Regular Research Article

Stroke Risk Among Elderly Users of Haloperidol and Typical Antipsychotics Versus Atypical Antipsychotics: A Real-World Study From a US Health Insurance Claims Database

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ABSTRACT

Background: *We estimated stroke risk associated with new exposure to haloperidol, or any typical antipsychotic, versus atypical antipsychotic among patients aged ≥65 years regardless of dementia status.* ***Methods:*** *IBM MarketScan Medicare Supplemental Database data (January 1, 2001 to December 31, 2017) were used. Stroke risk for new users of typical antipsychotics (T1 cohort) or haloperidol (T2 cohort) was compared with new users of atypical antipsychotics (C1 cohort) aged ≥65 years. Crude incidence rate (IR) and incidence proportion of stroke were estimated within each cohort and gender subgroup. Three propensity score (PS) matching strategies were employed: Unadjusted (crude), Sentinel PS replication, and a large-scale regularized regression model (adapted PS).* ***Results:*** *Overall, 36,734 (T1), 24,074 (T2), and 226,990 (C1) patients were included. Crude IRs for stroke per 1000 person-years were 17.67 (T1), 23.74 (T2), and 14.17 (C1). In preplanned analyses, PS-matched calibrated hazard ratio (cHR) for stroke T1 versus C1 cohort was 1.08 (95% calibrated confidence interval [cCI] = 0.75, 1.55) with Sentinel PS strategy and 1.31 (95% cCI = 1.07, 1.60) with adapted PS strategy. The cHR for stroke in patients of T2 versus C1 was 1.69 (95% cCI = 1.08, 2.75) with Sentinel PS strategy and 1.45 (95% cCI = 1.17, 1.80) with adapted PS strategy.* ***Conclusion:*** *Stroke risk in elderly new users of haloperidol was elevated compared to new users of atypical antipsychotics and was elevated for typical antipsychotics using the adapted PS strategy.* (Am J Geriatr Psychiatry 2021; 29:499−510)

Highlights

- It is uncertain whether stroke risk associated with the use of antipsychotic medications in elderly patients (aged ≥65 years) differs between the typical antipsychotics and atypical antipsychotics. Therefore, this study estimated and compared the stroke risk among elderly new users of typical antipsychotics and haloperidol versus atypical antipsychotics, regardless of dementia status.
- Results of the study showed that the propensity score (PS) matched calibrated hazard ratio (cHR) for stroke in patients exposed to typical antipsychotics versus atypical antipsychotics was 1.08 (95% calibrated confidence interval [cCI] = 0.75, 1.55) with Sentinel PS strategy and 1.31 (95% cCI = 1.07, 1.60) with adapted PS strategy. The cHR for stroke in patients exposed to haloperidol versus atypical antipsychotics was 1.69 (95% cCI 1.08, 2.75, Sentinel PS strategy) and 1.45 (95% cCI 1.17, 1.80, adapted PS strategy).
- Risk of stroke in elderly new users of haloperidol and other typical antipsychotics was elevated as compared with new users of atypical antipsychotics. However; as most of the patients included in the typical antipsychotics' cohort were users of haloperidol, the increased stroke risk associated with typical antipsychotics cannot be considered strong evidence of a class effect.

INTRODUCTION

Antipsychotics are approved and prescribed to treat various conditions such as schizophrenia, mania, major depressive disorder, agitation, delusional disorder, psychosis, and Tourette's syndrome.[1] The haloperidol prescribing information[2] in the United States (US) does not warn about the risk of stroke but has a black box warning for an increased risk of death among elderly patients with dementia-related psychosis treated with antipsychotic drugs. Nonetheless, antipsychotics are used for indications such as neuropsychiatric symptoms of dementia, in the presence or absence of psychosis; such use is not approved by the Food and Drug Administration (FDA) and this off-label use has increased over the past few years.[3] Furthermore, off-label use of antipsychotics is becoming more common among elderly patients, i.e., those aged 65 years or older.[4]

A post-hoc combined analysis of selected randomized placebo-controlled studies of two second-generation antipsychotics, risperidone and olanzapine, showed a statistically and clinically significant excess of cerebrovascular events in those elderly patients who received active medication when compared to those who received placebo.[5,6] The magnitude of the difference persisted but was less if the events were restricted to stroke. Individual studies were neither designed nor powered to evaluate cerebrovascular adverse events. A similar evaluation of randomized controlled trials including typical antipsychotic agents was limited by the size of the studies available and greater heterogeneity in design.[7]

Multiple retrospective studies have reported an increased risk of stroke among elderly and nonelderly users of antipsychotics[8–11] and the risk may be increased even after brief exposure to an antipsychotic agent.[12] In addition, several retrospective studies have provided evidence regarding the risk of stroke in elderly users of antipsychotics,[13–15] especially among those who have been diagnosed with dementia.[16,17] Retrospective studies comparing typical with atypical antipsychotics for stroke risk have shown mixed results. Douglas et al. in a case-only study from the General Practice Research Database of the United Kingdom showed that exposure to atypical antipsychotics was associated with a higher risk of stroke as compared to typical antipsychotics but the confidence intervals (CIs) for the two estimates overlapped slightly.[17] In contrast, Sacchetti et al. in a study from the Italian Heath Search Database, including patients ≥65 years, compared several typical and atypical antipsychotic medications and showed contrasting results as compared to Douglas et al.[8] Similarly, Shin et al. conducted a retrospective cohort study by utilizing data from the National Claims Database from the Korean Health Insurance Review and Assessment Service (HIRA) and compared the risk of stroke in elderly users of typical and atypical

antipsychotics. The study showed that elderly users of haloperidol—a typical antipsychotic—had a greater risk of stroke as compared with elderly users of risperidone—an atypical antipsychotic agent.[16] A recent retrospective study by Taylor et al.[18] used the Sentinel distributed database to study stroke risk among non-elderly patients without dementia. They reported that the crude risk of stroke was higher among users of haloperidol and typical antipsychotics than among users of atypical antipsychotics, but after adjustment for confounding, the relative risk was not significantly increased.

