



## Original Contribution

# The Explanatory Role of Stroke as a Mediator of the Mortality Risk Difference Between Older Adults Who Initiate First- Versus Second-Generation Antipsychotic Drugs

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Antipsychotic drugs are used to treat dementia-related symptoms in older adults, and observational studies show higher risks of death and stroke associated with the use of first-generation antipsychotic drugs (FGAs) compared with second-generation antipsychotic drugs (SGAs). However, the extent to which stroke explains the differential mortality risk between FGA use and SGA use in older adults is unclear. We followed those who initiated use of antipsychotic drugs (9,777 FGA users and 21,164 SGA users) aged 65 years or older, and who were enrolled in Medicare and either the New Jersey or Pennsylvania pharmacy assistance program during 1994 to 2005, over 180 days for the outcomes of stroke and death. We estimated direct and indirect effects by comparing 180-day mortality risks associated with the use of FGAs versus SGAs as mediated by stroke on the risk ratio scale, as well as the proportion mediated on the risk difference scale. FGA use was associated with marginally higher risks of stroke (risk ratio = 1.24, 95% confidence interval (CI): 1.01, 1.53) and death (risk ratio = 1.15, 95% CI: 1.08, 1.22) compared with SGA use, but stroke explained little (2.7%) of the observed difference in mortality risk. The indirect effect was null (risk ratio = 1.004, 95% CI: 1.000, 1.008), and the direct effect was equal to the total effect of antipsychotic drug type (FGA vs. SGA) on mortality risk (risk ratio = 1.15, 95% CI: 1.08, 1.22). These results suggest that the difference in mortality risk between users of FGAs and SGAs may develop mostly through pathways that do not involve stroke.

aged; antipsychotic drugs; cerebrovascular disease; death; mediation analysis; mortality risk; pharmaco-epidemiology; stroke

Abbreviations: CI, confidence interval; FGA, first-generation antipsychotic drug; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; SGA, second-generation antipsychotic drug.

Older adults with dementia are often prescribed antipsychotic drugs “off label” to treat behavioral and psychiatric symptoms, such as hallucinations, agitation, and aggression (1). Although short-term use of antipsychotic drugs in older adults can modestly improve symptoms of agitation and aggression (2), it can also pose significant health risks, including higher risk of death.

Randomized trials have demonstrated that second-generation antipsychotic drugs (SGAs) are associated with a 1.6- to 1.7-fold increase in risk of death compared with placebo (3, 4), and several retrospective cohort studies show even higher mortality risk associated with first-generation

antipsychotic drugs (FGAs) (5–8). In turn, regulatory agencies issued warnings to communicate the higher mortality risk associated with the use of both FGAs and SGAs (3, 9). Elucidating the mechanisms by which FGAs produce greater mortality risk than SGAs could help reduce the overall risk of death associated with the use of antipsychotic drugs. Nevertheless, after nearly a decade of research, we still do not know which medical events are responsible for the mortality risk difference between FGAs and SGAs.

One plausible contributor to the mortality risk difference is antipsychotic drug-induced stroke. In 2002 and 2004, results from placebo-controlled randomized trials raised concerns

that the SGAs risperidone and olanzapine were associated with higher risk of cerebrovascular events (10, 11). Antipsychotic medications may affect neurotransmitter systems in ways that may increase the risk of stroke, including orthostatic hypotension, anticholinergic effects, and impaired mobility from extrapyramidal symptoms. These side effects develop soon after initiation and occur more frequently with the use of FGAs than with SGAs (12).

Evidence from some (13–19), but not all (20–24), observational studies showed higher risk of stroke associated with use of FGAs compared with SGAs. These results suggest that differences in stroke risk between FGAs and SGAs may exist, but they cannot tell us the extent to which this relationship explains the mortality risk difference, nor what the mortality risk difference would be if we could prevent strokes after starting antipsychotic therapy. In this paper, we confirm the higher stroke and mortality risks for FGA users versus SGA users and then apply recent advances in mediation analysis to examine these questions directly using longitudinal claims data on older US Medicare beneficiaries.

