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# Long-Term Antidepressant Use and the Risk of Type 2 Diabetes Mellitus: A Population-Based, Nested Case-Control Study in Taiwan

*Chi-Shin Wu, MD, MSc; Susan Shur-Fen Gau, MD, PhD; and Mei-Shu Lai, MD, PhD*

**ABSTRACT**

***Objective:*** Antidepressant drugs might induce weight gain and increase diabetes risk. We examined the diabetes risk with long-term antidepressant use in a general population.

***Method:*** This study was a population-based, nested case-control study using Taiwan's National Health Insurance Research Database between 1998 and 2009. A total of 47,885 patients with type 2 diabetes mellitus (ICD-9 codes: 250.x; excluding 250.x 1 and 250.x 3) and 95,770 controls were identified. We used a conditional logistic regression model for data analysis and 1-year latent period before the diabetes diagnosis to account for the quantification of treatment duration of antidepressant (defined by Anatomic Therapeutic Chemical classification code N06A). Sensitivity analyses were performed using a propensity score matching method, as well as different lengths of latent periods.

***Results:*** Compared with nonusers, patients with cumulative antidepressant use (> 2 years) had an increased risk of diabetes (adjusted OR = 1.20; 95% CI, 1.05–1.37). Moreover, increasing mean daily dose or use of selective serotonin reuptake inhibitors or serotonin antagonist and reuptake inhibitors was associated with increased diabetes risk. The increased diabetes risk with long-term antidepressant therapy in patients aged 44 years or less (adjusted OR = 2.39; 95% CI, 1.46–3.90) was higher than that in older adults (adjusted OR = 1.15; 95% CI, 1.00–1.32).

***Conclusions:*** The findings suggest that long-term antidepressant use may be associated with an increased risk of type 2 diabetes mellitus, especially for young adults. Therefore, long-term antidepressant use should be evaluated more cautiously for its benefits and the potential risk of diabetes.

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***Corresponding author:*** *Susan Shur-Fen Gau, MD, PhD, Department of Psychiatry, National Taiwan University Hospital & College of Medicine, No. 7, Chung-Shan South Rd, Taipei 10002, Taiwan. (gaushufe@ntu.edu.tw).*

Diabetes mellitus is a chronic metabolic disorder associated with severe medical complications.[1] The prevalence of diabetes has increased markedly throughout the world and in Taiwan.[2,3] Depression might be an independent risk factor for diabetes mellitus; however, the underlying mechanism remains unclear.[4–6] Furthermore, the role of antidepressant use in the association between depression and diabetes has not been well explored.

Emerging evidence has indicated that antidepressant drug use might induce weight gain[7,8] and elevated blood glucose.[9] However, data from clinical trials and previous observational studies have produced conflicting results regarding the association between antidepressant use and diabetes.[10–22] The discrepant findings may be partially explained by

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heterogeneity of sample sizes, the duration of follow-up, and the characteristics of study populations. In addition, diabetes usually is not diagnosed immediately after onset. It is unclear whether disturbed glucose homeostasis would affect the presentation of mood symptoms and the prescription pattern of antidepressants.[23,24] Inclusion of the exposure status during the latent period immediately preceding clinical diagnosis may lead to bias, especially in situations in which early symptoms or signs of outcome were associated with the exposure of interest.[25,26] The use of lagging exposure has been suggested[27] as a means to avoid such kind of bias.

Therefore, we investigated the association between duration of antidepressant drug use and the risk of type 2 diabetes mellitus using lagging exposure to account for the diabetes latent period in a nationwide population-based study.

**Clinical Points**

- Long-term use of antidepressants for 2 years or more is associated with a modest increased risk of type 2 diabetes mellitus.
- Clinicians should evaluate antidepressant use more cautiously for its benefits and potential long-term risks for diabetes.

## METHOD

### Data Source

The National Health Insurance Research Database (NHIRD) is an administrative database containing claims records from Taiwan's universal National Health Insurance (NHI) program; about 22.6 million (98% of the population) Taiwanese were enrolled in 2007. Patients' demographic characteristics, diagnoses, prescriptions, and hospitalizations were all recorded in the NHIRD.[28] The database has been used for research into several diseases, including type 2 diabetes mellitus.[3]

This study utilized a representative subset of the original NHIRD and contains a total of 1,000,000 individuals randomly selected from the NHI Registry for Beneficiaries 2005.[29] This study was approved by the Research Ethics Review Committee of Far Eastern Memorial Hospital.

### Study Sample

We assembled a cohort of Taiwan's NHI participants to undertake a nested case-control study between 1998 and 2009. We identified all individuals who were aged 18 years or older at the cohort entry date, January 1, 1998 (N = 651,539). An observation period of at least 1 year prior to the cohort entry date was required to ensure complete ascertainment of prior medication use. Subjects with less than a 1-year observation period (n = 38,871) or those who had used antidepressants in 1997 (n = 16,250) were excluded. Patients with diagnosis of diabetes before the cohort entry date were excluded (n = 25,700). Moreover, we excluded patients with a diagnosis of type 1 diabetes mellitus (*ICD-9* codes 250.x1 and 250.x3) (n = 1,614).[3] Finally, the study population consisted of 569,104 individuals. The cohort members were followed up until the development of type 2 diabetes mellitus, disenrollment from the NHI program, or the end of the study (December 31, 2009).