We performed the current study that sought to emulate the Sentinel study by Taylor et al.[18] in a different database, using the same methods to compare the risk of stroke specifically among new users ≥65 years old, regardless of dementia status, of haloperidol versus atypical antipsychotics, and typical versus atypical antipsychotics. The comparison of stroke risk among new users of haloperidol versus atypical antipsychotics, and typical versus atypical antipsychotics in new users aged 18−64 years, regardless of dementia/no recent dementia, will be described in a separate report.

METHODS

Data Sources

Data were obtained from the IBM MarketScan Medicare Supplemental Database (MDCR) that represents health services of retirees in the United States with employer-sponsored Medicare supplemental coverage through privately insured fee-for-service, point-of-service, or capitated health plans. The data include adjudicated health insurance claims including outpatient pharmacy dispensing claims coded with National Drug Codes, inpatient and outpatient medical claims including diagnosis codes coded in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or ICD-10-CM, and procedure codes. The database was converted to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). A database converted to the OMOP CDM is a transformation of the source structure and content to a standardized structure and vocabulary for encoding healthcare information (such as drug utilization and condition occurrences), which allows for consistent application of standardized analytics for research.[19] As described by the Kaiser Family Foundation, employer-sponsored plans provide coverage to about 30% of traditional Medicare beneficiaries, or about 10 million persons. These beneficiaries tend to have both higher incomes and higher education levels, and are disproportionately white.[20]

The use of MDCR was reviewed by the New England Institutional Review Board and determined to be exempt from broad Institutional Review Board approval, as this research project did not involve human patient research.

Study Design and Study Population

This retrospective comparative cohort study included data available from January 1, 2001 through December 31, 2017 with the earliest cohort entry starting July 1, 2001, where prior data from 2001 contributed information on the conditions required for cohort inclusion. Thus, the start and end dates were similar to those of the Sentinel study (January 1, 2001−September 30, 2015).

The present study used databases that have been converted to the OMOP CDM. This model standardizes both the structure and content of data by mapping coding systems like ICD-9-CM to SNOMED-CT concepts by leveraging relationships that have been curated by the Unified Medical Language System.[21] Typically, we define the cohorts in SNOMED-CT by walking up and down the comprehensive hierarchy. The relationships between SNOMED-CT and ICD-9-CM (and ICD-10-CM) dictate the codes that are included in the definition. In this case, we were limited to the ICD-9-CM codes used in the Sentinel study by Taylor et al.[18] to define stroke. We used a similar approach and cross-walked from ICD-9-CM to SNOMED-CT. From there, we examined the relationships between SNOMED-CT and ICD-10-CM. We did not have a reference from Taylor et al.[18] regarding the ICD-10-CM codes to be used and therefore relied on the mappings provided by the Unified Medical Language System. These ICD-10-CM codes were used for the incidence comparison (see Supplementary Figure 1). As these figures indicated a change in incidence estimates after September 30, 2015, we did a post-hoc analysis that was limited

to the data through September 30, 2015 (see in the following sections).

New users of typical antipsychotics, haloperidol, or atypical antipsychotics who were ≥65 years old entered the study cohort when they first met all of the following conditions: Received a dispensing of a typical or atypical antipsychotic, had at least 183 days of continuous observation before that dispensing, during the 183 days up to and including the dispensing date had no diagnosis of stroke or cancer, and during the 183 days before that dispensing had received no dispensing of a typical or atypical antipsychotic. The dispensing date was the patient's index date. Patients who were exposed to typical and atypical antipsychotics on their index date were excluded.

The present study focused on two target cohorts (T1: new users of typical antipsychotics and T2: new users of haloperidol) and one comparator cohort (C1: new users of atypical antipsychotics). We compared the stroke risk in T1 cohort to the stroke risk in the C1 cohort, and the stroke risk in T2 cohort to the stroke risk in the C1 cohort. For each pairwise comparison, patients contributed "on-treatment" time at risk in the cohort for which they first qualified starting from the day after they entered that cohort until the first of: receiving a medication associated with the other cohort, having the study outcome (see in the following sections), having a gap of more than 30 days in the supply of the cohort-defining drug (more than 30 days from the end of the days' supply one dispensing to the next dispensing), reaching the end of insurance enrollment, or reaching the end of the study. Stroke as the study outcome was defined by a diagnosis code for stroke (using the same code list as the Sentinel study[18]) as the primary condition in the insurance claim associated with an inpatient stay. The protocol was preregistered at https://clinicaltrials.gov/ct2/show/NCT04002700. The full protocol and an accompanying file of code lists used for identifying typical antipsychotics, haloperidol, atypical antipsychotics, and stroke are both publicly available at https://data.ohdsi.org/StrokeRiskInElderlyApUsers/.

Reimbursement coding requirements in the US changed from ICD-9-CM to ICD-10-CM on October 1, 2015 (see Supplementary Figure 1). We therefore calculated and visualized the yearly incidence rate per 1000 person-years of the stroke outcome in the database population. We observed a considerable decrease in the yearly incidence rate after 2015,

reflective of the coding change and indicating that the ICD-9-CM codes used for stroke correspond to ICD-10-CM codes that identify a clinically different patient population. Because this change appeared likely to affect the incidence of stroke in the study population, we conducted a post-hoc analysis where the study end-date was redefined as September 30, 2015. That end-date for the post-hoc analysis was selected to reflect the end-date of the Sentinel study,[18] whose end date coincided with the switch of many US health care databases from ICD-9-CM to ICD-10-CM.

