Cerebrovascular Events Among Elderly Nursing Home Patients Treated With Conventional or Atypical Antipsychotics

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Objective: Concern exists about a possible increased risk of cerebrovascular events (CVEs) among elderly patients receiving risperidone or olanzapine. We estimated the effect of atypical and conventional antipsychotics on the risk of CVEs among elderly nursing home patients with dementia.

Method: We conducted a case-control study on residents of nursing homes in 6 U.S. states by using the Systematic Assessment of Geriatric drug use via Epidemiology database, which includes data from the Minimum Data Set linked to Medicare inpatient claims. Participants were diagnosed with Alzheimer's disease or other forms of dementia on the basis of clinical criteria and medical history (including medical records and neuroradiologic documentation). Cases included patients hospitalized for stroke or transient ischemic attack between June 30, 1998, and December 27, 1999. For each case, we identified up to 5 controls hospitalized for septicemia or urinary tract infection residing in the same facility during the same time period. The sample consisted of 1130 cases and 3658 controls.

Results: After controlling for potential confounders, the odds ratio of being hospitalized for CVEs was 0.87 (95% CI = 0.67 to 1.12) for risperidone users, 1.32 (95% CI = 0.83 to 2.11) for olanzapine users, 1.57 (95% CI = 0.65 to 3.82) for users of other atypical agents, and 1.24 (95% CI = 0.95 to 1.63) for conventional antipsychotic users compared to nonusers of antipsychotics. A history of CVEs appeared to modify the effect of atypical antipsychotics other than risperidone on the risk of new events.

Conclusion: Overall, no increased risk of CVEs seems to be conferred by atypical or conventional antipsychotics. Preexisting cerebrovascular risk factors might interact with some atypical antipsychotics to increase the risk of events. These results should be interpreted in light of the limitations of the study and need to be confirmed.

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Atypical antipsychotics have been introduced in the United States for the treatment of schizophrenia.[1] However, due to their reported superior side effect profiles relative to conventional agents, atypical antipsychotics have rapidly become the mainstay of treatment in a wide spectrum of neurologic and psychiatric disorders.[2,3] Indeed, over 70% of atypical antipsychotic prescriptions are for off-label indications,[4] and recent studies testify to an increasing use, especially in nursing homes.[5] Furthermore, atypical antipsychotics have been recently endorsed as treatment of choice for behavioral disturbances and psychotic symptoms of dementia.[6]

However, information regarding the safety and tolerability of these agents is limited, especially in the elderly population. Some evidence, for example, indicates that atypical antipsychotic use may increase the risk of obesity, dyslipidemia, and diabetes.[7,8] No conclusive evidence has been attained concerning the effect of these drugs on QT-interval prolongation and related arrhythmias.[9,10] Likewise, a suspiciously high rate of venous thromboembolism linked to the use of atypical agents, mostly clozapine, has been reported.[11]

More recently, there has been a warning about a possible increased risk of stroke and transient ischemic attack (TIA) among elderly patients with dementia being treated with risperidone or olanzapine.[12,13] In 4 placebo-controlled trials,[12,14–16] cerebrovascular events (CVEs) were twice as common in the risperidone-treated group as in the placebo group. Moreover, the maker of olanzapine has recently warned physicians about an increased risk of death and stroke in 5 clinical trials among patients with dementia.[13,17,18]

To date, the association between the use of atypical antipsychotics and the risk of stroke or TIA remains controversial. We conducted a case-control study to estimate the effect of atypical and conventional antipsychotics on the risk of CVEs among nursing home residents with dementia in 6 U.S. states.

METHOD

Data Source

We used the Systematic Assessment of Geriatric drug use via Epidemiology (SAGE) database, which contains data from the Minimum Data Set (MDS).[19,20] The MDS is a standardized, clinically based instrument that collects information on each resident's demographic, functional, medical, psychological, and cognitive status. Each Medicare/Medicaid-certified nursing home conducts an MDS assessment of all residents upon admission and quarterly thereafter. Since 1998, the Centers for Medicare & Medicaid Services has maintained a centralized repository of all MDS data, and these are used for administrative and research purposes.

