

Association of Cerebrovascular Events with Antidepressant Use

Chi-Shin Wu MD, MSc
Far Eastern Memorial Hospital
National Taiwan University Hospital

Background

- Stroke
 - The 2nd leading cause of death
 - The 6th leading cause of disease burden globally
 - Depression
 - An independent risk factor for stroke
 - Antidepressant
 - One of standard treatment of depression
-

Antidepressant use

- Prevalence
 - Increases in many countries (Chien et al. 2007)
 - Could antidepressants reverse depression-related cardiovascular complications
 - Inconclusive
 - Concerns
 - Bleeding complications (esp. SSRI)
 - Vasoconstriction of the large cerebral arteries
-

Previous Findings

- Negative findings
 - In randomized trials and case-control studies (Swenson et al. 2006; Bak et al, 2002; Barbui et al. 2005; de Abajo et al. 2000; Kharofa et al. 2007)
 - Recent large-scale observational studies
 - Increased risk in hemorrhagic (Smoller et al. 2009) and ischemic stroke (Chen et al. 2008)
 - Discrepant findings
 - Sample size
 - Unmeasured confounders
 - Current users vs. non-user
 - Current users: new users and long-term regular users
-

Aims

- Using a national representative database
 - Case-crossover design
 - Acute effects and transient exposures
 - Self-controlled
 - Hypothesis
 - Acute exposure to antidepressant would increase stroke risk
 - To characterize patients at risk
 - To identify the type of antidepressants with increased risk for stroke
-

Methods

Data Resources

- National Health Insurance program
 - A single-payer, covering 98% of 23 million Taiwanese population
 - Since March 1, 1995
 - National Health Insurance Research Database
 - Patients' demographic characteristics, diagnoses, medical expenditures, and prescription claims data
 - All individuals enrolled between Jan 1, 1997 and December 31, 2007
-

Study Subjects

- Patients with an incident cerebrovascular event
 - a hospitalization for a primary diagnosis
 - Cerebrovascular events
 - Hemorrhagic stroke (ICD-9-CM: 430, 431, and 432)
 - Ischemic stroke (ICD-9-CM: 433, 434, and 435)
 - Other type (ICD-9-CM: 436)
 - The index date:
 - The date when the case subjects were diagnosed as having a first hospitalization for a stroke.
-

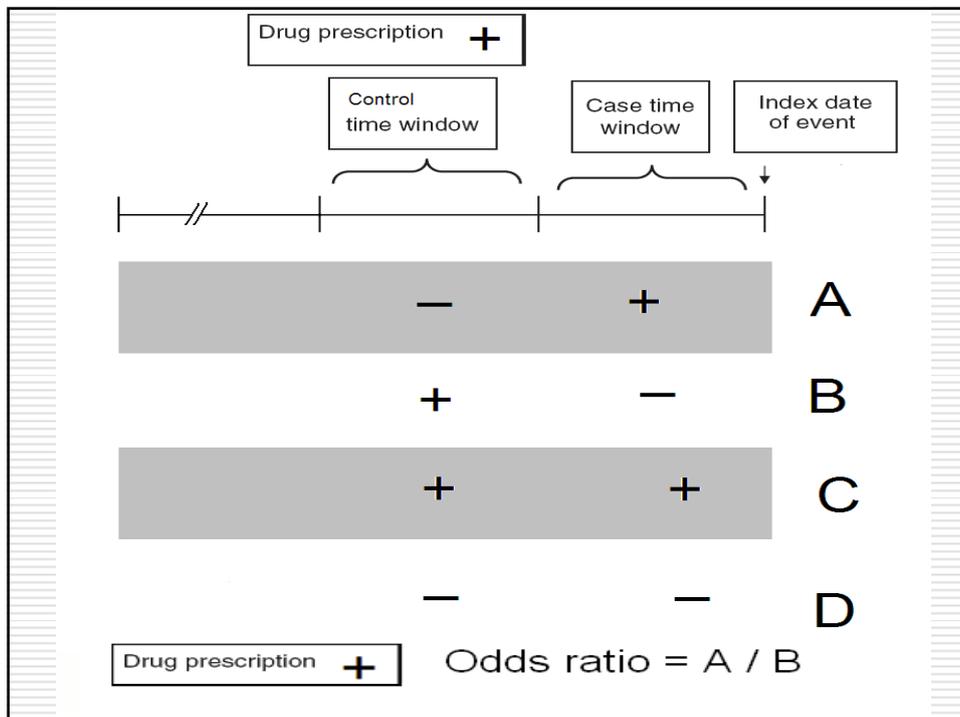
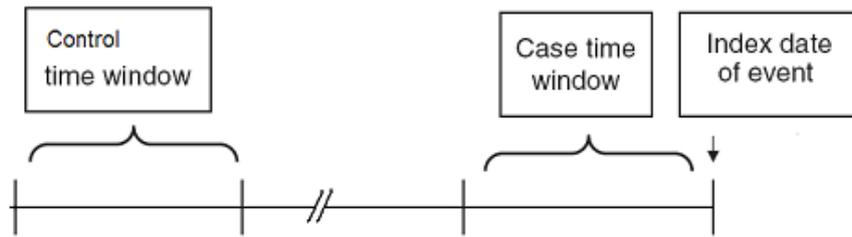
Exclusion Criteria

