Article

Association of Cerebrovascular Events With Antidepressant Use: A Case-Crossover Study

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Objective: The authors sought to assess the risk of cerebrovascular events associated with use of antidepressant medications.

Method: The authors conducted a case-crossover study of 24,214 patients with stroke enrolled in the National Health Insurance Research Database in Taiwan from 1998 to 2007. The authors compared the rates of antidepressant use during case and control time windows of 7, 14, and 28 days. Adjustments were made for time-dependent variables, such as health system utilization and proposed confounding medications. Stratified analyses were performed for valuing the interaction between the stroke risk of antidepressant use and age, sex, presence of mood disorder, stroke type, severity of chronic illness, and duration of antidepressant treatment. A conditional logistic regression model was used to determine the odds of antidepressant use during case time windows.

Results: The adjusted odds ratio of stroke risk with antidepressant exposure was 1.48 (95% confidence interval=1.37–1.59) using 14-day time windows. Stroke risk was negatively associated with the number of antidepressant prescriptions reported. Use of antidepressants with high inhibition of the serotonin transporter was associated with a greater risk of stroke than use of other types of antidepressants.

Conclusions: These findings suggest that antidepressant use may be associated with an increased risk of stroke. However, the underlying mechanisms remain unclear.

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Stroke is the second leading cause of death and the sixth leading cause of disease burden globally (1). Depression is an independent risk factor for stroke and the leading cause of years lost to disability (1–3). The prevalence of antidepressant use has increased in many countries, including the United States (4) and Taiwan (5). Whether treating depression with antidepressants reverses depression-related cardiovascular complications remains inconclusive (6–9), and concerns about the cerebrovascular effects of antidepressants have increased since a growing body of evidence has shown that antidepressants (especially selective serotonin reuptake inhibitors) may induce bleeding complications (10–12) and vasoconstriction of the large cerebral arteries (13–15). In this regard, the benefit-risk profile of the cerebrovascular effect of antidepressant use remains unclear (14).

Despite negative findings in randomized trials (16) and case-control studies (17–20), recent cohort studies revealed that current users of antidepressants had a higher risk of ischemic stroke (21) and hemorrhagic stroke (22). The discrepant findings may be partially explained by small sample sizes, lack of controls for potential confounders (such as confounding by indication [14]), and comparison between current users and nonusers in most of the case-control studies. The current users category contained both new users and long-term regular users. Antidepressants may have acute adverse effects but chronic beneficial effects on stroke risk by treating depression or psychological distress. Thus, the sum of different cerebrovascular effects in new users and long-term users may confound the results (23).

To overcome the limitations of previous studies, we conducted a case-crossover study to analyze the association between stroke risk and antidepressant exposure in a nationwide population-based claims data set. The case-crossover design is an efficient method for examining the association of transient drug exposure with acute effects (23, 24). In this design, study subjects serve as their own controls, removing between-subject time-invariant confounders, which remain unmeasured or unknown (23). We hypothesized that acute exposure to antidepressants, particularly those with high inhibition of the serotonin transporter, would increase the risk of stroke.

Method

Data Source

Taiwan introduced a single-payer National Health Insurance program, covering 98% of the Taiwanese population, on March 1, 1995. Since 1996, the National Health Insurance reimbursement claims data have been transferred to and managed by the National Health Research

This article is featured in this month's AJP **Audio**, is the subject of a **CME** course (p. 559), is discussed in an editorial by Dr. Smoller (p. 457), and is an article that provides **Clinical Guidance** (p. 521).

Institute in Taiwan to establish the National Health Insurance Research Database, a medical claims database. The database includes patients' demographic characteristics, diagnoses, medical expenditures, and prescription claims data (25). Each prescription record contains type of medication, dosage, time of prescription, and duration of drug supply. Information that could be used to identify beneficiaries and medical care providers is scrambled by the Bureau of National Health Insurance (26). All investigators must sign an agreement that guarantees patient confidentiality before using the database.

Data for this study were obtained from the ambulatory and inpatient claims database. The database has been used for the study of several diseases (26–28), including stroke (28). We included data from all individuals who were enrolled between January 1, 1997, and December 31, 2007.

Study Subjects

We defined patients with an incident cerebrovascular event as those with a hospitalization for a primary diagnosis of a cerebrovascular event under ICD-9-CM codes 430, 431, and 432.x for hemorrhagic stroke; 433.x, 434.x, and 435.x for ischemic stroke; and 436.x for other stroke. The index date was defined as the date when the case subjects were diagnosed as having a first hospitalization for a stroke.

In this study, the patients in whom an incident stroke was suspected had to be at least 18 years of age at the time of first hospitalization for stroke (index day) in the years 1998 to 2007 (N=489,852). Three groups of patients were excluded: those who had any inpatient or outpatient diagnosis of cerebrovascular disease with an ICD-9-CM code (430–438.x) in 1997; those who had diagnoses of head injury (ICD-9-CM code: 800.x–804.x, 850.x–854.x, or 959.x) at the time of first hospitalization for stroke; and those who had been hospitalized within 1 year before the index date (so that we would have a full 1-year observation period). After these exclusions, 334,249 patients were eligible for the study. Among them, 26,171 (7.8%) had at least one antidepressant prescription within 1 year before the onset of stroke. We further excluded patients who had prescriptions of melitracen-flupentixol (N=1,957), which combines a tricyclic agent and a conventional antipsychotic. After these exclusions, 24,214 patients remained in the study.

