Antipsychotic Use and Stroke:
A Retrospective Comparative Study in a Non-Elderly Population

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ABSTRACT

Objective: To evaluate stroke risk among users of typical antipsychotics compared to users of atypical antipsychotics in a non-elderly and non-demented US population.

Methods: New users of antipsychotics aged 18–64 years without dementia were identified via electronic health care data from 13 health plans participating in the Sentinel System from January 2001 to September 2015. The risk of hospitalized stroke events, identified via *ICD-9-CM* diagnostic criteria, was compared between typical and atypical antipsychotic users using 1:1 matching on propensity score. Adjusted hazard ratios (HRs) and 95% CIs during the entire follow-up period and during 1- to 15-day and 16- to 90-day risk windows were estimated. The risk associated with haloperidol use was estimated separately.

Results: A total of 45,495 typical antipsychotic users were matched 1:1 to atypical antipsychotic users. While unmatched HRs suggest an increased stroke risk among typical antipsychotic users compared to atypical antipsychotic users, no increased risk was observed after matching during the entire follow-up period (HR = 0.87; 95% CI, 0.54–1.41), the 1- to 15-day risk window (HR = 1.16; 95% CI, 0.41–3.32), or the 16- to 90-day risk window (HR = 0.52; 95% CI, 0.20–1.36). The adjusted HR for haloperidol was 1.31 (95% CI, 0.54–3.21).

Conclusion: These findings were not suggestive of an increased stroke risk in typical antipsychotic users compared to atypical antipsychotic users in a non-elderly and non-demented population.

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Typical and atypical antipsychotics are widely prescribed for treatment of schizophrenia, bipolar disorder, major depressive disorder (as adjunctive therapy), and Tourette syndrome. Unapproved indications for antipsychotics, including anxiety, dementia, posttraumatic stress disorder, and obsessive-compulsive disorder, have also been studied and described in the literature.[1]

Among all antipsychotic medications, 3 atypical antipsychotics (olanzapine, aripiprazole, and risperidone) have warnings of stroke risk in the medication label. These warnings are based on results of clinical trials in the development program conducted in elderly patients with dementia. Results from several observational studies[2–8] conducted in predominantly elderly populations over the last decade suggested that users of typical antipsychotics may also have an increased risk of stroke, and 3 of these studies[3,7,8] reported a higher risk for typical antipsychotics compared to atypical antipsychotics. Mechanistically, authors of one of these studies[7] speculated that a higher stroke risk with typical antipsychotics may be related to their hemodynamic effects, mediated by muscarinic and α_2 blockade. Two of these observational studies[3,9] reported that the highest risk for stroke occurred within the first few weeks of initiating antipsychotic treatment. Moreover, studies have reported that patients taking the typical antipsychotic haloperidol had an increased stroke risk when compared to those taking risperidone[10] and to non-users of haloperidol.[2]

Most of the research to date on antipsychotic and stoke risk has been conducted in elderly and demented populations, who have higher baseline risk of stroke relative to younger populations. However, antipsychotic use is common in the non-elderly and non-demented populations for both indicated and off-label treatment. One US study[11] using commercial claims data from 2010 reports that the prevalence of any antipsychotic use in the non-elderly population was 0.95%, 1.46%, and 1.54% in those aged 20–34 years, 35–59 years, and 60–64 years, respectively, with higher prevalence reported for women than for men across all age groups. In sum, despite the fact that younger adults commonly use these medications, the occurrence of stroke among non-elderly users of antipsychotics has remained largely unexamined. To begin to address this knowledge gap, we chose to explore whether the previously observed higher risk for stroke with typical antipsychotics relative to atypical antipsychotics might extend to antipsychotic use in a non-elderly population. Thus, we assessed the risk of stroke among new users of typical antipsychotics compared to new users of atypical antipsychotics in a population of primarily commercially insured non-elderly and non-demented patients.