### Cases of Type 2 Diabetes Mellitus and Comparison Subjects

The study outcome was incident type 2 diabetes, defined as any hospitalization for type 2 diabetes mellitus or at least 3 outpatient diagnoses within 1 year, based on *ICD-9-CM* codes 250.x (except 205.x1 and 205.x3). The validation of this definition of diabetes showed a 96.9% sensitivity and 93.9% positive predictive value in a study using a questionnaire assessment of patients with diabetes from the NHIRD.[30] The date of the first diabetes claim was defined as the date of clinical diagnosis. For each incident diabetes case, we randomly selected 2 comparison subjects who did not have diabetes at the time of the case diagnosis and were individually matched with that case by the year of birth and gender. The sampled date of each comparison subject was equal to the date of clinical diagnosis of his or her matched case. If there was no eligible comparison subject, the case was excluded.

Given that diabetes mellitus may have an insidious onset and may not be diagnosed immediately, calculating the cumulative period until the date of diagnosis would not take into account the change in prescription pattern during the latent period, which might bias our estimates. Therefore, we subtracted 1 year from the date of the clinical diagnosis for cases, as well as the sampled date of comparison subjects, as the index date. The follow-up period was calculated from the cohort entry date to the index date. If the follow-up period was less than 1 year, cases and comparison subjects would be excluded due to inadequate duration to assess long-term exposure status. In total, 47,885 incident cases of type 2 diabetes mellitus from 2000 to 2009 and 95,770 controls matched by gender and year of birth were included.

### Antidepressant Exposure

Using the Anatomic Therapeutic Chemical (ATC) classification system,[31] we identified antidepressants (N06A) and classified them into groups according to their proposed mechanism of action: tricyclic or tetracyclic antidepressants (amitriptyline, clomipramine, dothiepin, doxepin, imipramine, maprotiline, and melitracen); selective serotonin reuptake inhibitors (SSRIs [citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline]); and serotonin-norepinephrine reuptake inhibitors (SNRIs [duloxetine, milnacipran, and venlafaxine]), serotonin antagonist and reuptake inhibitors (SARIs [trazodone]), and other agents (bupropion, mirtazapine, moclobemide).

### Statistical Analysis

We used conditional logistic regression to estimate the effect of duration of antidepressant treatment on the risk of new-onset diabetes mellitus. The overall cumulative period

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**Table 1. Demographic and Clinical Characteristics of Patients With Diabetes and Comparison Subjects Between 2000 and 2009**

| | Cases (n = 47,885) | | Controls (n = 95,770) | | | |
|---|---|---|---|---|---|---|
| Characteristic | n | % | n | % | Crude OR | 95% CI |
| Age at the date of clinical diagnosis, y | | | | | | |
| < 45 | 7,982 | 16.7 | 15,964 | 16.7 | | |
| 45–54 | 12,933 | 27.0 | 25,866 | 27.0 | | |
| 55–64 | 11,835 | 24.7 | 23,670 | 24.7 | | |
| ≥ 65 | 15,135 | 31.6 | 30,270 | 31.6 | | |
| Male gender | 25,906 | 54.1 | 51,812 | 54.1 | | |
| Medical illness, preceding 1 year | | | | | | |
| Hypertension | 13,135 | 27.4 | 14,952 | 15.6 | 2.08 | 2.02–2.13 |
| Dyslipidemia | 3,923 | 8.2 | 3,764 | 3.9 | 2.03 | 1.95–2.12 |
| Cerebrovascular disease | 1,881 | 3.9 | 2,534 | 2.6 | 1.48 | 1.40–1.57 |
| Chronic heart failure | 1,096 | 2.3 | 1,150 | 1.2 | 1.84 | 1.70–1.99 |
| Chronic pulmonary disease | 2,694 | 5.6 | 3,900 | 4.1 | 1.39 | 1.32–1.46 |
| Chronic renal failure | 419 | 0.9 | 564 | 0.6 | 1.45 | 1.28–1.63 |
| Malignancy | 926 | 1.9 | 1,715 | 1.8 | 1.08 | 1.00–1.16 |
| Psychiatric illness, preceding 1 year | | | | | | |
| Mood disorders | 790 | 1.6 | 1,174 | 1.2 | 1.32 | 1.21–1.44 |
| Psychotic disorders | 321 | 0.7 | 370 | 0.4 | 1.66 | 1.44–1.92 |
| Anxiety disorders | 1,932 | 4.0 | 3,190 | 3.3 | 1.20 | 1.14–1.27 |
| Sleep disorders | 2,466 | 5.1 | 4,036 | 4.2 | 1.22 | 1.16–1.28 |
| Alcohol-related disorder | 160 | 0.3 | 123 | 0.1 | 2.60 | 2.06–3.29 |
| Concomitant use of medication, preceding 1 year | | | | | | |
| Antithrombotic agents | 8,737 | 18.2 | 11,365 | 11.9 | 1.67 | 1.62–1.72 |
| Antihypertensive agents | 18,869 | 39.4 | 23,458 | 24.5 | 2.07 | 2.02–2.12 |
| Corticosteroids | 10,065 | 21.0 | 17,189 | 17.9 | 1.20 | 1.17–1.23 |
| Diuretics | 7,438 | 15.5 | 8,353 | 8.7 | 1.89 | 1.83–1.95 |
| Lipid-lowering agents | 4,675 | 9.8 | 4,371 | 4.6 | 2.10 | 2.02–2.19 |
| Female sex hormones | 3,246 | 6.8 | 5,800 | 6.1 | 1.13 | 1.08–1.18 |
| Antipsychotics | 2,076 | 4.3 | 3,050 | 3.2 | 1.34 | 1.27–1.42 |
| Mood stabilizers | 770 | 1.6 | 1,140 | 1.2 | 1.32 | 1.21–1.45 |
| Health system utilization, preceding 1 year | | | | | | |
| No. of outpatient visits/y | | | | | | |
| < 10 | 15,538 | 32.4 | 40,853 | 42.7 | 1.00 | Referent |
| 10–19 | 12,286 | 25.7 | 24,220 | 25.3 | 1.35 | 1.31–1.39 |
| ≥ 20 | 20,061 | 41.9 | 30,697 | 32.1 | 1.76 | 1.71–1.80 |
| Hospitalization | 5,152 | 10.8 | 8,016 | 8.4 | 1.30 | 1.26–1.35 |