Study Population

Data collected in the nursing homes of 6 states (Ohio, Maine, Illinois, Mississippi, South Dakota, and New York) were used in this study. Eligible candidates were residents 65 years of age or above who were diagnosed with Alzheimer's disease or other forms of dementia on the basis of clinical criteria and medical history (including medical records and neuroradiologic documentation). Residents with schizophrenia were excluded, as they might have a different risk profile compared to patients with dementia only, especially with respect to smoking and alcohol consumption.

Case Selection

We calculated the required sample size to detect effects of this magnitude with a conventional α level of 0.05 and a β level of 0.20 (power = 80%).[21] Relative to nonusers of antipsychotics, we assumed a relative risk of 2.0 for risperidone and of 3.0 for olanzapine, based on the findings in clinical trials.[12,13] Given an estimated prevalence of 10.8% for risperidone and 2.4% for olanzapine in the study population, we calculated that we would have needed at least 222 cases and 222 controls in the case of risperidone, and at least 307 cases and 307 controls in the case of olanzapine.

The SAGE database links MDS data to the Medicare inpatient claim files (part A) that contain information on residents' health service use. The Medicare inpatient claim data provide the admission diagnosis and up to 10 discharge diagnoses for any hospitalizations recorded by using the *International Classification of Diseases*, Ninth Revision (ICD-9) codes. Cases included hospitalized residents for whom the primary discharge diagnosis was either ischemic stroke (ICD-9 codes: 433.0–434.9) or TIA (ICD-9 codes: 435–435.9). We used the first event for persons with multiple hospitalizations. We identified 1908 such hospitalizations between June 30, 1998, and December 27, 1999.

Control Selection

For the control group, we selected myocardial infarction, gastrointestinal bleeding, urinary tract infection, and septicemia from a list of the most common discharge diagnoses. We excluded patients with gastrointestinal bleeding or myocardial infarction because these conditions are associated with the use of antiplatelet agents, which in turn are related to a decreased incidence of CVEs. Thus, controls were residents for whom the primary diagnosis at discharge was either septicemia (ICD-9 codes: 038–038.9) or urinary tract infection (ICD-9 code: 599.0). We identified 7064 potential controls.

It has been shown that structural factors of the facility may affect rates and patterns of hospitalization.[22] To minimize this potential confounding effect, we matched cases and controls within the same facility. Each case could be matched to a maximum of 5 controls residing within the same facility during the same period. We excluded cases for whom we could not identify at least 1 eligible control (N = 778). We compared the excluded cases with those included in the study on all main characteristics. We found that there were no significant differences between the 2 groups. The final matched sample consisted of 1130 cases and 3658 controls. Cases included residents hospitalized for ischemic stroke (77.7%) and transient ischemic attack (22.3%).

Antipsychotic Exposure

Nursing home staff recorded the name, dose, frequency, and route of administration for up to 18 medications taken by the resident in the 7 days before the assessment.

We identified the most proximal assessment before the hospitalization and defined it as the index assessment. We defined as exposed those residents for whom any antipsychotic use was reported at the index assessment. Exposed residents were classified as users of risperidone, users of olanzapine, users of other atypical antipsychotics (clozapine and quetiapine), and users of conventional

agents (chlorpromazine, chlorprothixene, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, promazine, thioridazine, thiothixene, and trifluoperazine). We defined as unexposed those residents for whom no antipsychotic use was reported at the index assessment.

Potential Confounders

Residents' sociodemographic characteristics (age, sex, and race/ethnicity) along with body mass index (BMI); indicators of functional, cognitive, and behavioral status; comorbid conditions; and concurrent drug use were considered as potential confounders. To evaluate functional status, we used the Activities of Daily Living scale (ADL),[23] a 7-item, 6-level score based on the resident's performance in 7 areas: dressing, eating, toileting, bathing, locomotion, transferring, and incontinence. We classified the degree of dependence as mild (ADL score = 0–1), moderate (ADL score = 2–3), or severe (ADL score = 4–5). The Cognitive Performance Scale (CPS) was used to measure cognitive status.[24] The CPS is a validated scale embedded in the MDS that ranges from 0 (intact cognition) to 6 (severe dementia) and has a good correlation with the Mini-Mental State Examination.[25] We categorized cognitive impairment as follows: minimal (CPS score = 0–1), moderate (CPS score = 2–3), and severe (CPS score = 4–6).