Clinical Points

- Previous studies conducted primarily in elderly and demented patients reported that users of typical antipsychotics had a higher risk of stroke compared to users of atypical antipsychotics; however, comparative stroke risk in younger populations using these medications remains largely uninvestigated.
- No increased stroke risk was observed among users of typical antipsychotics relative to atypical antipsychotics in this study, suggesting that any increased risk present in elderly users of typical antipsychotics may not exist in younger, generally healthier populations.

METHODS

Data Source

This analysis was conducted using data from the US Food and Drug Administration's Sentinel System, which was launched in 2016 to perform active safety surveillance for approved medical products. An overview and description of the Sentinel System has been previously published.[12] Briefly, the Sentinel System is a distributed network of 18 data partners, consisting mainly of commercial health insurers, who contribute electronic health care (eg, insurance claims) data using a common data model. The common data model permits standardized data queries across the participating data partners and includes a rigorous data quality assurance process.[13] At the time of this analysis, Sentinel contained data on over 150 million patient lives. This analysis included administrative data (eg, health plan enrollment, demographics) and health services claims (eg, inpatient, outpatient, and emergency department encounters documented with clinical diagnoses and procedure data; outpatient pharmacy dispensings) from 13 data partners from January 2001 to September 2015.

Study Population, Exposure, and Outcome

We identified new users of typical and atypical antipsychotics aged 18–64 years based on the presence of product-specific National Drug Codes in electronic outpatient pharmacy dispensing records. We excluded typical and atypical antipsychotic users who had no continuous enrollment in the insurance plan for at least 6 months prior to the antipsychotic dispensing (index dispensing) and who in the past 183 days had a history of any antipsychotic use or diagnosis of dementia (*International Classification of Diseases, 9th Revision, Clinical Modification* [*ICD-9-CM*] codes 290, 290.x, 290.xx, 291.2, 292.82, 294.1–2, 294.1x, 294.2x, 331.0–2, 331.8–9, 331.1x, and 331.8x), cancer, or stroke.

The primary outcome was a hospitalized ischemic or hemorrhagic stroke, identified using *ICD-9-CM* codes 430, 431, 433.x1, 434.x1, and 436 recorded as a primary inpatient diagnosis. The positive predictive value of the outcome algorithm was 97% for ischemic or hemorrhagic stroke based on prior validation studies.[14]

Statistical Analyses

We followed new users of typical and atypical antipsychotics from the date of the index dispensing through the duration of the treatment episode, allowing for a maximum of a 30-day gap between dispensings in the treatment episode. Patients were followed until the first stroke event or censored upon the earliest occurrence of the following: dispensing of a comparator drug (ie, a user of a typical antipsychotic switched to an atypical, or vice versa), disenrollment from the insurance plan, recorded death, the end of data availability, or the end of the query period (September 2015).

We used Cox proportional hazards models with and without 1:1 propensity score matching to estimate the hazard ratio (HR) and 95% CI of stroke events in typical versus atypical antipsychotic users. The propensity score model included patient demographics, medical history/comorbidity variables, medication use history, and health service utilization variables assessed in the 183 days prior to antipsychotic initiation. Comorbidity/clinical history variables were included in the model based on either 1 inpatient diagnosis or 2 outpatient diagnoses for each condition, while medication uses were ascertained by a record for a single outpatient dispensing of each type of drug (eg, statin, β-blocker). We also generated Kaplan-Meier survival curves for stroke among typical and atypical antipsychotic users through the first 90 days of follow-up in the propensity score–matched cohort.

Given the results from previously published studies,[3,6,9] we performed secondary analyses to assess stroke risk on days 1–15 and 16–90 after antipsychotic initiation as well as among users of haloperidol exclusively.

