Seizure Risk Associated With Antidepressant Treatment Among Patients With Depressive Disorders:
A Population-Based Case-Crossover Study

Chi-Shin Wu, MD, PhD[a,b,‡]; Hsin-Yen Liu, BS[c,‡]; Hui-Ju Tsai, MPH, PhD[d,e,f]; and Shi-Kai Liu, MD[g,h,*]

ABSTRACT

Objective: To assess the risk of seizure associated with antidepressant use among patients with depressive disorders.

Methods: Individuals visiting the emergency department or hospitalized because of new-onset seizure (*ICD-9-CM* diagnostic code 345 or 780.3; our primary study outcome) after receiving antidepressants for depressive disorders, were identified from a Taiwanese total population health insurance database. Using a case-crossover study design, relative risk of antidepressant-related seizure was estimated by comparing the rates of antidepressant exposure during the case periods vs control periods. The effects of class and dose of antidepressant on seizure risk were explored, using a conditional logistic regression model adjusting for concomitant medications. Several sensitivity analyses were conducted to attest the results of primary analyses.

Results: A total of 10,002 patients were included between 2002 and 2012. Overall, antidepressant exposure was positively associated with increased seizure risk (OR = 1.48, 95% CI, 1.33–1.64). Among the antidepressants, the increases in seizure risk of bupropion (OR = 2.23, 95% CI, 1.58–3.16), selective serotonin reuptake inhibitors (OR = 1.76, 95% CI, 1.55–2.00), serotonin and norepinephrine reuptake inhibitors (OR = 1.40, 95% CI, 1.10–1.78), and mirtazapine (OR = 1.38, 95% CI, 1.08–1.77) showed clear dose-response effects. Furthermore, the seizure risk was highest among patients aged between 10 and 24 years and patients with major depression. The results of sensitivity analyses largely confirmed those from the primary analyses.

Conclusions: The seizure-inducing propensity and dose-response relationship pattern, as well as potential risk factors, associated with individual antidepressants should be taken into consideration when choosing antidepressants during clinical practice.

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[a]Department of Psychiatry, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan
[b]Department of Psychiatry, Far Eastern Memorial Hospital, New Taipei City, Taiwan
[c]Health Science Program, McMaster University, Hamilton, Ontario, Canada
[d]Division of Biostatistics and Bioinformatics, Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan
[e]Department of Public Health, China Medical University, Taichung, Taiwan
[f]Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, Illinois
[g]Centre for Addiction and Mental Health, Toronto, Ontario, Canada
[h]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
‡Both authors share equal contributions to this research.
**Corresponding author:* Shi-Kai Liu, MD, Centre for Addiction and Mental Health, Department of Psychiatry, University of Toronto, 1001 Queen St West, Toronto, Ontario, Canada M6J 1H4 (shi-kai_liu@camh.net).

Seizure can cause serious accidents, injuries, and mortality.[1,2] Notably, a substantial proportion of new-onset seizures resulting in hospitalization are drug-related.[3] Conventional antidepressants have been demonstrated to be among the most common medications responsible for drug-induced seizures. Recently, the prescription of the new-generation antidepressants has increased tremendously, but information regarding their seizure-inducing propensity, despite its clinical import, has been scarce and mainly anecdotal.[4,5] New-generation antidepressant–related seizure hence warrants systematic investigation.[3]

Seizure risks associated with antidepressants reported so far have varied widely. In one study using European multinational pharmacovigilance data, the seizure rate of tricyclic or tetracyclic antidepressants (TCAs) among psychiatric inpatients was twice as high as those of the selective serotonin reuptake inhibitors (SSRIs) and other new-generation antidepressants.[6] In contrast, one study using pooled data from clinical trials showed that new-generation antidepressants were not associated with increased seizure risk.[7] Among the 3 recent large-scale population-based cohort studies in England,[8–10] one demonstrated that, among elderly patients, SSRIs and other new-generation antidepressants were associated with higher seizure risk than TCAs.[8] Another found that seizure risk increased in current users of SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) but not in TCA users.[9] Conversely, the third study did not find significant differences in seizure risk across antidepressant classes in patients with depression and aged between 20 and 64 years.[10]

Given the diversities in scope, design, and outcome indices across the studies, such discrepant findings are not surprising. Methodologically, pharmacovigilance data cannot be used to estimate the incidence rate because the number and characteristics of exposed individuals were unknown. Furthermore, previous antidepressant clinical trials were not designed to examine seizure as a primary outcome. Also, the sample sizes were insufficient to estimate the incidence of seizure as a rare event. Finally, although the naturalistic, observational studies could procure information from a larger number of exposed subjects, potential confounding factors and their impacts on seizure incidence could not be properly controlled for and estimated.

The aforementioned methodologic shortcomings in determining seizure risk following antidepressant

Clinical Points

- The seizure risk of new-generation antidepressants has been underinvestigated.
- Clinicians should evaluate cautiously for the potential seizure risks of some antidepressants, including SSRIs, SNRIs, bupropion, and mirtazapine.

exposure can best be rectified by applying a case-crossover study design to a representative total population sample to eliminate the effects of all known or unknown time-invariant confounders. Because the complete record of disease-related health insurance claims of the Taiwanese population is available from the National Health Insurance Research Database, the current study is able to determine the seizure-inducing propensity of the traditional and new-generation antidepressants in patients with depressive disorders with improved methodologic rigor.

METHODS

Data Source

The universal, single-payer National Health Insurance program (NHI) in Taiwan covers more than 99% of the population, and its complete reimbursement claims data have been compiled into the National Health Insurance Research Database (NHIRD). The NHIRD includes comprehensive information about patients' demographics, clinical diagnosis, medical expenditure, and prescription records.[11] Each prescription record contains information about the name of medication, dosage, duration of drug supply, and date of prescription. For the current study, data from all subjects who were enrolled in NHI between 2002 and 2012 were included in the screening stage. This study protocol was approved by the Institutional Review Board of the National Taiwan University Hospital (201505001RINB).

Study Subjects

The primary study outcome was new-onset seizure. Pending diagnostic codes for seizure in the *ICD-9*,[12] we used convulsion (*ICD-9-CM* code: 780.3) or epilepsy (*ICD-9* code: 345) as proxy codes to identify patients with new-onset seizure through emergency department visits or hospitalizations. To ensure those were incident cases, prevalent cases with diagnostic records of convulsion or epilepsy or prescription records of non–mood-stabilizing antiepileptic drugs before 2002 were excluded. As the NHIRD did not provide detailed clinical information about the manifestation of the seizures, we attempted to validate the diagnoses by examining whether these diagnoses led to further confirmatory examinations or treatments, interventions reflecting the degree of clinical certainty. Indeed, the majority of cases (86.4%) did receive follow-up electroencephalography (EEG) examination and/or antiepileptic drug prescription within 90 days after the seizure diagnosis.

To avoid indication bias, we restricted our study subjects to those who received antidepressants with concomitant diagnoses of depressive disorders (n = 1,570,442). Among them, we identified 26,180 patients with new-onset seizure after antidepressant use. The index date was defined as the first date of diagnosis of seizure. We further excluded patients younger than 10 years, those diagnosed with schizophrenia or bipolar disorder, and those with seizure occurring concomitantly with or after major neurologic risk factors, including head injury, central nervous system infection, brain tumor, stroke, dementia, and organic brain syndrome. We further excluded patients hospitalized within 6 months before new-onset seizures because the prescription dates during hospitalization could not be ascertained. The final study sample thus consisted of 10,002 patients who had new-onset seizure after receiving antidepressants for depressive disorders (see Supplementary eFigure 1 at Psychiatrist.com).

