RESEARCH ARTICLE

Antidopaminergic Medications and Clinical Changes in Measures of Huntington's Disease: A Causal Analysis

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ABSTRACT: Background: Antidopaminergic medications (ADM) are often used for symptom management of Huntington's disease (HD). Evidence from past research suggests that ADMs are associated with worse clinical outcomes in HD, but their impact on various domains remains underexplored.
Objective: We used causal inference analysis to understand the impact of ADM use on measures of clinical progression in HD across multiple domains over 2 years.
Methods: We used the Enroll-HD database with a new-user design, which compared a cohort that initiated ADM use after the first visit with an unexposed cohort that remained *off* ADMs. To control for 27 covariates, we used a doubly robust *targeted maximum likelihood estimation* and conducted two analyses. First, we analyzed ADM treatment 2 years post-baseline and separately for 12 outcome measures. Second, we examined the association of ADM dose with measures of clinical outcomes.
Results: The ADM-exposed group exhibited faster change in measures of clinical outcome compared with the *off*-ADM group, which was statistically reliable in cognitive and functional outcome measures, and the composite Unified Huntington's Disease Rating Scale (cUHDRS). Motor domain analyses showed faster change in bradykinesia in the ADM-exposed group versus *off*-ADM but no difference in chorea or total motor score (TMS). Higher ADM doses also showed greater differences compared to the *off*-ADM group.
Conclusions: ADM use was associated with more rapid change in clinical measures, particularly in cognitive and functional domains. However, assumptions required to establish causation between ADM use and disease progression may not have been fully met, and further research is warranted.

Key Words: Huntington's disease; antidopaminergic; antipsychotic; vesicular monoamine transporter 2; targeted maximum likelihood estimation

In Huntington's disease (HD), antidopaminergic medications (ADM) are often used for symptomatic treatment of chorea and behavioral disturbances. These medications consist of first- and second-generation antipsychotics and vesicular monoamine transporter 2 (VMAT2) inhibitors. These medications carry dose-dependent risks for serious side effects that affect cognition, motor function, and overall quality of life.

Importantly, ADMs provide only palliative treatment without affecting disease progression, and the risk–benefit of off-label antipsychotics in HD remains controversial.[1–4] Well-documented common side effects of

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ADMs include sedation, impaired cognition, somnolence, depression, apathy, and suicidality as well as extrapyramidal side effects (EPSE).[5–11] It is well established that the concomitant use of VMAT2 inhibitors, multiple antipsychotics, or medications that inhibit ADM metabolism (eg, CYP2D6) increases the risk and severity of ADM side effects.

Strong evidence from large prospective HD studies in Europe and the United States consistently shows ADM use is associated with worsening measures of cognition and functional capacity. For example, data from the European REGISTRY cohort showed that patients treated with ADMs ($n = 320$) experienced accelerated functional decline compared to patients not taking ADMs ($n = 331$), measured using total functional capacity (TFC), Functional Assessment (FA), and Independence Scale (IS).[6] In agreement, a recent longitudinal observational study from the Enroll-HD dataset demonstrated that propensity-matched patients, for example, for disease stage, prescribed ADMs ($n = 466$) exhibited a more rapid decline in measures of function and cognition compared to those not using ADMs ($n = 466$). Moreover, patients demonstrated increased worsening measures of cognitive symptoms after initiating ADMs, such as Stroop Word Reading (SWR) and Symbol Digit Modalities Test compared to the period before ADM initiation.[5]

In a pivotal, double-blind, placebo-controlled trial of tetrabenazine, and the open-label follow-up study, though chorea improved, tetrabenazine treatment led to worse measures of functional and cognitive outcomes (composite Unified Huntington's Disease Rating Scale-Functional Assessment [UHDRS-FA]).[12,13] Interestingly, modern machine learning applied to the Enroll-HD dataset confirmed that antipsychotic and VMAT2 inhibitor use independently predicted worsening of clinical variables: cUHDRS, TFC, Symbol Digit Modalities Test (SDMT), and SWR.[14] The study evaluated 102 baseline variables to predict annual HD progression.

The cUHDRS, which integrates motor, cognitive, and functional domains, is one of the most powerful and sensitive outcome measures in HD clinical trials.[15] However, most studies have focused on ADMs' impact on motor signs and either function or cognition,[5,6] without assessing ADM impact across multiple domains, simultaneously. Taken together, it remains unclear whether ADMs negatively influence the underlying biology of HD progression, confound clinical outcome measures, or perform both.

In this study, we performed a causal analysis, emulating a randomized controlled trial (RCT) using the most recent Enroll-HD dataset,[16] the largest observational study of HD, to assess the impact of antipsychotics and VMAT2 inhibitors on motor, cognitive, and functional outcomes. Here we assessed the impact of antipsychotics and VMAT2 inhibitors, combined and separately, and examined their dose-dependent association with multiple outcome domains. To evaluate if the association between ADMs and clinical progression is restricted to this class of medications, we similarly evaluated the association between antidepressants use (ie, selective serotonin reuptake inhibitors [SSRI]) and clinical HD progression. Our analysis focused on a treatment population comparable to those in recent pivotal clinical trials with a 2-year follow-up. Our main findings show that ADM use was strongly associated with a more rapid decline in clinical outcome measures of HD, particularly in cognitive and functional domains. Although the assumptions necessary to establish a causal relationship between ADM use and disease progression may not have been fully met, these results provide a strong rationale for further investigation.

Patients and Methods

Participants

Participants were from the Enroll-HD study, Periodic Data Set 6 (PDS6), downloaded December 2022.[16] The initial database was filtered as follows: the first filter was to select *HTT* gene-expanded participants with CAG ≥36. The database was further filtered for "early manifest" criteria that were similar to those used in recent pivotal clinical trials (GenerationHD1 and PROOF-HD).[17] Inclusion criteria were age ≥25, UHDRS Diagnostic Confidence Level = 4, TFC ≥7, IS ≤90, and total motor score (TMS) ≥20. By definition, participants on more than one medication could qualify only for the ADM group, and the sample size varied slightly by outcome. A dosage group analysis was conducted with sample sizes reported here.