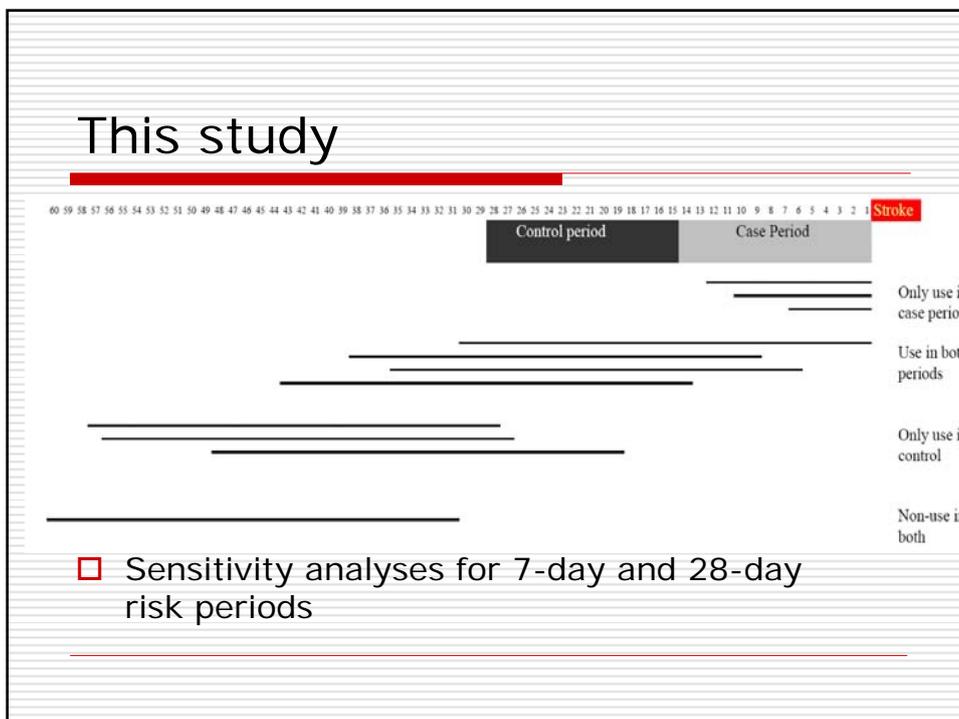
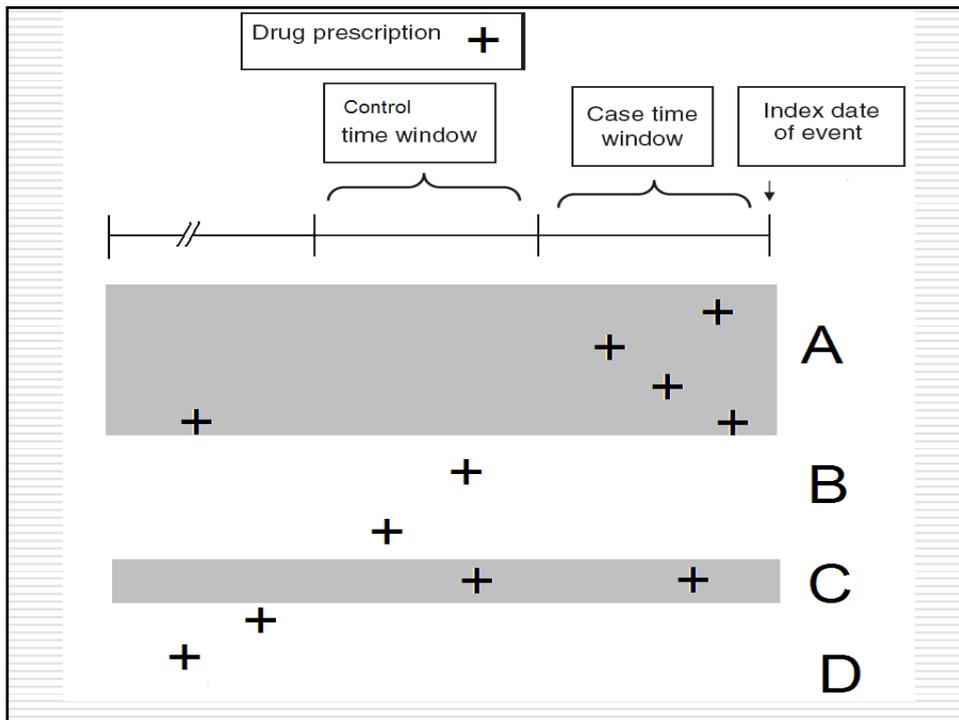
- Age < 18 years
 - Prevalent case
 - Any stroke diagnoses (ICD-9: 430-438) in 1997
 - Head injury
 - ICD-9: 800.x–804.x, 850.x–854.x, or 959.x
 - Hospitalization within 1 year before the index date
 - Patients used the followings drug within 1 year before the index date
 - Melitracen/flupentixol
-