Statistical Analysis

The crude incidence rate (IR) and incidence proportion (IP) of stroke were estimated within each exposure cohort and predefined gender subgroup. IRs were calculated as the number of patients with the outcome during each time-at-risk window divided by the total time-at-risk in years and were reported as IR/1000 person-years. IP was calculated as the number of patients with the outcome during each time-at-risk window divided by the total number of patients with time-at-risk and were reported as IP/1000 patients. Population-level effect estimation analyses were performed using a comparative cohort design including two pairwise comparisons: T1 versus C1 and T2 versus C1.

Propensity score (PS) matching was used to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates.[22] Three PS adjustment approaches were used in the present study. First was the unadjusted (crude) estimate. Second was the Sentinel PS replication (Sentinel PS strategy), which involved 1:1 matching on a PS based on the 31 covariates used in the Sentinel study[18] with a caliper of 0.05 on the PS scale. Third was the large-scale regularized regression model involving PS estimation (adapted PS strategy) using predicted probability from a large-scale regularized logistic regression model, fit with a Laplace prior (LASSO) using all observed covariates, including a recent diagnosis of dementia as input and 1:10 variable ratio matching with a caliper of 0.2 of the standard deviation of the logit of PS.[23] Covariate balance was summarized by computing, before and after PS matching, the mean value and the associated standardized mean difference for each baseline covariate.

Negative control outcomes (outcomes that are not causally associated with any of the exposure cohorts) were used for empirical calibration. Positive control outcomes were based on these negative controls with the true effect size artificially increased to a desired effect size by addition of simulated outcomes. Using the negative and positive controls, a systematic error model was fitted against the control estimates and used to calibrate the hazard ratio (HR) and CI for the stroke estimate to account for potential unmeasured confounding.[24]

The HRs for the outcome during the time-at-risk was estimated by applying a Cox proportional hazards model conditioned on the PS matched sets. For each outcome model, the uncalibrated and empirically calibrated HR, 95% CI, and p-value[25] were reported. For both cohorts being compared, patients were required to have at least 1 day of continuous observation after the time-at-risk start. The time-to-event of the outcome was determined by calculating the number of days from start of the time-at-risk window to the date of the outcome event.

RESULTS

All study results are publicly available through an interactive, online tool at the URL given above.

Patient Characteristics

During the study period (January 1, 2001 through December 31, 2017), 36,734 patients were identified for inclusion in the T1 cohort, 24,074 patients in the T2 cohort, and 226,990 patients in the C1 cohort. Before matching, the mean ages of the patients in T1, T2, and C1 were, 80.9 years, 83.7 years, and 80.5 years, respectively, and the proportions of women were 54.4%, 60.8%, and 63.3%, respectively (Supplementary Table 1). The distribution of baseline covariates before and after matching 1:1 on the variables used in the Sentinel PS strategy are shown in Supplementary Table 2 and after 1:10 matching on the variables used in the large-scale, regularized logistic regression PS strategy are shown in Table 1.

The covariate balance before and after PS matching for T1 versus C1 and T2 versus C1 comparisons using 1:1 PS matching and 1:10 PS matching is illustrated in Figure 1 and Figure 2, respectively. The stroke incidence rates and proportions before and after matching are shown in Supplementary Table 3. The 1:10 PS matching addressed more sources of covariate imbalance as compared with the 1:1 PS matching.

Crude Stroke Incidence

The crude IR for stroke per 1000 person-years (PY) was 17.67 for patients of the T1 cohort, 23.74 for the T2 cohort, and 14.17 for the C1 cohort during the pre-planned analyses. These IRs were similar in the post-hoc analyses (T1: 18.29, T2: 25.22, C1: 14.88 per 1000 PY) (Table 2).

Risk of Stroke: Time to First Postindex Stroke Analyses

The preplanned analyses for time-to-first-postindex primary inpatient stroke analyses showed that the calibrated HR (cHR) for stroke in patients of T1 versus C1 cohort was 1.08 (95% calibrated confidence interval [cCI] = 0.75, 1.55) with the Sentinel PS strategy (Fig. 3) and 1.31 (95% cCI = 1.07, 1.60) with the adapted PS strategy (Fig. 4). The cHR for stroke in patients of T2 versus C1 cohort was 1.69 (95% cCI = 1.08, 2.75) with the Sentinel PS strategy (Fig. 3) and 1.45 (95% cCI = 1.17, 1.80) with the adapted PS strategy (Fig. 4). Results of the post-hoc analyses were broadly similar to that of preplanned analyses (Table 3).