Case-Crossover Design

The case-crossover study design is a well-established method to examine the effect of short-term or intermittent exposures on acute outcomes.[13,14] Case-crossover design is a variant of case-control study; however, the odds ratio (OR) is estimated by comparing cases' exposure status immediately before the study outcome (the case period) with the exposure status at other past time periods (the control period), rather than comparing with other individuals (Figure 1). In the current study, we used a 30-day period as the exposure time window: 1st to 30th day before the index date as the case period and 91st to 120th day before the index date as the control period. As each case serves as his or her own control in such case-crossover design, time-invariant between-person confounding factors, such as genetic vulnerability or chronic medical conditions, will be automatically controlled, a superiority of the case-crossover design over cohort or case-control studies in controlling for confounding factors.

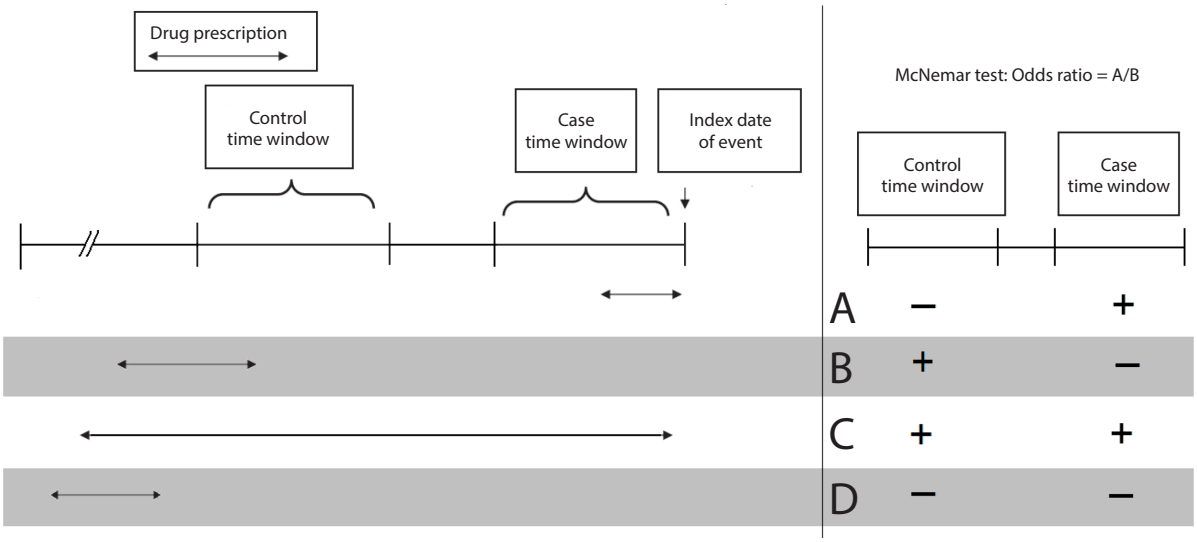
Characteristics of the Study Subjects

In addition to sex and age groups (10–24 y, 25–44 y, 45–64 y, and ≥ 65 y), we classified depression according to its severity as major (*ICD-9* code: 296.2x, 296.3x) or minor depression (*ICD-9* code: 300.4 or 311). The general health status was assessed using the Charlson comorbidity index, which is the sum of the weighted score of 19 comorbid conditions and is widely used to control for confounding in epidemiologic studies.[15] Psychiatric comorbid conditions possibly associated with lower seizure threshold, including mental retardation, autistic disorder, alcohol use disorder, substance use disorder, anxiety disorder, and sleep disorder, were also assessed.

Exposure to Antidepressants

Based on the Anatomical Therapeutic Chemical classification system,[16] antidepressants (N06A) were identified and classified according to their proposed mechanisms of action: TCAs (amitriptyline, clomipramine,

Figure 1. Case-Crossover Design[a]



[a]The case time window is the period between the 1st and 30th day prior to the index date (the date seizure is first diagnosed). The control time window is the period between the 91st and 120th day prior to the index date. If seizure and antidepressant use are unrelated, the exposure to antidepressants should be randomly distributed along the study timeline and hence similar across the case and control time windows. However, if the antidepressant use is associated with an increased risk of seizure, the rate of antidepressant exposure in the case time window would be higher than that in the control time window. The sample can be further divided into 4 subgroups according to the exposure status during case and control time windows (A to D), the crude odds ratio is calculated by the ratio of the number of patients exposed only in the case time window to those exposed only in the control time window (A/B). Conditional logistic regression model is used to adjust time-dependent confounders and estimate the adjusted odds ratios.

dothiepin, doxepin, imipramine, maprotiline, and melitracen/flupentixol), SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), SNRIs (venlafaxine, duloxetine, milnacipran), and other agents (ie, mirtazapine, bupropion, moclobemide, and trazodone).

The exposure to antidepressant was defined as the prescription of a particular antidepressant occurring in the case or control period or an earlier prescription that extended into these periods. We used the defined daily dose (DDD), "the assumed average maintenance dose per day for a drug used for its main indication in adults," to calculate standardized antidepressant daily doses (see eAppendix 1).[16] We further categorized the study population into 4 average daily dose groups: 0 (nonuse; reference group), >0 and ≤0.5, >0.5 and ≤1, and >1 DDD. Given the small number of cases using dosage >1 DDD of bupropion and trazodone, users of these 2 drugs were categorized into 3 groups only: 0, >0 and ≤0.5, and >0.5 DDD. A dose-response relationship trend was then examined by considering averaged daily dose as a continuous variable. Compliance to medication was estimated by the medication possession ratio (MPR)—the number of days patients were in possession of any antidepressant within the 1-year period prior to the index day, divided by 365.

Table 1. Demographic and Clinical Characteristics of Individuals With Depressive Disorder and First-Time Hospitalization or Emergency Room Visits for Seizure, 2002–2012 (N = 10,002)

Characteristic	n (%)
Age at new-onset seizure, y	
10–24	824 (8.2)
25–44	3,000 (30.0)
45–64	3,004 (30.0)
≥65	3,174 (31.7)
Sex	
Female	4,918 (49.2)
Male	5,084 (50.8)
Depressive disorder	
Major depression	4,018 (40.2)
Minor depression	5,984 (59.8)
Comorbidity	
Mental retardation	138 (1.4)
Autistic spectrum disorder	28 (0.3)
Alcohol use disorder	1,225 (12.2)
Substance use disorder	777 (7.8)
Sleep disturbance	4,218 (42.2)
Anxiety disorder	3,491 (34.9)
Drug overdose[a]	208 (2.1)
Charlson comorbidity index score	
0	3,333 (33.3)
1–2	3,132 (31.3)
≥3	3,537 (35.4)

[a]Drug overdose was assessed in the 7-day period before index date.