Case-Crossover Design

The case-crossover design is one method for examining the effect of transient exposures on acute outcomes (24). In this study design, each patient serves as his or her own control. The odds ratio was estimated by the ratio of patients exposed only during the 14-day case period (1–14 days before the index date) to patients exposed only during the 14-day control period (15–28 days before the index day). We also computed odds ratios using two other time windows, set at 7 days (i.e., 1–7 days and 8–14 days before the index day, for the case and control periods, respectively) and 28 days (i.e., 1–28 days and 29–56 days before the index day, for the case and control periods, respectively) for sensitivity analysis.

Characteristics of Study Subjects

In addition to age and sex, we assessed general health status by the Charlson comorbidity index, which is the sum of the weighted score of 19 comorbid conditions (29) and is widely used to control confounding in epidemiological studies (30). The presence of mood disorders was defined as any of ICD-9-CM codes 296.x, 300.4, and 311 at outpatient diagnosis within the year before onset of stroke. New-onset mood disorders were defined as the first date of diagnosis of a mood disorder during the study period after observation for 2 years without any diagnosis of mood disorders before the index date. Durations of antidepressant treatment were assessed by the number of antidepressant prescriptions during the year before stroke; this measure reflected the number of times an antidepressant medication was prescribed, including refills of the same prescription.

Exposure to Antidepressants

We identified antidepressants according to the Anatomical Therapeutic Chemical (ATC) classification system (31). Antidepressants were classified into four groups according to their proposed mechanisms of action: tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and other antidepressants.

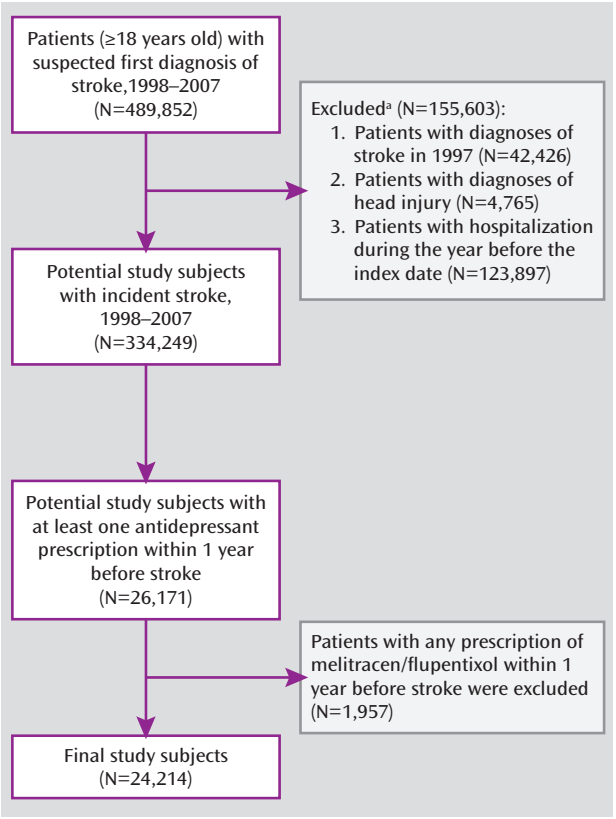
Based on the dissociation constant (K_d) for the serotonin transporter, antidepressants with serotonin transporter reuptake inhibition were categorized into three groups: high K_d (<1 nmol/liter), intermediate K_d (1–10 nmol/liter), and low K_d (>10 nmol/liter). For the degree of inhibition of norepinephrine reuptake, we used the K_d for the norepinephrine transporter and categorized antidepressants into three groups: high (<100 nmol/liter), intermediate (100–1,000 nmol/liter), and low K_d (>1,000 nmol/liter) (32, 33).

The exposure variable in this study was antidepressant medication, which was retrieved from the medical expenditure and prescription claims data (including refills) in the national database. The presence of exposure to an antidepressant was defined as the prescription of a particular antidepressant at least 1 day during the case or control time periods. Defined daily dose, which was defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults," was used to quantify an individual's average daily dose. We assessed the average daily dose by cumulative doses divided by cumulative exposure days during the case or control periods. For the analyses of the dose-response effect of antidepressants on stroke risk, the average daily dose was categorized into four ranges in relation to defined daily dose (31): 0, >0 to <0.5, ≥0.5 to <1, and ≥1 defined daily dose.

Time-Variant Confounding Factors

The confounding variables analyzed included health care utilization, measured as the number of outpatient

FIGURE 1. Flow Chart of Selection of Study Subjects From Among Patients With Incident Cerebrovascular Events Recorded and Antidepressant Prescriptions in Taiwan's National Health Insurance Research Database



[a] The Ns for these three exclusion criteria add up to more than the total N because some patients met more than one exclusion criterion.