DISCUSSION

PS matching seeks to control confounding in observational studies that compare two nonrandomized interventions. Effective confounding control through PS matching results from its ability to balance patient baseline characteristics that otherwise predicts both treatment assignment and the outcome (i.e., confounders). The large-scale PS used in this study included all observed baseline characteristics as potential confounders for model input, including versions of the 31 variables used in the Sentinel study PS. Therefore, in the current study, the large-scale PS was expected to balance on more patient baseline characteristics than the PS matching from the Sentinel study, thereby reducing the likelihood that observed baseline differences between intervention groups could
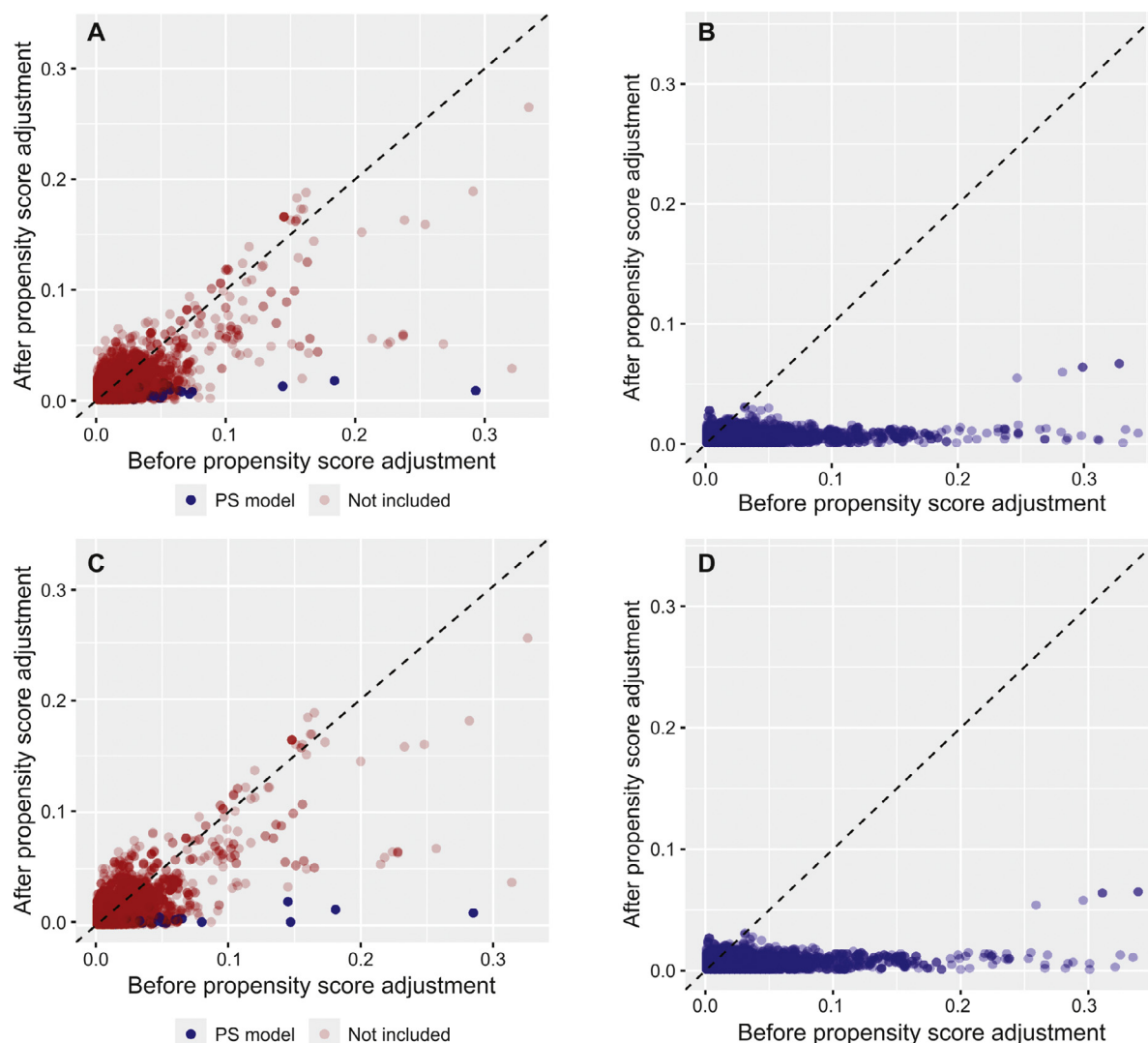
TABLE 1. Distribution of Selected Baseline Characteristics After 1:10 Variable Ratio Propensity Score Matching Using the Large-Scale Logistic Regression Model Across the Cohorts Included in the Study