Concomitant Medications as Time-Variant Confounding Factors

Although the case-crossover design automatically controls for patients' chronic medical conditions and vulnerability to seizure, time-variant factors, especially those medications that might affect seizure threshold, could still confound the results. Thus, the exposure status of the following medications was assessed during the case and control periods to be adjusted in statistical analysis: antipsychotics, benzodiazepines, mood-stabilizing antiepileptic agents, anticholinergic agents, analgesics, antiasthmatics, antibacterials, and antihistamines (see eAppendix 2).[17]

Table 2. Exposure to Antidepressants Between the 30-Day Case and Control Periods for Risk of Seizure

	Use Only in Case Period	Use Only in Control Period	Crude OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Overall antidepressant use	1,189	701	1.70 (1.54–1.86)***	1.48 (1.33–1.64)***
TCAs	393	317	1.24 (1.07–1.44)**	1.07 (0.91–1.25)
Amitriptyline	41	52	0.79 (0.51–1.21)	0.67 (0.44–1.02)
Clomipramine	9	6	1.50 (0.48–5.12)	1.46 (0.50–4.20)
Dothiepin	4	7	0.57 (0.12–2.25)	0.48 (0.14–1.66)
Doxepin	49	51	0.96 (0.64–1.45)	0.88 (0.59–1.32)
Imipramine	153	118	1.30 (1.01–1.66)*	1.22 (0.95–1.57)
Maprotiline	13	17	0.76 (0.34–1.67)	0.57 (0.27–1.22)
Melitracen/flupentixol	187	131	1.43 (1.14–1.80)**	1.18 (0.94–1.49)
SSRIs	804	406	1.98 (1.76–2.24)***	1.76 (1.55–2.00)***
Citalopram	116	66	1.76 (1.29–2.42)***	1.56 (1.14–2.14)**
Escitalopram	125	83	1.51 (1.13–2.01)**	1.36 (1.02–1.82)*
Fluoxetine	288	165	1.75 (1.44–2.13)***	1.59 (1.30–1.94)***
Fluvoxamine	53	33	1.61 (1.02–2.56)*	1.57 (1.00–2.47)
Paroxetine	154	85	1.81 (1.38–2.39)***	1.71 (1.30–2.25)***
Sertraline	252	115	2.19 (1.75–2.76)***	2.00 (1.59–2.51)***
SNRIs	178	119	1.50 (1.18–1.90)***	1.40 (1.10–1.78)**
Duloxetine	48	30	1.60 (0.99–2.62)	1.66 (1.03–2.67)*
Milnacipran	6	5	1.20 (0.31–4.97)	1.21 (0.36–4.04)
Venlafaxine	131	89	1.47 (1.12–1.95)**	1.31 (0.99–1.73)
Others				
Mirtazapine	173	112	1.54 (1.21–1.98)***	1.38 (1.08–1.77)*
Bupropion	109	48	2.27 (1.60–3.26)***	2.23 (1.58–3.16)***
Moclobemide	41	29	1.41 (0.86–2.36)	1.18 (0.72–1.93)
Trazodone	431	327	1.32 (1.14–1.53)***	1.08 (0.93–1.25)
Covariates				
Antipsychotics	706	386	1.83 (1.61–2.08)***	1.51 (1.33–1.72)***
Benzodiazepines	1,152	1,152	1.00 (0.92–1.09)	1.11 (1.00–1.23)
Mood stabilizers	320	184	1.74 (1.45–2.10)***	1.51 (1.25–1.82)***
Anticholinergic agents	594	430	1.38 (1.22–1.57)***	1.21 (1.06–1.37)**
Analgesics	167	99	1.69 (1.31–2.19)***	1.49 (1.15–1.92)**
Antiasthmatics	350	228	1.54 (1.30–1.82)***	1.44 (1.22–1.71)***
Antibacterials	833	598	1.39 (1.25–1.55)***	1.31 (1.18–1.46)***
Antihistamines	764	539	1.42 (1.27–1.59)***	1.31 (1.17–1.46)***

[a]Calculated by McNemar 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, benzodiazepines, mood stabilizers, anticholinergic agents, analgesics, antiasthmatics, antibacterials, and antihistamines.
*Significant at the .05 probability level.
**Significant at the .01 probability level.
***Significant at the .001 probability level.
Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic or tetracyclic antidepressant.

Data Analysis

We conducted the McNemar test comparing the ratio of patients exposed only in the case period with those exposed only in the control period to estimate the crude ORs of seizure risk for each antidepressant and used conditional logistic regression models to estimate the adjusted ORs (aORs), controlled for the aforementioned time-dependent confounding medication use.

To explore the modifying effects of patient characteristics on the association between seizure risk and antidepressant use, subgroup analyses were performed after stratifying by various patient characteristics, including age, sex, severity of mood disorder, and Charlson comorbidity index score. A modifying effect of a specific confounder would manifest as a significant interaction between antidepressant exposure and subject characteristics in the regression model.

To test the robustness of the results of the primary analyses, we conducted serial follow-up sensitivity analyses, including using different time windows (15 or 60 days) for the case and control periods, applying case-case-time-control design to eliminate exposure trend (see Supplementary eFigure 2), restricting analyses to only those patients with new or intermittent antidepressant use, excluding those with drug overdose, and stratifying analyses for those with newly diagnosed epilepsy (*ICD-9-CM*: 345) or convulsion (*ICD-9-CM*: 780.3), respectively (see eAppendix 3). Statistical significance was assessed by P value < .05, and 95% confidence intervals (CIs) were constructed. Data management and statistical analysis were performed using SAS 9.4 software (SAS Institute Inc, Cary, North Carolina).

RESULTS

The demographic and clinical characteristics of study subjects are detailed in Table 1. The mean age at new-onset seizure was 52.7 ± 19.8 years; 49.2% of the study subjects were

Table 3. Dose-Response Relationship Between Risk of First-Time Seizure and Dose of Antidepressant

Dose-Response Relationship[a]	Crude OR (95% CI)	Adjusted OR[b] (95% CI)	*P* Trend[c]
TCAs			NS
≤0.5 DDD	1.15 (0.96–1.37)	1.01 (0.84–1.22)	
>0.5–1 DDD	1.39 (1.10–1.77)	1.12 (0.87–1.44)	
>1 DDD	1.51 (0.91–2.51)	1.27 (0.75–2.14)	
SSRIs			***
≤0.5 DDD	1.48 (1.14–1.92)	1.38 (1.06–1.80)	
>0.5–1 DDD	1.98 (1.72–2.27)	1.75 (1.51–2.02)	
>1 DDD	2.60 (2.06–3.29)	2.29 (1.79–2.92)	
SNRIs			*
≤0.5 DDD	1.60 (1.00–2.55)	1.21 (0.89–1.64)	
>0.5–1 DDD	1.32 (0.99–1.77)	1.79 (1.09–2.93)	
>1 DDD	1.97 (1.23–3.16)	1.57 (0.87–2.82)	
Mirtazapine			*
≤0.5 DDD	1.77 (1.01–3.11)	1.57 (0.87–2.82)	
>0.5–1 DDD	1.48 (1.13–1.93)	1.31 (0.99–1.72)	
>1 DDD	1.72 (0.97–3.03)	1.70 (0.93–3.10)	
Bupropion			***
≤0.5 DDD	1.97 (1.31–2.97)	1.91 (1.26–2.90)	
>0.5 DDD	2.85 (1.69–4.81)	2.89 (1.68–4.98)	
Moclobemide			NS
≤0.5 DDD	1.62 (0.63–4.20)	1.34 (0.51–3.54)	
>0.5–1 DDD	1.33 (0.72–2.44)	1.17 (0.62–2.20)	
>1 DDD	1.44 (0.58–3.60)	1.16 (0.45–2.98)	
Trazodone			NS
≤0.5 DDD	1.32 (1.14–1.53)	1.08 (0.92–1.26)	
>0.5 DDD	1.24 (0.77–2.00)	0.93 (0.57–1.52)	

[a]Calculated by multivariate conditional logistic regression with adjustment for antipsychotics, benzodiazepines, mood stabilizers, anticholinergic agents, analgesics, antiasthmatics, antibacterials, and antihistamines.
[b]Doses of antidepressant per 1 DDD: amitriptyline 75 mg, clomipramine 100 mg, dothiepin 150 mg, doxepin 100 mg, imipramine 100 mg, maprotiline 100 mg, melitracen/flupentixol 10/0.5 mg, citalopram 20 mg, escitalopram 10 mg, fluoxetine 20 mg, fluvoxamine 100 mg, paroxetine 20 mg, sertraline 50 mg, duloxetine 60 mg, milnacipran 100 mg, venlafaxine 100 mg, mirtazapine 30 mg, bupropion 300 mg, moclobemide 300 mg, trazodone 300 mg.
[c]*P* trends for dose-response relationship were determined by considering averaged daily doses as continuous variables in regression model.
*Significant at the .05 probability level.
**Significant at the .01 probability level.
***Significant at the .001 probability level.
Abbreviations: DDD = defined daily dose, NS = nonsignificant (at .05 probability level), SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic or tetracyclic antidepressant.