We evaluated the degree of severity of psychotic and behavioral problems by using an MDS-based index previously used in research.[26] Residents were considered to have severe symptoms if they were verbally or physically abusive, and socially inappropriate every day. Residents with moderate symptoms exhibited wandering and verbally or physically abusive behavior and were socially inappropriate on occasions, but less than daily. If residents exhibited some of the mentioned symptoms or none of them, they were classified as mild/normal.

The MDS clinical diagnosis section was used to assess residents' comorbid conditions. The validity and accuracy of such diagnoses in the SAGE database have been previously shown.[19] Comorbid conditions considered were hypertension, heart failure, coronary artery disease, cardiac arrhythmias, other cardiac diseases, history of stroke/TIA, peripheral vascular disease, history of deep vein thrombosis, diabetes mellitus, Alzheimer's dementia, dementia other than Alzheimer's, depression, anxiety, and bipolar disorder. We also evaluated concomitant medications that may exert a protective effect on the risk of CVEs. These medications included diuretics, β blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, vasodilators, centrally acting antihypertensive drugs, antiarrhythmic drugs, lipid-lowering drugs, oral antidiabetic agents, insulin, coagulation modifiers, antiplatelets, nonsteroidal anti-inflammatory drugs (NSAIDs), and antidepressants.

Analytic Plan

To quantify the effect of antipsychotic use on the likelihood of hospitalization for CVEs controlling for all potential confounders, we used a conditional logistic regression model. The use of many covariates in the logistic regression model was done in accordance with the recommended analytic standard.[27] We derived crude and adjusted odds ratios (ORs) along with 95% confidence intervals (CIs) from this model.

Subgroup analyses were conducted restricting the outcome to only ischemic strokes (N = 881), and stratifying by sex and type of dementia (Alzheimer's disease vs. other forms). Then, based on the hypothesis that a history of previous stroke/TIA could modify the effect of antipsychotics on the risk of new CVEs, we tested the interaction between these 2 risk factors. According to the scheme suggested by Rothman and Greenland,[28] we combined the 2 risk factors, history of stroke/TIA (yes/no) and antipsychotic exposure, into 1 variable with several levels. We included this variable in a conditional logistic regression model with "no antipsychotic use/no history of stroke/TIA" as the reference category. We calculated crude and adjusted ORs along with 95% CIs from this model. We estimated the synergy index (S), which measures interaction as a departure from additivity of the effects.[26] The synergy index is defined as

$$S = \frac{OR(AB) - 1}{[OR(A\bar{B}) - 1] + [OR(\bar{A}B) - 1]}$$

where A and B denote the presence of and $\bar{A}$ and $\bar{B}$ the absence of the 2 risk factors. In the absence of interaction between the 2 risk factors, S equals 1. Statistical analysis was performed using SAS Version 8 (SAS Institute, Cary, N.C.).

RESULTS

Cases and controls did not differ with respect to age, sex, race/ethnicity, and BMI distribution (Table 1). Residents in the control group were more likely to present a severe degree of functional impairment (61.7% vs. 32.5%) and cognitive deficit (50.4% vs. 27.8%). Severity of behavioral problems did not differ between the 2 groups. Overall, cardiac diseases as well as history of stroke/TIA were slightly more prevalent among cases relative to controls. Controls were more likely than cases to be diagnosed with Alzheimer's dementia (30.0% vs. 23.8%). There was no substantial difference in the overall prevalence of antipsychotic use (25.3% among cases and 23.1% among controls), as well as in the pattern of antipsychotic prescribed.