The final analyzed dataset included 1173 participants for the combined analysis of antipsychotic and VMAT2 inhibitors ($n = 380$ exposed/793 unexposed). The same unexposed groups were used throughout (see CONSORT-like flowchart in Fig. S1). The antipsychotic-only analysis included 1060 participants (267 exposed, 793 unexposed), whereas the VMAT2 inhibitor-only analysis had 915 participants (122 exposed, 793 unexposed).

To emulate an RCT, a new-user design that required three contiguous annual visits was adopted (Fig. 1A).[18,19] There were two comparator arms: *on*- and *off*-ADMs. Similar to an RCT, the on-ADM participants were required to be *off* ADM medications for the first visit (designated as "baseline") and then *on*-ADMs for all follow-up visits—note that researchers did not control the time of the first visit or when ADM treatment started. *Off*-ADM participants had to be ADM naive during all visits, with no exposure within or beyond the analysis window.

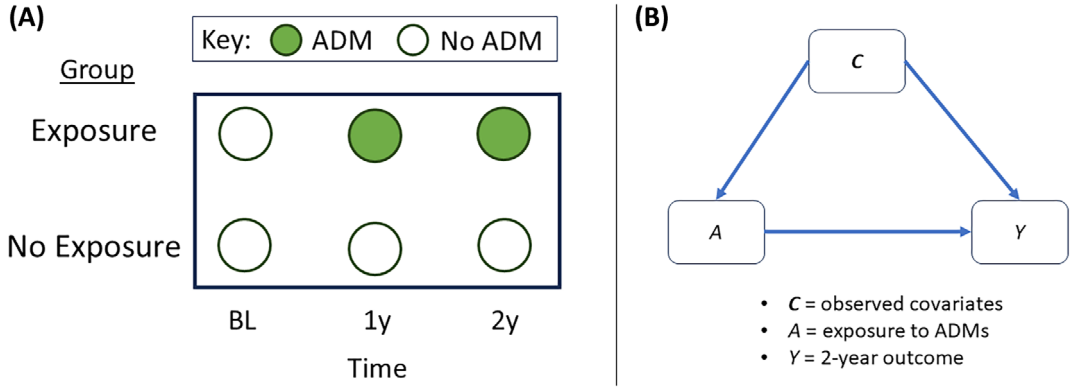

FIG. 1. Study design and causal analysis framework. (**A**) The new-user design in which both groups are *off* ADM (antidopaminergic medication) at baseline. The exposure group participants are on ADMs beginning sometime after baseline (not under researcher control). (**B**) The causal diagram for the analysis. The exposure mechanism is adjusted for the observed covariates (C-to-A arrow) and so is the outcome mechanism (C-to-Y arrow). [Color figure can be viewed at wileyonlinelibrary.com]

Clinical Outcome Measures

We separately analyzed 12 clinical outcome measures, all from the UHDRS.[20] This included the TFC, SDMT, SWR, TMS, and cUHDRS, which is a weighted combination of the TFC, SDMT, SWR, and TMS.[15] Subscales of the TMS were also analyzed, including chorea (7 items), gait balance (3 items), hand movement (5 items), bradykinesia scale (11 items), rigidity (2 items), dystonia (5 items), and oculomotor function (6 items).[21,22] For TFC, SDMT, SWR, and cUHDRS, lower scores indicate greater progression. Conversely, for TMS and all the motor subscales, larger values indicate greater progression. (Note that within the cUHDRS, the TMS is negatively weighted.) Importantly, for clarity, although TMS is part of the cUHDRS, we refer to TFC, SDMT, SWR, and cUHDRS as "nonmotor" and the TMS and motor subscales as "motor" variables.

Statistical Modeling and Causal Analysis

We conducted a causal analysis, accounting for 27 baseline covariates, focusing on exposure and outcome variables (Fig. 1B). Our analysis employed the *targeted maximum likelihood estimation* (*TMLE*), a semiparametric method that adjusts for covariates in both exposure (*on*/*off* medication) and outcome.[23] This approach shares similarities with propensity score weighting and g-computation.[24] For initial predictions, ensemble machine learning reduces bias by handling nonlinear relationships, whereas TMLE's double covariate adjustment minimizes model misspecification and yields smaller variances than methods like propensity score matching or inverse probability weighting.[25,26] TMLE estimates can be interpreted as causal effects with observational data when certain assumptions hold.[27] We performed two analyses using TMLE. First, we estimated the average treatment effect (ATE) for the *on*-ADM versus *off*-ADM groups at 2 years, separately analyzing 12 outcomes using the same set of baseline covariates and exposure (*on*- vs. *off*-ADM). Second, we assessed the ATE for low and high doses of medication groupings using the same methodology as in the first analysis.

In the *first analysis*, the ATE was defined as the counterfactual mean difference between the *on*-ADM and the *off*-ADM groups at 2 years (adjusting for covariates).[28] The 12 outcomes were analyzed separately, with the same set of baseline covariates and the same exposure (*on*/*off* ADM). For the *nonmotor variables*, that is, TFC, SDMT, SWR, and cUHDRS, a negative value of ATE indicates the *on*-ADM group is worse than the *off*-ADM group. For the *motor variables*, that is, TMS and other motor subscales, a positive value of ATE indicates the exposed group is worse than the unexposed group.

The exposure variable was binary: 0 = *off*-ADM (unexposed), 1 = *on*-ADM (exposed). Exposed or *on*-ADM was defined as participants taking any antipsychotic and/or VMAT2 inhibitor (ie, tetrabenazine or deutetrabenazine). Antipsychotics were further categorized into two subgroups based on their pharmacology and side-effect profiles: old and new antipsychotics. These antipsychotic drug classifications are based on the potency of these drugs for D2 receptor antagonism. For example, older antipsychotics, such as olanzapine and risperidone, are characterized by their high D2 receptor affinity and strong antagonism, often associated with a greater risk of EPSEs due to prolonged D2 receptor occupancy.[29,30] On the contrary, newer antipsychotics, including aripiprazole and quetiapine,[31,32] either have lower D2 receptor affinity or act as partial agonists (eg, aripiprazole), reducing the likelihood of EPS by providing more balanced dopamine activity.[30,33] Ancillary analysis of the subgroups is presented in the Supporting Information. Eleven antipsychotics were considered in the study (and including 2 VMAT2 inhibitors and 13 antidepressants, this totaled 26 medications). A full list of drugs for the exposed group is presented in Table S1. The most common medications for the exposed group were olanzapine (34%), tetrabenazine

(30%), risperidone (20%), citalopram (13%), and mirtazapine (13%). The other ADMs were used by less than 9% of the participants. Overall, 44% were on one ADM, 39% on two ADMs, 14% on three ADMs, and 3% on four ADMs.

