

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
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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
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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
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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
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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
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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.
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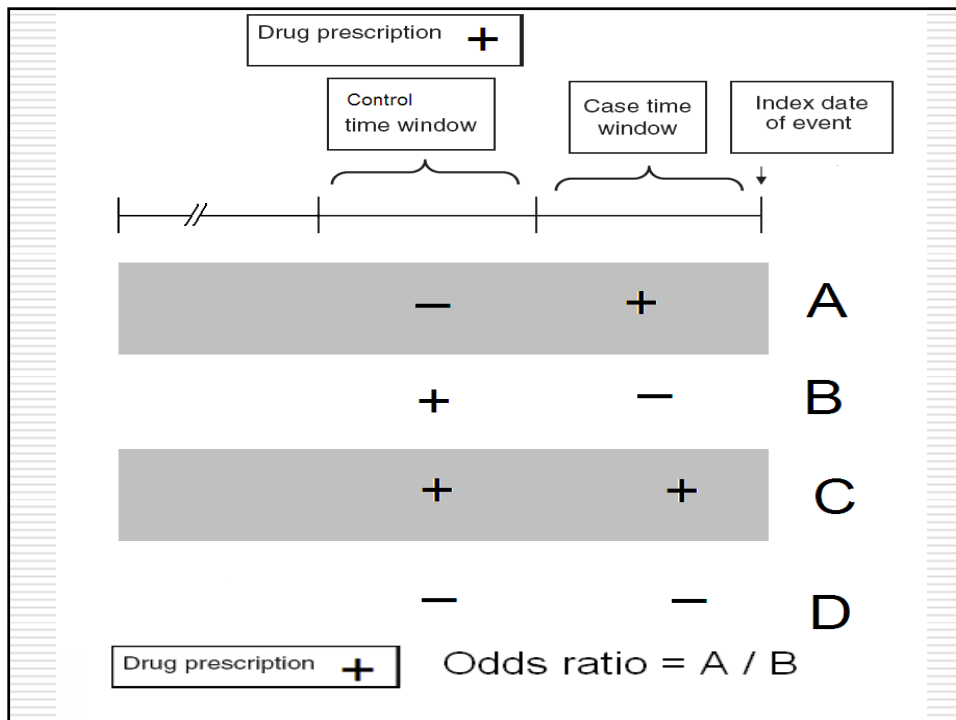
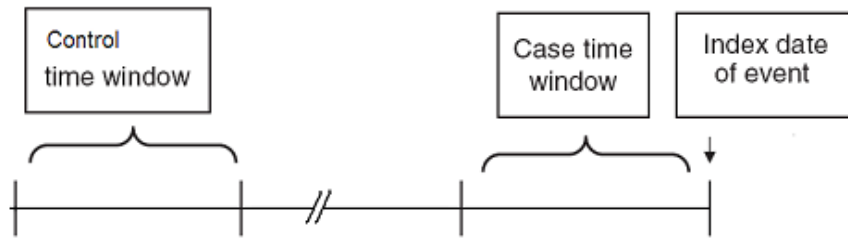
Exclusion Criteria