TABLE 1. Demographic and Clinical Characteristics of 24,214 Patients With Antidepressant Prescriptions and First-Time Hospitalization for Stroke, 1998–2007

Characteristic	N	%
Age group (years)		
18–64	7,956	32.9
65–74	8,299	34.3
≥75	7,959	32.9
Female	11,695	48.3
Charlson comorbidity index		
0–1	10,162	42.0
2–3	8,471	35.0
≥4	5,581	23.0
Mood disorders	8,785	36.3
Stroke type		
Ischemic	18,367	75.9
Hemorrhagic	3,912	16.2
Other	1,935	8.0
Number of antidepressant prescriptions in the year before stroke		
1	8,038	33.2
2	3,831	15.8
3–5	4,715	19.5
≥6	7,630	31.5

visits during the case or control periods, and medication related to strokes, defined as the prescription presence of any of the following medications (grouped by ATC classification) prescribed for at least for 1 day during the case or control periods (31): antipsychotics (N05A), antithrombotic agents (B01), antidiabetes agents (A10), diuretics (C03), antihypertensives (C07, C08, and C09), and lipid-modifying agents (C10).

Data Analysis

For the case-crossover analyses, we used conditional logistic regression models following the PHREG procedure in SAS, version 9.13 (SAS Institute, Cary, N.C.), to estimate the odds ratios and their 95% confidence intervals (CIs). The statistical significance of relationships was assessed by using 95% CIs or a p threshold of 0.05. The adjusted odds ratios of stroke for antidepressant use were estimated after controlling for the number of outpatient visits, mood disorders, and proposed confounding medication exposures.

We performed subgroup analyses by stratifying the various characteristics of the patients, including age, sex, Charlson comorbidity index (29), duration of treatment (number of prescriptions), and mood disorders. We tested the interactions between antidepressant exposure and these patient characteristics in the whole sample. We further conducted conditional logistic regression analyses to explore whether new-onset mood disorders were predictive of risk of stroke and to test the potential confounding effect of new-onset mood disorders on the relationship between antidepressant use and risk of stroke.

We further compared odds of the exposures of antidepressants between the case and control periods after the onset of stroke for the ischemic and hemorrhagic strokes stratified by the characteristics of antidepressant use, based on average daily dose, type of antidepressant, and degree of inhibition of serotonin or norepinephrine transporters. We also explored a potential dose-response relationship between stroke and antidepressant exposure by using conditional logistic regression analyses and considering average daily dose as a continuous variable. The trend toward an increasing risk of stroke with a higher average daily dose was determined by the Wald chi-square test. Finally, sensitivity analyses using 7-day and 28-day time windows were performed to test for the robustness of the results.

Results

Data for a total of 24,214 stroke patients with at least one antidepressant prescription in the year before a first hospitalization for stroke were analyzed (Figure 1). The mean age at stroke onset was 68.6 years (SD=12.0); 48.3% of the study subjects were women, 36.3% had mood disorders, and 75.9% had ischemic strokes. The mean number of antidepressant prescriptions in the previous year was

TABLE 2. Antidepressant Prescriptions During the Year Before Stroke Among 24,214 Patients With Antidepressant Prescriptions and First-Time Hospitalization for Stroke, 1998–2007[a]

Antidepressant Class and Agent	N	%	Defined Daily Dose (mg)	K_d^S	K_d^N
Tricyclics					
Imipramine	10,360	42.8	100	1.4	37
Amitriptyline	2,685	11.1	75	4.3	35
Doxepin	1,186	4.9	100	68	29.5
Maprotiline	438	1.8	100	5,800	11.1
Clomipramine	228	0.9	100	0.28	38
Dothiepin	143	0.6	75[b]	8.6	46
Viloxazine	1	0.0	200	17,300	155
SSRIs					
Fluoxetine	2,289	9.5	20	0.81	240
Sertraline	1,179	4.9	50	0.29	420
Paroxetine	941	3.9	20	0.13	40
Citalopram	439	1.8	20	1.16	4,070
Fluvoxamine	404	1.7	100	2.2	1,300
MAO inhibitors					
Moclobemide	953	3.9	300	>100,000	>100,000
Other					
Trazodone	7,009	28.9	300	160	8,500
Venlafaxine	527	2.2	100	8.9	1,060
Mirtazapine	260	1.1	30	>100,000	4,600
Bupropion	114	0.5	300	9,100	52,000
Duloxetine	17	0.1	60	0.07	1.17
Milnacipran	16	0.1	100[b]	8.44	22

[a] SSRIs=selective serotonin reuptake inhibitors; MAO=monoamine oxidase; K_d^S=dissociation constant for the serotonin transporter; K_d^N=dissociation constant for the norepinephrine transporter.
[b] For dothiepin and milnacipran, the defined daily dose was defined as the lowest recommended daily dose because of lack of data in the database.

5.3 (SD=6.5, range=1–138). The demographic characteristics, stroke types, and number of prescriptions are summarized in Table 1, and rates of antidepressant types are listed in Table 2.