For each outcome analysis, there were 27 baseline covariates that indexed demographic, progression, and behavioral domains for which the *on*/*off* ADM groups might differ. The covariates included the 12 baseline UHDRS variables, such as the baseline score of the outcome variable assessed at 2 years (within a ±6-month window), as well as age, CAG repeat expansion, CAP_{100},[34,35] sex, geographical region (coded as three dummy variables), age at motor onset, presence of a companion at the visit, and domain scores from the Problem Behavior Assessment-Short Form (PBA-s) for depression, irritability/aggression, psychosis, apathy, and executive function[35] (Table S7). Inference was based on the TMLE point estimate of the ATE and the 99% confidence interval (CI) (Table S8). When a CI did not contain 0, this was considered a statistically reliable result, indicating the means differed among the groups at 2 years. Per recommended practice,[36] each outcome was initially mapped to a [0,1] scale, and the resulting estimates of the ATE and the CIs were back transformed to the original metric.

In the *second analysis*, we estimated the ATE for dose groups of combinations of medications. Low- and high-dose groups were defined for each ADM medication based on labeling and expert knowledge[29,33,37–41] (Table S2). To maximize the sample size, combined dose groups were formed by aggregating the groups among certain medications. We formed five medication groups: (1) all ADMs, (2) antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, and tiapride), (3) newer antipsychotics (aripiprazole, quetiapine, and tiapride), (4) older antipsychotics (olanzapine and risperidone), and (5) VMAT2 inhibitors (deutetrabenizine and tetrabenazine). The exposed group sample size varied by medication class and outcome variable (see Table S4 and S5), but the largest was for ADM/TFC that had 163 high doses and 148 low doses. The same unexposed *off*-ADM group (N = 793) from the *first analysis* was used, as was TMLE and the same set of covariates. Each dose group was compared to the unexposed group constituting a set of two ATEs for each medication group: low versus unexposed and high versus unexposed.

The ensemble machine learning of TMLE used the general linear model, regularized regression, generalized additive models, Bayesian additive regression trees, and extreme gradient boosting (also see Supporting Information). The software packages of TMLE and SuperLearner were used in the R language for statistical computing.[25,42] Missing data with TMLE were handled by complete-case analysis (or list-wise deletion). Recent simulation results indicate that this approach can have very small bias unless the underlying causal model is complex (eg, if the outcome influences missingness in the predictor variables).[43] Both groups had similar profiles for the dropouts on key variables, such as cUHDRS, TFC, SWR/SDMT, TMS, and different PBA domains.

Results

Baseline Characteristics of Exposed and Unexposed Groups

Table 1 presents the unadjusted baseline descriptive statistics for the *off*-ADM group (unexposed, $n = 793$) and *on*-ADM group (exposed, $n = 380$). The last column (Z) lists the standardized mean difference. The largest Z difference was for chorea followed by TMS, with the exposed group having a larger mean in both instances. The exposed group also had a larger mean on all the PBA subscales, most pronounced for irritability/aggression, depression, and executive functioning (also see Table S7). CAP_{100} was also slightly larger for the exposed group. In addition, the exposed group had a slightly smaller mean for the cUHDRS, TFC, and cognitive variables (ie, worse on these variables relative to the unexposed group). Additional information regarding the importance of the covariates in the propensity score portion of the TMLE analysis and success of baseline balancing is presented in Figure S7 and Table S7.

Analysis 1: ADM Use and Clinical Change over 2 Years

The results of the first analysis are shown in Figure 2 (and Table S3), showing the ATE for each outcome, comparing the exposed (*on*-ADM) and unexposed (*off*-ADM) groups (box plots of key variables are shown in Fig. S2, and longitudinal trajectories are shown in Figs. S8 and S9). These graphs show the point estimate (vertical bar) of the ATE and the associated 99% CI. Faceting is by the class of ADM defining the exposure. A CI is colored black if it contains 0 (the 2-year mean difference is not statistically reliable) and red if it does not (the mean difference is statistically reliable). Additionally, to further evaluate the adjustment achieved by TMLE relative to a naive analysis, we compared the adjusted ATE estimates (see Figs. S6 and S7). Figure 2A shows the estimates for the *nonmotor variables* (a negative value indicates a smaller exposed group mean; cUHDRS, SDMT, SWR, and TFC). Here the *on*-ADM group exhibited significantly lower mean outcomes at 2 years compared to the *off*-ADM group across medication classes, except for cUHDRS in the VMAT2 group, which was not significant. Motor estimates (positive values) revealed consistently higher bradykinesia means in the exposed group for both ADM and antipsychotic medications (Fig. 2B), as well as larger means for gait balance and hand

TABLE 1 *Baseline descriptive statistics on key variables for the* off-*ADM group* (n = *793) (left) and the* on-*ADM group* (n = *380) (right)*

