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REVIEW

Antidepressant use and the risk of seizure: a meta-analysis of observational studies

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Abstract

Purpose The association between antidepressant use and the risk of seizures remains controversial. Therefore, this meta-analysis examined whether antidepressant use affects the risk of seizures.

Methods To identify relevant observational studies, we conducted systematic searches in PubMed and Embase of studies published through May 2023. Random-effects models were used to estimate overall relative risk.

Results Our meta-analysis included eight studies involving 1,709,878 individuals. Our results showed that selective serotonin reuptake inhibitors (SSRI) (odds ratio [OR] 1.48, 95% confidence interval [CI] 1.32–1.66; $P<0.001$) and selective noradrenalin reuptake inhibitors (SNRI) (OR 1.65, 95% CI 1.24–2.19; $P=0.001$), but not tricyclic antidepressants (TCA) (OR 1.27, 95% CI 0.84–1.92; $P=0.249$), were associated with an increased risk of seizures. Subgroup analyses revealed an OR of 2.35 (95% CI 1.7, 3.24; $P<0.001$) among short-term (< 30 days) antidepressant users.

Conclusions The findings of this meta-analysis support an increased risk of seizures in new-generation antidepressant users, expanding previous knowledge by demonstrating a more pronounced risk in short-term users.

Keywords Depression · Psychiatry · Epilepsy · Epilepsia

Introduction

Antidepressants are widely used to treat diseases such as depression, anxiety, obsessive compulsive disorder, neuralgia, and restless legs syndrome [1]. Their use has increased five-fold over the past 20 years in the United States and approximately three-fold over the past 15 years across 25 European countries [2]. Although antidepressants are effective and generally well-tolerated, there are increasing reports of potential adverse effects of antidepressants, including bone fractures [3], metabolic syndrome [4], bleeding [5], and a possible increased risk of seizures.

Epilepsy, a neurological disorder characterized by random recurring seizures of varying intensity, affects approximately 1% of the global population [6]. It most commonly involves intense shaking or twitching and loss of consciousness; mild seizures can produce a brief moment of blank staring or temporary changes in behavior. Seizure is caused by many factors, among which drug use is a common external cause [7]. Several cases of antidepressant-associated seizure have been identified in patients on high oral doses [8–10]. However, the risk of seizure at therapeutic doses remains unclear. In a cohort study, Hill et al. [11] found that all classes of antidepressant exposure were associated with an increased risk of seizures in people aged 20 to 64 years. However, Coupland et al. [12] reported that this risk varied according to the type or time of antidepressant exposure; they subsequently showed that antidepressant use increases the risk of seizures, but the results were inconsistent in a subgroup analysis based on individual antidepressants. Because various factors associated with antidepressant exposure (i.e., exposure time, antidepressant type, and

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individual antidepressant) may differentially affect the risk of fracture, these factors must be analyzed separately.

Considering the widespread use of antidepressants, it is important to determine whether there is a relationship between antidepressant exposure and the risk of seizures. In this study, we conducted a systematic literature review and meta-analysis to assess this association.

Methods

Data sources and search strategy

This work followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [13]. We comprehensively searched the PubMed and EMBASE for relevant English-language publications from the dates of inception to May 2022. The search strategy, performed using Medical Subject Heading terms and the free keywords, comprised 3 groups of keywords: 1 group was about intervention (e.g., "antidepressant OR tricyclic OR TCA OR monoamine oxidase inhibitor OR MAOI OR selective serotonin reuptake inhibitor OR SSRI OR selective noradrenalin reuptake inhibitor OR SNRI"), 1 about outcome of seizure (eg, "epilepsy OR epilepsia OR epileptic OR epilepticus OR seizure OR epilepsy OR aura"), and 1 about study design (eg, "risk OR ratio OR epidemiologic OR observational OR observation OR case-control OR cohort"). The reference lists of retrieved articles were manually examined to detect reports not found in the database search.

Study selection

Studies were initially identified based on titles and abstracts, then subjected to full-text evaluation. Studies were considered eligible if they met the following criteria: (1) population: adults receiving antidepressant, with or without a formal psychiatric disorder diagnosis; (2) exposure: antidepressant use; (3) comparison: no treatment or low dose antidepressant treatment; (4) primary outcome: incidence of seizures; and (5) study design: randomized-controlled trials, case-crossover or self-controlled case series, and cohort, nested case-control, and case-control studies.

The exclusion criteria were (1) reviews, letters to the editor, or conference abstracts; (2) basic or animal experiments; (3) case reports and series; (4) lack of a control group; and (5) inability to isolate seizure-related data.