Table 4. Factors Associated With Risk of Seizure With Antidepressant Use

	Adjusted OR[a] (95% CI)	*P* Interaction
Age at new-onset seizure, y		**
<25	2.73 (1.97–3.80)	
25–44	1.43 (1.19–1.70)	
45–64	1.35 (1.12–1.62)	
≥65	1.37 (1.13–1.67)	
Sex		NS
Female	1.58 (1.37–1.83)	
Male	1.35 (1.17–1.56)	
Mood disorder		*
Major depression	1.65 (1.41–1.94)	
Minor depression	1.35 (1.18–1.54)	
Charlson comorbidity index		NS
0	1.58 (1.31–1.92)	
1–2	1.56 (1.30–1.87)	
≥3	1.27 (1.07–1.51)	

[a]Calculated by multivariate conditional logistic regression with adjustment for antipsychotics, benzodiazepines, mood stabilizers, anticholinergic agents, analgesics, antiasthmatics, antibacterials, and antihistamines.
*Significant at the .05 probability level.
**Significant at the .01 probability level.
Abbreviation: NS = nonsignificant (at .05 probability level).

women. Only 2.1% among those with new-onset seizures had a concomitant diagnosis of drug overdose. There were 55,101 antidepressant prescriptions in the year prior to the index date (see Supplementary eTable 1). The average MPR of antidepressant within the 1-year period prior to the index date was 0.23.

Table 2 demonstrated that overall antidepressant use was associated with a 1.48-fold increased risk of new-onset seizure, adjusted for confounding medication use. The risk of new-onset seizure varied across different classes of antidepressants. We found that seizure risk was highest for bupropion use (aOR = 2.23; 95% CI, 1.58–3.16), followed by SSRIs (aOR = 1.76; 95% CI, 1.55–2.00), SNRIs (aOR = 1.40; 95% CI, 1.10–1.78), and mirtazapine (aOR = 1.38; 95% CI, 1.08–1.77). In contrast, TCAs, moclobemide, and trazodone were not associated with increased seizure risks. For individual antidepressants, all SSRIs, duloxetine, bupropion, and mirtazapine were associated with increased seizure risks (Table 3). In addition, dose-response relationship with seizure risk was significant for bupropion, SNRIs, SSRIs, and mirtazapine (Table 4).

Among the patient characteristics, age had a modifying effect on the association between antidepressant use and seizure risk ($P = .002$). The seizure risk was highest among patients younger than 25 years (aOR = 2.73; 95% CI, 1.97–3.80) (Table 4). Severity of depression ($P = .04$) also had a significant modifying effect on the association between antidepressant use and seizure; however, sex ($P = .11$) and Charlson comorbidity index ($P = .14$) did not. The results from the sensitivity analyses were largely consistent with those from the primary analysis (see Supplementary eTables 3–7).

DISCUSSION

Using the Taiwanese total population health claims data, the present study demonstrated that new-generation antidepressant use was indeed associated with increased risk of seizure in patients diagnosed with depressive disorders. Notably, the increase in seizure risk associated with short-term exposure to bupropion, SNRIs, SSRIs, and mirtazapine was dose related, with age and severity of depression as significant modifying factors, supporting a possible causal relationship between the risk and exposure. In addition, the increase in seizure-inducing propensity of SSRI and SNRIs was less pronounced compared with those in the 3 large-scale population-based cohort studies in England,[8–10] likely due to the exclusion of individuals with major neurologic comorbidities and the use of self-controlled design in which the time-invariant unmeasured confounders were eliminated. Understandably, if people with vulnerable concomitant physical conditions were included, as often

occurs in real-world situations, the seizure risks could have been higher. Overall, the current finding was of significant clinical import because it provided empiric information about the magnitude of the seizure-inducing propensity of the new-generation antidepressants to assist clinicians in making their choice while prescribing the antidepressants.

Neurophysiologically, mechanisms responsible for such associations between SSRIs/SNRIs and seizure remain unclear. Several SSRIs are inhibitors of G-protein–activated inwardly rectifying potassium (GIRK) channels.[18] Because GIRK channels normally inhibit neuronal excitability, the inhibition of these channels can increase neural excitability and lower seizure threshold.[18] In addition, hyponatremia, a precipitating factor of seizure,[19] might occur more frequently with the use of SSRIs/SNRIs and play a role in modifying the relationship between seizure and antidepressant use.[8,20]

Some, but not all, antidepressants in the current study demonstrated a dose-response association pattern between antidepressant exposure and induced seizure. For example, bupropion was found to have increased risk of seizure when the dose was above the recommended maximal dose,[21] whereas in the particular case of TCAs the findings were much less consistent.[8,9,22,23] Such discrepancies might be the result of different dosing strategies across the studies[24] and might have accounted for the lack of associations between TCA exposure and increased seizure risk in the current study—indeed, the majority of the TCA prescriptions in the current study were lower than 0.5 DDD (see Supplementary eTable 1), at the far lower end of the dose-response curve, and hence curtailed the possibility of finding an association. Notwithstanding such findings, clinicians should still err on the safe side and assume that TCAs could pose greater seizure risks at higher dosages, as the ORs did become higher as the dosage increased and the literature abounded in cases of seizure induced by TCA overdose.

Among the individual antidepressants, mirtazapine warrants some attention because it is increasingly prescribed for its sleep-inducing effect, substituting trazodone. In premarketing trials, mirtazapine was shown to have very low incidence of seizure,[25] and 3 recent large-scale observational studies showed that the increase in seizure risk associated with mirtazapine did not reach statistical significance.[8–10] However, several anecdotal case reports did suggest that mirtazapine might induce seizure or epileptiform EEG.[26,27] Although epileptiform EEG findings were not equivalents to clinical seizures, the dose-related increase in seizure-inducing risk of mirtazapine demonstrated by the current study did suggest that extra caution should be exercised with the usage of high doses of mirtazapine.

Among the modifying factors, age and type of depression had significant interactions with the risk of antidepressant-related seizures, with the age group of 25 to 44 and patients diagnosed with major depression at particularly increased risk. Although the nature of such associations was not specifically explored, age group difference has been reported and might partially explain the discrepancies from recent cohort studies.[8,10] For example, TCAs and trazodone were associated with increased seizure risks in young or middle-aged adults[10] but not in older adults.[8] Our findings showed a similar age-related trend (see Supplementary eTable 2). In addition, clinicians might prescribe higher doses of antidepressants for more severe cases of depression; hence, the higher seizure risk among patients with major depression. Alternatively, the severity of depression might have determined the dose-response relationship between antidepressant and seizure risk, wherein patients who took higher doses of antidepressants had higher risks of seizure only because they were naturally more prone to seizures. However, this was unlikely because large variations in seizure risks across different antidepressants reflected the epileptogenic effect of individual antidepressants, rather than differences in the severity of depression.