	Off-ADM					*On*-ADM					
Variable	**Mean**	**SD**	**Minimum**	**Md**	**Maximum**	**Mean**	**SD**	**Minimum**	**Md**	**Maximum**	**Z***
Age	54.1	12.2	25.3	54.4	86.1	53.8	12.3	27.1	53.9	85.1	−0.03
CAG length	43.6	3.6	36.0	43.0	65.0	43.9	3.3	39.0	43.0	58.0	0.08
CAP_{100}	108.0	13.6	59.4	108.0	162.5	109.9	12.7	67.9	110.4	152.6	0.15
Female	0.6	0.5	0.0	1.0	1.0	0.5	0.5	0.0	1.0	1.0	−0.07
Age at first motor signs	47.8	12.1	13.0	48.5	80.0	46.7	11.7	17.0	48.0	73.0	−0.09
Accompanied to visit	0.7	0.5	0.0	1.0	1.0	0.7	0.4	0.0	1.0	1.0	0.10
Region: Europe	0.7	0.4	0.0	1.0	1.0	0.7	0.5	0.0	1.0	1.0	−0.17
Region: North America	0.2	0.4	0.0	0.0	1.0	0.3	0.5	0.0	0.0	1.0	0.13
Region: Austrasia	0.0	0.1	0.0	0.0	1.0	0.0	0.2	0.0	0.0	1.0	0.10
Region: Latin America	0.0	0.1	0.0	0.0	1.0	0.0	0.1	0.0	0.0	1.0	0.04
PBA: depression	4.8	5.9	0.0	3.0	44.0	6.0	6.6	0.0	4.0	41.0	0.19
PBA: irritability/ aggression	2.7	4.0	0.0	1.0	32.0	4.1	5.7	0.0	2.0	32.0	0.26
PBA: psychosis	0.2	1.5	0.0	0.0	24.0	0.2	1.4	0.0	0.0	16.0	0.01
PBA: apathy	2.6	3.5	0.0	1.0	16.0	3.0	3.8	0.0	1.0	16.0	0.11
PBA: executive functioning	2.6	4.4	0.0	0.0	32.0	3.5	5.2	0.0	1.0	32.0	0.19
SDMT	23.6	9.3	0.0	22.0	63.0	22.5	8.7	0.0	21.0	51.0	−0.12
SWR	58.5	17.5	0.0	58.0	120.0	57.2	16.8	0.0	56.0	121.0	−0.07
TFC	9.5	1.7	7.0	9.0	13.0	9.1	1.6	7.0	9.0	13.0	−0.25
cUHDRS	8.3	2.4	0.8	8.3	15.5	7.7	2.2	1.9	7.7	13.4	−0.28
Motor: TMS	35.4	11.4	20.0	33.0	93.0	39.3	11.7	20.0	38.0	91.0	0.34
Motor: chorea	9.3	4.3	0.0	9.0	26.0	11.4	4.6	0.0	11.0	27.0	0.47
Motor: gait balance	3.5	1.8	0.0	3.0	12.0	3.8	1.9	0.0	4.0	12.0	0.14
Motor: hand movement	7.6	3.0	0.0	7.0	18.0	7.8	3.0	0.0	7.5	17.0	0.06
Motor: bradykinesia item	1.3	0.9	0.0	1.0	4.0	1.3	0.9	0.0	1.0	4.0	−0.03
Motor: bradykinesia scale	14.1	5.2	1.0	13.5	31.0	14.7	5.1	2.0	14.0	32.0	0.11
Motor: rigidity	1.4	1.4	0.0	1.0	7.0	1.2	1.3	0.0	1.0	6.0	−0.12
Motor: dystonia	2.7	3.1	0.0	2.0	20.0	3.2	3.3	0.0	2.0	17.0	0.16
Motor: oculomotor	8.0	3.9	0.0	7.0	24.0	8.8	4.1	0.0	8.0	23.0	0.21

*Standardized group mean difference based on the pooled standard error.
[a]Abbreviations: ADM, antidopaminergic medication; SD, standard deviation; Md, median; PBA, Problem Behavior Assessment; SDMT, Symbol Digit Modalities Test; SWR, Stroop Word Reading; TFC, total functional capacity; cUHDRS, composite Unified Huntington's Disease Rating Scale; TMS, total motor score.

movement. No significant motor differences were observed in the VMAT2 group.

Analysis 2: ADM Dosage Effects on Clinical Change

We performed a second analysis to investigate the dose-dependent effects of ADM use and variable changes in clinical measures of HD (Fig. 3). As mentioned earlier, the *on*-ADM group was split into high- and low-dose subgroups, each compared to the unexposed, *off*-ADM group. Negative values in the *on*-ADM group for *non-motor variables* indicate smaller means (Fig. 3A). In most cases, the high-dose *on*-ADM group exhibited smaller clinical outcome means than the *off*-ADM group, though some differences were not statistically significant.