Data extraction and quality assessment

The following data were extracted: first author, publication year, study design, study location, ascertainment of antidepressant exposure, assessment of seizures, number of participants, follow-up year, statistical adjustments, and study quality. The most adjusted effect-size estimate was included in the analysis if more than one estimate was listed. The risk of bias in an individual study was evaluated by two independent reviewers; areas of disagreement were resolved by consensus. The methodological quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS) [14], as recommended by the Cochrane Collaboration for evaluation of observational study quality. A score of >7 points was considered an indicator of a high-quality study.

Outcome assessment

The primary outcome assessed was the risk of seizures during antidepressant use compared with no treatment. To test the robustness of the association and the influence of each study on our estimates, a sensitivity analysis was performed by omitting one study at a time. In an attempt to explain possible heterogeneity between studies, we performed subgroup analyses based on the study design (case-crossover, cohort, nested case-control, or case-control), antidepressant type (selective serotonin reuptake inhibitors [SSRI], serotonin and norepinephrine reuptake inhibitors [SNRI], and others), individual antidepressants, and the definition of the exposure window (within 30 days or after antidepressant use). Following the results of the subgroup analysis, we conducted meta-regression analyses.

Data synthesis and analysis

Data were analyzed using STATA ver. 13 (Stata Corp., College Station, TX, USA). Quantitative meta-analyses were conducted for outcomes reported in at least two eligible studies. Heterogeneity among studies was assessed using the χ^2 test and I^2 statistic; an I^2 value of 0–25% represents insignificant heterogeneity, 26–50% represents low heterogeneity, 51–75% represents moderate heterogeneity, and $>75\%$ represents severe heterogeneity [15]. The DeSimonian and Laird random-effects model was used when studies were heterogeneous; otherwise, the Mantel–Haenszel fixed-effects model was used. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the associations between antidepressant exposure and subsequent risk of seizures [16]. Splitting one study into several estimates leads to substantial more weight is assigned to this study in the meta-analysis, especially in random effects model. Thus, we explored fix effects model to generate a pooled OR if more than 3 estimates from one study are included, and then this pooled OR was used in the meta-analysis. Potential publication bias was assessed using funnel plots and quantified

with Egger's regression test [17, 18]. *P*-values < 0.05 were assumed to indicate statistical significance.

Results

Search results

The initial systematic literature search of two databases identified 3,704 articles. After the exclusion of 1,321 duplicates, the titles and abstracts of 2,383 studies were screened. 63 potentially eligible studies were retrieved for full-text review. 55 articles were excluded after the full-text review because they did not meet the inclusion criteria. Two British studies extracted data from the QResearch primary care database, with distinct age ranges for the individuals included. Furthermore, the remaining two British studies obtained data from two different data sources. Consequently, all four British studies were included in the current review. Two studies conducted in Taiwan were also included in this study because they had different study designs, although there was some overlap in terms of study period and participants. We performed a sensitivity analysis to assess the influence of each study on heterogeneity, and a summary estimate by excluding each of these studies from the same database one at a time. Ultimately, eight studies [11, 12, 19–24] satisfied the predetermined eligibility criteria. No related randomized controlled trials were identified. The selection process and exclusion justification are presented in Fig. 1.

Characteristics of the included studies

Table 1 presents the main characteristics of the studies included in the systematic review. The eight studies were published from 2011 to 2023, with sample sizes ranging from 4,325 to 1,317,532 individuals, for a total of 1,709,878