**METHODS**

**Mediation analysis framework**

We used the causal mediation framework to decompose the total effect of antipsychotic drug type on mortality risk into the natural direct effect and the natural indirect effect as mediated by stroke (25, 26) (Figure 1). On the risk-difference scale, the ratio of the natural indirect effect to the total effect equals the proportion of the total effect mediated by stroke. We also estimated a controlled direct effect to address the policy-relevant question of what the effect of antipsychotic drug type on mortality risk would be if we were

able to prevent stroke from occurring after antipsychotic drug initiation, perhaps through prophylactic monitoring or intervention.

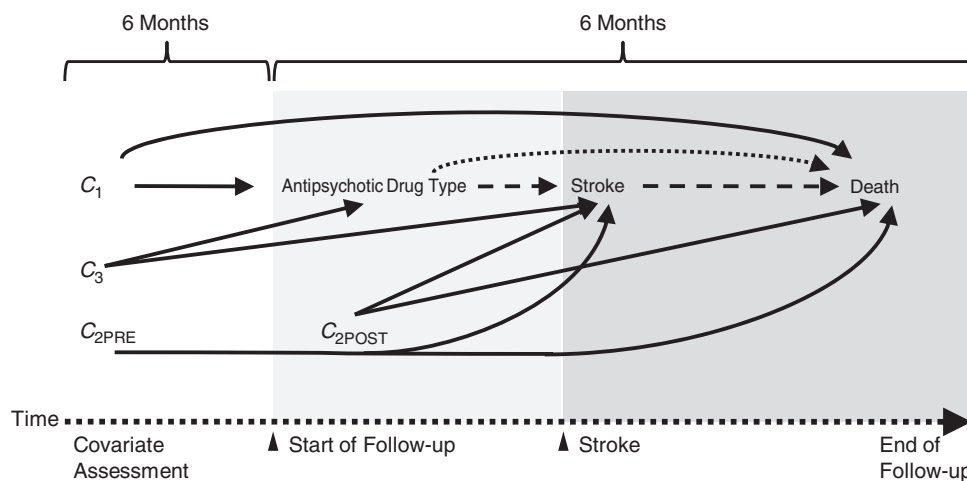
**Data source**

Prescription dispensing records were obtained for patients enrolled in the New Jersey Pharmacy Assistance for the Aged and Disabled or the Pennsylvania Pharmaceutical Assistance Contract for the Elderly programs from January 1, 1994, to December 31, 2005. These programs accept individuals earning up to twice the federal poverty level, have low copays, and offer relatively comprehensive drug coverage with open formularies (27, 28).

Data on prescription drug use were extracted from pharmacy records and linked via personal identifiers to Medicare claims data containing information on inpatient and outpatient diagnoses, related procedures, dates of service, short-term rehabilitative stays, and death records from the Social Security Administration Death Master File (<http://www.ssdmf.com>). Institutional review board approval was granted by Brigham and Women’s Hospital (Boston, Massachusetts). This project was covered under a signed data use agreement with the Centers for Medicare and Medicaid Services (Woodlawn, Maryland).

**Population and study design**

We assembled a retrospective cohort of persons aged 65 years or older who filled a new prescription for an oral antipsychotic drug (listed in Web Appendix 1, available at <http://aje.oxfordjournals.org/>) and who had no antipsychotic drug dispensing in the preceding 180 days. We retained individuals who, in the 180 days prior to this index date, were



**Figure 1.** Illustrative directed acyclic graph showing mediation of the effect of antipsychotic drug type (first-generation vs. second-generation) on death from stroke over 180 days of follow-up.  $C_1$ , mortality risk factors associated with antipsychotic drug type initiation (assessed before start of follow-up);  $C_{2PRE}$ , dual risk factors for death and stroke (assessed before start of follow-up);  $C_{2POST}$ , dual risk factors for death and stroke (assessed after start of follow-up);  $C_3$ , stroke risk factors associated with antipsychotic drug type initiation (assessed before start of follow-up). The dotted arrow represents the direct effect; the dashed arrow represents the indirect effect; and the solid arrows represent sources of noncausal association from confounding by  $C_1$ ,  $C_2$ , and  $C_3$ .

continuously enrolled in Medicare and either New Jersey Pharmacy Assistance for the Aged and Disabled or Pennsylvania Pharmaceutical Assistance Contract for the Elderly and who had at least 1 health service encounter or prescription fill. We excluded persons who had at least 2 health care encounters for diagnoses for cancer or other psychiatric or neurological conditions (based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes) or whose initial antipsychotic drug dispensing suggested schizophrenia treatment or pro re nata use (Web Appendix 2). Follow-up began on the first dispensing date and lasted for 180 days or until death. We also formed a propensity-matched subcohort for descriptive and confirmatory analyses (Web Appendices 3 and 4).