The data in Table 3 show that antidepressant use in the 2 weeks before the stroke was associated with a higher risk of stroke by 48%, adjusting for health system utilization and proposed confounding medications. In patients with mood disorders, univariate analysis revealed that new-onset mood disorders were associated with a higher risk of stroke (odds ratio=1.33; 95% CI=1.10–1.60). Including new-onset mood disorders as one of the covariates in multivariate analysis, we found that the stroke risk with antidepressant use was slightly lower, with the adjusted odds ratio dropping from 1.48 to 1.44 (95% CI=1.27–1.64), and the effect of new-onset mood disorders was not statistically significant (adjusted odds ratio=1.16; 95% CI=0.96–1.41, p=0.13).

There were no interactions between antidepressant use and age, the Charlson comorbidity index, or mood disorders on the risk of cerebrovascular events. However, the stroke risk with antidepressant use in the 2 weeks before the stroke was negatively associated with the number of antidepressant prescriptions in the previous year (p<0.001). There was no statistical association between antidepressant use in the 2 weeks before the stroke and the risk of stroke for patients with prescription numbers ranging from three to five in the previous year. Antidepressant use was associated with a lower stroke risk among patients with more than six antidepressant prescriptions. The greater stroke risk with antidepressant use was mainly attributable to patients who had one or two prescriptions in the previous year.

Table 4 summarizes the relationship between stroke type and antidepressant type among patients with fewer than three antidepressant prescriptions in the year before the stroke. We found that an excess risk of stroke with antidepressant use was more prominent for the ischemic type (adjusted odds ratio=2.52; 95% CI=2.23–2.84) than for the hemorrhagic type (adjusted odds ratio=1.92; 95% CI=1.49–2.47) of stroke, despite overlapping of the 95% confidence intervals of the two stroke types. We also observed a trend toward an increasing risk of stroke with a higher average daily dose (p trend <0.001, Wald χ^2=194.5, df=1) after adjusting for confounding factors. In addition, the risk of stroke associated with antidepressants with high inhibition of the serotonin transporter was greater than with antidepressants with low or intermediate inhibition (Figure 2). Antidepressants with high inhibition of the norepinephrine transporter were associated with a lower risk of stroke than those with low or intermediate inhibition. There was no significant difference between low and intermediate inhibitors of norepinephrine transporter.

TABLE 3. Exposure to Antidepressants Between the 14-Day Case and Control Periods for Risk of Stroke, Total and Stratified by Patient Characteristics

Measure	Use Only in the Case Period	Use Only in the Control Period	Use in Both Periods	Nonuse in Both Periods	Crude Odds Ratios[a]	95% CI	Adjusted Odds Ratio[b]	95% CI
All patients (N=24,214)	2557	1235	7096	13326	2.07	1.93–2.22	1.48	1.37–1.59
Subgroup analyses								
Age group (years)								
18-65 (N=7,956)	883	434	2103	4536	2.03	1.81–2.28	1.42	1.25–1.61
65-75 (N=8,299)	849	422	2530	4498	2.01	1.79–2.26	1.48	1.30–1.68
≥75 (N=7,959)	825	379	2463	4292	2.18	1.93–2.46	1.56	1.37–1.78
Gender								
Female (N=11,695)	1225	589	3377	6504	2.08	1.89–2.29	1.46	1.31–1.62
Male (N=12,519)	1332	646	3719	6822	2.06	1.88–2.27	1.49	1.35–1.65
Mood disorders								
Yes (N=8,785)	883	447	3421	4034	1.98	1.76–2.21	1.48	1.30–1.67
No (N=15,429)	1674	788	3675	9292	2.12	1.95–2.31	1.48	1.35–1.63
Charlson Comorbidity Index								
0-1 (N=10,162)	1142	551	2773	5696	2.07	1.87–2.29	1.43	1.28–1.60
2-3 (N=8,471)	840	394	2663	4574	2.13	1.89–2.40	1.57	1.38–1.78
≥4 (N=5,581)	575	290	1660	3056	1.98	1.72–2.28	1.42	1.22–1.66
Number of prescriptions in the year before stroke								
1 (N=8,038)	1457	341	357	5883	4.27	3.80–4.81	2.89	2.55–3.28
2 (N=3,831)	417	179	593	2642	2.33	1.96–2.77	1.68	1.39–2.02
3-5 (N=4,715)	329	267	1203	2916	1.23	1.05–1.45	0.91	0.77–1.09
≥6 (N=7,630)	354	448	4943	1885	0.79	0.69–0.91	0.62	0.53–0.72
Covariates[c]								
Use of confounding medication								
Antipsychotics	745	295	1422	17752	2.52	2.21–2.89	1.62	1.40–1.87
Antidiabetes agents	516	332	5709	13657	1.55	1.35–1.78	0.95	0.82–1.11
Diuretics	2297	703	5985	11229	3.27	3.00–3.56	1.06	0.93–1.21
Antithrombotic agents	728	439	2789	16258	1.66	1.47–1.87	2.21	2.02–2.43
Antihypertensive agents	1900	968	9838	7508	1.96	1.82–2.12	1.14	1.04–1.24
Lipid-modifying agents	702	415	3703	15394	1.69	1.50–1.91	1.02	0.89–1.17

[a] Calculated by McNemar's test: the ratio of subjects exposed only in the case period to subjects exposed in control period.
[b] Calculated by multivariate conditional logistic regression with adjustment for antipsychotics, antidiabetes agents, diuretics, antithrombotic agents, antihypertensive agents, lipid-modifying agents, and number of outpatient visits.
[c] For the covariates, adjusted odds ratios were estimated for all patients, and the adjusted odds ratio for the covariate examined was adjusted for the other covariates. A covariate not shown in the table is number of outpatient visits: control period, mean=1.78 (SD=1.86); case period, mean=2.48 (SD=2.14); crude odds ratio=1.36 (95% CI=1.34–1.38; adjusted odds ratio=1.30 (95% CI=1.29–1.32).