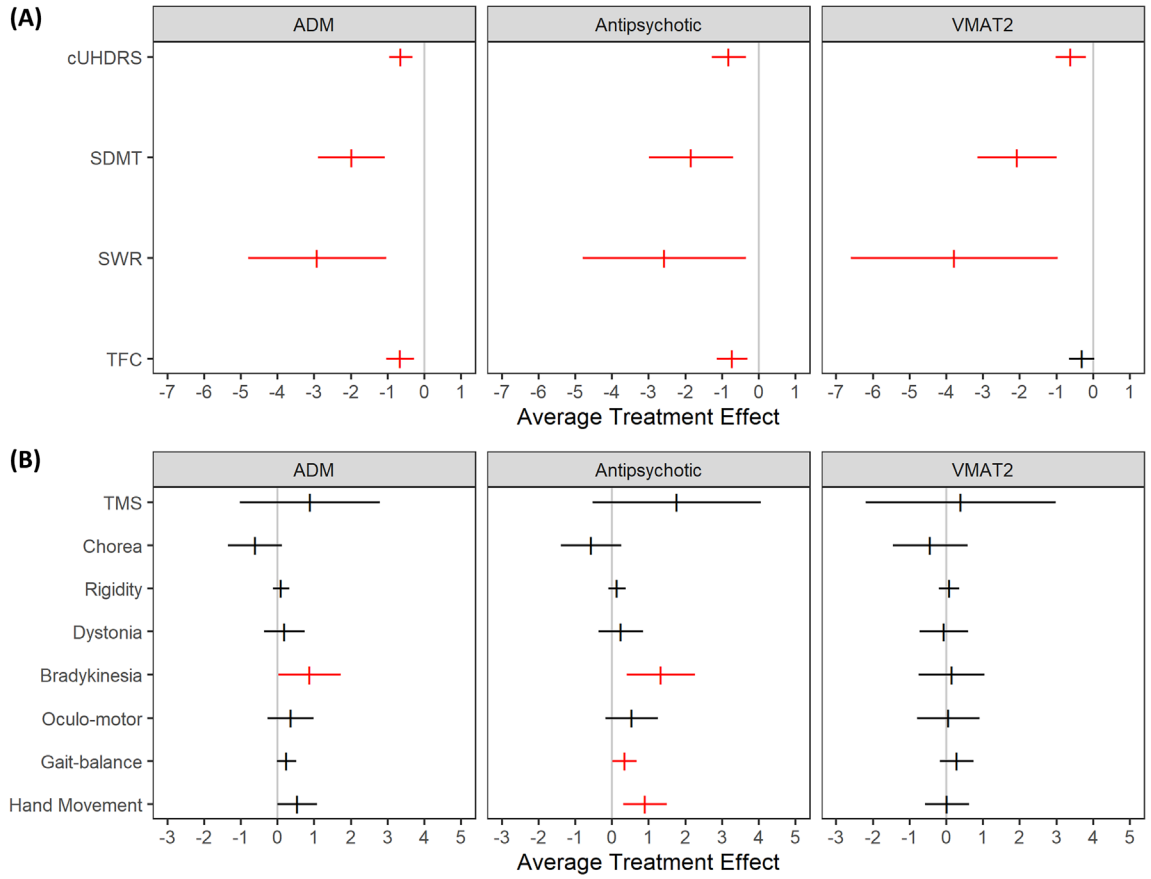

FIG. 2. TMLE (targeted maximum likelihood estimation) results by medication class. (**A**) The estimated average treatment effect (vertical bar) and 99% CI (confidence interval) for the nonmotor variables; a negative value indicates the exposed group had a smaller mean than the unexposed group at 2 years. (**B**) The results for the motor variables; a positive value indicates the exposed group had a larger mean than the unexposed group. A CI is black if it contains 0 (no mean difference) and red if it does not contain 0. [Color figure can be viewed at wileyonlinelibrary.com]

Specifically, high-dose groups for all ADMs and antipsychotics exhibited consistently smaller mean clinical outcomes for cUHDRS, SDMT, and SWR compared to the *off*-ADM group. For TFC, the lower-dose group's CI excluded 0 due to lower variability, not greater mean difference. For antipsychotics, the high-dose *on*-ADM group had reliably smaller means for SWR and TFC than the *off*-ADM group. For VMAT2 inhibitors, significant differences appeared only in SWR, whereas SDMT differed at both high and low doses between groups.

Figure 3B shows the results for *motor variable* outcomes, where positive values indicate larger means in the *on*-ADM group (Fig. 3B). Across all ADMs, antipsychotics, and VMAT2 inhibitors, most CIs showed no reliable differences between the high- or low-dose *on*-ADM groups and the *off*-ADM group. Exceptions included significant differences in TMS and dystonia for the VMAT2 inhibitor group, and hand movement in both antipsychotic- (high dose) and VMAT2 inhibitor-only groups (low dose). These results were corroborated using another analysis in which dose was treated as a continuous covariate (not defining any specific cutoff for lower/higher dose per drug). Higher doses were associated with increased worsening in clinical measures of cognition (SDMT and SWR) and in cUHDRS, which were statistically reliable. No statistically reliable dose effect was observed for the TFC, TMS, or motor subscores (Figs. S2 and S5). To assess the impact of antidepressant use, we similarly analyzed outcomes using antidepressants, for example, SSRIs. Here, no differences were found in any outcomes (cUHDRS, SDMT, SWR, TFC, TMS) between participants on antidepressants and those who were not (Fig. S3; Table S6).

Discussion

Our main findings support and extend previous observations that suggest that ADM use is associated with worsening outcome measures commonly studied in HD.[5,6] For the *on*-ADM group, there was worsening of outcome measures for cognitive performance, function, and the cUHDRS after 2 years. Our results for *motor variable* measures were mixed, with worsening