Abbreviation: OR = odds ratio.

of antidepressant treatment was calculated by summation of the daily supply of each antidepressant prescription during the follow-up period. On the basis of the cumulative period of antidepressant treatment, we categorized patients into nonuse, duration < 1 year, 1 to 2 years, and ≥ 2 years. We defined long-term antidepressant users as those with a cumulative period of treatment ≥ 2 years. We used defined daily dose (DDD), which is defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults,"[31(p22)] as a dose standard unit for various antidepressants. The mean daily dose of antidepressant treatment was calculated by the cumulative DDD divided by the cumulative period. In addition, we calculated the specific cumulative period of antidepressant classes based on their proposed mechanism of action.

The potential confounders that were assessed in the year preceding the index date included comorbid conditions of hypertension, hyperlipidemia, cerebrovascular disease, chronic heart failure, chronic pulmonary disease, chronic renal failure, malignancy, mood disorders, psychotic disorders, anxiety disorders, sleep disorders, and alcohol-related disorder, as well as medications related to metabolic disturbance (antithrombotic agents, antihypertensive agents, diuretics, lipid-lowering agents, corticosteroids, female sex hormones, antipsychotics, and mood stabilizers). To control for a potential detection bias, which indicates that patients receiving antidepressant treatment may be more likely to have a blood glucose test, thereby increasing the chance of a diabetes diagnosis,[14] we also assessed health system utilization using number of outpatient visits and history of hospitalization 1 year before the index date.

We undertook stratification analyses to examine whether the association would be modified by the patients' characteristics, including age group, sex, comorbidity with hypertension or hyperlipidemia, presence of mood disorders, or use of antipsychotics. We also tested the interactions between long-term antidepressant use and patient characteristics on the risks for diabetes in the whole sample for the modifying effects from patient characteristics.

To test for the robustness of the results, we performed several sensitivity analyses. First, the actual latent period of diabetes is unclear. To address the influence of different lengths of the latent period, we assessed the antidepressant exposure using a latent period of 2 or 4 years, as well as no latent period. Second, we used a propensity score–matching method to further control for indication bias. The propensity

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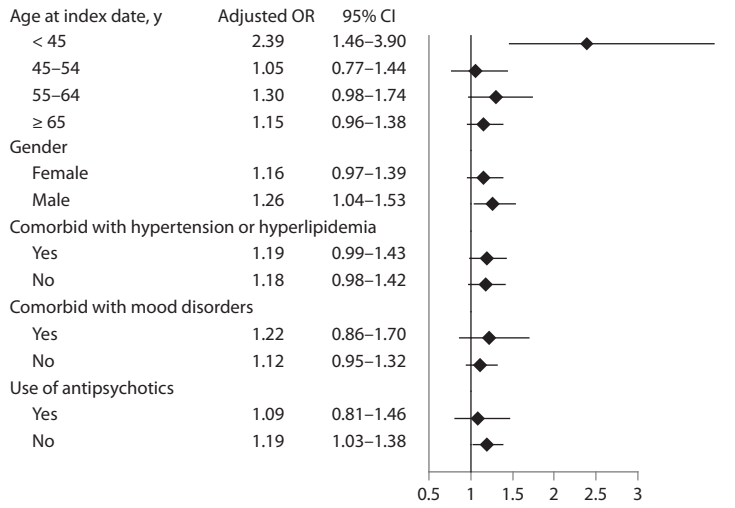
**Table 2. Diabetes Risk Associated With Antidepressant Use, by Duration, Dose, and Classes**

| | Cases (n = 47,885) | | Controls (n = 95,770) | | | | | |
|---|---|---|---|---|---|---|---|---|
| Variable | n | % | n | % | Crude OR | 95% CI | Adjusted OR | 95% CI |
| Nonuse | 38,884 | 81.2 | 80,218 | 83.8 | 1.00 | Referent | 1.00 | |
| Overall cumulative period, y | | | | | | | | |
| < 1 | 8,036 | 16.8 | 14,192 | 14.8 | 1.18 | 1.15–1.22 | 0.99 | 0.96–1.02 |
| 1–2 | 465 | 1.0 | 719 | 0.8 | 1.35 | 1.20–1.52 | 1.01 | 0.89–1.14 |
| ≥ 2 | 500 | 1.0 | 641 | 0.7 | 1.64 | 1.46–1.84 | 1.20 | 1.05–1.37 |
| Mean daily dose and cumulative period | | | | | | | | |
| < 0.5 DDD and < 2 y | 5,253 | 11.0 | 9,514 | 9.9 | 1.15 | 1.11–1.20 | 0.97 | 0.93–1.01 |
| < 0.5 DDD and ≥ 2 y | 199 | 0.4 | 289 | 0.3 | 1.45 | 1.21–1.74 | 1.07 | 0.88–1.30 |
| ≥ 0.5 DDD and < 2 y | 3,248 | 6.8 | 5,397 | 5.6 | 1.25 | 1.20–1.31 | 1.01 | 0.97–1.06 |
| ≥ 0.5 DDD and ≥ 2 y | 301 | 0.6 | 352 | 0.4 | 1.79 | 1.54–2.09 | 1.32 | 1.11–1.56 |
| Antidepressant classes and cumulative period | | | | | | | | |
| Overall antidepressants < 2 y | 8,501 | 17.8 | 14,911 | 15.6 | 1.19 | 1.15–1.23 | 0.99 | 0.96–1.02 |
| Tricyclic and tetracyclic antidepressants ≥ 2 y | 162 | 0.3 | 220 | 0.2 | 1.56 | 1.27–1.91 | 1.06 | 0.86–1.31 |
| SSRIs ≥ 2 y | 101 | 0.2 | 111 | 0.1 | 1.91 | 1.46–2.51 | 1.50 | 1.12–2.00 |
| SNRIs ≥ 2 y | 10 | 0.0 | 15 | 0.0 | 1.36 | 0.61–3.04 | 1.00 | 0.44–2.28 |
| SARIs ≥ 2 y | 84 | 0.2 | 88 | 0.1 | 2.00 | 1.48–2.70 | 1.58 | 1.15–2.17 |
| Others ≥ 2 y | 14 | 0.0 | 13 | 0.0 | 2.29 | 1.08–4.87 | 1.70 | 0.78–3.71 |
| Polypharmacy ≥ 2 y[a] | 129 | 0.3 | 194 | 0.2 | 1.39 | 1.11–1.74 | 1.02 | 0.81–1.30 |