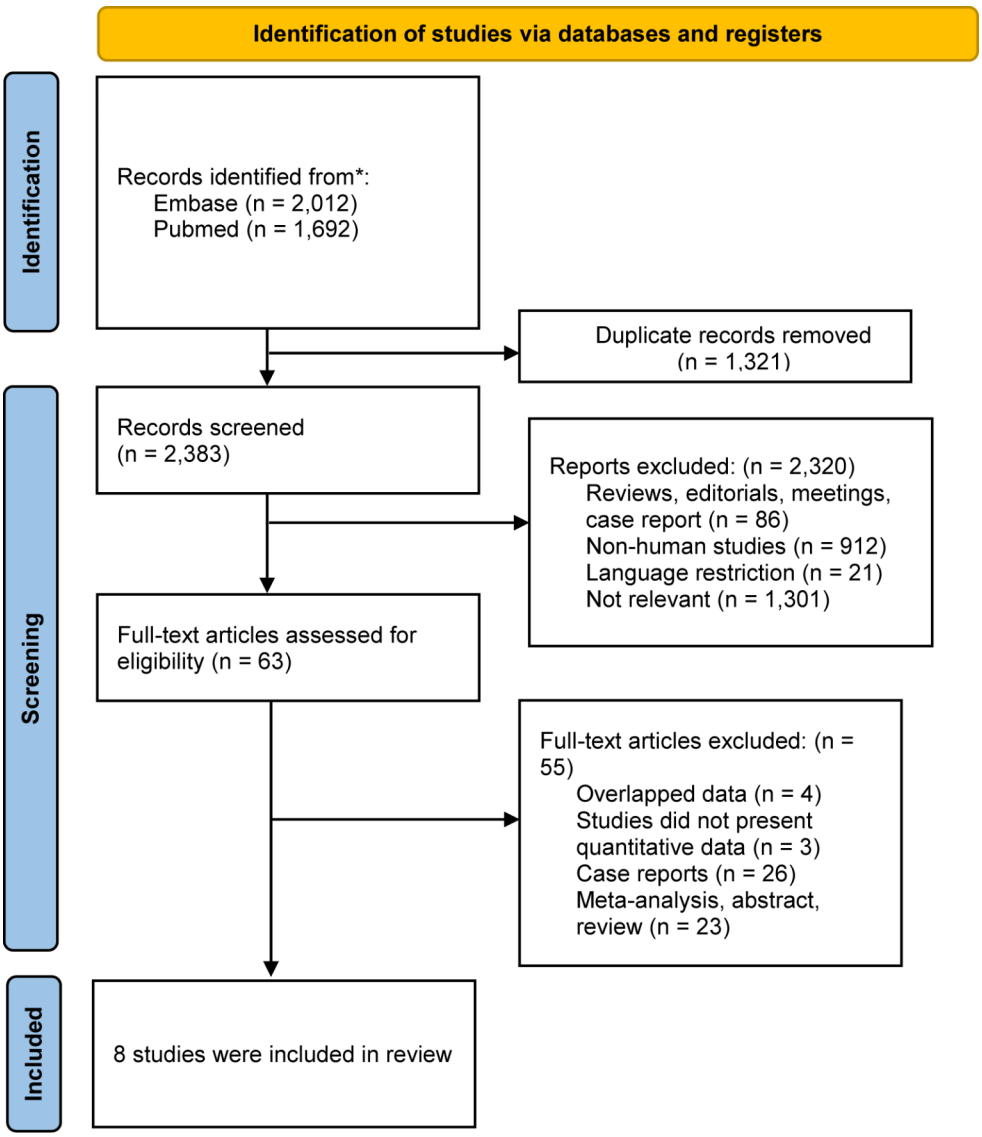

Fig. 1 Flow chart of the search process and study selection

Table 1 Characteristics of the included studies

Author, year	Location, setting	Study design/ period	Age	Ascertainment of antidepressant use	Epilepsy/ seizure assessment	Sample size	Duration of follow up (year)	Adjustment	NOS score
Coupland et al., 2011	UK, population-based	Cohort and case-cross-over/1996–2008	65–100 years diagnosed with depression	QResearch database	ICD-9/ICD-10	Total 59,793	1–12 years	Gender, age, year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, aspirin, antihypertensives, hypnotics/ anxiolytics	Cohort 8 Case-cross-over 9
Hill et al., 2015	UK, population-based	Cohort/2000–2012	20 to 64 years diagnosed with depression	QResearch database	ICD-9/ICD-10	Exposure 209,476 No-exposure 29,487	more than 5 years	Age at study entry, gender, year of index diagnosis of depression, severity of index diagnosis of depression, smoking status, alcohol intake and ethnicity categorised	Cohort 8 Case-cross-over 9
Bloechliger et al., 2016	UK, population-based	nested case–control/1998–2012	18 to 89 years diagnosed with depression	UK-based Clinical Practice Research Datalink	ICD-10	Case 619 Control 2,476	more than 3 years	Alcohol consumption, other antidepressant drugs, benzodiazepines, antipsychotics, opioids, schizophrenia, affective disorders other than depression, compulsive disorders, suicidal ideation, dementia, Parkinson's disease, transient ischemic attack, and stroke	8
Saez et al., 2016	UK, population-based	Nested case-control/2005–2013	20–84 years	The Health Improvement Network	Read codes	Case 8,605 Control 40,000	more than 2 years	Demographic characteristics, lifestyle factors, the most relevant comorbidity	7
Wu et al., 2017	Taiwan, population-based	Case-cross-over/2002–2012	> 10 years	Taiwan national Health Insurance Database	ICD-10	10,002 exposure	120 days	Antipsychotic,benzodiazepine, mood stabilizers, analgestic, anticholinergic agents, antiasthmatics, antibacterials, and antihistamines	9
Finkelstein et al., 2018	Canada, population-based	Case-control/2002–2015	> 65 years	Database	ICD-10	Case 5,701 Control 21,872	13 years	Age, sex, date and a seizure-specific disease risk index	8
Chu et al., 2023	Taiwan, population-based	Case-control/1998–2013	NA	Taiwan national Health Insurance Database	ICD-9-CM	Case 863 Control 3,452	3.53 years	Demographic data, Charlson Comorbidity Index score, physical comorbidities, and indications of antidepressant use	7
Wiggs et al., 2023	Sweden, population-based	Cohort and case-cross-over/2006–2013	12 to 65 years	Database	ICD-10	Exposure 658,766 No-exposure 658,766	more than 1 year	Mood and anxiety diagnoses	Cohort 6 Case-cross-over 8