Table 2 illustrates the use of concomitant medications. Relative to controls, cases were more likely to use cardiovascular drugs, particularly β blockers (18.2% vs. 12.2%, respectively), ACE inhibitors (23.9% vs. 18.8%, respectively), calcium channel blockers (21.1% vs. 15.6%,

Table 1. Principal Characteristics of Case and Control Elderly Nursing Home Residents (%)

Characteristic	Cases (N = 1130)	Controls (N = 3658)
Age group, y		
≤ 74	11.4	10.9
75–84	36.1	39.0
≥ 85	52.5	50.1
Sex		
Women	70.5	71.1
Race/ethnicity		
White	86.2	83.2
Black	11.7	14.4
Other	2.1	2.3
Body mass index (kg/m^2)		
< 18.5	11.6	15.7
18.5–24.9	50.5	53.8
25.0–29.9	27.2	22.1
≥ 30.0	10.7	8.4
Functional impairment (ADL score)		
Mild (0–1)	12.9	4.0
Moderate (2–3)	54.6	34.2
Severe (4–5)	32.5	61.7
Cognitive deficit (CPS score)		
Mild (0–1)	12.3	6.2
Moderate (2–3)	59.9	43.3
Severe (4–6)	27.8	50.4
Behavior index		
Normal/mild	61.9	64.8
Moderate	31.5	28.0
Severe	6.6	7.1
Hypertension	55.2	48.5
Heart failure	27.1	27.2
Cardiac ischemic disease	22.8	21.4
Arrhythmias	17.7	15.4
Other heart disease	26.0	23.4
History of stroke	25.6	21.8
History of transient ischemic attack	7.5	3.7
Peripheral vascular disease	12.5	14.4
History of deep vein thrombosis	1.8	2.7
Diabetes	26.0	25.5
Alzheimer's dementia	23.8	30.0
Dementia other than Alzheimer's	82.9	79.5
Depression	34.9	32.3
Anxiety/bipolar disorder	13.1	13.0
Psychotic symptoms	4.8	4.6
Sleep cycle disturbances	11.3	10.6
Antipsychotic use		
Risperidone	10.5	10.8
Olanzapine	3.0	2.4
Other atypical (clozapine/quetiapine)	0.9	0.5
Conventional	10.9	9.4

Abbreviations: ADL = Activities of Daily Living scale, CPS = Cognitive Performance Scale.

Table 2. Medication Use of Case and Control Elderly Nursing Home Residents (%)

Medication	Cases (N = 1130)	Controls (N = 3658)
Diuretics	38.2	34.6
β blockers	18.2	12.2
Angiotensin-converting enzyme inhibitors	23.9	18.8
Calcium channel blockers	21.1	15.6
Vasodilators	20.6	16.2
Centrally acting antihypertensive drugs	3.5	3.0
Antiarrhythmic drugs	29.1	24.3
Lipid-lowering drugs	7.6	8.7
Oral antidiabetic agents	10.7	9.0
Insulin	10.4	11.6
Coagulation modifiers	9.7	10.3
Aspirin/antiplatelet agents	34.1	25.2
Nonsteroidal anti-inflammatory drugs	37.7	29.3
Antidepressants	33.5	28.3
Benzodiazepines	11.3	10.9
Anticonvulsants	11.6	11.2
Lithium	0.8	0.4

Table 3. Number of Prescriptions and Drug Regimens Among Elderly Nursing Home Residents Taking Antipsychotics

Drug	N	Daily Dose, Mode (mg)	Daily Dose, Range (mg)
Atypical			
Clozapine	11	50.0	25.0–400.0
Olanzapine	169	5.0	2.5–10.0
Quetiapine	32	50.0	25.0–300.0
Risperidone	611	1.0	0.25–4.0
Conventional			
Chlorpromazine	18	10.0	10.0–150.0
Chlorprothixene	2	…	…
Fluphenazine	24	10.0	7.5–30.0
Haloperidol	341	1.0	0.5–40.0
Loxapine	13	…	5.0–30.0
Mesoridazine	3	…	20.0–75.0
Molindone	10	10.0	5.0–25.0
Perphenazine	54	2.0	2.0–24.0
Promazine	23	…	…
Thioridazine	73	50.0	5.0–150.0
Thiothixene	26	2.0	1.0–20.0
Trifluoperazine	13	5.0	0.5–8.0

Symbol: … = missing data.

respectively), and antiarrhythmic drugs (29.1% vs. 24.3%, respectively). Also, cases were more likely than controls to be prescribed antiplatelet agents (34.1% vs. 25.2%), NSAIDs (37.7% vs. 29.3%), and antidepressants (33.5% vs. 28.3%).