[a]Patients with use of 2 or more antidepressant classes ≥ 2 years.
Abbreviations: DDD = defined daily dose, OR = odds ratio, SARI = serotonin antagonist and reuptake inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

**Figure 1. Diabetes Risk for Long-Term Antidepressant Use: Stratification Analysis by Patients' Characteristics**




scores, a patient's probability of receiving an antidepressant, were constructed using a multivariate logistic regression model, which included all above-mentioned covariates in the year prior to the date of first antidepressant prescription or a randomly selected date among nonusers. Diabetes cases and controls were matched 1:1 by the estimated propensity score using a greedy matching algorithm. All of the analyses were performed using SAS version 9.2 (SAS Institute; Cary, North Carolina). The statistical significance of relationships was assessed by using 95% CIs or a *P* value less than .05.

## RESULTS

Table 1 shows the demographic and clinical characteristics of diabetic cases and comparison subjects. The mean follow-up period was 6.30 (SD = 2.80) years. The diabetes cases were more likely to have a medical or psychiatric diagnosis and to have received medications that are known to be associated with the risk of diabetes.

As shown in Table 2, the multivariate-adjusted OR for diabetes associated with long-term antidepressant use was 1.20 (95% CI, 1.05–1.37). Among users of antidepressants for 2 years or more, we found the adjusted OR of the mean daily dose with ≥ 0.5 of the DDD for diabetes was 1.32 (95% CI, 1.11–1.56); however, the risk of diabetes among those with a mean daily dose < 0.5 of the DDD was not statistically significant. In terms of antidepressant classes, we found the long-term use of SSRIs and SARIs, but not tricyclic or tetracyclic antidepressants or other antidepressants, was associated with an increased risk of diabetes.

In subgroup analysis (Figure 1), the positive association between long-term antidepressant therapy and diabetes was strongest among patients aged 44 years or less (adjusted OR = 2.39; 95% CI, 1.46–3.90); the test for interaction between long-term antidepressant use and age was statistically significant ($P < .001$). The effects of mean daily dose or certain types of antidepressant on diabetes risk were also higher in young adults (age < 45 years) than in middle age or the elderly (Table 3). There was no significant modifying effect on diabetes risk across gender ($P = .09$), comorbidity with hypertension or hyperlipidemia ($P = .36$), presence of mood disorder ($P = .18$), or use of antipsychotics ($P = .11$).

We performed sensitivity analyses with different latent periods and used a propensity score–matching method. The results based on these sensitivity analyses were grossly consistent with our main analysis. Table 4 presents the results based on a latent period of 4 years, as well as the estimated ORs using propensity score analyses. Details of the propensity

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**Table 3. Diabetes Risk Associated With Antidepressant Use by Age Groups**

| | Age < 45 y | | Age ≥ 45 y | |
|---|---|---|---|---|
| | Adjusted OR | 95% CI | Adjusted OR | 95% CI |
| Nonuse | 1 | Referent | 1 | Referent |
| Overall cumulative period, y | | | | |
| < 1 | 1.02 | 0.92–1.13 | 0.99 | 0.95–1.02 |
| 1–2 | 1.12 | 0.72–1.74 | 1.00 | 0.88–1.15 |
| ≥ 2 | 2.39 | 1.46–3.90 | 1.15 | 1.00–1.32 |
| Mean daily dose and cumulative period | | | | |
| < 0.5 DDD and < 2 y | 1.00 | 0.87–1.14 | 0.97 | 0.93–1.02 |
| < 0.5 DDD and ≥ 2 y | 2.26 | 1.03–4.98 | 1.02 | 0.83–1.25 |
| ≥ 0.5 DDD and < 2 y | 1.05 | 0.91–1.20 | 1.01 | 0.96–1.06 |
| ≥ 0.5 DDD and ≥ 2 y | 2.44 | 1.35–4.43 | 1.26 | 1.05–1.50 |
| Antidepressant classes and cumulative period | | | | |
| Overall antidepressants < 2 y | 1.02 | 0.92–1.13 | 0.99 | 0.96–1.02 |
| Tricyclic and tetracyclic antidepressants ≥ 2 y | 1.66 | 0.55–5.07 | 1.07 | 0.86–1.33 |
| SSRIs ≥ 2 y | 2.70 | 1.16–6.26 | 1.41 | 1.03–1.93 |
| SNRIs ≥ 2 y | 3.36 | 0.33–34.57 | 0.81 | 0.32–2.03 |
| SARIs ≥ 2 y | 7.33 | 1.88–28.61 | 1.39 | 0.99–1.94 |
| Others ≥ 2 y | NA[a] | | 1.64 | 0.74–3.64 |
| Polypharmacy ≥ 2 y[b] | 1.30 | 0.57–3.00 | 1.00 | 0.78–1.29 |