### Stroke and death during follow-up

We assessed strokes occurring between the index prescription date (inclusive) and the end of follow up (180 days) or death. Using the ICD-9-CM, we classified individuals as having a stroke if any of the following codes were present as the primary diagnosis on an inpatient Medicare claim during follow-up: intracranial hemorrhage (code 430.xx, 431.xx, or 432.xx; positive predictive value  $\geq 80\%$ ) or ischemic stroke (code 433.x1 or 434.x1; positive predictive value  $\geq 70\%$ ) (29). Vital status and dates of death were obtained from the Social Security Death Master File.

### Patient characteristics

Patient characteristics included demographic factors, health service and medication use, medical and psychiatric illnesses, and indicators of frailty; these were defined as present when a related ICD-9-CM code appeared in the 180 days preceding the index date. We also assessed stroke risk factors after antipsychotic drug initiation until the occurrence of stroke, death, or the end of follow-up (Web Appendices 5 and 6).

### Statistical analysis

We calculated the baseline prevalence of each covariate and the prevalence difference by comparing FGA users with SGA users (Web Table 1). For each antipsychotic drug group, we calculated the difference in covariate prevalence by comparing patients who developed stroke during follow-up with those who did not (Web Table 2). We estimated crude and adjusted risk ratios (using the propensity-matched subcohort) for the effect of antipsychotic drug type on stroke and for the effect of antipsychotic drug type on mortality risk over 14, 30, 60, 120, and 180 days of follow-up. To estimate direct and indirect effects on the risk ratio scale and the proportion mediated on the risk difference scale (30), we combined parameters from a logistic regression model for stroke conditional on antipsychotic drug type and baseline patient characteristics and a Poisson regression model for death conditional on these covariates and stroke allowing for exposure-mediator interaction (26). We used 500 bootstrap samples and the percentile method to produce 95% confidence intervals. These analyses were repeated at 30, 60, 120, and 180 days of follow-up and for subgroups

defined by (treated) dementia, cerebrovascular disease, and duration of use. We repeated the mediation analysis for drug-specific comparisons, examined ischemic and hemorrhagic stroke separately as mediators, and further adjusted for calendar year (Web Appendices 7–9). We performed sensitivity analyses for a binary unmeasured confounder of the stroke-death relationship and for various ICD-9-CM–based definitions of stroke (Web Appendices 10 and 11).

## RESULTS

### Patients

We identified 9,777 FGA and 21,164 SGA initiators who were aged 65 years or older and who received at least 30 days' drug supply at the start of follow-up (Web Figure 1). The full cohort was mostly female (80.6%) and older (mean = 82.0 years), and approximately one-third or more had medical

**Table 1.** Risk of Stroke and Death Over 180 Days of Follow-up Among Adults Aged 65 Years or Older With Dual Enrollment in Medicare and Pharmacy Assistance Programs in New Jersey or Pennsylvania, 1994–2005

Outcome and Length of Follow-up, days	Full Cohort				Matched Cohort (1:1)	
	SGA (n = 21,164)		FGA (n = 9,777)		FGA vs. SGA (n = 8,892 Pairs)	
	No. of Events	Risk, %	No. of Events	Risk, %	Risk Ratio <sup>a</sup>	95% CI
Stroke						
14	36	0.17	23	0.24	1.13	0.57, 2.20
30	80	0.38	54	0.55	1.31	0.85, 2.04
60	131	0.62	91	0.93	1.52	1.07, 2.15
120	220	1.04	135	1.38	1.44	1.09, 1.89
180	299	1.41	163	1.67	1.30 <sup>b</sup>	1.02, 1.65
Death						
14	213	1.01	140	1.43	1.22	0.93, 1.59
30	501	2.37	290	2.97	1.20	1.00, 1.44
60	1,004	4.74	570	5.83	1.20	1.06, 1.37
120	1,931	9.12	1,059	10.83	1.19	1.08, 1.30
180	2,764	13.06	1,442	14.80	1.12 <sup>c</sup>	1.04, 1.20

Abbreviations: CI, confidence interval; FGA, first-generation antipsychotic drug; SGA, second-generation antipsychotic drug.