Drug regimens among antipsychotic users are shown in Table 3. Risperidone was the most commonly prescribed atypical antipsychotic, accounting for over 70% of prescriptions. The use of other atypical agents was infrequent, particularly that of clozapine and quetiapine. Among conventional agents, haloperidol was the most commonly used (over 50% of prescriptions), followed by thioridazine.

No significant increase in the risk of being hospitalized for ischemic stroke or TIA was found among antipsychotic users (Table 4). After controlling for potential confounders, the OR was 0.87 (95% CI = 0.67 to 1.12) for risperidone users, 1.32 (95% CI = 0.83 to 2.11) for olanzapine users, 1.57 (95% CI = 0.65 to 3.82) for users of other atypical agents, and 1.24 (95% CI = 0.95 to 1.63) for conventional antipsychotic users. These results were unchanged when the outcome was restricted to only ischemic strokes or the analysis was stratified by type of dementia and sex.

Table 5 shows that users of risperidone and of conventional antipsychotics had no increased risk of being hospi-

Table 4. Crude and Adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs) of Being Hospitalized With a Diagnosis of Stroke or Transient Ischemic Attack in Elderly Nursing Home Residents Taking Antipsychotics

Variable	Crude OR	Adjusted OR[a]	95% CI
Risperidone versus no use	0.95	0.87	0.67 to 1.12
Olanzapine versus no use	1.37	1.32	0.83 to 2.11
Other atypical antipsychotic[b] versus no use	1.77	1.57	0.65 to 3.82
Conventional antipsychotic versus no use	1.27	1.24	0.95 to 1.63

[a]Adjusted for age, sex, race/ethnicity, body mass index, Activities of Daily Living scale score, Cognitive Performance Scale score, behavior index score, hypertension, cardiac ischemic disease, heart failure, cardiac arrhythmias, other cardiac diseases, history of cerebrovascular events (stroke/transient ischemic attack), peripheral vascular disease, history of deep vein thrombosis, diabetes mellitus, Alzheimer's disease, other dementias, depression, anxiety disorder, bipolar disorder, and concomitant drug use including diuretics, systemic β blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, vasodilators, centrally acting antihypertensive drugs, antiarrhythmic drugs, lipid-lowering drugs, oral antidiabetic agents, insulin, coagulation modifiers, antiplatelets, nonsteroidal anti-inflammatory drugs, and antidepressants.
[b]Other atypical antipsychotics include clozapine and quetiapine.

Table 5. Modification of Antipsychotic Effect by History of Cerebrovascular Events (CVEs) on the Risk of Being Hospitalized With a Diagnosis of Stroke or Transient Ischemic Attack Among Elderly Nursing Home Residents

Variable	Crude OR	Adjusted OR[a]	95% CI
CVEs history and risperidone use	1.74	1.49	0.93 to 2.38
CVEs history and olanzapine use	3.69	3.71	1.55 to 8.84
CVEs history and other atypical antipsychotic use[b]	4.99	4.63	1.35 to 32.63
CVEs history and conventional antipsychotic use	1.21	1.23	0.68 to 2.23
No CVEs history and risperidone use	0.88	0.83	0.62 to 1.12
No CVEs history and olanzapine use	1.07	1.04	0.60 to 1.80
No CVEs history and other atypical antipsychotic use[b]	1.04	1.02	0.29 to 2.99
No CVEs history and conventional antipsychotic use	1.42	1.36	1.01 to 1.83
CVEs and no use	1.33	1.50	1.22 to 1.84
No CVEs and no use	1.00	1.00	