RESULTS

We identified 45,576 new users of typical antipsychotics and 806,611 new users of atypical antipsychotics before propensity score matching (Table 1). New users of typical antipsychotics were on average older than new users of atypical antipsychotics, were more commonly male, and were more likely to have risk factors for stroke. The mean follow-up time was 0.2 person-years in new users of typical antipsychotics and 0.4 person-years in new users of atypical antipsychotics. The crude incidence rate per 1,000 person-years was 2.5 in new users of typical antipsychotics and 1.2 in new users of atypical antipsychotics. When typical antipsychotic users were compared with atypical antipsychotic users, the unmatched, site-adjusted HR was 1.75 (95% CI, 1.17–2.63) overall, 3.06 (95% CI, 1.37–6.83) during the 1- to 15-day risk window and 1.23 (95% CI, 0.54–2.80) during the 16- to 90-day risk widow (Table 2).

After 1:1 matching on propensity score, 45,495 typical antipsychotic users were matched to the same number of atypical antipsychotic users. Clinical and demographic differences between cohorts were greatly reduced after matching (Table 1). Overall, stroke incidence in the study population was low in both cohorts after propensity score

Table 1. Selected Demographic and Medical Characteristics[a] of New Users of Typical and Atypical Antipsychotics, Before and After 1:1 Propensity Score Matching[b]

	Unmatched			1:1 Propensity Score–Matched		
Characteristic	Typical Antipsychotics (n = 45,576)	Atypical Antipsychotics (n = 806,611)	Standardized Difference[c]	Typical Antipsychotics (n = 45,495)	Atypical Antipsychotics (n = 45,495)	Standardized Difference[c]
Age, mean (SD), y	44.0 (12.6)	39.9 (12.8)	0.324	44.0 (12.6)	44.2 (12.7)	−0.020
Female	21,206 (46.5)	489,469 (60.7)	−0.287	21,194 (46.6)	20,987 (46.1)	0.009
Atrial fibrillation/flutter	648 (1.4)	4,745 (0.6)	0.084	620 (1.4)	660 (1.5)	−0.007
Acute myocardial infarction	899 (2.0)	7,789 (1.0)	0.084	879 (1.9)	928 (2.0)	−0.008
Diabetes	5,226 (11.5)	52,950 (6.6)	0.172	5,182 (11.4)	5,393 (11.9)	−0.014
Hypertension	9,800 (21.5)	120,258 (14.9)	0.171	9,754 (21.4)	9,886 (21.7)	−0.007
Renal failure	1,869 (4.1)	11,495 (1.4)	0.164	1,817 (4.0)	1,855 (4.1)	−0.004
Depression	10,603 (23.3)	324,387 (40.2)	−0.370	10,586 (23.3)	10,860 (23.9)	−0.014
Schizophrenia	5,687 (12.5)	56,550 (7.0)	0.185	5,676 (12.5)	5,998 (13.2)	−0.021
Angiotensin-converting enzyme inhibitor use	6,152 (13.5)	75,035 (9.3)	0.132	6,125 (13.5)	6,228 (13.7)	−0.007
β-Blocker use	5,786 (12.7)	76,471 (9.5)	0.103	5,753 (12.6)	5,857 (12.9)	−0.007
Oral anticoagulant use	1,025 (2.2)	9,540 (1.2)	0.082	993 (2.2)	981 (2.2)	0.002
Statin use	6,787 (14.9)	91,915 (11.4)	0.104	6,762 (14.9)	6,928 (15.2)	−0.010
No. of ambulatory encounters, mean (SD)[d]	8.7 (11.1)	9.5 (10.4)	−0.071	8.7 (11.1)	8.7 (10.7)	−0.005
No. of inpatient encounters, mean (SD)[d]	0.4 (1.0)	0.3 (0.7)	0.149	0.4 (1.0)	0.4 (1.1)	0.003

[a]Medical conditions assessed as the presence of 1 inpatient or 2 outpatient diagnoses in the 183 days prior to antipsychotic initiation; medication use assessed as a dispensing for any of the categories of medications in the 183 days prior to antipsychotic initiation.
[b]Data from the Sentinel distributed database, January 2001–September 2015. Data are shown as n (%) unless otherwise noted.
[c]A standardized difference smaller than −0.1 or greater than 0.1 usually indicates a meaningful difference.
[d]Number of encounters in the 183 days prior to antipsychotic initiation.