<sup>a</sup> Estimated in the FGA versus SGA 1:1 propensity score–matched cohort unless otherwise noted (see Web Appendices 3 and 4 for details). The propensity model score included demographic characteristics, health services usage, comorbid chronic and psychiatric conditions, and concomitant medication use occurring before the index date, as listed in Web Table 1.

<sup>b</sup> The corresponding risk ratio for stroke over 180 days of follow-up in the full cohort, estimated (as an odds ratio) via logistic regression with the same covariates used in the propensity score model, was 1.24 (95% CI: 1.01, 1.53).

<sup>c</sup> The corresponding risk ratio for death over 180 days of follow-up in the full cohort, estimated via Poisson regression with the same covariates used in the propensity score model was 1.15 (95% CI: 1.08, 1.22). Nonparametric bootstrapping ( $n = 500$  samples) was used to obtain the 95% confidence interval.

**Table 2.** Direct and Indirect Effects of Exposure (to FGAs vs. SGAs) on Mortality Risk, Mediated by Stroke, Over 180 Days of Follow-up Among Adults Aged 65 Years or Older With Dual Enrollment in Medicare and Pharmacy Assistance Programs in New Jersey or Pennsylvania, 1994–2005

Analysis	Controlled Direct Effect		Natural Direct Effect		Natural Indirect Effect		Total Effect		Proportion Mediated, %
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	
Unadjusted <sup>a</sup>	1.13	1.08, 1.21	1.13	1.07, 1.20	1.004	0.999, 1.009	1.13	1.07, 1.20	3.27
Multivariable adjusted <sup>b</sup>									
Days since initiation									
14	1.43	1.11, 1.81	1.42	1.10, 1.80	1.000	1.000, 1.000	1.42	1.10, 1.80	–0.01
30	1.25	1.06, 1.47	1.25	1.06, 1.47	1.001	1.000, 1.003	1.25	1.07, 1.47	0.38
60	1.22	1.09, 1.36	1.22	1.10, 1.36	1.005	1.001, 1.012 <sup>c</sup>	1.23	1.11, 1.36	2.73
120	1.21	1.12, 1.31	1.21	1.12, 1.30	1.004	1.001, 1.012 <sup>c</sup>	1.21	1.13, 1.31	2.34
180	1.15	1.08, 1.22	1.15	1.08, 1.22	1.004	1.000, 1.008 <sup>c</sup>	1.15	1.08, 1.22	2.70
Stroke subtype <sup>a</sup>									
Ischemic	1.15	1.08, 1.22	1.17	1.08, 1.22	1.003	1.000, 1.006	1.15	1.08, 1.22	2.02
Hemorrhagic	1.15	1.08, 1.22	1.15	1.08, 1.22	1.000	0.999, 1.002	1.15	1.08, 1.22	0.22

Abbreviations: CI, confidence interval; FGA, first-generation antipsychotic drug; RR, risk ratio; SGA, second-generation antipsychotic drug.

<sup>a</sup> All analyses were conducted over 180 days since initiation unless noted otherwise.

<sup>b</sup> Multivariable analyses adjusted for demographic characteristics, health services usage, comorbid chronic and psychiatric conditions, and concomitant medication use occurring before the index date, as listed in Web Table 1.

<sup>c</sup> The lower confidence bound for indirect effect is above the null.

claims related to cardiovascular disorders and dementia; they used, on average 7.1 different medications (Web Table 1). FGA users appeared to be healthier than SGA users in terms of chronic disease and psychiatric diagnoses in the full cohort, but they were similar in the propensity score–matched cohort (Web Table 2; Web Figure 2). Most of the cohort discontinued use of antipsychotic medications during the course of follow-up (79.5% of FGA users and 70.7% of SGA users).

### Differential risk of stroke and death between FGA and SGA users

The crude mortality risk was high for both FGA users (14.8%) and SGA users (13.1%) over the 180 days of follow-up (Table 1), whereas the risk of stroke was low for both groups (1.41% and 1.67%, respectively). The excess mortality risk comparing those who experienced stroke ( $n = 462$ ) during follow-up with those who did not was 23.7% and was similar for both groups. FGA users were more likely to experience a stroke during 180 days of follow-up after adjustment for baseline covariates (for undifferentiated stroke, odds ratio = 1.24, 95% confidence interval (CI): 1.01, 1.53; for ischemic stroke, odds ratio = 1.25, 95% CI: 0.99, 1.58; for hemorrhagic stroke, odds ratio = 1.17, 95% CI: 0.72, 1.89), as well as death from any cause (risk ratio = 1.15, 95% CI: 1.08, 1.22).