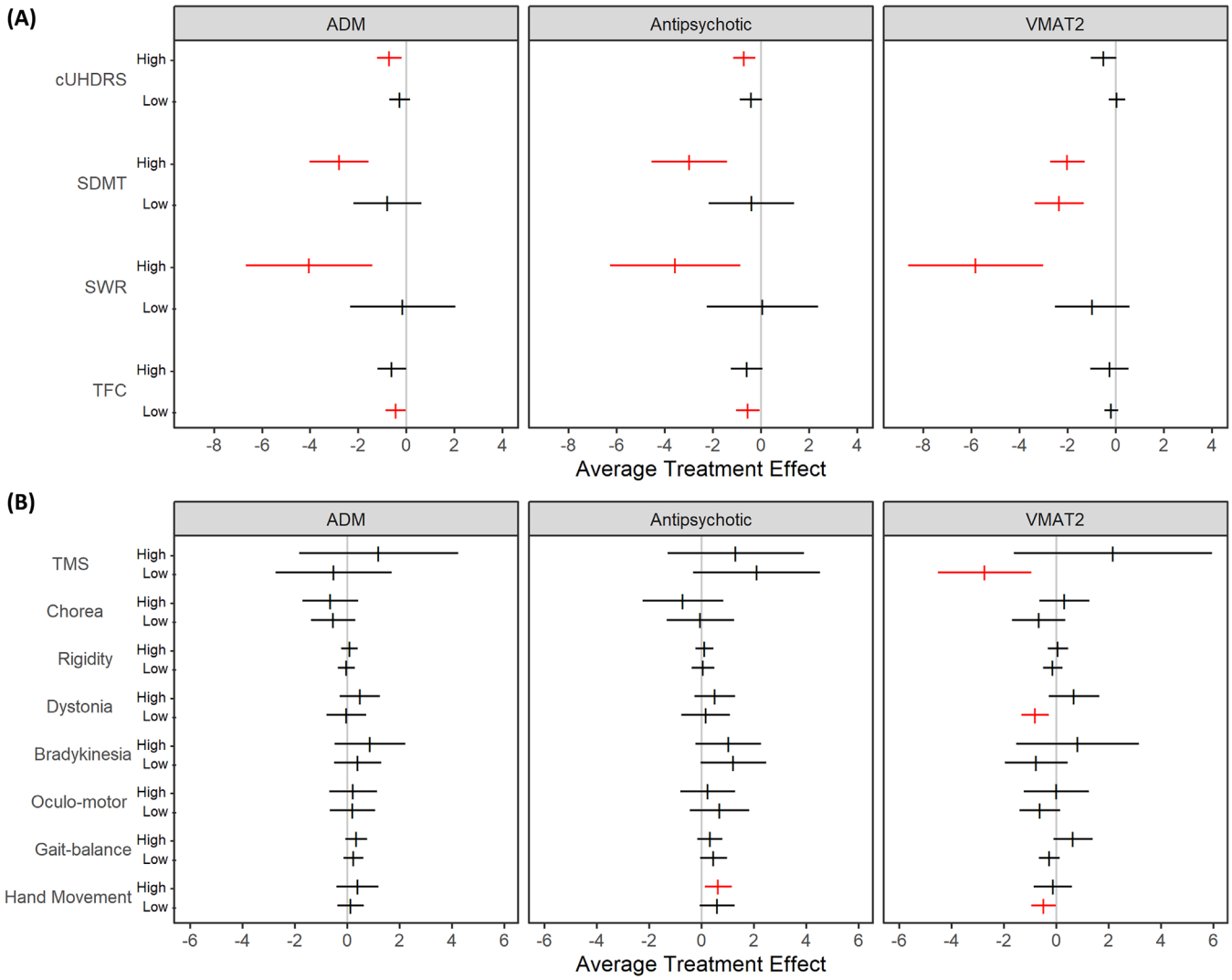

FIG. 3. Dose group results by ADM (antidopaminergic medication) class. (**A**) The estimated average treatment effect (vertical bar) and 99% CI (confidence interval) for the nonmotor variables for low- and high-dose exposure groups; a negative value indicates the exposed group had a smaller mean (ie, was worse) than the unexposed group at 2 years. (**B**) The results for the motor variables; positive values indicate the exposed group had a larger mean (ie, was worse) than the unexposed group. A CI is black if it contains 0 (no difference) and red if it does not contain 0. [Color figure can be viewed at wileyonlinelibrary.com]

in outcomes measures for bradykinesia but not for chorea or TMS. In our dosage study, participants receiving high-dose ADMs exhibited a statistically reliable difference in worsening measures of clinical progression relative to the *off*-ADM group. The results for motor signs were more complex, underscoring a need to examine subdomains. In agreement with previous reports,[6] we observed worsening for bradykinesia but not for oculomotor outcomes.

The biological effects of ADMs in the central nervous system still require investigation. Although VMAT2 inhibitors like tetrabenazine and deutetrabenazine are approved for treating chorea in HD, regulatory labels warn of risks, including cognitive decline, reduced alertness, mood changes, and decreased functional capacity. The use of VMAT2 inhibitors may also contribute to sedation and other dose-dependent side effects that can confound the interpretation of clinical variable change in clinical care settings.[12] Only one short-term, 12-week-long, placebo-controlled study has shown that ADM use was associated with worsening cognition and function in HD patients, that is, tetrabenazine.[12] As such, most evidence linking ADM use to clinical change comes from observational, natural history studies rather than extended RCTs, which precludes establishing a definitive causal relationship. A clearer understanding of ADM's impact on cognitive, motor, and functional outcomes would improve clinical decisions and trial designs for HD treatments. In the present study, we performed a series of analyses to investigate a potential causal relationship between ADM use and increased progression in HD clinical measures.

We employed a new-user design and adjusted for a large number of baseline covariates using state-of-the-

art statistical methods for causal analysis. The analytical platform captures baseline characteristics before the initiation of ADM use which helps control for possible confounding factors, that is, disease severity, prior medication use, psychiatric comorbidities, age, sex, and genetic predispositions, ensuring a more accurate estimation of treatment effects.

A limitation of our study is the lack of precision in participants' medical history on prior ADM use, hindering our ability to confidently determine causality. Certainly for these individuals, the baseline visit may have acted as a brief wash-out period, but "exposure during the first follow-up" would not represent a true first-time ADM use. In this respect, the *on*-ADM group may have been qualitatively different from the *off*-ADM group, in regard to outcome measures prior to or at baseline. Quantitative initial differences were also present at baseline—the *on*-ADM group had a more progressed profile (Table 1). Baseline differences may have influenced our results, as patients who are more progressed at baseline tend to experience slower rates of decline in TFC as the disease advances,[21] potentially masking functional changes over time. Our analyses successfully adjusted for these baseline differences (Fig. S6), but this may have been an inadequate approximation to random assignment of exposure. Statistical adjustment for confounders is necessary with exposure groups that are not randomly assigned.[27] Although the doubly robust procedure has several advantages, causal conclusions from its application require no omitted confounders (among other assumptions). We accounted for 27 baseline covariates, but it was not exhaustive, and likely missed relevant confounders necessary to equate the groups. It is also possible that the estimated exposure effect size in our analysis may not be sufficient to translate into clinically meaningful differences.[44] Finally, a determination of causation between ADM use and HD clinical progression was limited due to an inconsistent definition of exposure among participants—ADM dose varied within the low-/high-dose groups, and duration of use after baseline was not controlled. Nonetheless, our study shows that (1) HD participants using ADMs exhibited statistically reliable worsening of clinical measures after adjusting for a large number of baseline covariates, and that (2) high ADM dosing was associated with worsening of clinical measures compared to low ADM doses. Of course, due to the limitations of our analytical assumptions, our results should not be used to inform reconsideration of the current standard of care. Antipsychotics remain important tools for managing HD symptoms, and this study's data should not guide clinical practice.

