total sample size is \( n = 1500 \), to be consistent with the numerical studies presented in Yang et al.. The treatment model coefficients are given by

\[
\begin{align*}
\beta_1^T &= (0, 0, 0, 0, 0, 0) \\
\beta_2^T &= \kappa_2 \times (0, 1, 1, 1, -1, 1, 1) \\
\beta_3^T &= \kappa_3 \times (0, 1, 1, 1, 1, 1, 1)
\end{align*}
\]

with \((\kappa_2, \kappa_3) = (0.2, 0.1)\) to simulate the “adequate overlap” scenario, \((\kappa_2, \kappa_3) = (0.7, 0.4)\) to simulate the ‘inadequate overlap” scenario, and \((\kappa_2, \kappa_3) = (0, 0)\) for the RCT setting. The outcome model settings for moderate event rates are

\[
\begin{align*}
\gamma_1^T &= (-1.5, 1, 1, 1, 1, 1), \\
\gamma_2^T &= (-3, 2, 3, 1, 2, 2), \quad \text{and} \\
\gamma_3^T &= (1.5, 3, 1, 2, -1, -1, -1).
\end{align*}
\]

For low event rates,

\[
\begin{align*}
\gamma_1^T &= (-4, 1, -2, -1, 1, 1), \\
\gamma_2^T &= (-2, 1, -1, -1, -1, -4), \quad \text{and} \\
\gamma_3^T &= (3, 3, -1, 1, -2, -1, -2).
\end{align*}
\]

Finally, in the “no treatment effect” setting, we specify \(\gamma_1^T, \gamma_2^T, \gamma_3^T = (0, 0, 0, 0, 0, 0)\).
Figure B1. Simulations: observed treatment probabilities.
FIG B2. Simulations: observed outcomes under each treatment.
**FIG B3.** Simulation: average bias for the ATE over all 3 pairwise comparisons.
FIG B4. Simulations: average coverage probability for the ATE over all 3 pairwise comparisons.
FIG B5. Simulations: widths of estimated confidence intervals for the ATE for each 3 pairwise comparisons.
Supplement C: Additional results from empirical application.

Table C1
Cross-validated error and weights for classification algorithms in super learner ensembles.

| Algorithm                                      | Weight | Mean CV error | SE  |
|------------------------------------------------|--------|---------------|-----|
| Elastic net regression, nlambdas = 100, α = 0.25 (glmnet) | 0.000  | 1.498        | 0.003 |
| Elastic net regression, nlambdas = 100, α = 0.50 (glmnet) | 0.000  | 1.498        | 0.003 |
| Elastic net regression, nlambdas = 100, α = 0.75 (glmnet) | 0.064  | 1.498        | 0.003 |
| Lasso regression, nlambdas = 100, α = 1 (glmnet)       | 0.121  | 1.498        | 0.003 |
| Random forests, num.trees = 50 (ranger)               | 0.123  | 1.479        | 0.003 |
| Random forests, num.trees = 100 (ranger)              | 0.000  | 1.471        | 0.003 |
| Random forests, num.trees = 500 (ranger)              | 0.691  | 1.465        | 0.003 |
| Ridge regression, nlambdas = 100, α = 0 (glmnet)       | 0.000  | 1.501        | 0.003 |
| Super learner (sl3)                                    | 1.000  | 1.463        | 0.003 |

Table C2
Summary statistics and ESS of estimated multinomial probabilities using GLM.

| Antipsychotic | Min. | Mean | Max. | S.d. | ESS_j | \(ESS_j/n_j\) |
|---------------|------|------|------|------|-------|---------------|
| Reference     | 0.001| 0.172| 0.554| 0.076| 5101  | 0.76          |
| A             | 0.000| 0.060| 0.392| 0.054| 520   | 0.22          |
| B             | 0.000| 0.163| 0.394| 0.075| 4612  | 0.73          |
| C             | 0.039| 0.266| 0.967| 0.120| 8355  | 0.81          |
| D             | 0.002| 0.255| 0.607| 0.085| 5084  | 0.51          |
| E             | 0.002| 0.084| 0.342| 0.032| 2801  | 0.86          |

Notes: ‘Mean CV error’ is the average cross-validated error across \(V = 5\) folds in terms negative log likelihood for each algorithm and the super learner ensemble; ‘SE’ is the standard error for the mean CV error; and ‘Weight’ is the ensemble weight for each algorithm; \(R\) package used for implementing each algorithm in parentheses. The parameters for the \(glmnet\) models are the number of regularization parameters to fit (nlambdas) and the elastic net mixing parameter \(α\); for random forests, the number of trees used to grow the forest (num.trees); and for gradient boosting, the number of fitting iterations (nrounds).
Table C3. Coefficients and standard errors for GLM implementation of binomial outcome model and multinomial treatment model. Notes: The dummy indicator variable for the state of California and the continuous Drug B-equivalent dose variable are dropped to prevent bias due to multicollinearity. Statistically significant coefficients at conventional levels of significance in bold.