[a]There was only 1 diabetes case, and no control aged less than 45 years used other antidepressants more than 2 years.
[b]Patients with use of 2 or more antidepressant classes ≥ 2 years.
Abbreviations: DDD = defined daily dose, NA = not applicable, SARI = serotonin antagonist and reuptake inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

**Table 4. Sensitivity Analysis for Diabetes Risk With Antidepressant Use by Latent Periods and Analytic Methods**

| | Conditional Logistic Regression Analysis | | | | Propensity Score Analysis With Matching | | | |
|---|---|---|---|---|---|---|---|---|
| | Latent Period of 1 Year (n = 143,655) | | Latent Period of 4 Years (n = 106,839) | | Latent Period of 1 Year (n = 66,960) | | Latent Period of 4 Years (n = 28,192) | |
| | Adjusted OR | 95% CI | Adjusted OR | 95% CI | Adjusted OR | 95% CI | Adjusted OR | 95% CI |
| Nonuse | 1 | Referent | 1 | Referent | 1 | Referent | 1 | Referent |
| Overall cumulative period, y | | | | | | | | |
| < 1 | 0.99 | 0.96–1.02 | 1.01 | 0.97–1.06 | 1.04 | 1.01–1.08 | 1.05 | 1.00–1.11 |
| 1–2 | 1.01 | 0.89–1.14 | 1.06 | 0.88–1.28 | 1.09 | 0.96–1.24 | 1.14 | 0.97–1.35 |
| ≥ 2 | 1.20 | 1.05–1.37 | 1.25 | 1.01–1.56 | 1.20 | 1.06–1.36 | 1.22 | 1.05–1.41 |
| Average daily dose and cumulative period | | | | | | | | |
| ≤ 0.5 DDD and < 2 y | 0.97 | 0.93–1.01 | 1.00 | 0.94–1.05 | 1.03 | 1.00–1.07 | 1.04 | 0.98–1.10 |
| ≤ 0.5 DDD and ≥ 2 y | 1.07 | 0.88–1.30 | 1.17 | 0.85–1.62 | 1.10 | 0.91–1.33 | 1.13 | 0.91–1.41 |
| > 0.5 DDD and < 2 y | 1.01 | 0.97–1.06 | 1.04 | 0.98–1.10 | 1.06 | 1.01–1.12 | 1.10 | 1.02–1.18 |
| > 0.5 DDD and ≥ 2 y | 1.32 | 1.11–1.56 | 1.32 | 1.00–1.74 | 1.29 | 1.09–1.52 | 1.30 | 1.07–1.57 |
| Antidepressant classes and cumulative period | | | | | | | | |
| Overall antidepressants < 2 y | 0.99 | 0.96–1.02 | 1.02 | 0.97–1.06 | 1.04 | 1.01–1.08 | 1.06 | 1.01–1.11 |
| Tricyclic and tetracyclic antidepressants ≥ 2 y | 1.06 | 0.86–1.31 | 1.01 | 0.71–1.44 | 1.25 | 1.01–1.54 | 1.22 | 0.96–1.56 |
| SSRIs ≥ 2 y | 1.50 | 1.12–2.00 | 1.74 | 1.06–2.88 | 1.42 | 1.06–1.89 | 1.44 | 1.05–1.98 |
| SNRIs ≥ 2 y | 1.00 | 0.44–2.28 | 0.93 | 0.17–5.13 | 1.11 | 0.53–2.31 | 1.16 | 0.49–2.73 |
| SARIs ≥ 2 y | 1.58 | 1.15–2.17 | 1.43 | 0.84–2.42 | 1.10 | 0.82–1.48 | 1.29 | 0.92–1.80 |
| Others ≥ 2 y | 1.70 | 0.78–3.71 | 4.31 | 0.44–42.52 | 1.03 | 0.43–2.47 | 0.28 | 0.07–1.22 |
| Polypharmacy ≥ 2 y[a] | 1.02 | 0.81–1.30 | 1.23 | 0.84–1.79 | 1.10 | 0.86–1.42 | 1.14 | 0.85–1.53 |

[a]Patients with use of 2 or more antidepressant classes ≥ 2 years.
Abbreviations: DDD = defined daily dose, OR = odds ratio, SARI = serotonin antagonist and reuptake inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

score analysis are shown in the supplementary tables (see Supplementary eTables 1–3 at PSYCHIATRIST.COM).

## DISCUSSION

With the improvement of methodology by using the population-based, nested case-control study design with a large-scale sample size and careful consideration of the latent period of diagnosis of diabetes, the current study shows a 20% increased risk of diabetes for patients with long-term antidepressant treatment for 2 or more years.

Our results are consistent with those of previous observational studies[10,13,15,17–19] that have shown a positive association between antidepressant use and diabetes risk. In addition, we found a duration-response effect, which further supports our hypotheses. Such a duration-response relationship also has been noted in previous studies.[10,13,15,19] The negative or nonsignificant findings in 5 previous studies have been attributed to the small sample sizes,[11,12,14] limited follow-up period,[16,20] and lack of assessment for treatment duration.[11,12,16,20]

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Our finding that young adults (aged < 45 years) with long-term antidepressant use had a greater risk of new-onset diabetes mellitus indicates that age had a significant modifying effect on this association. Patients who were aged 45 years or older had risk factors other than antidepressants that increased the diabetes risk; therefore, long-term antidepressant use may play a relatively less important role in developing diabetes and accounts for only a slightly increased risk. Our findings are partially in line with a previous study[32] showing that a history of depression, which was defined as an antidepressant prescription with a diagnosis of depression, would increase the risk of diabetes in younger adults rather than older ones.