Our study does raise the question of whether there is a direct biological impact of ADMs on HD severity and progression. Although not part of the main study, the antidepressant results revealed no reliable differences among any of the outcome measures for those participants only on antidepressants (though the sample size was smaller, the point estimates were closest to 0; see Fig. S4). Although there are differences in the reasons for prescribing an ADM versus an antidepressant, it seems that general medication exposure (for any reason) does not account for faster clinical change in our results. Thus, our study findings suggest that ADMs may exert a pronounced and specific influence on clinical measurement of HD progression rate compared to other types of medications. ADMs help control chorea by modulating dopaminergic signaling, but they may also negatively impact neuronal function. Chronic dopamine inhibition, for example, may lead to compensatory changes in other neurotransmitter systems or exacerbate neuronal dysfunction, especially in HD-vulnerable regions like the striatum.[30,45] However, it is not clear whether the worsening of clinical measures associated with ADM use is permanent. Here, an RCT involving the withdrawal of ADMs would be necessary to observe if improvements or stabilization occurs after ADM washout. High-dose antipsychotics carry increasing risks of cognitive and functional impairments due to dopamine D2 receptor antagonism. Prolonged blockade can worsen motor symptoms and lead to EPSEs, which is common in HD.[30] The deterioration of motor function, particularly through prolonged D2 receptor antagonism, raises significant concerns, potentially reflecting more severe neurodegeneration and necessitating more aggressive clinical intervention. Second-generation antipsychotics, for example, aripiprazole[32], could potentially have proapoptotic effect in nonneuronal cells such as breast cancer cell lines, increasing proapoptotic markers, including CASP3 and BCL10.[46] Both haloperidol and olanzapine have also been shown to increase messenger RNA levels of CASP3.[47] In this context, clinicians could consider second-generation antipsychotics, but with careful evaluation of dosage, including reduction or tapering—as indicated by regulatory-approved labeling.

In conclusion, our study provides further evidence that ADM use is strongly associated with worsening in clinical measures of HD progression. Although we used a novel naturalistic study design and rigorous statistical methods appropriate for causal inference, limitations remain, and our methods cannot substitute for true physical balanced randomization of patients regarding the use of ADMs at baseline. Our results also strongly suggest that ADMs may have a powerful influence on the rate of change of HD clinical measures; and therefore, future clinical trials should ensure balanced randomization of patients regarding ADM use at baseline or include a statistical plan that evaluates outcomes both with and without ADMs.

Author Roles: M.G.: Conceptualized the study, provided input on study design, contributed to drafting and editing the manuscript, and was involved in the final manuscript production.

Y.P.G.: Provided scientific input on study design and data interpretation, participated in project management, and contributed to manuscript drafting and revision.
H.S.: Involved in coordination of study activities and manuscript review.
J.L.: Contributed to the study design, performed core statistical analyses and data interpretation, contributed to writing the first draft and the final manuscript.
A.M.T.: Provided scientific input and contributed to data interpretation, supervised all aspects of manuscript production, and wrote the final manuscript copy.
M.R.H.: Supervised the project, conceptualized the study, contributed to data interpretation and manuscript production.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. Dean M, Sung V. Review of deutetrabenazine: a novel treatment for chorea associated with Huntington's disease. Drug Des Devel Ther 2018;12:313–319.
2. Yero T, Rey JA. Tetrabenazine (Xenazine), an FDA-approved treatment option for Huntington's disease-related chorea. PT Peer Rev J Formul Manag 2008;33(12):690–694.
3. Ross CA, Tabrizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. Lancet Neurol 2011;10(1):83–98.
4. Armstrong MJ, Miyasaki JM, American Academy of Neurology. Evidence-based guideline: pharmacologic treatment of chorea in Huntington disease: report of the guideline development subcommittee of the American Academy of Neurology. Neurology 2012;79(6):597–603.
5. Harris KL, Kuan WL, Mason SL, Barker RA. Antidopaminergic treatment is associated with reduced chorea and irritability but impaired cognition in Huntington's disease (Enroll-HD). J Neurol Neurosurg Psychiatry 2020;91(6):622–630.
6. Tedroff J, Waters S, Barker RA, Roos R, Squitieri F, EHDN Registry Study Group. Antidopaminergic medication is associated with more rapidly progressive Huntington's disease. J Huntingt Dis 2015;4(2):131–140.
7. package insert. Ingrezza (valbenazine) [package insert]. Neurocrine Biosciences, Inc; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218390s000lbl.pdf
8. package insert deutetrabenazine. Austedo (deutetrabenazine) [package insert]. Silver Spring, MD, USA: Teva Pharmaceuticals USA, Inc; 2017 Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208082s000lbl.pdf.
9. package insert tetrabenazine. Xenazine (tetrabenazine) [package insert]. Lundbeck; 2019. https://www.lundbeck.com/content/dam/lundbeck-com/americas/united-states/products/neurology/xenazine_pi_us_en.pdf
10. package insert risperidone. Risperdal (risperidone) [package insert]. Janssen Pharmaceuticals, Inc. 2025. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/RISPERDAL-pi.pdf
11. package insert olanzapine. Zyprexa (olanzapine) [package insert]. Eli Lilly and Company; 2009. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020592s062021086s040021253s048lbl.pdf
12. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. Neurology 2006;66(3):366–372.
13. Huntington Study Group/TETRA-HD Investigators, Frank S. Tetrabenazine as anti-chorea therapy in Huntington disease: an open-label continuation study. BMC Neurol 2009;9:62.
14. Ghazaleh N, Houghton R, Palermo G, Schobel SA, Wijeratne PA, Long JD. Ranking the predictive power of clinical and biological features associated with disease progression in Huntington's disease. Front Neurol 2021;12:678484.
15. Schobel SA, Palermo G, Auinger P, Long JD, Ma S, Khwaja OS, et al. Motor, cognitive, and functional declines contribute to a single progressive factor in early HD. Neurology 2017;89(24):2495–2502.
16. Landwehrmeyer GB, Fitzer-Attas CJ, Giuliano JD, et al. Data analytics from enroll- HD, a global clinical research platform for Huntington's disease. Mov Disord Clin Pract 2017;4(2):212–224. https://doi.org/10.1002/mdc3.12388
17. McColgan P, Thobhani A, Boak L, et al. Tominersen in adults with manifest Huntington's disease. N Engl J Med 2023;89(23):2203–2205. https://doi.org/10.1056/NEJMc2300400
18. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. Nat Rev Rheumatol 2015;11(7):437–441.
19. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158(9):915–920.
20. Unified Huntington's disease rating scale: reliability and consistency. Mov Disord 1996;11(2):136–142.
21. Marder K, Zhao H, Myers RH, et al. Rate of functional decline in Huntington's disease. Neurology 2000;54(2):452–458.
22. Vaccarino AL, Anderson K, Borowsky B, Duff K, Giuliano J, Guttman M, et al. An item response analysis of the motor and behavioral subscales of the unified Huntington's disease rating scale in huntington disease gene expansion carriers. Mov Disord 2011;26(5):877–884.
23. Van Der Laan MJ, Rose S. Targeted Learning: Causal Inference for Observational and Experimental Data [Internet]. New York, NY: Springer New York; 2011 [cited 2024 Sep 26]. (Springer Series in Statistics). Available from: https://link.springer.com/10.1007/978-1-4419-9782-1.
24. Robins J. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. Math Model 1986;7(9–12):1393–1512.
25. Gruber S, Laan MJVD. Tmle: an R package for targeted maximum likelihood estimation. J Stat Softw [Internet] 2012 [cited 2024 Sep 26];51(13):2–22. Available from: http://www.jstatsoft.org/v51/i13/
26. Smith MJ, Phillips RV, Luque-Fernandez MA, Maringe C. Application of targeted maximum likelihood estimation in public health and epidemiological studies: a systematic review. Ann Epidemiol 2023;86:34–48.e28.