Limitations

The current study has several limitations. First, the accuracy of the diagnosis of new-onset seizure was limited by the nature of the NHIRD. Psychogenic seizures might also be misdiagnosed as genuine seizures, leading to overestimation of seizure risks from antidepressant use. However, there is no evidence that such a misdiagnosis occurred only with specific antidepressants. It was thus unlikely that misdiagnosis led to spurious associations.

Second, although we used a case-crossover study design to eliminate time-invariant confounders and controlled for time-variant concomitant medications, there were still unmeasured confounding factors that could have influenced the current results. For example, the withdrawal status of alcohol or sedative medication might increase seizure risk and confound our findings. However, use of alcohol or sedatives was more likely to be concomitant with depressive episodes and hence antidepressant use. Therefore, withdrawal status was less likely to occur during periods of antidepressant use.

Third, there might be concerns that the case-crossover design, which is based on the assumption of short-term exposure, would not be applicable when the course of antidepressant treatment is recommended for at least 6 months. We examined the pattern of use in Taiwan and found that less than 20% of patients continued antidepressant treatment up to 6 months. Such common early termination and interruption of antidepressant therapy rendered the issue with short-term exposure less controversial.[28] Furthermore, our sensitivity analyses examined the issue of prolonged exposure in case-crossover design by lengthening the exposure assessment windows,[29] and the results were consistent when patients with prolonged regular use were excluded.

Finally, our results may or may not be generalizable to contexts outside of Taiwan. The high prevalence of slow metabolizers of antidepressant drugs in Taiwan might influence the estimate of seizure risk.[30] In addition, our study was conducted among patients with depressive disorder. The results might not be generalizable to antidepressant use for other psychiatric disorders, such as anxiety disorder or obsessive-compulsive disorder.

CONCLUSION

The current study demonstrated that SSRIs, SNRIs, bupropion, and mirtazapine were associated with increased seizure risks, probably in a dose-dependent manner. Although the cumulative seizure rate was only 0.68% (10,002/1,469,693) in a mean follow-up period of 5.4 years, the induced seizure may result in severe health consequences. Such findings highlighted the importance of taking into consideration factors associated with increased vulnerability to seizure (eg, young age and higher doses), and the dose-dependent increase in seizure risk, when choosing among types and dosages of antidepressant. The current findings can improve clinical practice by providing evidence-based information to supplement the current knowledge base derived mainly from product information or anecdotal case reports.

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Additional information: Information on the National Health Insurance Research Database can be found at http://nhird.nhri.org.tw/en/index.htm. The data are managed and supervised by the Bureau of National Health Insurance (BNHI). They can only be accessed by local researchers, and utilization of NHI data is only allowed at specific computer sites designated by the BNHI.

Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Seizure Risk Associated With Antidepressant Treatment Among Patients With Depressive Disorders: A Population-Based Case-Crossover Study

Authors: Chi-Shin Wu, MD, PhD; Hsin-Yen Liu, BS; Hui-Ju Tsai, MPH, PhD; and Shi-Kai Liu, MD

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12. **eTable 7** Stratified Analyses for Seizure Risk With Antidepressant Use, by the ICD-9-CM Diagnostic Code

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eAppendix 1. Calculation for average defined daily dose

We used the Defined Daily Dose (DDD), "the assumed average maintenance dose per day for a drug used for its main indication in adults," to calculate standardized antidepressant daily doses. We first calculated the cumulative dose by multiplying the tablet size in DDD by the number of tablets prescribed per day and the duration of drug supply within the case or control period. The average daily dose was then calculated by dividing the cumulative dose by the number of exposed days during the case or control period. If there were two or more prescriptions, the cumulative doses and durations were summed up; however, overlapped days were counted only once.

For example, based on the WHO's survey, the average maintenance dosage of fluoxetine is 20 mg. If a patient receives 40 mg of fluoxetine per day for major depressive disorder, the average daily dose will be 2 (40/20) DDD per day. If there are two prescriptions of fluoxetine in the case period, one with a total of 1 DDD per day for 14 days and the other 2 DDD per day for 21 days with a 7-day overlapping period, the average daily dose will then be calculated by (1*14 + 2*21) DDD/ (14+21-7) days= 2 DDD per day.

eAppendix 2. Details of Concomitant Medications

Antipsychotics	amisulpride, aripiprazole, chlorpromazine, chlorprothixene, clothiapine, clozapine, flupentixol, haloperidol, olanzapine, paliperidone, perphenazine, prochlorperazine, thioridazine, trifluoperazine, quetiapine, risperidone, sulpiride, ziprasidone, and zotepine
Benzodiazepine	alprazolam, bromazepam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, fludiazepam, flunitrazepam, flurazepam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordazepam, oxazepam, oxazolam, triazolam, zaleplon, zolpidem, and zopiclone.
Mood-stabilizing antiepileptic agents	carbamazepine, valproic acid, and lamotrigine
Anticholinergic agents	atropine, benzhexol, benzatropine, biperiden, cyclopentolate, scopolamine, and trihexyphenidyl
Analgesics	alfentanil, morphine, pentazocine, pethidine, meperidine, dextropropoxyphene, propoxyphene, and tramadol
Antiasthmatics	salbutamol, terbutaline, and theophylline
Antibacterials	cefalosporins, erythromycin, gentamicin, fluoroquinolones, nalidixic acid, and penicillins
Antihistamines	astemizole, brompheniramine, chlorphenamine, diphenhydramine, hydroxyzine, pheniramine, and terfenadine

eAppendix 3. Sensitivity analyses

To test the robustness of the results of the primary analyses, we conducted serial follow-up sensitivity analyses.

First, we computed odds ratios using different time windows, set at 15 days (i.e., 1-15 days and 91-105 days prior to the index date, for the case and control periods, respectively) and 60 days (i.e., 1-60 days and 91-150 days prior to the index date, for the case and control periods, respectively). The use of different time windows could address the issue that the ideal length of a time window for drug exposure is unknown and could be different for each drug.[1] The results were shown in supplementary eTable 3.

Second, since case-crossover design could be vulnerable to changes in exposure prevalence over time,[2] we applied the case-case-time-control design to the same study sample, [3] In this design, we first estimated the odds ratio for exposure trend using correspondent "case" period as 181-210 days prior to the index date and correspondent "control" period as 271-300 days prior to the index date; both periods were assumed to be representative of the trend of antidepressant exposure but unrelated to the onset of seizure. We then calculated the "actual" effect of antidepressant on seizure risk by dividing the odds ratios from index case and control periods by those from corresponding "case" and "control" periods in the case-case-time-control design. Such practice could eliminate the exposure trend bias to provide better estimates of the odds ratio for the actual effect of antidepressant use on seizure risk (Supplementary Figure 2). The results were demonstrated in supplementary eTable 4.

Third, in order to meet the requirement of a short-term exposure in case-crossover design, we restricted the analysis to patients with new or intermittent antidepressant use and excluded patients with long-term regular antidepressant treatment, as defined by a medication possession ratio (MPR) of >0·8 (MPR was calculated by summing the days' supply from all antidepressant prescriptions within the one-year period prior to the index day, and then dividing the sum by 365 days). The results were revealed in supplementary eTable 5.

Fourth, we excluded those with drug overdose to obtain the seizure risk of normal antidepressant use. The results were revealed in supplementary eTable 6.