Table 2. Unmatched and 1:1 Propensity Score–Matched Hazard Ratios (HRs) and 95% CIs for the Association Between Typical Antipsychotic Use and Stroke as Compared to Atypical Antipsychotic Use[a]

	Unmatched (Data Partner–Adjusted Only[b])				1:1 Propensity Score–Matched[c]			
Variable	Exposed, n	No. of Person-Years	No. of Events	HR (95% CI)	Exposed, n	No. of Person-Years	No. of Events	HR (95% CI)
Overall								
Typical	45,576	10,125.82	25	1.75 (1.17–2.63)	45,495	10,113.92	25	0.87 (0.54–1.41)
Atypical	806,611	338,987.22	396	1 (Reference)	45,495	20,646.19	53	1 (Reference)
1–15 Days after exposure								
Typical	45,576	1,534.75	7	3.06 (1.37–6.83)	45,495	1,532.82	7	1.16 (0.41–3.32)
Atypical	806,611	32,431.81	42	1 (Reference)	45,495	1,829.06	7	1 (Reference)
16–90 Days after exposure								
Typical	30,204	3,109.76	6	1.23 (0.54–2.80)	30,186	3,107.76	6	0.52 (0.20–1.36)
Atypical	757,812	96,228.27	124	1 (Reference)	30,186	3,885.00	14	1 (Reference)
Haloperidol only								
Haloperidol	13,882	3,369.51	9	1.80 (0.93–3.48)	13,841	3,366.33	9	1.31 (0.54–3.21)
Atypical	801,275	336,212.38	397	1 (Reference)	13,841	6,482.65	11	1 (Reference)

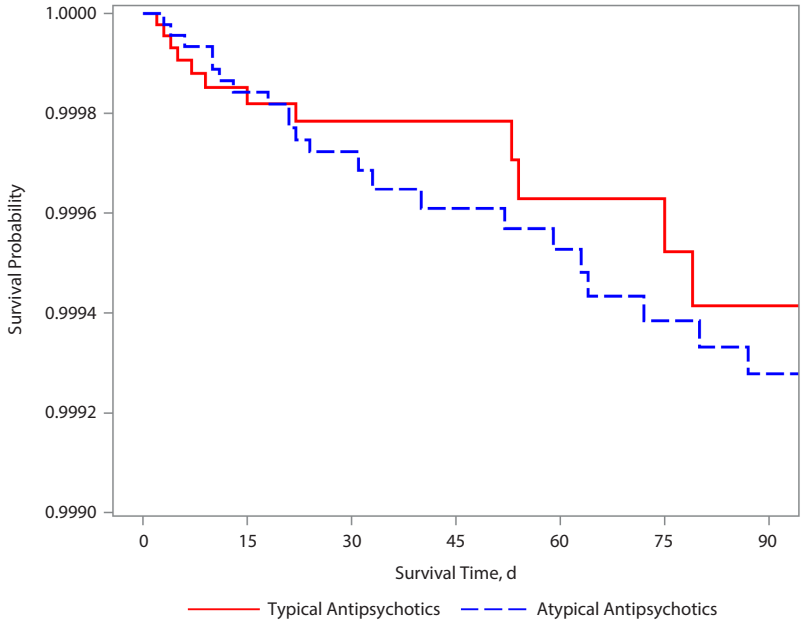
[a]Data from the Sentinel distributed database, January 2001–September 2015.
[b]Matching occurs at the data partner level; unmatched results are otherwise crude.
[c]The following variables were included in the propensity score: age (continuous); year of exposure; sex; acute myocardial infarction history; diabetes; heart failure; hypercholesterolemia; hypertension; kidney failure (acute or chronic); obesity; transient ischemic attack; atrial fibrillation/flutter; peripheral vascular disease; coagulation defects; other cardiovascular disease; anxiety; bipolar disorder; depression; posttraumatic stress disorder; schizophrenia/psychotic disorder; substance abuse; use of angiotensin-converting-enzyme inhibitors, antiarrhythmics, β-blockers, statins, oral anticoagulants, non-oral anticoagulants, angiotensin-receptor blockers, antiplatelets, or diuretics; health services, including number of inpatient stays, number of nonacute institutional stays, number of emergency department visits, number of outpatient visits, and number of other ambulatory encounters (eg, telemedicine, e-mail consults); and drug utilization metrics (number of dispensings, number of unique generics dispensed, number of unique drug classes dispensed; and combined comorbidity index (see Gagne et al[15]).