27. Schuler MS, Rose S. Targeted maximum likelihood estimation for causal inference in observational studies. Am J Epidemiol 2017; 185(1):65–73.
28. Dang LE, Balzer LB. Start with the target trial protocol, then follow the roadmap for causal inference. Epidemiology 2023;34(5): 619–623.
29. Divac N, Prostran M, Jakovcevski I, Cerovac N. Second-generation antipsychotics and extrapyramidal adverse effects. Biomed Res Int 2014;2014:1–6.
30. Siafis S, Wu H, Wang D, et al. Antipsychotic dose, dopamine D2 receptor occupancy and extrapyramidal side-effects: a systematic review and dose-response meta-analysis. Mol Psychiatry 2023;28(8): 3267–3277. https://doi.org/10.1038/s41380-023-02203-y
31. package insert quetiapine. Seroquel (quetiapine) [package insert]. Astrazeneca.pdf; 2021. https://www.astrazeneca.ca/content/dam/az-ca/downloads/productinformation/seroquel-product-monograph-en.pdf
32. package insert. Aripiprazole (Abilify Asimtufii) [package insert]. Otsuka America Pharmaceutical, Inc.pdf; 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217006s000lbl.pdf
33. Sykes DA, Moore H, Stott L, Holliday N, Javitch JA, Lane JR, et al. Extrapyramidal side effects of antipsychotics are linked to their association kinetics at dopamine D2 receptors. Nat Commun 2017; 8(1):763.
34. Ross CA, Aylward EH, Wild EJ, et al. Huntington disease: natural history, biomarkers and prospects for therapeutics. Nat Rev Neurol 2014;10(4):204–216. https://doi.org/10.1038/nrneurol.2014.24
35. Warner JH, Long JD, Mills JA, Langbehn DR, Ware J, Mohan A, et al. Standardizing the CAP score in Huntington's disease by predicting age-at-onset. J Huntingt Dis 2022;11(2):153–171.
36. Frank HA, Karim ME. Implementing TMLE in the presence of a continuous outcome. Res Methods Med Health Sci 2024;5(1):8–19.
37. Stahl SM. Stahl's essential psychopharmacology: Neuroscientific basis and practical applications. 4th ed. New York, NY, US: Cambridge University Press; 2013 xv, 608.
38. Markowitz JS, Brown CS, Moore TR. Atypical antipsychotics part I: pharmacology, pharmacokinetics, and efficacy. Ann Pharmacother 1999;33(1):73–85.
39. Schotte A, Bonaventure P, Janssen PF, Leysen JE. In vitro receptor binding and in vivo receptor occupancy in rat and Guinea pig brain: risperidone compared with antipsychotics hitherto used. Jpn J Pharmacol 1995;69(4):399–412.
40. Shapiro DA, Renock S, Arrington E, Chiodo LA, Liu LX, Sibley DR, et al. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology 2003;28(8): 1400–1411.
41. Huys D, Hardenacke K, Poppe P, Bartsch C, Baskin B, Kuhn J. Update on the role of antipsychotics in the treatment of Tourette syndrome. Neuropsychiatr Dis Treat 2012;8:95. https://doi.org/10.2147/ndt.s12990
42. Polley E. ecpolley/SuperLearner [Internet]; 2024. [cited 2024 Oct 15]. Available from: https://github.com/ecpolley/SuperLearner.
43. Dashti SG, Lee KJ, Simpson JA, White IR, Carlin JB, Moreno-Betancur M. Handling missing data when estimating causal effects with targeted maximum likelihood estimation. Am J Epidemiol 2024;193(7):1019–1030.
44. Hamilton JL, Mills JA, Stebbins GT, Long JD, Fuller RLM, Sathe S, et al. Defining clinical meaningfulness in Huntington's disease. Mov Disord 2023;38(6):1036–1043.
45. Cramb KML, Beccano-Kelly D, Cragg SJ, Wade-Martins R. Impaired dopamine release in Parkinson's disease. Brain 2023; 146(8):3117–3132.
46. Badran A, tul-Wahab A, Zafar H, Mohammad N, Imad R, Ashfaq Khan M, et al. Antipsychotics drug aripiprazole as a lead against breast cancer cell line (MCF-7) in vitro. Pizzo SV, editor. PLoS One 2020;15(8):7–14.
47. Osacka J, Kiss A, Bacova Z, Tillinger A. Effects of antipsychotics, haloperidol and olanzapine, on the expression of apoptosis-related genes in mouse mHippoE-2 cells and rat hippocampus. Endocr Regul 2023;57(1):152–161.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.