Case-Crossover Study

- An efficient method to examine the association of transient exposure with acute effects.
 - Subjects serve as their own matched controls,
 - Removing between-subjects time-invariant confounders, which remain unmeasured or unknown
-

Case-crossover design





Characteristics of study patients

- Age
 - Sex
 - General health status
 - Charlson comorbidity index
 - Presence of mood disorder
 - ICD-9: 296.x, 300.4, and 311
 - Duration of antidepressants treatment
 - Number of antidepressant prescriptions
-

Exposure to antidepressant

- Anatomical therapeutic chemical (ATC) classification system (N06A)
- Four groups
 - Tricyclic antidepressants,
 - Selective serotonin reuptake inhibitors
 - Monoamine oxidase inhibitors
 - Other antidepressants.
- Serotonin transporter reuptake inhibition :
 - (<1 , 1–10 , >10 nmol/liter).
- Norepinephrine transporter reuptake inhibition
 - (<100, 100–1,000, >1,000 nmol/liter)

Time-variant confounding factors

- Medications:
 - Antithrombotic agents
 - Antidiabetes agents
 - Diuretics
 - antihypertensive agents
 - Lipid-modifying agents
 - Antipsychotics
 - Health system utilization
 - Number of outpatients visits
-

Data analyses

- Conditional logistic regression
 - PHREG procedure, SAS
 - Crude odds ratios
 - Adjusted odds ratios
 - Adjustment for antidiabetes, diuretics, antithrombotic agents, antihypertensive drugs, lipid modifying agents, antipsychotics and number of outpatient visits.
-

Subgroup analyses

- stratifying the various characteristics
 - Age
 - Sex
 - Charlson comorbidity index
 - Presence of mood disorder
 - Duration of treatment
 - Interactions between antidepressants and these patients' characteristics
-

