THE JOURNAL OF CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

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

DOI Number: 10.4088/JCP.16m11377

List of Supplementary Material for the article

1. **eAppendix 1** Calculation for Average Defined Daily Dose
2. **eAppendix 2** Details of Concomitant Medications
3. **eAppendix 3** Sensitivity Analyses
4. **eFigure 1** Flow Chart of the Dataset of Patients With New-Onset Seizure After Antidepressant Use From the National Health Insurance Research Database
5. **eFigure 2** Case-Crossover and Case-Case-Time-Control Design
6. **eTable 1** Number of Prescriptions, Length of Drug Supply, and Daily Dose for Antidepressant Prescription
7. **eTable 2** Subgroup Analyses for Seizure Risk with Antidepressant Use, by Age Groups
8. **eTable 3** Sensitivity Analysis for Seizure Risk with Antidepressant Use, by Time-Windows
9. **eTable 4** Sensitivity Analysis for Seizure Risk with Antidepressant Use, by Case-Case-Time-Control Design
10. **eTable 5** Seizure Risk With Antidepressant Use, Among Patients With New Or Intermittent Use (medication possession ratio ≤0·8; n=9,010)
11. **eTable 6** Seizure Risk With Antidepressant Use, Excluding Patients With Drug Overdose (n=9794)

THE JOURNAL OF CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

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

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

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.

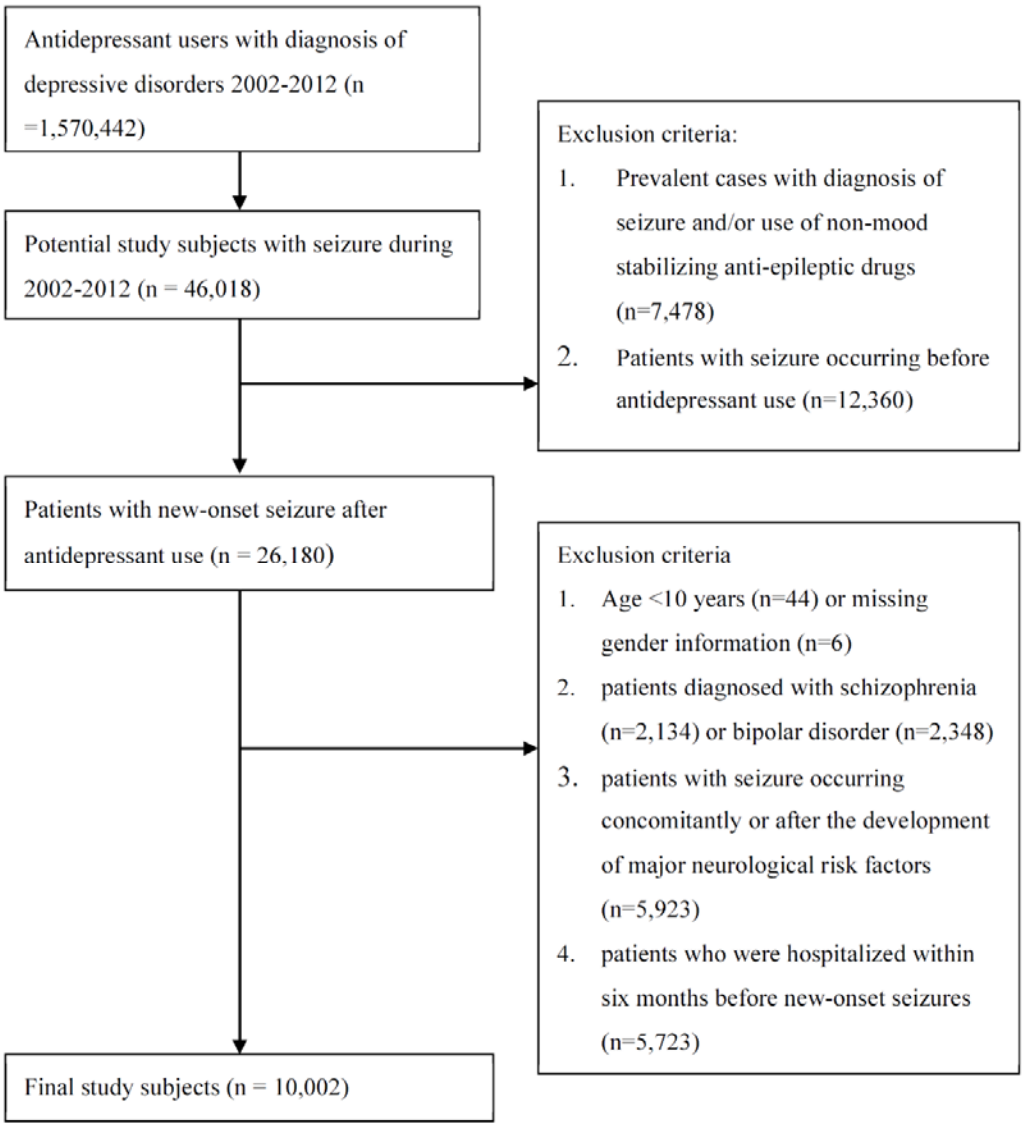
Third, in order to meet the requirement of a short-term exposure in case-crossover design, we restricted the analysis to patients with new or intermittent antidepressant use and excluded patients with long-term regular antidepressant treatment, as defined by a medication possession ratio (MPR) of >0·8 (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.