We performed sensitivity analysis with 7-, 14-, and 28-day time windows as the case and control periods for our results (Table 5). The results were grossly consistent for the three time periods. However, compared with the use of low serotonin transporter inhibitors, the stroke risk with high inhibitors remained but was statistically nonsignificant in the 7-day and 28-day windows.

Discussion

This is the first study to investigate the association between use of antidepressants and risk of cerebrovascular events in a nationwide population-based cohort using a case-crossover design with a population-wide sample. We found that antidepressant use was associated with a 48% greater risk of stroke, after taking confounding factors into account, and that the magnitude of associations was greater in high-potency inhibitors of the serotonin transporter than in low- and intermediate-potency inhibitors.

Our findings are in agreement with those of previous studies showing that antidepressant use was associated with an increased risk of stroke, both ischemic (21) and hemorrhagic (22) types. Contrary to the findings from Chen and colleagues (34), in which a much smaller sample was studied, our findings here provide strong evidence supporting the thesis that degree of inhibition of the serotonin transporter is associated with risk of hemorrhagic stroke. Our findings are compatible with those of studies showing that a high inhibition of the serotonin transporter has a more potent antiplatelet effect and is associated with a higher risk of abnormal bleeding in other organ systems (12, 35). Surprisingly, we also found that antidepressants with high inhibition of the serotonin transporter were associated with a greater risk of ischemic stroke. A possible

TABLE 4. Risk of Stroke With Antidepressant Use Within the 14-Day Risk Period, by Characteristics of Antidepressants and Subtypes of Stroke Among Patients With Fewer Than Three Antidepressant Prescriptions During the Year Before Stroke[a]

Measure	Use Only in the Case Period	Use Only in the Control Period	Use in Both Periods	Nonuse in Both Periods	Adjusted Odds Ratio[b]	95% CI
All stroke (N=11,869)						
Antidepressant use	1874	520	950	8525	2.48	2.23–2.75
Average daily dose[c]						
<0.5 defined daily dose	1188	384	588	9709	2.17	1.92–2.46
0.5–1 defined daily dose	408	129	180	11152	2.45	1.98–3.04
≥1 defined daily dose	320	49	140	11360	5.10	3.71–7.01
Antidepressant type						
Tricyclic	991	328	500	10050	2.14	1.87–2.45
SSRI	319	54	163	11333	4.22	3.12–5.72
Other antidepressants	540	142	254	10933	3.17	1.78–5.66
MAO inhibitor	83	15	21	11750	2.46	2.02–3.00
Degree of serotonin transporter inhibition						
Low	647	173	299	10750	2.42	2.03–2.90
Intermediate	996	306	506	10061	2.25	1.96–2.58
High[d]	282	53	140	11394	3.87	2.85–5.26
Degree of norepinephrine transporter inhibition						
Low	661	158	306	10744	2.67	2.22–3.22
Intermediate	213	40	104	11512	4.00	2.81–5.70
High[e]	1049	337	532	9951	2.18	1.91–2.49
Ischemic stroke (N=8,938)						
Antidepressant use	1428	392	755	6363	2.52	2.23–2.84
Average daily dose[c]						
<0.5 defined daily dose	894	287	469	7288	2.20	1.90–2.54
0.5–1 defined daily dose	320	101	144	8373	2.46	1.93–3.14
≥1 defined daily dose	247	37	109	8545	5.32	3.68–7.69
Antidepressant type						
Tricyclic	759	246	397	7536	2.19	1.87–2.56
SSRI	254	44	130	8510	4.11	2.93–5.76
Other antidepressants	399	105	202	8232	2.95	1.57–5.55
MAO inhibitor	65	13	15	8845	2.50	1.99–3.15
Degree of serotonin transporter inhibition						
Low	476	127	235	8100	2.45	1.98–3.02
Intermediate	770	231	404	7533	2.30	1.96–2.70
High	222	43	112	8561	3.81	2.70–5.37
Degree of norepinephrine transporter inhibition						
Low	495	119	242	8082	2.68	2.16–3.32
Intermediate	163	32	85	8658	3.84	2.57–5.72
High	809	254	421	7454	2.24	1.92–2.61
Hemorrhagic stroke (N=1,958)						
Antidepressant use	271	96	130	1461	1.92	1.49–2.47
Average daily dose[c]						
<0.5 defined daily dose	177	74	78	1629	1.60	1.19–2.16
0.5–1 defined daily dose	53	18	24	1863	2.33	1.31–4.12
≥1 defined daily dose	47	10	22	1879	3.72	1.82–7.58
Antidepressant type						
Tricyclic	141	61	72	1684	1.56	1.13–2.15
SSRI	43	8	23	1884	4.24	1.95–9.26
Other antidepressants	85	28	31	1814	5.40	0.66–44.16
MAO inhibitor	10	1	3	1944	1.99	1.25–3.17
Degree of serotonin transporter inhibition						
Low	100	34	38	1786	1.95	1.28–2.97
Intermediate	136	55	74	1693	1.67	1.19–2.33
High	42	9	17	1890	3.55	1.68–7.49
Degree of norepinephrine transporter inhibition						
Low	98	29	40	1791	2.22	1.42–3.48
Intermediate	36	7	13	1902	4.29	1.85–9.94
High	145	62	76	1675	1.57	1.14–2.17