| Covariate                      | Outcome model | Multinomial treatment model |
|-------------------------------|---------------|------------------------------|
|                               | Diabetes or death | Drug A | Drug B | Drug C | Drug D | Drug E |
| Reference drug                | 0.042         | (0.081) |       |       |       |       |
| Drug B                        | -0.002        | (0.081) |       |       |       |       |
| Drug C                        | **0.207**     | (0.077) |       |       |       |       |
| Drug D                        | 0.096         | (0.075) |       |       |       |       |
| Drug E                        | **0.245**     | (0.088) |       |       |       |       |
| State: Georgia                | 0.163         | (0.052) | 0.711 | 0.392 | 0.478 | 0.729 | 0.663 |
| State: Iowa                   | 0.115         | (0.062) | 0.425 | -0.475 | -0.344 | -0.048 | -0.039 |
| State: Mississippi            | **0.224**     | (0.067) | 0.611 | 0.075 | 0.007 | 0.244 | 0.419 |
| State: Oklahoma               | **0.288**     | (0.057) | -0.026 | -0.211 | 0.021 | 0.065 | 0.104 |
| State: West Virginia          | **0.293**     | (0.073) | 0.386 | 0.384 | 0.398 | 0.396 | 0.797 |
| Race/ethnicity: black         | 0.022         | (0.079) | 0.602 | 0.037 | 0.250 | 0.238 | 0.278 |
| Race/ethnicity: latino        | **0.217**     | (0.081) | 0.136 | -0.208 | 0.122 | -0.072 | 0.133 |
| Race/ethnicity: white         | -0.063        | (0.069) | -0.245 | -0.186 | 0.085 | -0.202 | 0.066 |
| Primary diag.: MDD            | -0.087        | (0.047) | -0.225 | -0.278 | -0.046 | 0.046 | -0.428 |
| Primary diag.: schiz.         | 0.020         | (0.042) | 1.660 | 0.572 | -0.438 | 0.755 | 0.072 |
| Index year                    | -0.001        | (0.020) | -0.001 | -0.001 | 0.001 | 0.001 | -0.001 |
| Female                        | **-0.085**    | (0.013) | -0.589 | -0.754 | -0.235 | -0.514 | 0.094 |
| Payer: Medicare               | **-0.088**    | (0.040) | 0.145 | -0.100 | 0.032 | -0.026 | 0.112 |
| Psychiatric comorbidity       | 0.090         | (0.044) | -0.323 | -0.068 | 0.177 | -0.070 | 0.038 |
| Metabolic risk                | 0.408         | (0.103) | -0.395 | -0.496 | -0.358 | -0.240 | -0.155 |
| Other chronic conditions      | **0.255**     | (0.255) | -0.120 | -0.014 | 0.051 | 0.050 | 0.089 |
| Variable                                      | Coefficient 1 | Coefficient 2 | Coefficient 3 | Coefficient 4 | Coefficient 5 | Coefficient 6 | Coefficient 7 | Coefficient 8 |
|-----------------------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Antipsychotic drug use (days)                 | -0.095        | 0.074         | 0.402         | 0.173         | 0.252         | 0.301         |               |               |
| Lipid or glucose lab tests                    | 0.109         | -0.138        | 0.061         | 0.079         | 0.100         | 0.060         |               |               |
| Antidiabetic drugs                            | 2.721         | 0.048         | -0.697        | -0.101        | 0.035         | 0.042         |               |               |
| Other drugs (CM disorders)                    | 0.419         | -0.123        | -0.163        | -0.065        | -0.170        | 0.007         |               |               |
| Other drugs (CM effects)                      | 0.019         | -0.517        | -0.360        | -0.052        | -0.303        | 0.038         |               |               |
| Age                                           | 0.347         | 0.335         | 0.227         | 0.146         | 0.143         | -0.006        |               |               |
| Psychiatric ER visits                         | -0.006        | 0.088         | 0.053         | 0.043         | 0.060         | -0.008        |               |               |
| Non-psychiatric ER visits                     | 0.024         | 0.054         | 0.001         | 0.060         | -0.026        | 0.031         |               |               |
| Injury-related ER visits                      | 0.020         | 0.011         | -0.030        | 0.045         | -0.032        | -0.006        |               |               |
| Psychiatric outpatient visits                 | 0.014         | -0.021        | -0.073        | -0.103        | -0.004        | -0.044        |               |               |
| Non-psychiatric outpatient visits             | 0.042         | -0.209        | -0.101        | -0.002        | -0.114        | -0.058        |               |               |
| Injury-related outpatient visits              | 0.013         | -0.056        | -0.055        | 0.008         | 0.002         | 0.018         |               |               |
| Psychiatric inpatient (days)                  | 0.023         | 0.087         | 0.105         | 0.101         | 0.108         | 0.066         |               |               |
| Non-psychiatric inpatient (days)              | 0.095         | 0.060         | 0.074         | 0.095         | 0.070         | 0.036         |               |               |
| Injury-related inpatient (days)               | 0.010         | -0.017        | 0.065         | 0.062         | 0.079         | 0.068         |               |               |
| Constant                                      | 0.912         | -0.218        | 1.179         | -0.295        | -0.310        | -0.309        |               |               |
| Constant (std)                                | (42.137)      | (0.001)       | (0.001)       | (0.001)       | (0.001)       | (0.001)       |               |               |
FIG C1. CATE estimates for each pairwise comparison (relative to Reference) on the probability of diabetes diagnosis or death within 36 months, conditional on schizophrenia diagnosis at baseline. Horizontal ranges are 95% confidence intervals calculated using standard errors estimated from the influence function.
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