patients. Among the eight studies, four were conducted in the UK [11, 12, 19, 20], two were conducted in Taiwan [21, 23], one was conducted in Canada [22], and one was conducted in Sweden [24]. The studies included two case-control studies [22, 23], two nested case-control studies [19, 20], one cohort study [11], and one case-crossover study [21]. The remaining two studies [12, 24] used case-crossover and cohort study designs. Three studies [11, 12, 19] selected exclusively depressive patients without antidepressant exposure as a control, one [22] enrolled patients with depression who were exposed to bupropion as a control, and one [23] enrolled patients with depression who were exposed to low-dose antidepressant as control. The overall NOS score was 51 of 63 (81%), which is considered representative of overall high quality; the details of the critical appraisal are provided in Tables S2 and S3.

Meta-analysis

Overall-analysis

A meta-analysis of all studies with 1,709,878 individuals revealed that antidepressant use significantly increased the risk of subsequent epilepsy (OR 1.59, 95% CI 1.39–1.83; $P < 0.001$), with high heterogeneity ($I^2 = 89.2\%$) (Fig. 2). As shown in Figure S1, there was no evidence of publication bias. Sensitivity analysis showed that the significance of the comprehensive effect did not significantly change after studies using the same data source were eliminated one by one.

Subgroup analysis

Table 2 presents the results of the subgroup analyses. The subgroup analyses according to study design showed significant associations for the case-crossover studies (OR 2.35, 95% CI 1.7–3.24; $P < 0.001$), cohort studies (OR 2.03, 95% CI 1.57–2.6; $P < 0.001$), nested case-control studies (OR 1.74, 95% CI 1.41–2.15; $P < 0.001$), and case-control