[a] SSRI=selective serotonin reuptake inhibitor; MAO=monoamine oxidase.
[b] Adjustment for antipsychotics, antidiabetes agents, diuretics, antithrombotic agents, antihypertensive agents, lipid-modifying agents, and number of outpatient visits.
[c] For average daily dose, the p trend was p<0.001. Conditional logistic regression analysis was used in which average daily dose was treated as a continuous variable (Waldχ^2=194.5, df=1).
[d] High > low (odds ratio=1.70, 95% CI=1.19–2.41); high > intermediate (odds ratio=1.81, 95% CI=1.30–2.52).
[e] Intermediate > high (odds ratio=1.92, 95% CI=1.32–2.79); low > high (odds ratio=1.26, 95% CI=1.01–1.58).

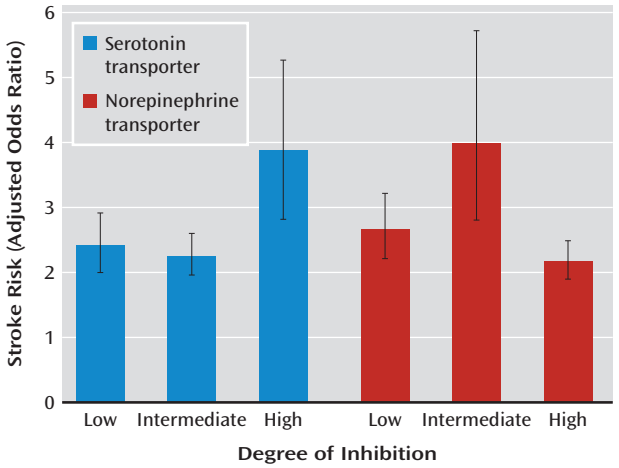
mechanism is antidepressant-induced vasoconstriction, which is mediated by the serotonin receptors on smooth muscle cells and can prompt thromboembolic formation in atherosclerotic cerebral arteries (14, 36). However, even the use of low-potency inhibitors of the serotonin transporter is associated with an excess risk of stroke, regardless of stroke type. Thus, other underlying mechanisms for stroke risk in relation to antidepressant use warrant further investigation.

This is the first study to explore the role of norepinephrine transporter inhibition in the relation between antidepressant use and stroke risk. We found that low or intermediate inhibitors of the norepinephrine transporter were associated with higher stroke risks than were high inhibitors. A possible explanation is that high norepinephrine transporter inhibition helps prevent vasovagal reaction (37), which reduces the possibility of hypoperfusion of cerebral circulation and lowers the stroke risk. However, highly selective norepinephrine reuptake inhibitors, such as reboxetine, are not available for patients who participate in the National Health Insurance program. Further studies are needed to explore the cerebrovascular effect of norepinephrine reuptake inhibition and other underlying mechanisms of stroke risk.

One new finding of this study is that the risk of stroke increased with average daily antidepressant dose. The increasing trend was significant ($p<0.001$) across the three different time windows we used. Another new finding is that the magnitude of stroke risk with antidepressant use varied according to the duration of antidepressant treatment. The increasing stroke risk associated with antidepressant use is largely attributable to patients who had few antidepressant prescriptions in previous years. Patients who used antidepressants over longer periods (three or more prescriptions) had no excess risk of stroke. This may partially explain the inconsistent findings of previous studies (17–20), in which the category of current users included both new users and long-term users. The different cerebrovascular effects of antidepressants among new users and long-term users would move the estimated effect toward the null. The failure to show the effect of duration of treatment on the relationship between antidepressant use and stroke in previous studies may be due to limited case numbers (17–19).

In contrast, we found that there may be a protective effect of antidepressant use on stroke risk among long-term users. The antiplatelet effect of antidepressants may play a role in preventing thrombus formation. Depression and psychological distress themselves are risk factors for stroke, and antidepressants may eliminate the harmful effects of these factors after an adequate duration of treatment. However, the interpretation of such findings is not clear. In a case-crossover study, a protective effect would be indicated by the rates of nonuse being higher during the case period than during the control period. Thus, another possible explanation for such findings is that withdrawal from long-term antidepressant use may increase the risk of stroke. Indeed, antidepressant discontinuation syndrome is associated with autonomic nervous system instability (38), which may have an adverse effect on the cardiovascular and cerebrovascular systems. Furthermore, the depletion of susceptible cases might explain the decreased stroke risk among patients with long-term antidepressant use (39). Those who are likely to have had strokes due to antidepressants may have already had them before the observation period and therefore were not included in this study.