Characteristic	T1 versus C1			T2 versus C1		
	T1 N = 31,223	C1 N = 178,897	Std. diff	T2 N = 21,941	C1 N = 153,864	Std. diff
Mean age (years)	81.4	81.2	0.02	83.7	83.8	−0.02
Women (%)	56.8	57.1	<0.01	60.9	60.8	<0.01
Index year (%)						
2001	3.7	3.7	<0.01	2.9	2.9	<0.01
2002	4.6	4.6	<0.01	3.4	3.4	<0.01
2003	6.4	6.4	<0.01	5.6	5.6	<0.01
2004	7.7	7.7	<0.01	7.2	7.2	<0.01
2005	9.1	9.2	<0.01	8.5	8.4	<0.01
2006	5.8	5.8	<0.01	5.3	5.4	<0.01
2007	5.9	5.9	<0.01	5.9	6	<0.01
2008	6	6	<0.01	6.1	6.3	−0.01
2009	6.1	6.1	<0.01	6.5	6.5	<0.01
2010	6.6	6.6	<0.01	6.9	6.9	<0.01
2011	8.3	8.2	<0.01	8.9	8.5	0.02
2012	7.2	7.2	<0.01	7.9	7.9	<0.01
2013	6.8	6.8	<0.01	7.4	7.5	<0.01
2014	5.4	5.4	<0.01	6	6	<0.01
2015	4	4.1	<0.01	4.4	4.5	<0.01
2016	3.7	3.7	<0.01	4.3	4.2	<0.01
2017	2.6	2.6	<0.01	2.9	2.8	<0.01
Medical history						
Acute respiratory disease	14.2	14.5	−0.01	13.9	14.1	<0.01
Chronic obstructive lung disease	14.1	14.4	−0.01	15.4	15.4	<0.01
Dementia	29.5	29.5	<0.01	38.4	39.0	−0.01
Diabetes mellitus	20.8	20.9	<0.01	20.2	20.4	<0.01
Hypertension	45.8	45.9	<0.01	47.5	47.6	<0.01
Osteoarthritis	19.6	19.8	<0.01	19.8	19.6	<0.01
Urinary tract infections	16.5	16.8	−0.01	19.4	19.8	−0.01
Coronary arteriosclerosis	17.7	17.9	<0.01	17.9	18	<0.01
Heart disease	44.2	44.5	−0.01	47.3	47.8	<0.01
Heart failure	16.7	17	−0.01	19.4	19.9	−0.01
Peripheral vascular disease	20	20.1	<0.01	21.6	21.8	<0.01
Medication use						
Agents acting on the renin-angiotensin system	41.5	41.5	<0.01	40.8	40.8	<0.01
Antibacterials for systemic use	48.9	49.4	−0.01	49.1	49.2	<0.01
Antidepressants	46.4	47	−0.01	47	45.7	0.03
Antithrombotic agents	24.8	25	<0.01	25.6	25.9	−0.01
Beta blockers	41.2	41.5	−0.01	42.5	42.8	−0.01
Calcium channel blockers	26.8	27	<0.01	27.1	27.1	<0.01
Drugs for acid related disorders	34.1	34.6	−0.01	32.7	32.5	0.01
Psycholeptics	38.9	39.4	−0.01	40.1	39.8	0.01
Health services utilization 183 days						
Inpatient visit	0.5	0.6	−0.02	0.6	0.6	−0.02
Emergency room visit	0.8	0.9	−0.02	1	1	−0.02
Outpatient visit	12.5	12.6	−0.01	12.6	12.7	<0.01
Health services utilization 30 days						
Inpatient visit	0.2	0.3	−0.02	0.3	0.3	−0.03
Emergency room visit	0.3	0.3	−0.01	0.3	0.3	−0.01
Outpatient visit	3.1	3.2	−0.03	3.2	3.2	−0.01

Notes: New users of typical antipsychotics (T1), new users of haloperidol (T2), new users of atypical antipsychotics (C1), standardized difference in means (Std. diff.)

The population sizes reported are subsets of the initial exposure populations, where patient attrition resulted from (a) excluding patients from the cohorts if they switched from another cohort, (b) requiring patients to have at least 1 day time-at-risk after exposure, and (c) 1:10 variable ratio matching on the propensity score.

FIGURE 1. Covariate balance before and after propensity score matching for T1 versus C1 cohorts Footnote: (A) 1:1 PS matching of selected covariates (preplanned analyses); (B) 1:10 PS matching of full covariates (preplanned analyses); (C) 1:1 PS matching of selected covariates (post-hoc analyses); (D) 1:10 PS matching of full covariates (post-hoc analyses). Each data point represents the standardized difference of means for a single covariate before (x-axis) and after (y-axis) propensity score (PS) adjustment. Data points that are below the dashed diagonal line represent covariates for which the standardized difference of means decreases after PS adjustment. Standardized difference of means <0.1 represent negligible imbalance between exposure cohorts. In panels A and C, the blue data points represent the before and after matching standardized difference in means for variables that were included in the Sentinel PS model and were well-balanced after matching. The red data points represent covariates that were not included in the Sentinel PS model of which many show considerable imbalance after matching. In panels B and D, the blue data points represent the before and after matching standardized difference in means for all observed covariates.
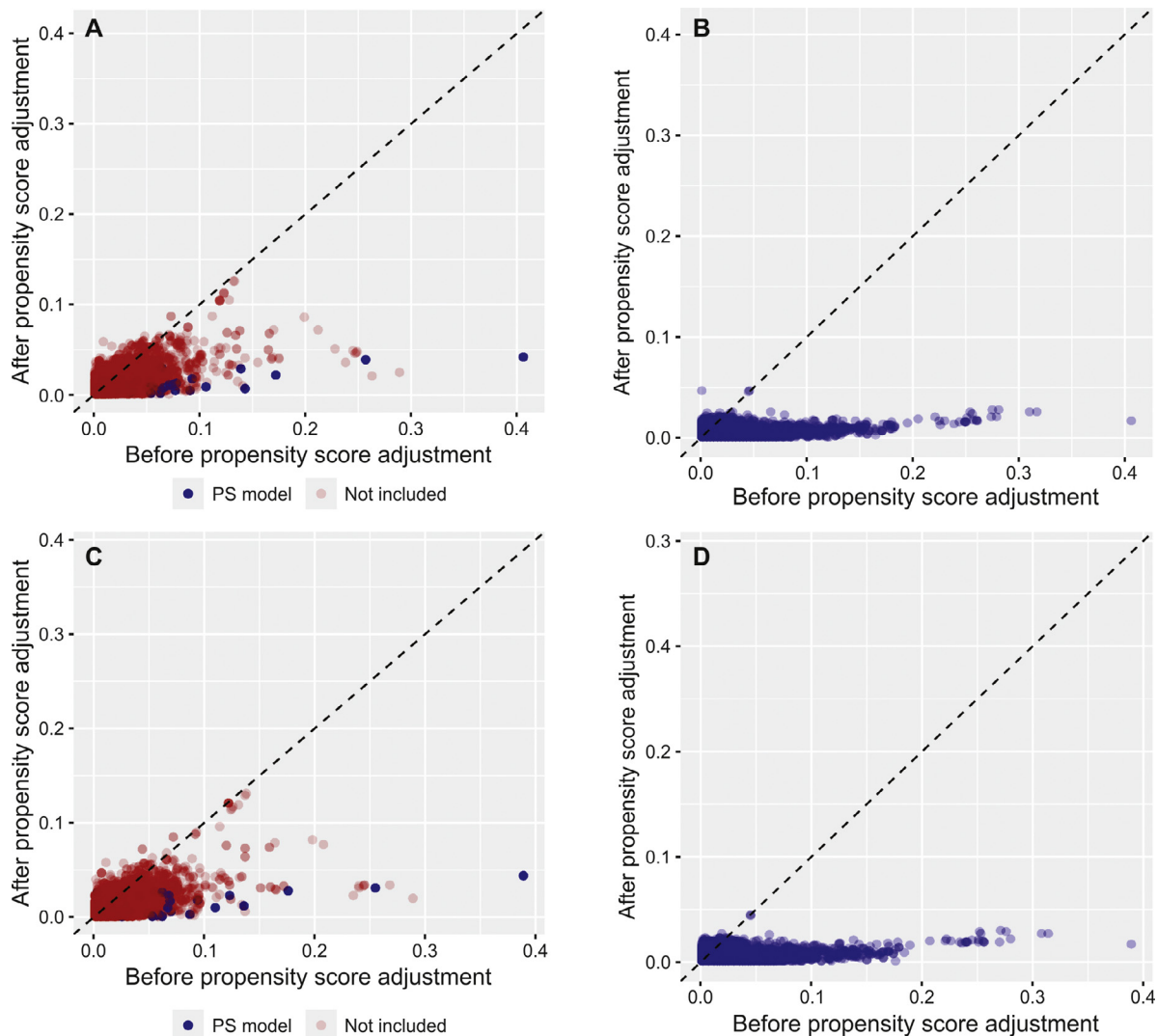