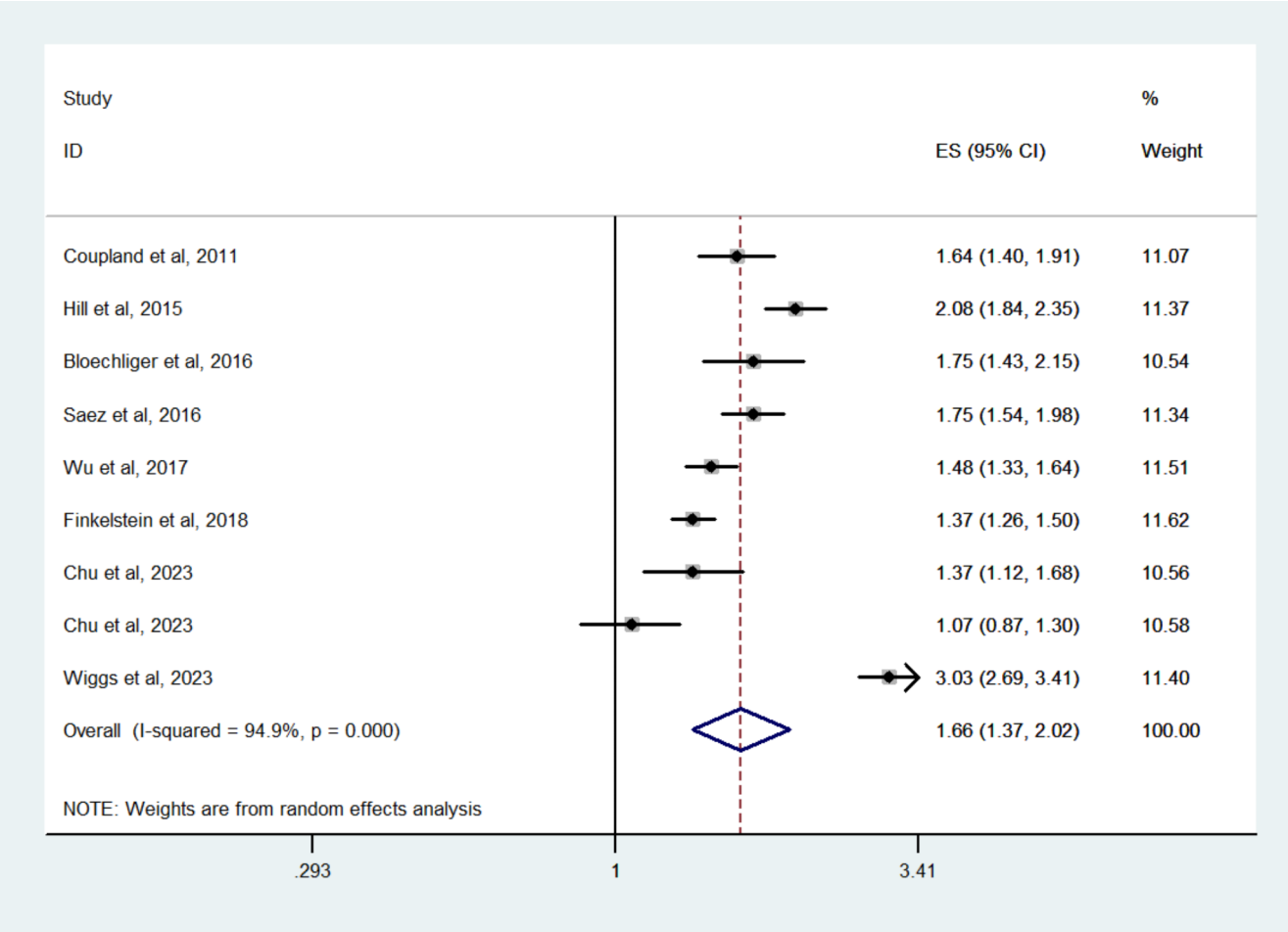

Fig. 2 Forest plot of the risk of seizure in relation to antidepressant exposure

Table 2 meta-analysis for studies included in this analysis

Analysis	No. of studies	Pooled OR (95% CI), I^2 statistics (%),	Model used
Overall analysis	8	1.66 (1.37–2.02); $I^2 = 94.9\%$	Random effects
Study design			
Case-crossover	4	2.35 (1.7–3.24); $I^2 = 89.3\%$	Random effects
Cohort	3	2.03 (1.57–2.6); $I^2 = 89.8\%$	Random effects
Nested case–control	2	1.74 (1.41–2.15); $I^2 = 88\%$	Random effects
Case–control	2	1.32 (1.15–1.51); $I^2 = 68.9\%$	Random effects
Type of antidepressant			
TCA	4	1.27 (0.84–1.92); $I^2 = 89.4\%$	Random effects
SSRI	6	1.48 (1.32–1.66); $I^2 = 70.4\%$	Random effects
SNRI	6	1.65 (1.24–2.19); $I^2 = 81.9\%$	Random effects
Others	4	1.77 (1.4–2.25); $I^2 = 38.3\%$	Random effects
Individual antidepressant			
Citalopram	6	1.62 (1.35–1.95); $I^2 = 61.9\%$	Random effects
Escitalopram	6	1.62 (1.39–1.9); $I^2 = 0\%$	Random effects
Fluoxetine	6	1.44 (1.2–1.73); $I^2 = 66.8\%$	Random effects
Paroxetine	6	1.56 (1.3–1.87); $I^2 = 32.6\%$	Random effects
Sertraline	6	1.76 (1.35–2.29); $I^2 = 74.8\%$	Random effects
Mirtazapine	5	1.48 (1.24–1.78); $I^2 = 0\%$	Random effects
Venlafaxine	6	1.88 (1.36–2.61); $I^2 = 81.6\%$	Random effects
Fluvoxamine	3	1.38 (1.03–1.83); $I^2 = 28.8\%$	Random effects
Amitriptyline	4	1.22 (0.75–1.98); $I^2 = 79.3\%$	Random effects
Dosulepin	3	0.86 (0.27–2.72); $I^2 = 86.9\%$	Random effects
Lofepramine	2	2.12 (0.96–4.69); $I^2 = 66.8\%$	Random effects
Trazodone	3	2.03 (0.67–6.13); $I^2 = 93\%$	Random effects
Duloxetine	2	0.97 (0.75–1.25); $I^2 = 0\%$	Random effects
Definition of exposure window			
Within 30 days	4	2.35 (1.7–3.24); $I^2 = 89.3\%$	Random effects
After antidepressant use	4	1.49 (1.26–1.76); $I^2 = 84.9\%$	Random effects

studies (OR 1.32, 95% CI 1.15–1.51; $P < 0.001$) (Figure S2).

In the analysis limited to five studies that enrolled controls, including depressive patients with or without exposure to low-dose antidepressants, who had an indication for antidepressant use; notably, a significant association was observed among patients using antidepressants (OR 1.53, 95% CI 1.34–1.74; $P < 0.001$) (Figure S3).

In the analysis limited to three studies that exclusively enrolled depressive patients, a positive relationship was observed among patients using antidepressants (OR 1.83, 95% CI 1.54–2.17; $P < 0.001$; Figure S3).

In subgroup analyses according to antidepressant type, significant associations were observed for the use of an SSRI (OR 1.48, 95% CI 1.32–1.66; $P < 0.001$, SNRI (OR 1.65, 95% CI 1.24–2.19; $P = 0.001$), or other antidepressant (OR 1.77, 95% CI 1.4–2.25; $P < 0.001$). However, the use of a TCA (OR 1.27, 95% CI 0.84–1.92; $P = 0.249$) (Figure S5) was not significantly associated with an increased risk of seizures.

