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Selective Serotonin Reuptake Inhibitors and Poststroke Epilepsy: A Population-Based Nationwide Study

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Abstract

Objective: To investigate the effects of selective serotonin reuptake inhibitors (SSRIs) on poststroke epilepsy in a population-based nationwide study.

Patients and Methods: The SSRI group included patients who received a stroke diagnosis from January 1, 2000, through December 31, 2009, and were prescribed SSRIs after stroke. The non-SSRI group enrolled patients with stroke who were not prescribed SSRIs from the Taiwan National Health Insurance Research Database and used propensity score matching based on the index year, duration time, sex, age, type of stroke, and duration of hospitalization. Cox proportional hazards models were used to estimate the risk of epilepsy between the SSRI and comparison groups.

Results: A total of 4688 patients with stroke (2344 in each of the SSRI and non-SSRI cohorts) were enrolled. The cumulative incidence of epilepsy in the SSRI group was significantly higher than that in the comparison group (log-rank $P<.001$). In the SSRI group, the risk of poststroke epilepsy increased 2.45-fold (95% CI, 1.69- to 3.57-fold) compared with that in the comparison group. Furthermore, the risk of poststroke epilepsy increased with the defined daily dose of SSRIs. For patients with ischemic stroke, SSRIs users had a 2.74-fold higher risk of epilepsy than non users (95% CI, 1.79- to 4.22-fold).

Conclusion: In this study, SSRI users had a higher risk of poststroke epilepsy than nonusers. Further study is warranted to investigate the causal relationship between SSRI exposure and poststroke epilepsy.

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Poststroke epilepsy is a critical complication of stroke and further reduces the quality of life of people who have a stroke; it occurs in 2% to 4% of patients with stroke.[1] The major risk factors for poststroke epilepsy are stroke severity and hemorrhagic stroke; other possible factors include younger age at stroke onset and the cortical involvement of stroke.[1,2] Some commonly prescribed medications for patients with stroke, including antibiotics, antipsychotics, analgesics, and antidepressants, may also provoke seizures.

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressant drugs for poststroke depression, the mechanism of which blocks serotonin reuptake in the brain.[3] In addition, some evidence has shown that SSRIs may benefit motor recovery in patients with stroke.[4,5] However, the effects of SSRIs on poststroke epilepsy remain unclear. The SSRIs are considered convulsants, particularly in patients with a high defined daily dose (DDD) of SSRIs; however, some studies have reported that SSRIs are potential anticonvulsants.[6-9]

In the present population-based nationwide study, we investigated the incidence of poststroke epilepsy and the relationships between poststroke epilepsy and SSRI exposure in Taiwan.

MATERIALS AND METHODS

Data Source

Taiwan's National Health Insurance (NHI) program, which is a single-payer universal insurance system established in 1995, covers more than 99% of the population and has contracts with 97% of the hospitals and clinics in Taiwan. The NHI Research Database (NHIRD), established by the National Health

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Research Institutes, contains annual registration files and original claims data for reimbursement. We analyzed the Longitudinal Health Insurance Database 2000 (LHID2000), a subset of the NHIRD, and information from the NHI program. The LHID2000 contains the insurance data of 1 million patients randomly sampled from the NHIRD and includes all inpatient claims, ambulatory care claims, and prescriptions for each patient from 1996 through 2011.

We used *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* coding to define the disease diagnostic codes. This study was exempted from full review by the Institutional Research Ethics Committee of China Medical University, Taichung, Taiwan. To secure confidential details and prevent ethical violations, we linked the files through encoded personal identification numbers and obtained the longitudinal medical history of all the patients. Therefore, the institutional review board also specifically waived the consent requirement.

Study Population

We conducted a retrospective population-based cohort study to examine the association between SSRI exposure and epilepsy risk in patients with stroke. The study population comprised inpatients with newly diagnosed stroke (*ICD-9-CM* codes 430-438) from the LHID2000. The SSRI group enrolled patients who received a stroke diagnosis from January 1, 2000, through December 31, 2009, and were prescribed SSRIs after the diagnosis; the date of the first use of SSRIs was defined as the index date. In the non-SSRI group, propensity score matching was used to select patients with stroke who were not prescribed SSRIs.[10] For the non-SSRI group, we randomly selected a date from January 1, 2000, through December 31, 2009, as the index date. The propensity score was calculated using logistic regression to estimate the probability of the SSRI group assignment according to the baseline variables, including age, sex, type of stroke (hemorrhagic or ischemic), index year (the year of the index date), duration time (the period between the date of newly diagnosed stroke and the index date), and duration of hospitalization (the period of hospitalization for newly diagnosed stroke).

We excluded patients who had received a diagnosis of brain tumor (*ICD-9-CM* codes 225, 191, 192, 1943, and 1944) or head injury (*ICD-9-CM* codes 850-854 and 95901) and had a history of epilepsy before stroke. The SSRIs considered in this study included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, and escitalopram.

The primary study outcome was the diagnosis of epilepsy (*ICD-9-CM* code 345). All the patients were followed from the index date to the end date, which was defined as the date when they stopped claiming insurance or showed evidence of epilepsy or December 31, 2011. The following comorbidities occurring before the end date were also defined for adjustment in the analysis model: hypertension (*ICD-9-CM* codes 401-405), hyperlipidemia (*ICD-9-CM* code 272), diabetes (*ICD-9-CM* code 250), dementia (*ICD-9-CM* codes 2900-2904 and 3310), depression (*ICD-9-CM* codes 2962, 2963, 29682, 3004, 3090, 3091, 30928, and 311), anxiety (*ICD-9-CM* codes 3000, 3002, 3003, 3083, and 30981), and sleep disorder (*ICD-9-CM* codes 3074 and 7805).

In the SSRI group, the SSRI medication history of each patient was evaluated and presented by the annual average DDD of SSRIs from the index date until the end date. We calculated the average number of SSRI exposure days by dividing the total number of SSRI exposure days by the total follow-up time. We categorized the exposure dose of SSRIs (none, <7, 7-28, 29-122, and ≥ 123 DDDs per year) according to the quartile method. Furthermore, the annual number of SSRI exposure days was also classified according to the quartile method (none, <10, 10-40, 41-171, and ≥ 172 days).

Statistical Analyses

A statistical software package (SAS version 9.4; SAS Institute Inc) was used for all the statistical analyses conducted in this study. R software (R Foundation for Statistical Computing) was used to plot the cumulative incidence of stroke in the SSRI and non-SSRI groups. Results with $P<.05$ were considered statistically significant in the 2-tailed tests performed in this study.

The *t* test was used to analyze differences in the distribution of continuous variables

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