Finally, there are no specific ICD-9 codes for drug-induced seizure, the clinicians need to rely on proxy codes to indicate this condition, including convulsion (ICD-9-CM: 780.3) or epilepsy (ICD-9 code: 345). However, the diagnostic code of epilepsy might imply there are pre-existing seizures. Although we included incident case only, there might be possibilities that subjects had previous convulsions or seizures and they were recognized but not formally registered. In that case, the clinicians will be inclined to avoid the use of antidepressants commonly recognized to have higher seizure-inducing property, such as buproprion, as well as higher dosages for certain antidepressants, especially TCAs. This might lead to under-estimation of the actual seizure risks. We found there was 5020 diagnosed with epilepsy and 4982 cases with convulsion. We conduct stratified analyses for the potential difference in these two groups. The results were demonstrated in supplementary eTable 7.

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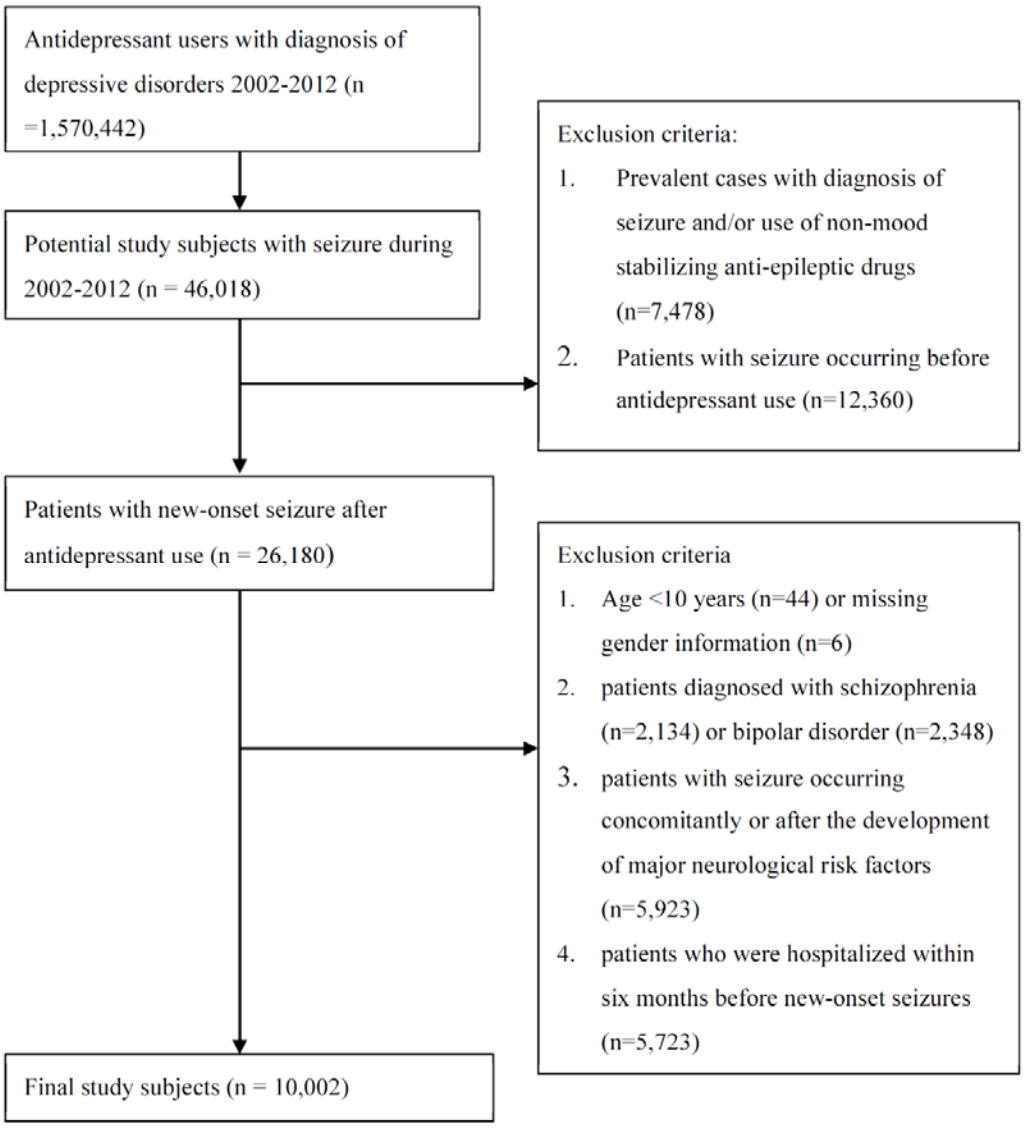
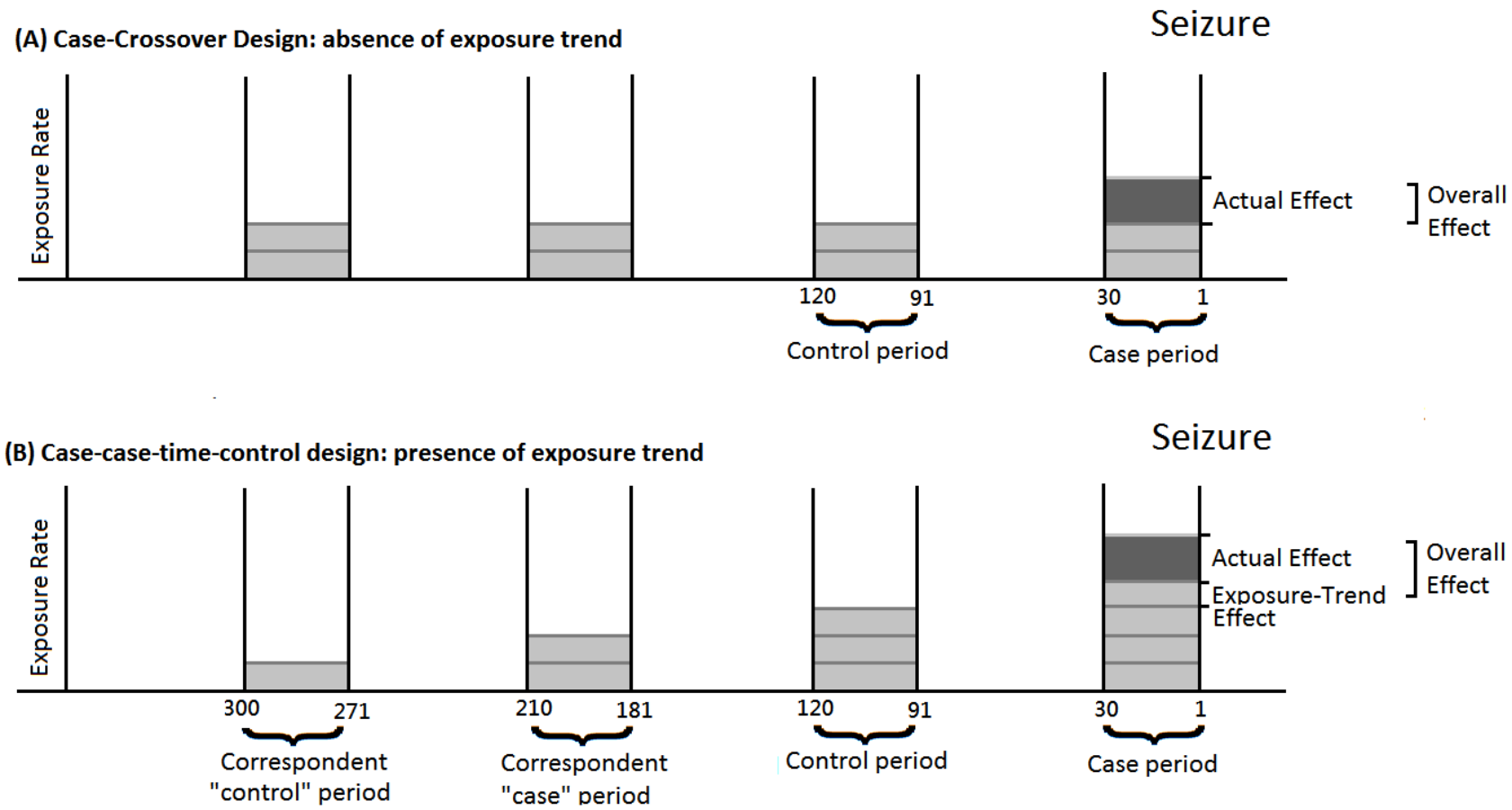
eFigure 1. Flow chart of the dataset of patients with new-onset seizure after antidepressant use from the National Health Insurance Research Database



eFigure 2. Case-crossover and case-case-time-control design



eTable 1. Number of prescriptions, length of drug supply, and daily dose for antidepressant prescription