When studies were grouped according to individual antidepressants, positive relationships were detected for the use of citalopram (OR 1.62, 95% CI 1.35–1.95; $P < 0.001$), escitalopram (OR 1.62, 95% CI 1.35–1.95; $P < 0.001$), fluoxetine (OR 1.44, 95% CI 1.2–1.73; $P < 0.001$), paroxetine (OR 1.56, 95% CI 1.3–1.87; $P < 0.001$), sertraline (OR 1.76, 95% CI 1.35–2.29; $P < 0.001$), mirtazapine (OR 1.48, 95% CI 1.24–1.78; $P < 0.001$), venlafaxine (OR 1.88, 95% CI 1.36–2.61; $P < 0.001$), and fluvoxamine (OR 1.38, 95% CI 1.03–1.83; $P = 0.029$). No significant association was observed among patients using amitriptyline (OR 1.22, 95% CI 0.75–1.98; $P = 0.427$), dosulepin (OR 0.86, 95% CI 0.27–2.72; $P = 0.797$), lofepramine (OR 2.12, 95% CI 0.96–4.69; $P = 0.065$), trazodone (OR 2.03, 95% CI 0.67–3.16; $P = 0.21$), or duloxetine (OR 0.97, 95% CI 0.75–1.25; $P = 0.818$) (Figure S6).

In subgroup analyses based on the definition of the exposure window, a significant association was observed between studies that evaluated seizure development within 30 days after antidepressant use (OR 2.35, 95% CI 1.7–3.24; $P < 0.001$) and those that evaluated seizure development after antidepressant use (OR 1.49, 95% CI 1.26–1.76; $P < 0.001$; Figure S7).

Meta-regression analysis

Considering the higher combined OR associated with shorter-term antidepressant exposure, a univariate meta-regression analysis was conducted to investigate the potential sources of variation in the exposure window. This analysis revealed no significant differences in seizure risk (standard error (SE) = 0.132, P = 0.104; Figure S8).

Discussion

By combining data from available studies, this study demonstrated that antidepressant exposure was associated with an increased risk of seizures. Subgroup analyses indicated that this risk varied according to antidepressant type and individual antidepressant.

An investigation of the association between antidepressant exposure and seizures should consider antidepressant indications, which have been associated with an increased risk of seizure [25]. Thus, the ideal control for confounding according to indication is a reference group of patients with psychiatric disorders who did not take antidepressants. Five of the included studies limited their cohorts to patients diagnosed with psychiatric disorders or exposed to low-dose antidepressants to reduce potential indication bias. The significant association persisted when data from these five studies were pooled; the pooling partially controlled for indication confounding. The pooled analysis of the four case-crossover studies [11, 12, 21, 24] also supported a positive relationship. Case-crossover is a novel strategy that controls for between-person confounders by comparing the risk and reference periods in each patient. Risk periods are defined as the time during or after an exposure. Thus, although a psychiatric disorder itself is associated with a risk of seizures, our findings suggest that confounding according to indication could not explain the observed association.

Our further analyses demonstrated that only new-generation antidepressants were associated with an increased risk of seizures. The precise biological mechanisms underlying the relationship between SSRIs/SNRIs and seizures are unclear. Several SSRIs inhibit G-protein-activated inwardly rectifying potassium (GIRK) channels. It has been suggested that the activation of GIRK channels induces neuron membrane hyperpolarization via potassium ion efflux, ultimately reducing neural excitability [26]. Thus, the inhibition of these channels by SSRI exposure may increase neural excitability and produce a lower seizure threshold. Additionally, antidepressant use has been linked to hyponatremia [27], which may represent an additional potential mechanism underlying the association between antidepressants and seizures [28]. Furthermore, previous epidemiological investigations demonstrated that the risk of seizures was higher for SSRIs than for TCAs [27], which may partially explain the findings of subgroup analyses based on antidepressant type and individual antidepressant.

Another important issue is the definition of the antidepressant exposure window, which varied among the included studies. In our study, we used a 30-day period as the exposure time window among case-crossover studies. After data from the case-crossover studies had been pooled, a more pronounced risk of seizures was observed, suggesting an acute effect of antidepressants. This finding was reinforced by the relatively lower, but significant, risk observed in the overall analysis. The lower risk present in more long-term antipsychotic users might be related to the effects of tolerance and cross-tolerance to antidepressant drugs.