confound the risk estimates. This is supported by the observation (Figs. 1 and 2) that 1:10 matching on the large-scale PS was more successful at balancing baseline characteristic differences than the 1:1 matching on the PS that used the variables employed by the Sentinel study. The estimates based on the large-scale

PS indicate an increased stroke risk in elderly patients newly exposed to typical antipsychotics or haloperidol compared to patients exposed to atypical antipsychotics.

The US label for haloperidol (injections and tablets) contains prominent warnings of an increased risk of

FIGURE 2. Covariate balance before and after propensity score adjustment for T2 versus C1 cohorts Footnote: (A) 1:1 PS matching of selected covariates (preplanned analyses); (B) 1:10 PS matching of full covariates (preplanned analyses); (C) 1:1 PS matching of selected covariates (post-hoc analyses); (D) 1:10 PS matching of full covariates (post-hoc analyses). Each data point represents the standardized difference of means for a single covariate before (x-axis) and after (y-axis) propensity score (PS) adjustment. Data points that are below the dashed diagonal line represent covariates for which the standardized difference of means decreases after PS adjustment. Standardized difference of means <0.1 represent negligible imbalance between exposure cohorts. In panels A and C, the blue data points represent the before and after matching standardized difference in means for variables that were included in the Sentinel PS model and were well-balanced after matching. The red data points represent covariates that were not included in the Sentinel PS model of which many show considerable imbalance after matching. In panels B and D, the blue data points represent the before and after matching standardized difference in means for all observed covariates.

death among elderly patients with dementia-related psychosis treated with antipsychotic drugs and that haloperidol is not approved for treatment of patients with dementia-related psychosis. Though these warnings are based on data from multiple placebo-controlled trials conducted largely in patients taking atypical antipsychotics,[26,27] they refer to all antipsychotics. Therefore, the present study did not stratify patients based on dementia status, as such off-label usage (e.g., treatment of psychosis associated with dementia) would be inconsistent with the US label.

TABLE 2. Crude First Post-Index Event Incidence Rate (IR) and Incidence Proportion (IP) Within the Exposure Cohorts

Exposure Cohort	Strata	Number of Patients	IR/1000 PY	1P/1000 Patients
Pre-planned analyses				
T1	Overall	36,702	17.67	5.15
	Women	20,117	16.30	5.52
	Men	16,585	20.05	4.70
T2	Overall	24,048	23.74	5.70
	Women	14,665	22.68	5.66
	Men	9,383	25.57	5.75
C1	Overall	226,881	14.17	8.22
	Women	143,698	13.57	8.21
	Men	83,183	15.35	8.25
Post-hoc analyses				
T1	Overall	33,879	18.29	5.40
	Women	18,622	17.04	5.85
	Men	15,257	20.51	4.85
T2	Overall	21,965	25.22	6.10
	Women	13,357	24.66	6.21
	Men	8,608	26.19	5.92
C1	Overall	203,985	14.88	8.52
	Women	129,302	14.22	8.50
	Men	74,683	16.19	8.57

Notes: New users of typical antipsychotics (T1), new users of haloperidol (T2), new users of atypical antipsychotics (C1), incidence rate (IR), incidence proportion (IP), person-year (PY)s.

The population sizes reported are subsets of the initial exposure populations, where patient attrition resulted from requiring patients to have at least 1 day of time-at-risk after exposure.

Findings of the present report regarding the risk of stroke among elderly patients who were exposed to typical versus atypical antipsychotics are supported by some,[14,16,28] but not all[8, 29] recent studies in the sense that the former references found, among elderly patients, a higher stroke risk associated with exposure to typical antipsychotics than with exposure to atypical antipsychotics. Taking the broader perspective of comparing stroke risk in elderly patients who were exposed to antipsychotics, versus those who were not, one recent study[25] found no difference and another[30] found a statistically significant 70% increased risk among the exposed group.