FIGURE 2. Risk of Stroke With Antidepressant Use, by Degree of Serotonin or Norepinephrine Transporter Inhibition[a]



[a] Data are from 24,214 patients with antidepressant prescriptions and first-time hospitalization for stroke, 1998–2007. Error bars indicate 95% confidence intervals.

In addition to use of antidepressants, we found increased prescription rates of other medications and more number of outpatient visits in the case period. The clinical circumstance whether patients received an antidepressant prescription or not might be different. The conditions that patients used antidepressants would also increase the likelihood that they received other drugs and had increased number of outpatient visits. For example, patients with mood disorders would be more likely to have somatic complaints; therefore, they may seek professional help more frequently and used more drugs. However, after adjusting these confounding factors, the associations between antidepressant use and stroke risk were still significant.

Our study has several potential limitations. We identified incident cases as first-time hospitalization for stroke; although patients with any record of stroke in 1997 were excluded, remote recurrent cases may have been misclassified as incident cases. We excluded cases with hospitalization within 1 year before the stroke. Thus, the patients included as cases may have been healthier than those excluded from the study. Moreover, patients who died of stroke before hospitalization were not included in the study.

TABLE 5. Sensitivity Analysis for Stroke Risk With Antidepressant Use, by Risk Period[a]

Measure	Use Only in the Case Period	Use Only in the Control Period	Use in Both Periods	Nonuse in Both Periods	Adjusted Odds Ratio[b]	95% CI
7-Day window						
Antidepressant use	1817	908	6928	14561	1.40	1.29–1.53
Stroke type						
Ischemic	1408	700	5319	10940	1.43	1.29–1.50
Hemorrhagic	244	138	1068	2462	1.22	0.97–1.54
Other	165	70	541	1159	1.58	1.16–2.15
Number of prescriptions in the year before stroke						
1	1072	248	494	6224	2.87	2.47–3.32
2	239	135	636	2821	1.50	1.19–1.89
3–5	206	174	1152	3183	0.81	0.65–1.01
≥6	300	351	4646	2333	0.58	0.49–0.69
Average daily dose[c]						
<0.5 defined daily doses	825	259	693	10092	2.30	1.97–2.67
0.5–1 defined daily doses	279	99	219	11272	2.16	1.68–2.78
≥1 defined daily dose	233	51	192	11393	3.58	2.60–4.93
Antidepressant type[c]						
Tricyclic	682	238	571	10378	1.99	1.70–2.34
SSRI	211	51	220	11387	2.85	2.06–3.93
Other antidepressants	385	97	294	11093	5.15	2.26–11.71
MAO inhibitor	59	7	38	11765	2.93	2.30–3.72
Degree of inhibition of serotonin transporter[c]						
Low	418	116	314	11021	2.65	2.12–3.31
Intermediate	689	228	585	10367	2.06	1.75–2.42
High	182	45	195	11447	2.94	2.08–4.15
Degree of inhibition of norepinephrine transporter[c]						
Low	426	110	333	11000	2.80	2.24–3.51
Intermediate	146	32	139	11552	3.32	2.22–4.96
High	713	248	620	10288	2.01	1.72–2.34
14-day window						
Antidepressant use	2557	1235	7096	13326	1.48	1.37–1.59
Stroke type						
Ischemic	1961	942	5466	9998	1.50	1.37–1.63
Hemorrhagic	358	211	1092	2251	1.22	1.01–1.47
Other	238	82	538	1077	2.04	1.55–2.67
Number of prescriptions in the year before stroke						
1	1457	341	357	5883	2.89	2.55–3.28
2	417	179	593	2642	1.68	1.39–2.02
3–5	329	267	1203	2916	0.91	0.77–1.09
≥6	354	448	4943	1885	0.62	0.53–0.72
Average daily dose[c]						
<0.5 defined daily doses	1188	384	588	9709	2.17	1.92–2.46
0.5–1 defined daily doses	408	129	180	11152	2.45	1.98–3.04
≥1 defined daily dose	320	49	140	11360	5.10	3.71–7.01
Antidepressant type[c]						
Tricyclic	991	328	500	10050	2.14	1.87–2.45
SSRI	319	54	163	11333	4.22	3.12–5.72
Other antidepressants	540	142	254	10933	3.17	1.78–5.66
MAO inhibitor	83	15	21	11750	2.46	2.02–3.00
Degree of inhibition of serotonin transporter[c]						
Low	647	173	299	10750	2.42	2.03–2.90
Intermediate	996	306	506	10061	2.25	1.96–2.58
High	282	53	140	11394	3.87	2.85–5.26
Degree of inhibition of norepinephrine transporter[c]						
Low	661	158	306	10744	2.67	2.22–3.22
Intermediate	213	40	104	11512	4.00	2.81–5.70
High	1049	337	532	9951	2.18	1.91–2.49

One of the major limitations of the case-crossover design is that the exposure frequency changes over time. For example, the prevalence of antidepressant use increased from 2.2% in 1997 to 4.4% in 2004 in the general population in Taiwan (5). However, the effect of this time trend bias may be negligible since the study time windows were short. Second, the case-crossover design controls all between-subject time-invariant confounding factors but not time-variant factors. Our results may have been influenced by the confounding factors of acute indications, such as