Results

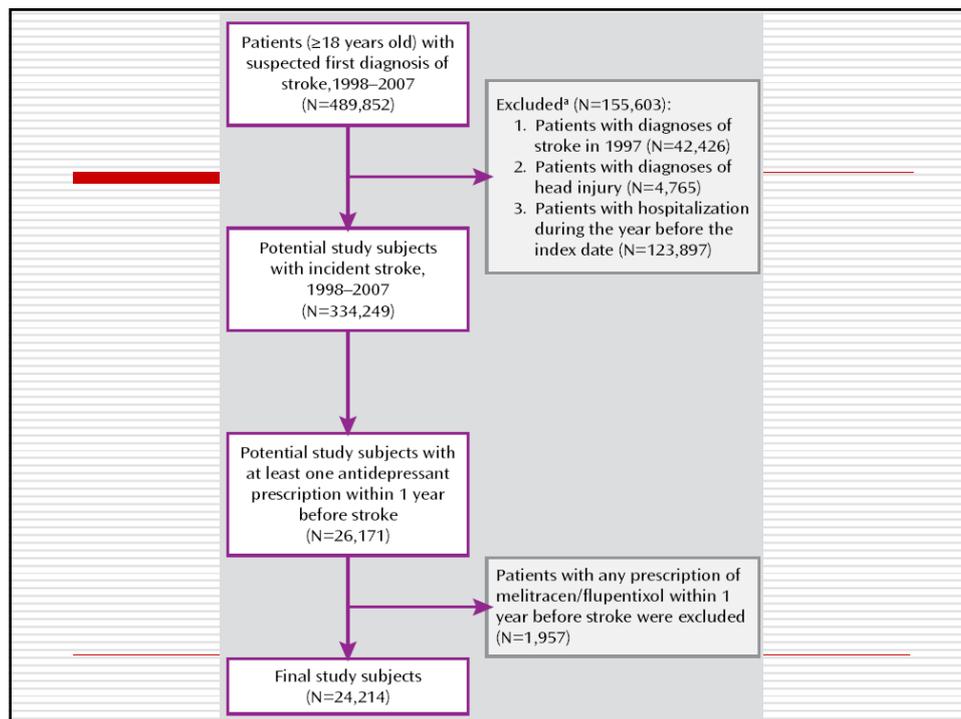


TABLE 1. Demographic and Clinical Characteristics of 24,214 Patients With Antidepressant Prescriptions and First-Time Hospitalization for Stroke, 1998–2007

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

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

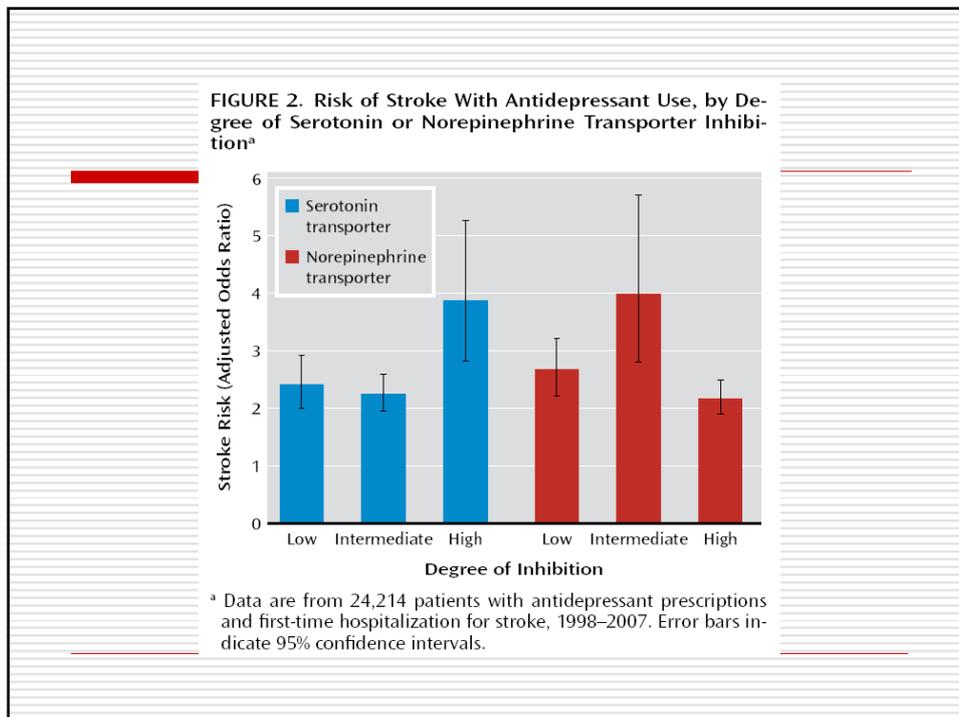
^a SSRIs=selective serotonin reuptake inhibitors; MAO=monoamine oxidase; K_d^S =dissociation constant for the serotonin transporter; K_d^N =dissociation constant for the norepinephrine transporter.
^b For dothiepin and milnacipran, the defined daily dose was defined as the lowest recommended daily dose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

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

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



schemic 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	0.66–44.1
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

Table 4. Sensitivity analysis for the stroke risk in antidepressant use by using 7, 14, and 28-day risk periods.