Regarding different regions of the world, Sacchetti et al.[8] studied the risk of incident stroke among elderly patients in the Health Search Database, a primary care Italian database with 800,000 patients. The cohort study reported that the adjusted stroke risk was $5.79\times$ higher for phenothiazines, $3.55\times$ higher for butyrophenones, and $2.46\times$ higher for atypical antipsychotics.[8] Shin et al. analyzed the incidence of ischemic stroke in a retrospective cohort study among elderly patients drawn from 50 million Koreans covered by the universal National Health Insurance System. Patients who were newly prescribed either of
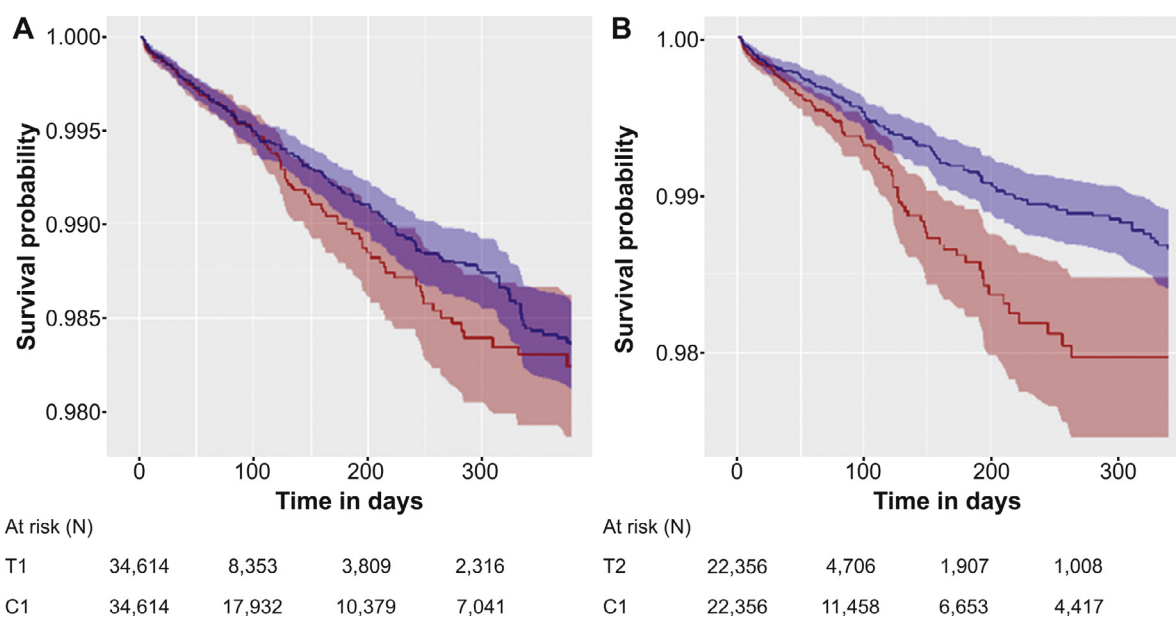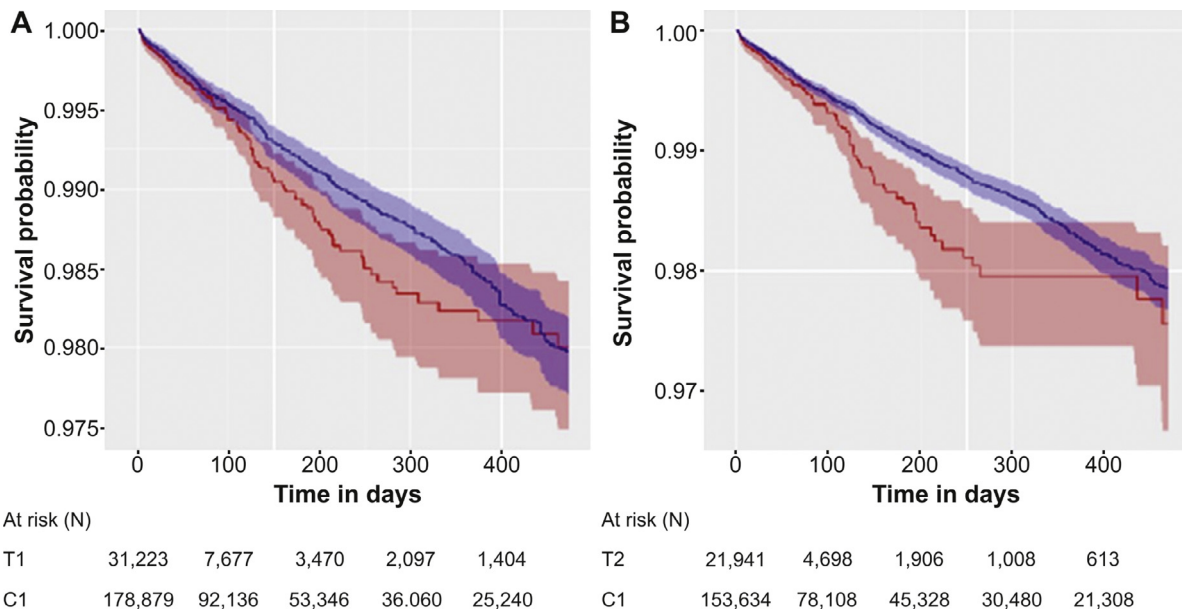
FIGURE 3. Kaplan Meier curves for sentinel approach propensity matched analyses (preplanned analysis) (A) T1 versus C1 (B) T2 versus C1.