[a]Adjusted for age, sex, race/ethnicity, body mass index, Activities of Daily Living scale score, Cognitive Performance Scale score, behavior index score, hypertension, cardiac ischemic disease, heart failure, cardiac arrhythmias, other cardiac diseases, peripheral vascular disease, history of deep vein thrombosis, diabetes mellitus, Alzheimer's disease, other dementias, depression, anxiety disorder, bipolar disorder, and concomitant drug use including diuretics, systemic β blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, vasodilators, centrally acting antihypertensive drugs, antiarrhythmic drugs, lipid-lowering drugs, oral antidiabetic agents, insulin, coagulation modifiers, antiplatelets, nonsteroidal anti-inflammatory drugs, and antidepressants.
[b]Other atypical antipsychotics include clozapine and quetiapine.
Abbreviations: CI = confidence interval, OR = odds ratio.

talized for CVEs regardless of the presence of a previous history of stroke/TIA. In contrast, olanzapine users and users of other atypical agents presenting a history of CVEs were 3.71 times and 4.63 times, respectively, more likely to be hospitalized for CVEs compared to nonusers without such history. The estimates of the synergy index showed an interaction between atypical antipsychotics and a history of stroke/TIA, which was strong in the case of olanzapine (S = 5.02) and for clozapine and quetiapine (S = 6.98). The synergy index in the case of risperidone was 1.48, suggesting no interaction.

DISCUSSION

The findings of this study suggest that, among nursing home residents with dementia, antipsychotics do not increase the risk of hospitalization for stroke or TIA.

The suggestion that risperidone might increase the risk of CVEs was based on a pooled analysis of data from all placebo-controlled trials of risperidone in elderly patients with dementia.[12] In particular, an Australian trial (AUS-5)[14] showed that the incidence of CVEs was 9% in the risperidone group and 2% in the placebo group. A second trial (INT-24)[15] documented that 8% of patients who received risperidone manifested CVEs compared to 2% of those who received placebo. This prompted the maker of risperidone to issue a worldwide warning, despite an additional placebo-controlled dementia trial (USA-63) and a small-scale pilot trial (BEL-14) that failed to show any difference in the incidence of CVEs between risperidone and placebo.[12,16] More recently, the maker of olanzapine also has warned physicians about an increased risk of death and stroke.[13] In particular, a 2-fold increase in mortality and 3-fold increase in CVEs were observed among elderly patients with dementia treated with olanzapine in 5 placebo-controlled clinical trials.[13,17,18] In contrast with these data, Herrmann and colleagues[29] recently published a large observational study examining the risk of hospitalization for stroke in a cohort of elderly antipsychotic users. These authors found no increased risk of hospital admission for stroke among risperidone or olanzapine users compared with users of conventional antipsychotics.

In our study, we defined as CVEs all cases of stroke and TIA that led to a patient's hospitalization. Events classified as CVEs in the AUS-5 and INT-24 trials included cases of syncope and obtundation, probably linked to the α-adrenergic–blocking properties of risperidone. Such differences in the operational definition of CVEs might have contributed to the observed discrepancy between the findings of the current study and those of the 2 clinical trials.

The estimated effect of olanzapine, that of other atypical agents, and that of conventional antipsychotics suggested a possible 20% to 50% increased risk of stroke or TIA. This increased risk did not reach statistical significance. However, case reports[30] and observational studies[31] have documented an increased risk of venous thromboembolism in recipients of conventional antipsychotics. Almost all data on venous thromboembolism during treat-

ment with atypical antipsychotics refer to clozapine.[32–34] More recently, there have been 3 cases of venous thromboembolism reported among elderly patients treated with olanzapine,[35] and an additional case in a young man with a psychotic disorder.[36]

The biological mechanisms responsible for a possible increased cerebrovascular risk are unknown. Certainly, antipsychotics might induce several metabolic abnormalities (increased triglycerides and cholesterol levels, increased plasma levels of leptin and glucose) known to be associated with a decreased fibrinolytic activity.[11,37] Secondly, lupus anticoagulant and anticardiolipin antibodies have frequently been reported to be raised in patients taking conventional antipsychotics[38] and clozapine.[39] An effect on platelet aggregation is also possible. There is evidence, for example, that phenothiazines increase serotonin-induced platelet aggregation.[40] Then, atypical antipsychotics would be expected to increase platelet aggregation due to their high affinity for the serotonin receptor type-2A. However, the event rate seems low enough to suggest that, even if any of these mechanisms are in place, individual susceptibility remains the most important determinant of the risk.