In this study, we found that long-term use of SSRIs and SARIs, rather than tricyclic or tetracyclic antidepressants and other antidepressants, would increase the risk of diabetes. Findings regarding differences in diabetes risk with the use of various classes of antidepressant drugs are inconsistent.[10,15,18,33] Our findings are in line with research using data from the Diabetes Prevention Program, which found that antidepressants, mainly SSRIs, would increase the diabetes risk of subjects with prediabetic conditions.[19] In addition, a cross-sectional survey[8] using data from the Hordaland Health Study in Norway found that use of SSRIs was associated with abdominal obesity and hypercholesterolemia. The association between SARIs and diabetes was consistent with previous studies that showed that trazodone use would increase body weight.[34] Of interest, we found that tricyclic or tetracyclic antidepressants were not associated with diabetes risk, although long-term tricyclic or tetracyclic antidepressant use was associated with body weight gain.[7] Our findings here contradict those of previous studies.[10,18] A possible explanation for the lack of association is that tricyclic or tetracyclic antidepressant users in Taiwan were older than users of SSRIs and other antidepressants,[35] and the risk of diabetes with antidepressant use was less predominant among the older age group. The adjusted OR for diabetes risk with long-term tricyclic or tetracyclic antidepressant use among young adults was 1.66 (95% CI, 0.55–5.07). The point estimates were increased, but not to a statistically significant extent due to the limited case numbers.

The underlying mechanism for the association between long-term antidepressant use and new-onset diabetes is still unclear. Antidepressant use might increase the diabetes risk via body weight gain.[10] However, body weight gain cannot completely explain such associations. Although the use of SSRIs and SARIs might induce weight gain,[7,8,36] the effect of tricyclic or tetracyclic antidepressants on body weight change was more predominant.[7] Under the assumption that body weight gain is the key attributable factor, we would expect to find a higher diabetes risk in tricyclic or tetracyclic antidepressant users. Nevertheless, we could not find a diabetes risk with long-term tricyclic or tetracyclic antidepressant use in this study. Previous studies[18,19] have found that antidepressant use has an independent effect on diabetes risk after adjustment for weight change during the follow-up period. Therefore, the direct effect of antidepressant use on glucose metabolism should be considered. In animal and in vitro studies,[37,38] administration of SSRIs might induce hyperglycemia via suppression of insulin release or increased insulin resistance. Clinical studies have found that long-term antidepressant use would induce down-regulation of the serotonin-2A (5-$HT_{2A}$) receptor,[39] as well as inactivation of the 5-$HT_{2A}$ receptor, which would impair insulin sensitivity[40] and thereby increase diabetes risk. However, the actual biological mechanism that induces diabetes risk relative to long-term antidepressant use is still unclear and warrants further investigation.

Our study has several potential limitations. First, we could not exclude prediabetic patients from healthy individuals. If depression is a prodrome of diabetes, antidepressants would be falsely interpreted as a causal factor of diabetes. However, we used a lag-time analysis to minimize the effect of prediabetic state. Second, there was no information on the severity of depression; therefore, we could not distinguish the effect of antidepressant use from any effect derived from the depressive disorders. One possible extreme explanation for the increased diabetes risk might be the severe or chronic depression (the reason for long-term antidepressant use) rather than the antidepressants per se. In this study, not all antidepressants were prescribed for depression. Of note, the prevalence of mood disorder was quite low in Taiwan.[41] Approximately 20% of antidepressants were prescribed for a mood disorder.[35] We found there was no significant difference in the diabetes risk with long-term antidepressant use among patients with or without mood disorders. In addition, previous studies also have shown that antidepressant use is an independent risk factor for diabetes after adjusting for the severity of depressive symptoms.[15,17–19] Furthermore, we found consistent results in our sensitivity analysis using a propensity score–matching method, which includes pertinent covariates related to the severity of depression, such as comorbid psychiatric disorders and concomitant psychotropic agents.

Another limitation of this study, the use of claims data, should be considered. First, lifestyle factors, including body weight and smoking, were not available in the NHIRD. We used hypertension, hyperlipidemia, and chronic pulmonary disease as proxy measures for these factors. In addition, the associations between obesity and depression varied across ethnic groups and countries.[42] Several longitudinal studies have demonstrated obesity is inversely associated with depression in Taiwan[43,44]; therefore, obesity would not increase the rate of antidepressant use and bias our results. The prevalence of smoking among women in Taiwan is quite low (< 5%).[45] Given that the diabetes risk with antidepressant use was similar between men and women, the effect of smoking might not confound these results markedly after adjusting proxy measures of smoking. Second, medication adherence was unknown, so, if patients had poor compliance, we would have underestimated the diabetes risk with long-term antidepressant use. Third, only the diagnosis of type 2 diabetes mellitus was validated in the NHIRD. The accuracy

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of covariates is unknown; therefore, it is difficult to evaluate the effect of a misclassification of covariates. Finally, we used a dataset randomly selected from the NHI Registry in 2005. Patients who died between 1998 and 2005 were not included in this study. Thus, our study population may have been slightly healthier than those excluded from this study.

To the best of our knowledge, this is the first such study conducted in an Asian population, an ethnic group with a high diabetes risk.[46] The strengths of our study design include the use of a nationwide representative population and a long follow-up period. We used a new user design to evaluate the cumulative period of antidepressant use and to avoid an overrepresentation of patients who tolerated antidepressants well. We comprehensively explored the duration, dose, and classes of antidepressants in exploring the diabetes risk. Moreover, our study used a previously validated method to define incident diabetes and controlled for pertinent confounding factors and potential detection bias. Finally, sensitivity analyses for different latent periods and a propensity score–matching method to control indication bias were conducted to confirm the robustness of the results.