matching (< 1.5 per 1,000 persons). After matching, new users of typical antipsychotics did not have an increased risk of stroke compared to new users of atypical antipsychotics (HR = 0.87; 95% CI, 0.54–1.41) (Table 2). Similarly, during the risk windows of 1–15 days and 16–90 days after initial exposure, typical antipsychotic users did not have an increased risk of stroke (HR = 1.16; 95% CI, 0.41–3.32 and HR = 0.52; 95% CI, 0.20–1.36, respectively). Figure 1 depicts the Kaplan-Meier survival curve for the propensity score–matched cohort during the first 90 days of follow-up. By 60 days after exposure, the proportion of patients remaining on treatment with typical and atypical antipsychotics was 27.4% and 53.4%, respectively.

The crude incidence rate of stroke was 2.7 per 1,000 person-years in new users of haloperidol. The HR comparing haloperidol to atypical antipsychotics was 1.80 (95% CI, 0.93–3.48) in the unmatched, site-adjusted analysis and 1.31 (95% CI, 0.54–3.21) in the propensity score–matched analysis.

For all associations, 1:1 matching on propensity score attenuated the association. For overall use and use in the 1–15 days after exposure, the 95% CIs no longer excluded the null after 1:1 propensity score matching.

Figure 1. Kaplan-Meier Survival Curves for Propensity Score–Matched Analysis During 90 Days of Treatment With Typical Antipsychotics Versus Atypical Antipsychotics[a]



Typical Antipsychotics, n	45,495	31,056	26,788	13,641	12,464	9,500	8,554
Atypical Antipsychotics, n	45,495	43,270	40,720	25,555	24,292	19,670	18,194

[a]Data from the Sentinel distributed database, January 2001–September 2015.

DISCUSSION

Findings from our analysis did not support an increased risk of stroke in new users of typical antipsychotics compared to atypical antipsychotic users in a non-elderly, non-demented population. Moreover, although the propensity score–matched HR was greater in the initial period after treatment initiation, the 95% CI was relatively wide and included the null. There was also no strong evidence to suggest a higher risk of stroke with haloperidol compared to atypical antipsychotics. These findings conflict with those of previous observational studies, primarily conducted in elderly demented populations.[2,3,7–9,16]

Four potential explanations could account for these discrepancies. First, conflicting results could possibly be explained by residual confounding in previous studies. Our unmatched, site-adjusted–only results also suggested an increased risk of stroke among users of typical antipsychotic compared to users of atypical antipsychotics. However, we adjusted for over 30 variables via propensity score matching. Baseline differences between new users of typical and atypical antipsychotics were minimal after matching, all risk estimates were attenuated, and the 95% CIs included the null in the propensity score–matched analysis. Second, a true increased stroke risk among users of typical antipsychotics may exist in an elderly or demented population but not in the non-elderly and non-demented population. That is, antipsychotic-associated stroke risk may vary by age. Third, given that stroke is a rare outcome in a non-elderly population, we lacked statistical power to detect a modest increase in stroke risk with typical antipsychotics over atypical antipsychotics, even if such an increase existed. Finally, our observed results could be spurious due to systematic error. However, extensive residual confounding was unlikely in our study given the directions of the risk estimates before and after confounding adjustment (ie, all risk estimates were attenuated toward or below the null). Also, our study would be subject to many of the same potential biases in the other studies using electronic health care databases (eg, exposure and outcome misclassification) that produced results quantitatively different from those in our study.