The main strength of our study was that we performed detailed subgroup analyses according to study design, antidepressant type, and individual antidepressant. We conducted additional analyses to control for confounding according to indication. Nevertheless, this work had several limitations. First, the robustness of our findings was hindered by the small number of included studies. Thus, the subgroup analysis was limited by the sample size, and further studies are needed. Second, similar to other meta-analyses of observational studies, uncontrolled confounding variables may have affected the results. Previous studies have shown that antidepressant use increases the risk of falls [29], and the associated traumatic brain injury is a strong risk factor for seizures. However, this potential confounder was considered in a single included study. Future studies should fully adjust for potential confounders to rule out alternative explanations. Third, there was evidence of high statistical heterogeneity for the pooled results. Subgroup analyses were performed to examine the source of the heterogeneity, but the variables (study design, type of antidepressant, individual antidepressant, or exposure window) evaluated did not thoroughly explain the source of heterogeneity. Thus, we can be less certain about these results. Finally, the definition of antidepressant dose in the included studies was inconsistent; therefore, we could not determine whether this parameter was associated with the risk of seizures.

In conclusion, the findings of this meta-analysis suggest that SSRI/SNRI, but not TCA, use is significantly associated with risk of seizures, especially among short-term users. Clinicians should ensure that antidepressants are prescribed only for patients with a clear indication and be cautious when prescribing antidepressants to patients who have an underlying increased risk of seizures.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00228-023-03597-y.

Author contributions AJL and WY searched the library and wrote the manuscript text. YHJ and HYJ extracted data and reviewed all articles. AJL designed the manuscript. All authors reviewed the manuscript.

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Declarations

Conflict of interest The authors declare no competing interest.

Details of ethical approval No ethical approval was required for this review as all data were already published in peer-reviewed journals.