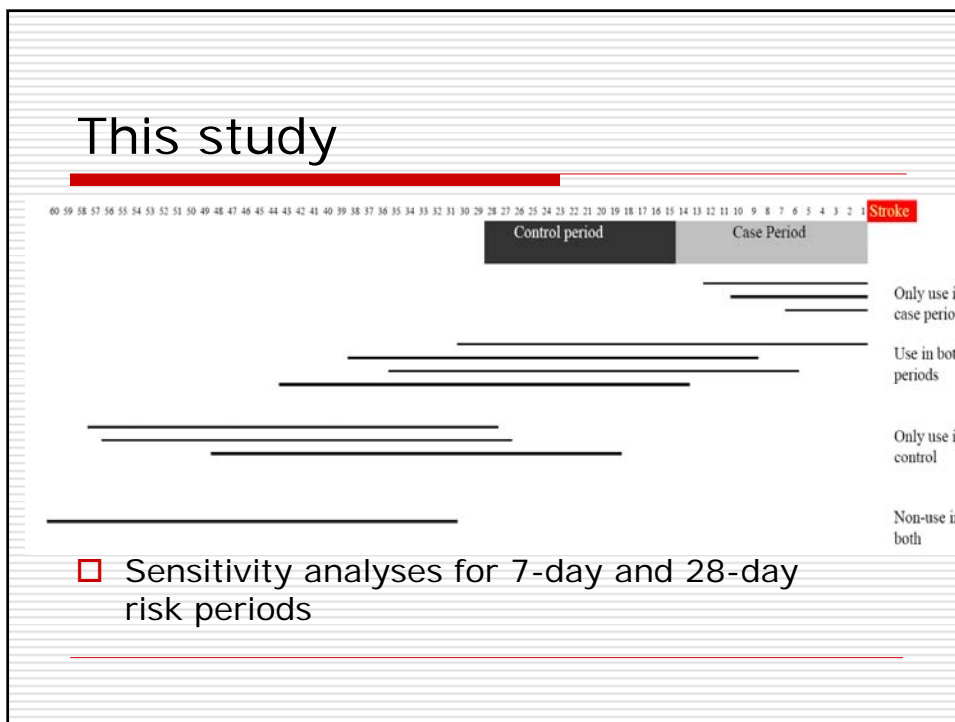
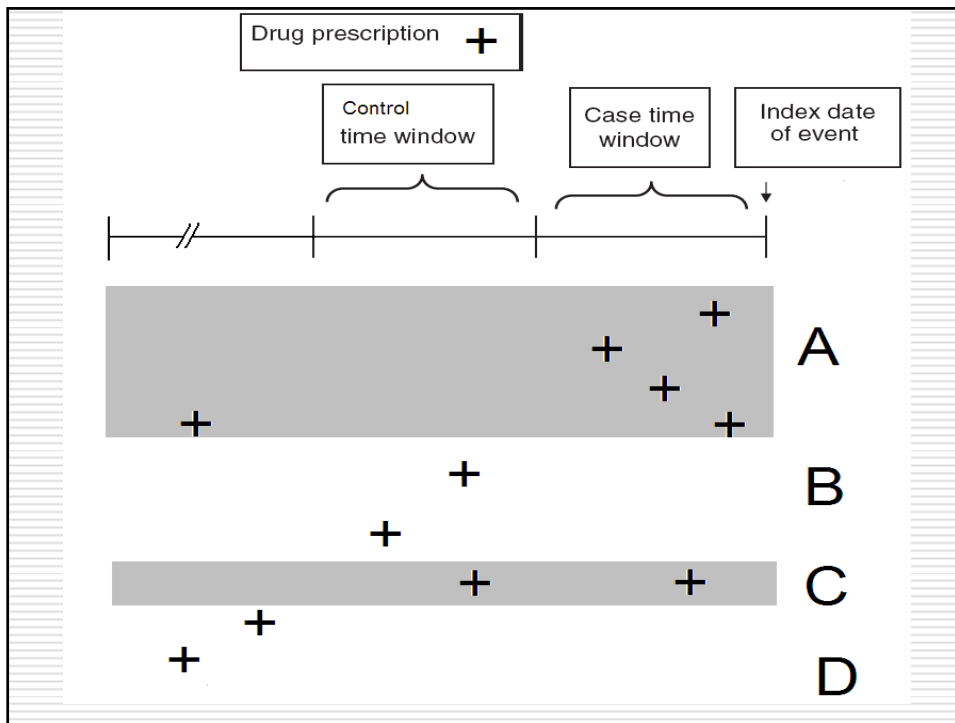
- Age < 18 years
 - Prevalent case
 - Any stroke diagnoses (ICD-9: 430-438) in 1997
 - Head injury
 - ICD-9: 800.x–804.x, 850.x–854.x, or 959.x
 - Hospitalization within 1 year before the index date
 - Patients used the followings drug within 1 year before the index date
 - Melitracen/flupentixol
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Case-Crossove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