	7 Days				14 Days				28 Days			
	Control Period	Case period	Adjusted OR ^b	(95% CI)	Control Period	Case period	Adjusted OR ^b	(95% CI)	Control Period	Case period	Adjusted OR ^b	(95% CI)
Antidepressant use	7836	8745	1.40	(1.29- 1.53)	8831	9653	1.48	(1.37- 1.59)	9039	10888	1.49	(1.40- 1.58)
Stroke type												
Ischemic	6019	6727	1.43	(1.29- 1.50)	6408	7427	1.50	(1.37- 1.63)	6872	8369	1.53	(1.42- 1.64)
Hemorrhage	1206	1312	1.22	(0.97- 1.54)	1303	1450	1.22	(1.01- 1.47)	1464	1661	1.32	(1.13- 1.54)
Other	611	706	1.58	(1.16- 2.15)	620	776	2.04	(1.55- 2.67)	703	858	1.53	(1.23- 1.90)
Number of prescriptions in one year before stroke												
1	742	1566	2.87	(2.47- 3.32)	698	1814	2.89	(2.55- 3.28)	793	2155	2.41	(2.18- 2.67)
2	771	875	1.50	(1.19- 1.89)	772	1010	1.68	(1.39- 2.02)	722	1189	1.91	(1.64- 2.22)
3-5	1326	1358	0.81	(0.65- 1.01)	1470	1532	0.91	(0.77- 1.09)	1683	1799	0.95	(0.82- 1.09)
≥ 6	4997	4946	0.58	(0.49- 0.69)	5391	5297	0.62	(0.53- 0.72)	5841	5745	0.59	(0.51- 0.68)
Average DDD per day^a												
<0.5 DDD	952	1518	2.30	(1.97- 2.67)	972	1776	2.17	(1.92- 2.46)	1007	2150	2.18	(1.97- 2.42)
0.5-1 DDD	318	498	2.16	(1.68- 2.78)	309	588	2.45	(1.98- 3.04)	315	700	2.18	(1.84- 2.60)
>=1 DDD	243	425	3.58	(2.60- 4.93)	189	460	5.10	(3.71- 7.01)	193	494	2.68	(2.16- 3.34)
Classification of antidepressants^a												
TCA	809	1253	1.99	(1.70- 2.34)	828	1491	2.14	(1.87- 2.45)	892	1819	2.00	(1.79- 2.23)
SSRI	271	431	2.85	(2.06- 3.93)	217	482	4.22	(3.12- 5.72)	204	536	2.83	(2.28- 3.53)
Other antidepressants	391	679	2.93	(2.30- 3.72)	396	794	2.46	(2.02- 3.00)	392	936	2.43	(2.07- 2.86)
MAOI	45	97	5.15	(2.26- 11.71)	36	104	3.17	(1.78- 5.66)	40	119	2.35	(1.47- 3.78)
Degree of inhibition of serotonin transporter^a												
Low	430	732	2.65	(2.12- 3.31)	472	946	2.42	(2.03- 2.90)	489	1119	2.22	(1.92- 2.56)
Intermediate	813	1274	2.06	(1.75- 2.42)	812	1502	2.25	(1.96- 2.58)	859	1808	2.11	(1.88- 2.35)
High	240	377	2.94	(2.08- 4.15)	193	422	3.87	(2.85- 5.26)	180	475	2.76	(2.20- 3.47)
Degree of inhibition of norepinephrine transporter^a												
Low	443	759	2.80	(2.24- 3.51)	464	967	2.67	(2.22- 3.22)	460	1125	2.49	(2.14- 2.89)
Intermediate	171	285	3.32	(2.22- 4.96)	144	317	4.00	(2.81- 5.70)	137	357	2.69	(2.07- 3.50)
High	868	1333	2.01	(1.72- 2.34)	869	1581	2.18	(1.91- 2.49)	927	1918	2.05	(1.84- 2.28)

Discussion

Summary of Our Findings

- ❑ Acute exposure to antidepressants associated with an increase in stroke risk (adjusted OR = 1.48)
 - ❑ Dose-response relationship
 - ❑ No difference in age, sex, and Charlson comorbidity index
-

Durations of treatment

- Acute effect among new users
- Protective effect ?

Number of prescriptions in the year before stroke	Adjusted	
	Odds Ratio ^b	95% CI
1 (N=8,038)	2.89	2.55–3.28
2 (N=3,831)	1.68	1.39–2.02
3-5 (N=4,715)	0.91	0.77–1.09
≥6 (N=7,630)	0.62	0.53–0.72

Possible Mechanism

- Hemorrhagic stroke
 - Anti-platelet effect
- Ischemic stroke
 - Vasoconstriction of cerebral arteries
- High norepinephrine transporter inhibition
 - Preventing vasovagal reaction
 - Reducing the possibility of hypoperfusion of cerebral circulation and lowers the stroke risk.

Limitations

- Study sample
 - Remote recurrent cases
 - Patients with stroke died before hospitalizations
 - Patients with hospitalization within one year before stroke
 - Case-crossover design
 - The increased trend of antidepressants use
 - 2.2% in 1997 and to 4.4% in 2004 (Chien et al, 2007)
 - Confounding by acute indications, psychological distress
 - Claims data
 - Accuracy of stroke-related coding
 - Adherence of antidepressants use
 - Unmeasured confounding factors
-

Thanks for your attention

Article

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

Chi-Shin Wu, M.D., M.Sc.

Sheng-Chang Wang, M.D., M.Sc.

Yu-Cheng Cheng, M.Sc.

Susan Shur-Fen Gau, M.D., Ph.D.

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 1996 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.

(*Am J Psychiatry* 2011; 168:511–521)