References

1. Harmer CJ, Duman RS, Cowen PJ (2017) How do antidepressants work? New perspectives for refining future treatment approaches. Lancet Psychiatry 4(5):409–418. https://doi.org/10.1016/s2215-0366(17)30015-9
2. Kazdin AE, Wu CS, Hwang I, Puac-Polanco V, Sampson NA, Al-Hamzawi A, Alonso J, Andrade LH, Benjet C, Caldas-de-Almeida JM, de Girolamo G, de Jonge P, Florescu S, Gureje O, Haro JM, Harris MG, Karam EG, Karam G, Kovess-Masfety V, Lee S, McGrath JJ, Navarro-Mateu F, Nishi D, Oladeji BD, Posada-Villa J, Stein DJ, Üstün TB, Vigo DV, Zarkov Z, Zaslavsky AM, Kessler RC (2023) Antidepressant use in low- middle- and high-income countries: a World Mental health surveys report. Psychol Med 53(4):1583–1591. https://doi.org/10.1017/s0033291721003160
3. Kumar M, Bajpai R, Shaik AR, Srivastava S, Vohora D (2020) Alliance between selective serotonin reuptake inhibitors and fracture risk: an updated systematic review and meta-analysis. Eur J Clin Pharmacol 76(10):1373–1392. https://doi.org/10.1007/s00228-020-02893-1
4. Wang XY, Ying XH, Jiang HY (2023) Antidepressant use during pregnancy and the risk for gestational Diabetes: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 36(1):2162817. https://doi.org/10.1080/14767058.2022.2162817
5. Jiang HY, Chen HZ, Hu XJ, Yu ZH, Yang W, Deng M, Zhang YH, Ruan B (2015) Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 13(1):42–50e43. https://doi.org/10.1016/j.cgh.2014.06.021
6. Elger CE, Hoppe C (2018) Diagnostic challenges in Epilepsy: seizure under-reporting and seizure detection. Lancet Neurol 17(3):279–288. https://doi.org/10.1016/s1474-4422(18)30038-3
7. Larson EA, Accardi MV, Zhong Y, Paquette D, Authier S (2021) Drug-Induced seizures: considerations for underlying Molecular mechanisms. Int J Toxicol 40(5):403–412. https://doi.org/10.1177/10915818211040483
8. Magli G, Conti M, Polano R, Luzzu G, Fadda M, Sotgiu S, Casellato S (2021) Seizures associated with selective serotonin reuptake inhibitors: a case of pharmacologically induced epileptic myoclonia. Seizure 88:75–77. https://doi.org/10.1016/j.seizure.2021.03.031
9. Saffaei D, Lovett S, Rech MA (2020) New-Onset Seizure in Patient Medicated with Bupropion for Smoking Cessation: a Case Report. J Emerg Med 58(3):e145–e147. https://doi.org/10.1016/j.jemermed.2019.12.020
10. Ye C, Ninneman M, Christian JS, Zhang F, Musselman D (2018) Seizure Induced by a therapeutic dose of Venlafaxine ER: a Case Report. J Psychiatr Pract 24(2):117–120. https://doi.org/10.1097/pra.0000000000000298
11. Hill T, Coupland C, Morriss R, Arthur A, Moore M, Hippisley-Cox J (2015) Antidepressant use and risk of Epilepsy and seizures in people aged 20 to 64 years: cohort study using a primary care database. BMC Psychiatry 15:315. https://doi.org/10.1186/s12888-015-0701-9
12. Coupland CA, Dhiman P, Barton G, Morriss R, Arthur A, Sach T, Hippisley-Cox J (2011) A study of the safety and harms of antidepressant drugs for older people: a cohort study using a large primary care database. Health Technol Assess 15 (28): 1-202, iii-iv https://doi.org/10.3310/hta15280
13. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational studies in Epidemiology (MOOSE) group. JAMA 283(15):2008–2012. https://doi.org/10.1001/jama.283.15.2008
14. Higgins JP (2014) Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane collaboration. Available at: www.cochrane-handbook.org [6 December 2014]
15. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21(11):1539–1558. https://doi.org/10.1002/sim.1186
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560. https://doi.org/10.1136/bmj.327.7414.557
17. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109):629–634. https://doi.org/10.1136/bmj.315.7109.629
18. Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I (2006) The case of the misleading funnel plot. BMJ 333(7568):597–600. https://doi.org/10.1136/bmj.333.7568.597
19. Bloechliger M, Ceschi A, Rüegg S, Kupferschmidt H, Kraehenbuehl S, Jick SS, Meier CR, Bodmer M (2016) Risk of seizures Associated with antidepressant use in patients with depressive disorder: follow-up study with a nested case-control analysis using the Clinical Practice Research Datalink. Drug Saf 39(4):307–321. https://doi.org/10.1007/s40264-015-0363-z
20. Sáez ME, González-Pérez A, Gaist D, Johansson S, Nagy P, García Rodríguez LA (2016) Risk of seizure associated with use of acid-suppressive Drugs: an observational cohort study. Epilepsy Behav 62:72–80. https://doi.org/10.1016/j.yebeh.2016.06.039
21. Wu CS, Liu HY, Tsai HJ, Liu SK (2017) Seizure risk Associated with antidepressant treatment among patients with depressive disorders: a Population-based case-crossover study. J Clin Psychiatry 78(9):e1226–e1232. https://doi.org/10.4088/JCP.16m11377
22. Finkelstein Y, Macdonald EM, Li P, Mamdani MM, Gomes T, Juurlink DN (2018) Second-generation anti-depressants and risk of new-onset seizures in the elderly. Clin Toxicol (Phila) 56(12):1179–1184. https://doi.org/10.1080/15563650.2018.1483025
23. Chu CS, Lee FL, Bai YM, Su TP, Tsai SJ, Chen TJ, Hsu JW, Chen MH, Liang CS (2023) Antidepressant Drugs use and Epilepsy risk: a nationwide nested case-control study. Epilepsy Behav 140:109102. https://doi.org/10.1016/j.yebeh.2023.109102
24. Wiggs KK, Lagerberg T, Quinn PD, Öberg AS, Larsson H, Chang Z, D'Onofrio BM (2023) A nationwide study of initiation of antidepressant pharmacotherapy and the risk of seizures. Epilepsy Res 192:107134. https://doi.org/10.1016/j.eplepsyres.2023.107134
25. Karadag N, Shadrin AA, O'Connell K, Hindley GFL, Rahman Z, Parker N, Bahrami S, Fominykh V, Cheng W, Holen B, Alvestad S, Taubøll E, Steen NE, Djurovic S, Dale AM, Frei O, Andreassen OA, Smeland OB (2023) Identification of novel genomic risk loci shared between common epilepsies and psychiatric disorders. Brain DOI. https://doi.org/10.1093/brain/awad038

26. Lesage F, Guillemare E, Fink M, Duprat F, Heurteaux C, Fosset M, Romey G, Barhanin J, Lazdunski M (1995) Molecular properties of neuronal G-protein-activated inwardly rectifying K + channels. J Biol Chem 270(48):28660–28667. https://doi.org/10.1074/jbc.270.48.28660
27. De Picker L, Van Den Eede F, Dumont G, Moorkens G, Sabbe BG (2014) Antidepressants and the risk of hyponatremia: a class-by-class review of literature. Psychosomatics 55(6):536–547. https://doi.org/10.1016/j.psym.2014.01.010
28. Halawa I, Andersson T, Tomson T (2011) Hyponatremia and risk of seizures: a retrospective cross-sectional study. Epilepsia 52(2):410–413. https://doi.org/10.1111/j.1528-1167.2010.02939.x
29. Warden SJ, Fuchs RK (2016) Do selective serotonin reuptake inhibitors (SSRIs) cause fractures? Curr Osteoporos Rep 14(5):211–218. https://doi.org/10.1007/s11914-016-0322-3