### Stroke as a potential mediator

Over the course of follow-up, the controlled direct effect and total effect of antipsychotic drug type on mortality risk

were the same (risk ratio = 1.15, 95% CI: 1.08, 1.22) (Table 2). Although the natural indirect effect did not change appreciably over the study period (risk ratio = 1.004, 95% CI: 1.000, 1.008), the proportion mediated increased slightly to 2.70% by 180 days of follow-up, due mostly to the declining total effect. The results were similar for patients with or without history of cerebrovascular disease, (treated) dementia, or recent nursing home stays (Web Tables 3 and 4). We observed similar results when comparing haloperidol users with olanzapine, risperidone, and quetiapine users, when evaluating ischemic and hemorrhagic strokes separately as mediators, and when further adjusting for potential confounders assessed after antipsychotic drug initiation, including statin and anti-coagulant use (Web Table 5). An attenuated indirect effect and an enlarged total effect (risk ratios ranging from 1.28 to 1.41) but similar and nonsignificant stroke effect were observed after stratifying by duration of use (Web Table 6). When we used alternate ICD-9-CM–based definitions, the proportion mediated was as high as 6.7% (Web Table 7).

### DISCUSSION

Although our study found higher risks of stroke and death over 180 days for FGA users, only a small portion (2.70%) of the effect of antipsychotic drug type on mortality risk was explained by stroke. Stroke prevention efforts would likely decrease the 180-day mortality risk in this population, but our results suggest that the mortality risk gap between FGA users and SGA users would persist.

Our finding of higher risks of stroke and death for FGA users compared with SGA users is consistent with much of

the previous literature. Prior studies showed that the relative risk of death was highest in the first month after antipsychotic drug initiation (hazard ratio = 1.55); it decreased over time, but remained elevated at 180 days (hazard ratios ranging from 1.27 to 1.37) (6) and was unlikely to be explained by unmeasured confounding (31).

With regard to stroke, only some studies of initiators found higher risks for FGA users compared with SGA users. Three cohort studies showed higher risk of cerebrovascular events for FGA users than SGA users in the first 180 days of follow-up (hazard ratios ranging from 1.20 to 2.34) (16, 17, 19). In contrast, another 3 cohort studies (20, 22, 32) found no difference in risk, but this discrepancy may be attributable to differences in study design (33), longer follow-up, or artificial (and potentially informative) censoring of patients who switched or discontinued their medications.

Despite evidence for modest effects of antipsychotic drug type on risks of both death and stroke, these 2 effects were only slightly related. Only 2.7% of the difference in mortality risk by antipsychotic drug type could be explained by differences in stroke onset. One potential explanation is measurement error in the ICD-9-CM–based algorithm used to identify stroke, which, if nondifferential, would tend to bias the indirect effect toward the null (34). The use of less restrictive algorithms to improve sensitivity increased the percent mediated from 2.7% to 6.7%.

Medicare insurance claims databases do not contain information on important behavioral cardiovascular risk factors. The sensitivity analyses for a binary unmeasured confounder (35) showed that, although strong unmeasured confounding of the stroke-death relationship could fully explain the observed indirect effect, downward bias from protective risk factors for stroke would be minimal (Web Figure 3). Adjustment for stroke risk factors assessed during follow-up and stratification by the duration of use yielded results that were similar to those of the main analyses (Web Tables 4 and 5). The mediation analysis framework we used requires that no stroke-death confounders be affected by antipsychotic drug type. In sensitivity analyses for violations of this condition (36), the small indirect effect we observed would be subject to such violations, but the large direct effect would be robust; our qualitative conclusions would not change.

Our study has a number of strengths. We approximated a new user design, which is suited for the evaluation of short-term drug effects (37), and the temporal ordering of covariate assessment, antipsychotic drug initiation, stroke occurrence, and death was clear. Mediation analyses typically suffer from unmeasured mediator-outcome confounders; we adjusted for a rich set of patient characteristics. The many sensitivity analyses support our overall conclusion that stroke does not explain much of the observed mortality risk difference between FGA users and SGA users.

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