To the best of our knowledge, this study is the first to assess antipsychotic-associated stroke risk in a non-elderly, non-demented population. While event rates were low in the non-elderly population, the size of the US Food and Drug Administration's Sentinel System, which includes data from a large, diverse, and primarily commercial population from multiple health plans across the United States, allowed for the assessment of a potentially rare drug-associated outcome. Electronic outpatient pharmacy dispensing data enabled us to ascertain antipsychotic use free from recall bias. We used previously validated algorithms[14] with high positive predictive values to identify stroke events. The use of propensity score methods allowed us to adjust for a large number of potential confounders.

We note that stroke events were generally rare in our non-elderly study population (2.5 and 1.2 events per 1,000 person-years for typical and atypical antipsychotic users, respectively). These rates suggest that even if a modest increase in stroke risk existed among typical versus atypical

non-elderly antipsychotic users, the absolute risk would be low and possibly of limited clinical relevance despite data suggesting stroke rates increasing among the non-elderly.[17,18] The incidence rate observed in our study is consistent with those reported in prior US population–based studies of non-elderly general populations. One study[19] reported a crude incidence rate of 2.2 per 1,000 person-years among adults aged 45–64 years; another study[18] reported incidence rates between 0.4 and 1.3 per 1,000 person-years among adults aged 20–54 years and 2.1 and 5.2 per 1,000 person-years among adults aged 55–64 years. Although patients treated with antipsychotics may be different from the general population of a similar age, our results suggest that users of antipsychotics might not have a notably higher risk of stroke than the general population.

Study strengths notwithstanding, our study had several limitations. Although 1:1 propensity score matching reduced confounding and increased internal validity, the analysis removed over 90% of atypical antipsychotic users from the adjusted analyses. Even if matching ratio was increased to 1:4, we would have still excluded over 75% of atypical antipsychotic users and potentially introduced more confounding by matching atypical antipsychotic users who were not as similar to the typical antipsychotic users.[20] Such an exclusion could potentially reduce the generalizability of the study findings to the larger non-elderly and non-demented population of atypical antipsychotic users. We did not separate ischemic and hemorrhagic stroke in our outcome definition due to the small numbers of stroke events. Therefore, we were unable to detect whether typical antipsychotics had different effects on ischemic versus hemorrhagic stroke. Average follow-up time was different between typical and atypical antipsychotic users, which could bias the analysis that included the entire follow-up period if censoring was informative. However, our results were consistent when we restricted the analysis to 1–15 days and 16–90 days, when follow-up was more comparable between the 2 groups.

In addition, we lacked information regarding the actual indications for which antipsychotics had been prescribed. Contrary to expectations, most patients initiating either typical or atypical antipsychotics did not have a diagnosis of depression or schizophrenia recorded during their 6-month baseline period. We speculate that diagnoses for chronic conditions (such as schizophrenia) may be recorded infrequently. However, by comparing users of one type of antipsychotic to users of another type of antipsychotic, rather than comparing antipsychotic users to nonusers, we sought to minimize confounding by indication. Variables such as race, alcohol use, substance abuse, and tobacco use are usually only partially captured or not captured at all in most claims data sources, including Sentinel. Thus, if there were notable imbalances in these variables between typical and atypical users and if these variables may also be risk factors for stroke in the non-elderly, our results may be confounded. However, by adjusting for some medical (eg, diabetes, hypertension, obesity) and psychiatric (depression, anxiety, bipolar) correlates for several of these missing or incompletely measured variables, we suspect any remaining confounding to be minimal. Finally, we did not perform subgroup analyses by dose or age group.

In summary, contrary to previous findings in primarily elderly and demented populations, we did not observe an increased risk of stroke among users of typical antipsychotics compared to users of atypical antipsychotics.

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