At risk (N)				
T1	34,614	8,353	3,809	2,316
C1	34,614	17,932	10,379	7,041

At risk (N)				
T2	22,356	4,706	1,907	1,008
C1	22,356	11,458	6,653	4,417

FIGURE 4. Kaplan Meier curves for large-scale logistic regression propensity score matched analyses (preplanned analysis) (A) T1 versus C1 (B) T2 versus C1.

At risk (N)					
T1	31,223	7,677	3,470	2,097	1,404
C1	178,879	92,136	53,346	36.060	25,240

At risk (N)					
T2	21,941	4,698	1,906	1,008	613
C1	153,634	78,108	45,328	30,480	21,308

two typical antipsychotics were at a greater risk of stroke (HR: 2.53; 95% CI: 1.96, 3.27) as compared to those newly prescribed any of three atypical antipsychotics.[14] Another study conducted by Shin et al.

reported similar results with elevated stroke risk observed among typical antipsychotic users.[16] Herrmann et al. evaluated elderly patients drawn from administrative healthcare claims databases in

TABLE 3. Propensity Score Matched Risk of Stroke in Elderly Patients

Analysis	Target Cohort (N)	Comparator Cohort (N)	HR (95% CI)	Cal. HR (95% CI)
T1 versus C1, Preplanned analyses				
Unadjusted	34,614	224,479	1.24 (1.06−1.44)	1.26 (0.95−1.71)
1:1 PS match	34,614	34,614	1.12 (0.86−1.45)	1.80 (0.75−1.55)
1:10 PS match	31,223	178,879	1.27 (1.05−1.53)	1.31 (1.07−1.60)
T2 versus C1 Preplanned analyses				
Unadjusted	22,356	225,224	1.63 (1.36−1.94)	1.87 (1.00−3.40)
1:1 PS match	22,356	22,356	1.47 (1.07−2.04)	1.69 (1.08−2.75)
1:10 PS match	21,941	153,834	1.38 (1.12−1.69)	1.45 (1.17−1.80)
T1 versus C1, Post-hoc analyses				
Unadjusted	32,023	201,823	1.22 (1.04−1.42)	1.19 (0.90−1.62)
1:1 PS match	32,023	32,023	1.28 (0.98−1.68)	1.18 (0.81−1.75)
1:10 PS match	28,913	163,795	1.26 (1.04−1.52)	1.27 (1.04−1.56)
T2 versus C1, Post-hoc analyses				
Unadjusted	20,475	202,502	1.65 (1.37−1.97)	1.83 (0.99−3.33)
1:1 PS match	20,475	20,475	1.28 (0.94−1.74)	1.36 (0.96−2.00)
1:10 PS match	20,135	139,967	1.34 (1.09−1.65)	1.39 (1.12−1.73)

Notes: New users of typical antipsychotics (T1), new users of haloperidol (T2), new users of atypical antipsychotics (C1), hazard ratio (HR), calibrated hazard ratio (Cal. HR), propensity score (PS), Sentinel propensity score approach (1:1 PS match), adapted propensity score strategy using large-scale regularized regression (1:10 PS match).

The population sizes reported are subsets of the initial exposure populations, where patient attrition resulted from a) excluding patients from the second exposure cohort after switching treatment from the first, b) requiring patients to have at least 1 day time-at-risk after exposure, and c) matching on the propensity score.

The 1:1 PS matching used a PS analogous to the Sentinel study PS and the 1:10 used the large-scale logistic regression PS.

Ontario, Canada and reported higher point estimates for the risk of stroke among atypical antipsychotic users as compared to typical antipsychotic users but the differences were not statistically significant.[28] Wang et al., in a nested case control study in Taiwan that included patients with known cardiovascular disease, reported a pronounced stroke risk (after adjustment for potential confounders) among atypical antipsychotic users which required hospitalization.[29] Although instructive, all of these regional studies present multiple potential limitations for extrapolation of results to the elderly US population prescribed antipsychotics, due to differences in ethnic populations, comorbidities, healthcare systems, social habits, selection criteria, and study methodology.

The present study has several limitations. Data related to socioeconomic and behavioural variables were not available, which may have impacted the validity for outcome identification, risk factor/confounding adjustment, or causal interpretation. Certain risk factors for stroke such as obesity, smoking, and other lifestyle factors were either excluded or underreported in the databases used for the study. In addition, the MDCR database used in the analysis is limited to Medicare patients with both prescription coverage and supplemental insurance including coverage for outpatient prescriptions. Health disparities between patients with and without supplemental insurance may limit the generalizability of the findings of the present study. Because the use of complimentary drug samples was not captured in claims databases, antipsychotic exposure for some patients might have been classified as nonexposure, or prevalent drug use might have been classified as new initiation. Some sensitivity analyses were not performed due to the limited sample size and changes in insurance plans over time. Study strengths include a large sample size from a claims database that covers a wide geographical region and that provided a nationally representative overview of stroke risk. Incorporating a PS that mimicked the PS used in the Sentinel study allowed comparison to Sentinel study results to focus on the difference in the analyzed populations. Use of the large-scale regularized regression model and empirical calibration allowed the study to identify and mitigate potential observed and unobserved confounding.

In conclusion, the present study found that the risk of stroke in elderly patients who were new users of haloperidol and other typical antipsychotics was elevated as compared with new users of atypical antipsychotics. Because most of the patients included in the typical antipsychotics' cohort were users of haloperidol, the increased stroke risk associated with typical antipsychotics cannot be considered strong evidence of a class effect.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jagp.2020.09.017.

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