Antidepressant classes	Number (%)	Length of drug supply (days)			Daily dose (DDD)		
		Mean ± S.D	Median	(IQR: 25th - 75th)	Mean ± S.D	Median	(IQR: 25th - 75th)
TCAs	11507 (20·9)	18·3 ± 10·1	14	(7 - 28)	0·6 ± 0·4	0·50	(0·25 - 1·00)
SSRIs	20389 (37·0)	21·2 ± 8·9	28	(14 - 28)	1·2 ± 0·6	1·00	(1·00 - 1·00)
SNRIs	4010 (7·3)	21·4 ± 8·6	28	(14 - 28)	1·0 ± 0·6	0·75	(0·75 - 1·50)
Others	19195 (34·8)	21·6 ± 8·8	28	(14 - 28)	0·5 ± 0·2	0·33	(0·17 - 0·50)
Individual antidepressant							
TCAs							
Amitriptyline	1897 (3·4)	16·9 ± 11·0	14	(3 - 28)	0·5 ± 0·4	0·33	(0·33 - 0·67)
Clomipramine	161 (0·3)	17·9 ± 7·5	14	(14 - 28)	0·7 ± 0·3	0·75	(0·50 - 0·75)
Dothiepin	53 (0·1)	21·6 ± 9·2	28	(14 - 28)	0·3 ± 0·2	0·33	(0·17 - 0·50)
Doxepin	1412 (2·6)	18·7 ± 10·0	21	(7 - 28)	0·3 ± 0·3	0·11	(0·25 - 0·50)
Imipramine	3621 (6·6)	18·1 ± 10·2	14	(7 - 28)	0·4 ± 0·3	0·25	(0·25 - 0·50)
Maprotiline	347 (0·6)	22·4 ± 8·1	28	(14 - 28)	0·5 ± 0·3	0·50	(0·25 - 0·75)
Melitracen/Flupentixol	4016 (7·3)	18·6 ± 9·7	14	(10 - 28)	0·9 ± 0·4	1·00	(0·50 - 1·00)
SSRIs							
Citalopram	2542 (4·6)	19·6 ± 8·8	21	(14 - 28)	1·2 ± 0·5	1·00	(1·00 - 1·25)
Escitalopram	2351 (4·3)	21·9 ± 8·1	28	(14 - 28)	1·0 ± 0·4	1·00	(1·00 - 1·00)
Fluoxetine	6133 (11·1)	20·9 ± 9·4	28	(14 - 28)	1·3 ± 0·8	1·00	(1·00 - 1·00)
Fluvoxamine	1108 (2·0)	19·9 ± 9·5	21	(14 - 28)	1·0 ± 0·7	0·50	(1·00 - 1·00)
Paroxetine	3183 (5·8)	21·9 ± 8·7	28	(14 - 28)	1·1 ± 0·5	1·00	(1·00 - 1·00)
Sertraline	5072 (9·2)	21·7 ± 8·4	28	(14 - 28)	1·1 ± 0·5	1·00	(1·00 - 1·00)
SNRIs							
Duloxetine	817 (1·5)	22·5 ± 7·8	28	(14 - 28)	0·9 ± 0·4	1·00	(0·50 - 1·00)
Milnacipran	165 (0·3)	18·0 ± 9·3	14	(7 - 28)	0·8 ± 0·5	0·50	(0·50 - 1·00)
Venlafaxine	3028 (5·5)	21·3 ± 8·7	28	(14 - 28)	1·1 ± 0·6	0·75	(0·75 - 1·50)
Others							
Mirtazapine	3365 (6·1)	21·9 ± 8·5	28	(14 - 28)	1·1 ± 0·4	1·00	(1·00 - 1·00)
Bupropion	1330 (2·4)	22·6 ± 8·0	28	(14 - 28)	0·7 ± 0·3	0·50	(0·50 - 1·00)
Moclobemide	1016 (1·8)	22·8 ± 9·5	28	(14 - 28)	1·0 ± 0·4	1·00	(0·50 - 1·00)

Trazodone	13484 (24·5)	21·3 ± 8·8	28	(14 - 28)	0·3 ± 0·2	0·17	(0·17 - 0·33)

Abbreviation: TCAs= tricyclic or tetracyclic antidepressants; SSRIs= selective serotonin reuptake inhibitors; SARIs= serotonin antagonist and reuptake inhibitors; SNRIs= serotonin-norepinephrine reuptake inhibitors; NaSSAs= noradrenergic and specific serotonergic antidepressants; RIMAs= reversible inhibitor of monoamine oxidase A; and NRDIs= norepinephrine dopamine reuptake inhibitors; DDD=defined daily dose

a Doses of antidepressant per 1 DDD: amitriptyline 75mg, clomipramine 100mg, dothiepin 150mg, doxepin 100mg, imipramine 100mg, maprotiline 100mg, melitracen/flupentixol 10/0·5mg, citalopram 20mg , escitalopram 10mg, fluoxetine 20mg, fluvoxamine 100mg, paroxetine 20mg, sertraline 50mg, duloxetine 60mg, milnacipran 100mg, venlafaxine 100mg, mirtazapine 30mg, bupropion 300mg, moclobemide 300mg, trazodone 300mg

eTable 2. Subgroup Analyses for Seizure Risk with Antidepressant Use, by Age Groups

	Age 10-24		Age 25-44		Age 45-64		Age ≥ 65		
	Adjusted OR[a] (95% CI)		Adjusted OR[a] (95% CI)		Adjusted OR[a] (95% CI)		Adjusted OR[a] (95% CI)		p-interaction
Antidepressant use	2·59	(1·76-3·82)	1·42	(1·17-1·72)	1·43	(1·18-1·74)	1·25	(1·03-1·51)	<·001
Classes of Antidepressant									
TCAs	1·47	(0·72-2·98)	1·08	(0·82-1·42)	1·22	(0·91-1·61)	0·85	(0·65-1·12)	0·099
SSRIs	2·19	(1·43-3·36)	1·70	(1·37-2·12)	1·65	(1·30-2·09)	1·66	(1·29-2·14)	0·056
SNRIs	1·51	(0·73-3·12)	1·29	(0·85-1·94)	1·32	(0·85-2·04)	1·55	(0·92-2·61)	0·940
Mirtazapine	1·97	(0·80-4·85)	1·42	(0·99-2·06)	1·03	(0·66-1·61)	2·29	(1·16-4·51)	0·933
Bupropion	4·19	(1·75-10·03)	3·29	(1·87-5·79)	0·54	(0·22-1·32)	1·54	(0·70-3·43)	0·008
Moclobemide	N/A	(0·00-0·00)	1·41	(0·58-3·43)	0·37	(0·14-0·97)	2·06	(0·79-5·39)	0·784
Trazodone	1·68	(0·93-3·06)	0·93	(0·73-1·17)	1·18	(0·89-1·56)	1·11	(0·79-1·55)	0·947