TABLE 5. Sensitivity Analysis for Stroke Risk With Antidepressant Use, by Risk Period[a] (*continued*)

Measure	Use Only in the Case Period	Use Only in the Control Period	Use in Both Periods	Nonuse in Both Periods	Adjusted Odds Ratio[b]	95% CI
28-day windows						
Antidepressant use	3556	1707	7332	11619	1.49	1.40–1.58
Stroke type						
Ischemic	2772	1275	5597	8723	1.53	1.42–1.64
Hemorrhagic	489	292	1172	1959	1.32	1.13–1.54
Other	295	140	563	937	1.53	1.23–1.90
Number of prescriptions in the year before stroke						
1	1916	554	239	5329	2.41	2.18–2.67
2	730	263	459	2379	1.91	1.64–2.22
3–5	530	414	1269	2502	0.95	0.82–1.09
≥6	380	476	5365	1409	0.59	0.51–0.68
Average daily dose[c]						
<0.5 defined daily doses	1684	541	466	9178	2.18	1.97–2.42
0.5–1 defined daily doses	574	189	126	10980	2.18	1.84–2.60
≥1 defined daily dose	414	113	80	11262	2.68	2.16–3.34
Antidepressant type[c]						
Tricyclic	1422	495	397	9555	2.00	1.79–2.23
SSRI	442	110	94	11223	2.83	2.28–3.53
Other antidepressants	754	210	182	10723	2.35	1.47–3.78
MAO inhibitor	102	23	17	11727	2.43	2.07–2.86
Degree of inhibition of serotonin transporter[c]						
Low	902	272	217	10478	2.22	1.92–2.56
Intermediate	1417	468	391	9593	2.11	1.88–2.35
High	395	100	80	11294	2.76	2.20–3.47
Degree of inhibition of norepinephrine transporter[c]						
Low	911	246	214	10498	2.49	2.14–2.89
Intermediate	297	77	60	11435	2.69	2.07–3.50
High	1504	513	414	9438	2.05	1.84–2.28

[a] SSRI=selective serotonin reuptake inhibitor; MAO=monoamine oxidase.
[b] Adjusted for antipsychotics, antidiabetes agents, diuretics, antithrombotic agents, antihypertensive agents, lipid-modifying agents, and number of outpatient visits.
[c] Analysis only for patients with fewer than three prescriptions for antidepressants (N=11,869).

abrupt emotional distress. However, we found that stroke risk with antidepressant use was not changed after adjustment for new-onset mood disorders. Moreover, mood disorders may have occurred insidiously, in which case the onset date would not have been accurately measured in this study. Thus, the association between antidepressant use and stroke might, to a varying degree, be related to the change in the severity of underlying psychiatric disorders between the case and control periods.

Several limitations inherent in using claims databases also need to be taken into consideration. First, because patients' identification was scrambled for protection of privacy, we have no way to assess for medication adherence. However, nonadherence would most likely result in nondifferentiated misclassification of the exposure, which would lead to underestimation of the actual risk. Second, there are no published studies of the accuracy of stroke-related coding in the National Health Insurance Research Database, although some studies examining the validity of stroke diagnoses in claims data showed high positive predictive values (40). Identifying patients hospitalized for a primary diagnosis of stroke, as we did, would minimize potential misclassification of cases. Third, a number of other potential confounding factors that might affect stroke risk, such as body mass index, alcohol use, and smoking status, were not available in the database. However, we used a case-crossover design for controlling such unmeasured variables. Finally, our findings may or may not extend to the population outside Taiwan. Further investigations are needed to explore such associations in different populations and ethnic groups.

The strengths of this study are the use of a nationwide sample (National Health Insurance covering 98% of the population of Taiwan), a very large sample, a well-defined method for identifying cases of stroke, detailed data on exposure to antidepressants and other medications, controls for all between-subject time-invariant confounding factors by using the case-crossover study design, and a sensitivity analysis to confirm the robustness of the results.

Conclusions

Our results in this study have major clinical and public health implications deserving careful consideration. Our findings suggest that antidepressant use contributes to an increased risk of stroke. The effects appear to be dose related and were noted only in the first few prescriptions. Thus, we recommend starting antidepressants at low dosages and closely monitoring the side effects for initial prescriptions, particularly for individuals at risk for cerebrovascu-

lar events. Although the use of antidepressants with a high affinity for the serotonin transporter seems to be associated with a higher risk of stroke, more investigation into the possible biological mechanisms underlying the relationship between stroke and antidepressants is indicated.

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Clinical Guidance: Risk of Stroke From Starting Antidepressant Treatment

Initiation of antidepressant treatment was associated with increased risk of stroke in this Taiwanese national sample. About 7% of adults hospitalized for a first stroke had received an antidepressant in the preceding year. The odds ratio of stroke during initiation of antidepressant use, compared to previous recent history of antidepressant use, was 1.48, adjusted for other concurrent medications and mood disorder. Antidepressants with high inhibition of the serotonin transporter, such as SSRIs, were associated with greater risk. Smoller (p. 457) points out that results are similar to those in the Women's Health Initiative, but neither study can fully differentiate the effects of depression versus medication.