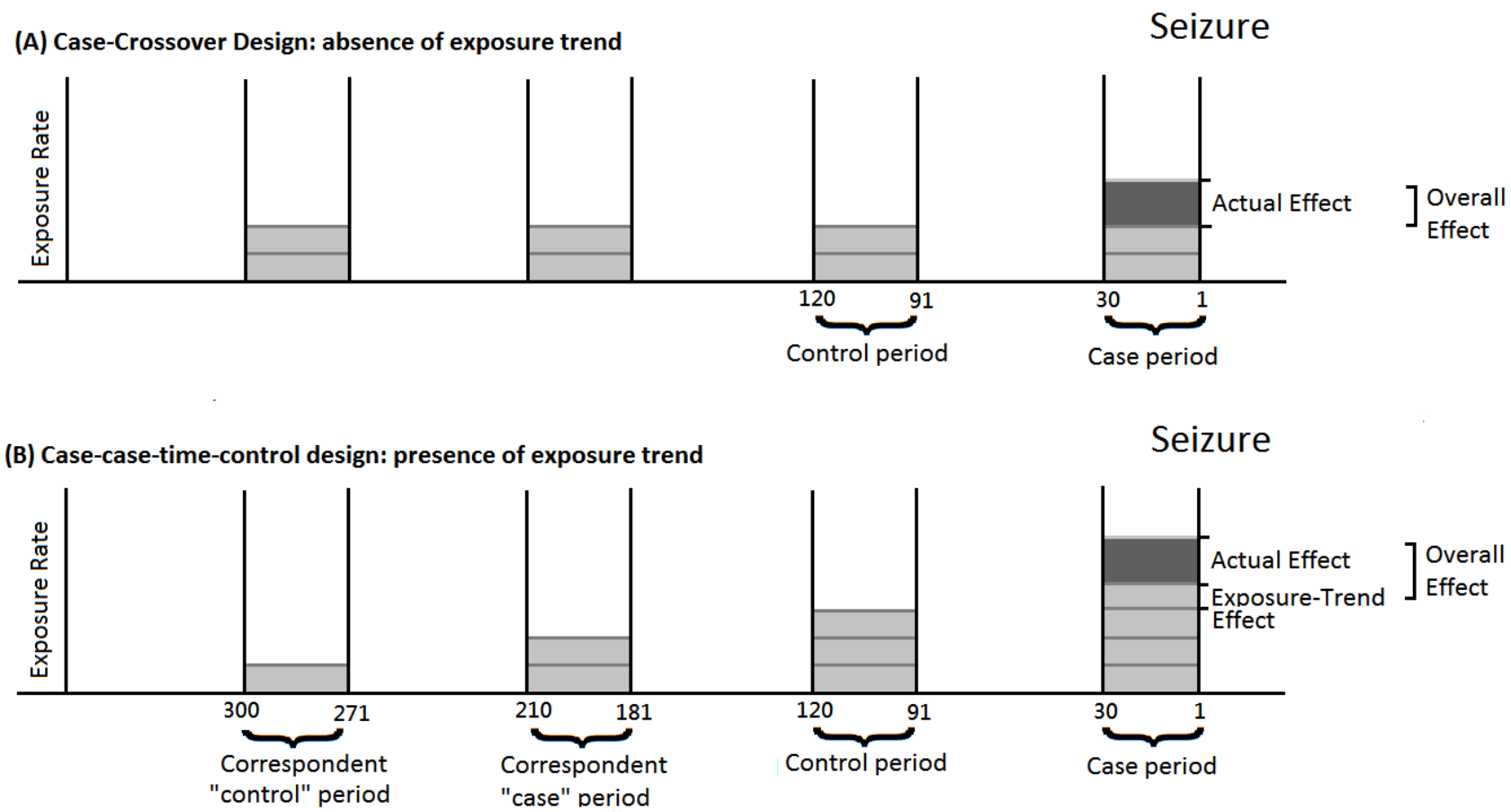
Finally, there are no specific ICD-9 codes for drug-induced seizure, the clinicians need to rely on proxy codes to indicate this condition, including convulsion (ICD-9-CM: 780.3) or epilepsy (ICD-9 code: 345). However, the diagnostic code of epilepsy might imply there are pre-existing seizures. Although 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.

1. Delaney JA, Suissa S. The case-crossover study design in pharmacoepidemiology. *Statistical methods in medical research.* 2009;18(1):53-65.
2. Schneeweiss S, Sturmer T, Maclure M. Case-crossover and case-time-control designs as alternatives in pharmacoepidemiologic research. *Pharmacoepidemiol Drug Saf.* 1997;6 Suppl 3:S51-59.
3. Wang SV, Gagne JJ, Glynn RJ, Schneeweiss S. Case-crossover studies of therapeutics: design approaches to addressing time-varying prognosis in elderly populations. *Epidemiology.* 2013;24(3):375-378.

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.