## CONCLUSION

We found that long-term use of antidepressants for 2 years or more is associated with a modest increased risk of type 2 diabetes mellitus. However, the underlying mechanism is still unclear. If the association reflects a causal effect, long-term antidepressant use should be evaluated more cautiously for its benefits and the potential risk of type 2 diabetes mellitus.

***Drug names:*** bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), doxepin (Silenor, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), milnacipran (Savella), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), trazodone (Oleptro and others), venlafaxine (Effexor and others).

***Disclosure of off-label usage:*** The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

***Author affiliations:*** Department of Psychiatry, Far Eastern Memorial Hospital, New Taipei City (Dr Wu); Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health (Drs Wu, Gau, and Lai); and Department of Psychiatry, National Taiwan University Hospital and College of Medicine (Drs Wu and Gau), National Taiwan University, Taipei, Taiwan.

***Author contributions:*** Drs Gau and Lai equally contributed to the supervision of this work.

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***Supplementary material:*** Available at PSYCHIATRIST.COM.

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## Posttest

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**1. This study showed an increased risk for type 2 diabetes mellitus among patients who had been taking antidepressants for ___.**

a. Less than 1 year

b. Between 1 and 2 years

c. At least 2 years

d. All of the above

**2. Among all patients taking antidepressants for 2 years or more, those taking which of the following antidepressants had the highest odds ratio for diabetes?**

a. Tricyclic antidepressants (TCAs)

b. Selective serotonin reuptake inhibitors (SSRIs)

c. Serotonin-norepinephrine reuptake inhibitors (SNRIs)

d. Polypharmacy (> 1 antidepressant)

**3. Ms A, who is 35 years old, and Ms B, who is 55 years old, are patients with major depressive disorder. Both patients have had chronic, recurrent depression and will need long-term treatment. Which antidepressant group would not increase the risk of diabetes in Ms B but would in Ms A, according to odds ratios in this study?**

a. TCAs

b. SSRIs

c. SNRIs

d. Polypharmacy

**4. Mr C is 40 years old and has been taking an SSRI for depression for 10 years. Mr D is also 40 years old and has been taking an SSRI for 10 years for generalized anxiety disorder. Mr C is at greater risk for diabetes because mood disorders were found to increase risk compared with other disorders.**

a. True

b. False

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THE JOURNAL OF CLINICAL PSYCHIATRY

# Supplementary Material

**Article Title:** Long-Term Use of Antidepressant and the Risk of Type 2 Diabetes Mellitus: A Population-Based, Nested Case-Control Study in Taiwan

**Author(s):** Chi-Shin Wu, MD, MSc; Susan Shur-Fen Gau, MD, PhD; and Mei-Shu Lai, MD, PhD

**DOI Number:** 10.4088/JCP.13m08421

## List of Supplementary Material for the article

1. eTable 1 Demographic and clinical characteristics of study population, by antidepressant use
2. eTable 2 Demographic and clinical characteristics of case with diabetes and comparison subjects between 2000 and 2009
3. eTable 3 Diabetes Risk Associated with Antidepressant Using Propensity Score-Matching Methods

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Supplementary eTable 1. Demographic and clinical characteristics of study population, by antidepressant use[a]

| | Antidepressant users (n=77,459) | | Non-users (n=491,645) | |
|---|---|---|---|---|
| | N | (%) | N | (%) |
| Age at index date, year | | | | |
| <45 | 34511 | (44.6) | 312854 | (63.6) |
| 45-54 | 17196 | (22.2) | 91270 | (18.6) |
| 55-64 | 11179 | (14.4) | 46523 | (9.5) |
| ≥65 | 14573 | (18.8) | 43524 | (8.9) |
| Gender, male | 31473 | (40.6) | 256676 | (52.2) |
| Medical illness | | | | |
| Hypertension | 17711 | (22.9) | 45431 | (9.2) |
| Dyslipidemia | 7478 | (9.7) | 21399 | (4.4) |
| Cerebrovascular disease | 7478 | (9.7) | 21399 | (4.4) |
| Chronic heart failure | 2800 | (3.6) | 5322 | (1.1) |
| Chronic pulmonary disease | 11003 | (14.2) | 36781 | (7.5) |
| Chronic renal failure | 2052 | (2.6) | 5577 | (1.1) |
| Malignancy | 2440 | (3.2) | 5646 | (1.1) |
| Psychiatric illness | | | | |
| Mood disorders | 15497 | (20.0) | 1710 | (0.3) |
| Psychotic disorders | 1609 | (2.1) | 1711 | (0.3) |
| Anxiety disorders | 20144 | (26.0) | 14435 | (2.9) |
| Sleep disorders | 15139 | (19.5) | 16500 | (3.4) |
| Alcohol related disorder | 855 | (1.1) | 1438 | (0.3) |
| Concomitant use of medication | | | | |
| Antithrombotic agent | 12161 | (15.7) | 26726 | (5.4) |
| Anti-hypertensive agent | 27732 | (35.8) | 57692 | (11.7) |
| Corticosteroid | 22403 | (28.9) | 99116 | (20.2) |
| Diuretic | 8945 | (11.5) | 21473 | (4.4) |