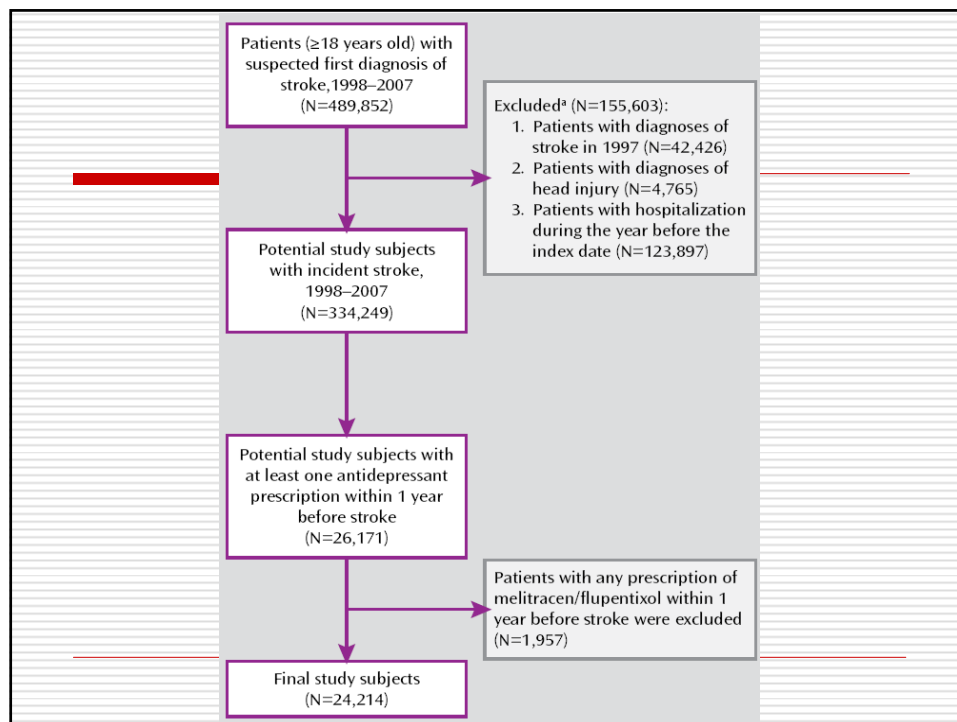


TABLE 1. Demographic and Clinical Characteristics of 24,214 Patients With Antidepressant Prescriptions and First-Time Hospitalization for Stroke, 1998–2007

| 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 |

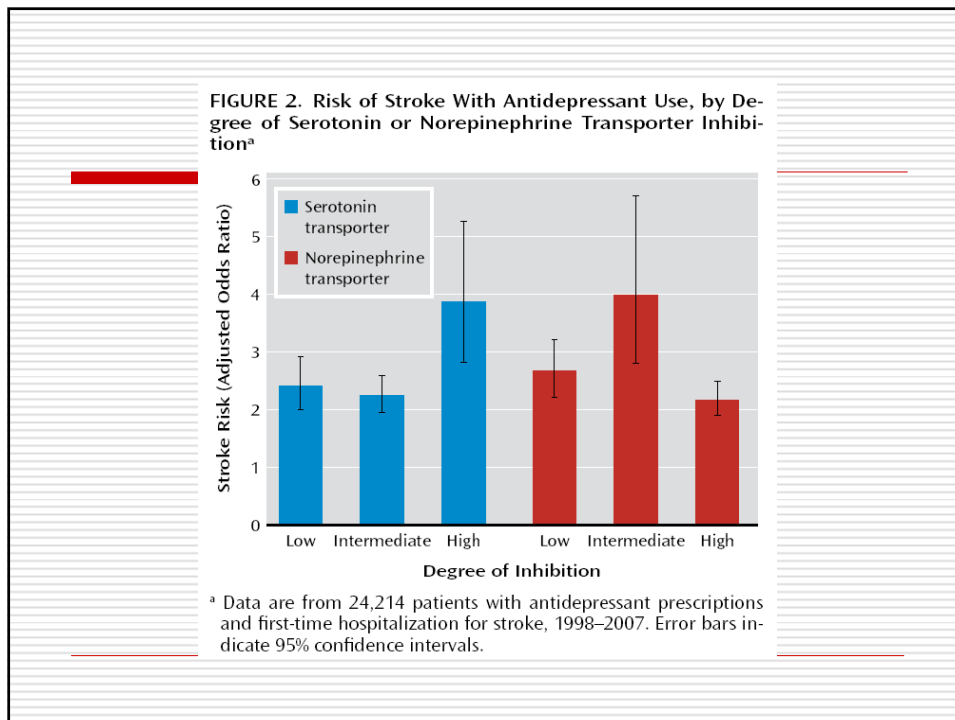
^a SSRIs=selective serotonin reuptake inhibitors; MAO=monoamine oxidase; K_d^S=dissociation constant for the serotonin transporter; K_d^N=dissociation constant for the norepinephrine transporter.
^b For dothiepin and milnacipran, the defined daily dose was defined as the lowest recommended daily dose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

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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