Abbreviation: TCAs= tricyclic or tetracyclic antidepressants; SSRIs= selective serotonin reuptake inhibitors; SNRIs= serotonin-norepinephrine reuptake inhibitors; DDD=defined daily dose

a Calculated by multivariate conditional logistic regression with adjustment for antipsychotics, benzodiazepine, mood stabilizer, anticholinergic agents, analgesics, antiasthmatics, antibacterials, and antihistamines.

eTable 3. Sensitivity Analysis for Seizure Risk with Antidepressant Use, by Time-Windows

	15-day time windows		30-day time windows		60-day time windows	
	Adjusted OR[a] (95% CI)		Adjusted OR[a] (95% CI)		Adjusted OR[a] (95% CI)	
Antidepressant use	1·40	(1·26-1·56)	1·48	(1·33-1·64)	1·61	(1·45-1·79)
Classes of Antidepressant						
TCAs	1·06	(0·91-1·25)	1·07	(0·91-1·25)	1·18	(1·02-1·36)
SSRIs	1·63	(1·43-1·86)	1·76	(1·55-2·00)	1·82	(1·60-2·07)
SNRIs	1·24	(0·97-1·59)	1·40	(1·10-1·78)	1·48	(1·16-1·88)
Mirtazapine	1·59	(1·22-2·06)	1·38	(1·08-1·77)	1·24	(0·97-1·57)
Bupropion	2·13	(1·49-3·03)	2·23	(1·58-3·16)	2·16	(1·53-3·05)
Moclobemide	1·16	(0·71-1·91)	1·18	(0·72-1·93)	1·38	(0·87-2·19)
Trazodone	1·06	(0·91-1·24)	1·08	(0·93-1·25)	1·14	(0·98-1·32)

Abbreviation: TCAs= tricyclic or tetracyclic antidepressants; SSRIs= selective serotonin reuptake inhibitors; SNRIs= serotonin-norepinephrine reuptake inhibitors

a Calculated by multivariate conditional logistic regression with adjustment for antipsychotics, benzodiazepine, mood stabilizer, anticholinergic agents, and number of outpatient visits

eTable 4. Sensitivity Analysis for Seizure Risk with Antidepressant Use, by Case-Case-Time-Control Design

	Case-crossover		Effect of Exposure-Trend		Case-Case Time-Controls	
	Adjusted OR[a] (95% CI)		Adjusted OR[a] (95% CI)		Adjusted OR[a] (95% CI)	
Overall antidepressant	1·48	(1·33-1·64)	1·08	(0·97-1·20)	1·37	(1·17-1·59)
Classes of Antidepressant						
TCAs	1·07	(0·91-1·25)	0·97	(0·82-1·14)	1·10	(0·88-1·38)
SSRIs	1·76	(1·55-2·00)	1·12	(0·97-1·28)	1·57	(1·30-1·90)
SNRIs	1·40	(1·10-1·78)	0·84	(0·62-1·13)	1·67	(1·14-2·45)
Mirtazapine	1·38	(1·08-1·77)	1·26	(0·94-1·68)	1·10	(0·75-1·61)
Bupropion	2·23	(1·58-3·16)	1·37	(0·89-2·10)	1·64	(0·94-2·85)
Moclobemide	1·18	(0·72-1·93)	1·01	(0·60-1·68)	1·17	(0·58-2·39)
Trazodone	1·08	(0·93-1·25)	1·07	(0·91-1·27)	1·00	(0·80-1·26)

Abbreviation: TCAs= tricyclic or tetracyclic antidepressants; SSRIs= selective serotonin reuptake inhibitors; SNRIs= serotonin-norepinephrine reuptake inhibitors

a Calculated by multivariate conditional logistic regression with adjustment for antipsychotics, benzodiazepine, mood stabilizer, anticholinergic agents, and number of outpatient visits

eTable 5. Seizure Risk with Antidepressant Use, among Patients with New or Intermittent Users (medication possession ratio ≤0·8; n=9010)

	Adjusted OR[a] (95% CI)	
Overall Antidepressant	1·50	(1·35-1·67)
Classes of Antidepressant		
TCAs	1·03	(0·87-1·21)
SSRIs	1·85	(1·62-2·12)
SNRIs	1·45	(1·12-1·89)
Mirtazapine	1·30	(0·99-1·70)
Bupropion	2·39	(1·62-3·52)
Moclobemide	1·16	(0·69-1·96)
Trazodone	1·15	(0·98-1·36)

Abbreviation: TCAs= tricyclic or tetracyclic antidepressants; SSRIs= selective serotonin reuptake inhibitors; SNRIs= serotonin-norepinephrine reuptake inhibitors

a Calculated by multivariate conditional logistic regression with adjustment for antipsychotics, benzodiazepine, mood stabilizer, anticholinergic agents, and number of outpatient visits

eTable 6. Seizure Risk with Antidepressant Use, excluding Patients with Drug Overdose (n=9794)

	Use only in case period	Use only in control period	Adjusted OR[a] 95% CI
Overall antidepressant	1081	698	1.37 (1.23-1.52)
TCAs	370	314	1.04 (0.89-1.21)
SSRIs	733	401	1.65 (1.45-1.88)
SNRIs	159	118	1.28 (1.00-1.64)
Others			
Mirtazapine	161	108	1.34 (1.04-1.72)
Bupropion	100	45	2.18 (1.52-3.12)
Moclobemide	33	29	0.96 (0.58-1.61)
Trazodone	405	323	1.05 (0.90-1.23)

Abbreviation: TCAs= tricyclic or tetracyclic antidepressants; SSRIs= selective serotonin reuptake inhibitors; SNRIs= serotonin-norepinephrine reuptake inhibitors

a Calculated by multivariate conditional logistic regression with adjustment for antipsychotics, benzodiazepine, mood stabilizer, anticholinergic agents, analgesics, antiasthmatics, antibacterials, and antihistamines.

eTable 7. Stratified Analyses for Seizure Risk with Antidepressant Use, by the ICD-9-CM Diagnostic Code

	Outcome diagnosed as new-diagnosed epilepsy (ICD-9-CM: 345) (n=5020)	Outcome diagnosed as new-diagnosed convulsion (ICD-9-CM: 780.3) (n=4982)	
	Adjusted OR[a] (95% CI)	Adjusted OR[a] (95% CI)	P-difference
Overall antidepressant use	1.48 (1.28-1.72)	1.48 (1.28-1.72)	0.859
Classes of Antidepressant			
TCAs	0.93 (0.75-1.17)	1.20 (0.97-1.49)	0.113
SSRIs	1.72 (1.44-2.07)	1.81 (1.51-2.17)	0.877
SNRIs	1.12 (0.79-1.58)	1.72 (1.23-2.41)	0.100
Mirtazapine	1.56 (1.10-2.23)	1.20 (0.85-1.70)	0.280
Bupropion	2.18 (1.34-3.55)	2.33 (1.42-3.85)	0.910
Moclobemide	1.47 (0.73-2.99)	0.93 (0.47-1.86)	0.395
Trazodone	1.17 (0.94-1.45)	1.01 (0.81-1.25)	0.294

Abbreviation: TCAs= tricyclic or tetracyclic antidepressants; SSRIs= selective serotonin reuptake inhibitors; SNRIs= serotonin-norepinephrine reuptake inhibitors

a Calculated by multivariate conditional logistic regression with adjustment for antipsychotics, benzodiazepine, mood stabilizer, anticholinergic agents, analgesics, antiasthmatics, antibacterials, and antihistamines.