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| | | | | |
|---|---|---|---|---|
| Lipid lowering agent | 3656 | (4.7) | 9039 | (1.8) |
| Female sex hormones | 11474 | (14.8) | 40351 | (8.2) |
| Antipsychotics | 8383 | (10.8) | 11337 | (2.3) |
| Mood stabilizer | 3035 | (3.9) | 2876 | (0.6) |
| Health system utilization | | | | |
| Number of outpatient visit per year | | | | |
| <10 | 14897 | (19.2) | 232595 | (47.3) |
| 10-19 | 22236 | (28.7) | 145342 | (29.6) |
| ≥20 | 40326 | (52.1) | 116234 | (23.6) |
| Hospitalization | 9709 | (12.5) | 29195 | (5.9) |

a all p-value <0.001

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Supplementary eTable 2. Demographic and clinical characteristics of case with diabetes and comparison subjects between 2000 and 2009

| | Cases (N=33,480) | | Controls (N=33,480) | | |
|---|---|---|---|---|---|
| | N | (%) | N | (%) | p-value |
| Age at index date, year | | | | | |
| <45 | 6299 | (18.8) | 6299 | (18.8) | |
| 45-54 | 9439 | (28.2) | 9439 | (28.2) | |
| 55-64 | 8019 | (24.0) | 8019 | (24.0) | |
| ≥65 | 9723 | (29.0) | 9723 | (29.0) | |
| Gender, male | 18331 | (54.8) | 18331 | (54.8) | |
| Medical illness | | | | | |
| Hypertension | 9157 | (27.4) | 9106 | (27.2) | .658 |
| Hyperlipidemia | 3109 | (9.3) | 3058 | (9.1) | .496 |
| Cerebrovascular disease | 1125 | (3.4) | 1132 | (3.4) | .881 |
| Chronic heart failure | 627 | (1.9) | 613 | (1.8) | .688 |
| Chronic pulmonary disease | 3795 | (11.3) | 3762 | (11.2) | .687 |
| Chronic renal failure | 428 | (1.3) | 424 | (1.3) | .890 |

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| | | | | | |
|---|---|---|---|---|---|
| Malignancy | 419 | (1.3) | 420 | (1.3) | .972 |
| Psychiatric illness | | | | | |
| Mood disorders | 853 | (2.5) | 855 | (2.6) | .961 |
| Psychotic disorders | 151 | (0.5) | 149 | (0.4) | .908 |
| Anxiety disorders | 2291 | (6.8) | 2297 | (6.9) | .927 |
| Sleep disorders | 1950 | (5.8) | 1945 | (5.8) | .934 |
| Alcohol related disorder | 112 | (0.3) | 106 | (0.3) | .684 |
| Concomitant use of medication | | | | | |
| Antithrombotic agent | 4151 | (12.4) | 4112 | (12.3) | .647 |
| Anti-hypertensive agent | 10292 | (30.7) | 10291 | (30.7) | .993 |
| Corticosteroid | 7468 | (22.3) | 7445 | (22.2) | .831 |
| Diuretic | 3654 | (10.9) | 3594 | (10.7) | .456 |
| Lipid lowering agent | 1444 | (4.3) | 1408 | (4.2) | .491 |
| Female sex hormones | 2581 | (7.7) | 2599 | (7.8) | .795 |
| Antipsychotics | 1055 | (3.2) | 1052 | (3.1) | .947 |
| Mood stabilizer | 264 | (0.8) | 273 | (0.8) | .697 |
| Health system utilization | | | | | |

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| | | | | | |
|---|---|---|---|---|---|
| Number of outpatient visit per year | | | | | |
| <10 | 10414 | (31.1) | 10453 | (31.2) | .912 |
| 10-19 | 9969 | (29.8) | 9982 | (29.8) | |
| ≥20 | 13097 | (39.1) | 13045 | (39.0) | |
| Hospitalization | 2069 | (6.2) | 2094 | (6.3) | .689 |

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Supplementary eTable 3. Diabetes Risk Associated with Antidepressant Using Propensity Score-Matching Methods

| | Cases (N=33,480) | | Controls (N=33,480) | | | |
|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | Adjusted OR | (95% CI) |
| Antidepressant exposure status | | | | | | |
| Non-use | 23923 | (71.5) | 24254 | (72.4) | 1 | referent |
| Overall cumulative period | | | | | | |
| <1 year | 5817 | (17.4) | 5587 | (16.7) | 1.04 | (1.01-1.08) |
| 1-2 years | 301 | (0.9) | 270 | (0.8) | 1.09 | (0.96-1.24) |
| ≥2 years | 306 | (0.9) | 232 | (0.7) | 1.2 | (1.06-1.36) |
| Average daily dose and cumulative period | | | | | | |
| ≤0.5 DDD and< 2 years | 3883 | (11.6) | 3773 | (11.3) | 1.03 | (1.00-1.07) |
| ≤0.5 DDD and ≥ 2 years | 126 | (0.4) | 112 | (0.3) | 1.1 | (0.91-1.33) |
| >0.5 DDD and < 2 years | 2235 | (6.7) | 2084 | (6.2) | 1.06 | (1.01-1.12) |
| >0.5 DDD and ≥ 2 years | 180 | (0.5) | 120 | (0.4) | 1.29 | (1.09-1.52) |
| Antidepressant classes and cumulative period | | | | | | |
| Overall antidepressants < 2 years | 6118 | (18.3) | 5857 | (17.5) | 1.04 | (1.01-1.08) |
| Tricyclic antidepressants≥ 2 years | 103 | (0.3) | 71 | (0.2) | 1.25 | (1.01-1.54) |
| SSRIs≥ 2 years | 61 | (0.2) | 34 | (0.1) | 1.42 | (1.06-1.89) |
| SNRIs ≥ 2 years | 8 | 0.0 | 7 | 0.0 | 1.11 | (0.53-2.31) |
| SARIs ≥ 2 years | 52 | (0.2) | 46 | (0.1) | 1.1 | (0.82-1.48) |

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| | | | | | | |
|---|---|---|---|---|---|---|
| Others ≥ 2 years | 6 | 0.0 | 6 | 0.0 | 1.03 | (0.43-2.47) |
| Polypharmacy ≥ 2 years [a] | 76 | (0.2) | 68 | (0.2) | 1.1 | (0.86-1.42) |

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