An additional finding of our study is that a history of CVEs appears to modify the effect of olanzapine and quetiapine/clozapine but not that of risperidone. This might be explained by a more severe worsening of the cardiovascular risk profile documented to occur with these agents relative to risperidone. For example, olanzapine causes a more marked increase in weight, serum lipid levels, glucose levels, and leptin levels relative to risperidone.[41–43] Other risk factors such as concomitant medication use may modify the effect of antipsychotics on the risk of stroke, and future studies exploring this issue are warranted.

The findings of this study have high clinical and public health relevance. In times when atypical antipsychotics are rapidly replacing conventional antipsychotics[5] and indications for their use are expanding,[44] there is a critical need for information concerning the safety of these substances. We studied the effect of antipsychotics in a population of frail elderly patients characterized by a high cardiovascular risk profile. Such a population is more likely than a clinical trial sample to reflect the characteristics of patients who are prescribed antipsychotics in clinical practice. Our study suggests that among those patients who are the most common users of these drugs, there appears to be no increased risk of CVEs linked to the use of antipsychotics. Our data also indicate that other cerebrovascular risk factors such as a previous history of CVEs may interact with some atypical antipsychotics to increase the risk of CVEs. This finding would suggest an extremely cautious use of atypical antipsychotics among patients with high baseline cerebrovascular risk.

Some limitations of our study are worth discussing. The potential for misclassification of the outcome based on claims data exists. However, ischemic stroke diagnoses derived from hospital-based registries and based on ICD codes have been proven to be reliable in the United States,[45] Canada,[46] and several European countries.[47] By definition, we have missed all cases of stroke or TIA resulting in death prior to hospital referral. This may be relevant since the fatality rate reported in the cited dementia trials was around 45% to 50%.[12,13]

An appropriate selection of controls is a critical issue. However, a reference group consisting of hospitalized controls appeared the most valid comparison group in our study. In fact, by doing so and by matching within facility, we have tried to control for patients' characteristics and other "forces" (structural and organizational characteristics of the facility) influencing the probability of being hospitalized from a nursing home.[22] Since many conditions that lead to hospitalization among nursing home residents may be characterized by psychotic and behavioral symptoms and may indeed be linked to the use of antipsychotics, we cannot rule out the possibility of a selection bias. However, we have tried to minimize this risk by verifying that there was no difference in the prevalence of antipsychotic use between the study control group and a sample of nonhospitalized residents from the same geographic areas and in the same time period as controls. In the case of clozapine, quetiapine, and some conventional agents, the low prevalence of use may have limited the precision in the estimates of effect. The distinction between Alzheimer's dementia and dementia other than Alzheimer's, mostly including vascular or mixed dementia, was based on clinical criteria and the resident's medical history. This practice could have led to some degree of misclassification, which can explain the lower prevalence of Alzheimer's dementia in the present study relative to previous studies. However, this limitation did not impact the validity and the generalizability of findings. We lack information on biochemical parameters to better characterize the individual baseline risk including information on platelet counts, coagulation parameters, inflammatory markers, leptin and lipid profiles, and blood glucose levels. We observed low variability among drug regimens, and we were not able to investigate dose-response relationships. Moreover, we lacked data on duration of treatment to investigate the relevant etiologic period. Finally, although we controlled for numerous confounders, residual confounding is always possible.

In conclusion, among patients with dementia living in nursing homes, there appears to be no increased risk of CVEs conferred by atypical or conventional antipsychotics. Yet, preexisting cerebrovascular risk factors might interact with at least some atypical antipsychotics, producing an increased risk of CVEs. Further studies are needed to corroborate these findings.

Drug names: chlorpromazine (Sonazine, Thorazine, and others), clozapine (Clozaril, FazaClo, and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), loxapine (Loxitane and others), molindone (Moban), olanzapine (Zyprexa), perphenazine (Trilafon and others), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), trifluoperazine (Stelazine and others).

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