

Antiepileptic Drugs and Suicide: A Systematic Review of Adverse Effects

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Key Words

Antiepileptic drugs · Suicide · Adverse effects · Review

Abstract

Background: Since the FDA (Food and Drug Administration) report on antiepileptic drugs (AEDs) and suicide risk was released (2008), several studies have been published on this controversial relationship. This systematic review (SR) gives an updated approach to this health issue. **Summary:** We searched 6 databases. We ultimately included 11 publications: 4 cohort studies, 1 case-crossover study, 2 community case-control studies, and 4 SRs. Overall, 1 SR described studies already included; 3 studies reported a 2- to 4-fold overall increase in risk; 1 study reported an increased risk of suicide among epilepsy patients on AEDs with high risk of depression; 1 study showed a protective effect among epilepsy patients; 2 studies were conducted with patients with bipolar disorder (1 showed a protective effect, whereas the other showed a 3-fold increase in risk of suicide), and the other 3 studies reported results for single AEDs. Several biases affected the published results. **Key Messages:** There is no clear evidence of an association between the use of AEDs and an increased risk of suicide because of the heterogeneity in the studies at the clinical and methodological level. A future

study should cover all indications for use, retrieve information from a healthcare database, and include a defined set of covariates to avoid bias.

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Introduction

Antiepileptic drugs (AEDs) have been described as potential risk factors for suicidal behavior [1]. In 2008, the Food and Drug Administration (FDA) in the USA reported a 2-fold increased risk of suicidal ideation or behavior for 11 AEDs (odds ratio, OR, 1.80, 95% confidence interval, CI, 1.24–2.66) [2].

Suicide is a serious public health concern around the world. In 2011, the prevalence rate in Europe was 13.9/100,000 persons per year [3], with the highest rates among men and older individuals, although the prevalence among adolescents and young adults has recently increased [4, 5]. These figures are even higher among people with epilepsy; the reported lifetime prevalence rate of suicide and suicide attempts are between 5 and 14.3% [6]. Psychological autopsy studies have demonstrated that 90% of suicide victims suffer from a psychiatric condition at the time of death [7].

The following trends and observations led to this systematic review (SR): (1) the high and widespread use of AEDs to treat epilepsy and other conditions including off-label indications [8–10]; (2) the use of new AEDs among the elderly [11, 12]; (3) the fact that AED users have the highest risk of suicide within their population age group [3], and (4) the potential public health implications of the association between AEDs and suicide. The aim of this review is to systematically summarize the available evidence from randomized clinical trials (RCTs) and observational studies on the association between AEDs and suicide.

Methods

Data Sources

We searched PubMed (1980–April 2012), the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (1980–February 2012), PsycINFO (1980–February 2012), and ClinicalTrials.gov (April 5, 2012). The search strategy included MeSH terms and free-text words. We combined the terms ‘antiepileptic drugs’ and each of the Anatomical Therapeutic Chemical Classification level 4 and 5 drugs for N03A (version 2012) with the terms ‘suicide’, ‘intentional self-murder’, ‘killing oneself’, ‘hastened death’, ‘subintended death’, ‘miscalculation’, ‘fatal self-harm’, ‘suicide intent’, ‘suicide attempt’ and ‘suicide behavior’, using the Boolean operator AND. We included studies published in any language mastered by the authors P.F., E.B., M.S. and L.I. – English, any Romance language, and Swedish. We also electronically searched the following peer-reviewed journals: *Neuropsychopharmacology*, *CNS Drugs*, *Neurology*, all of the Lancet group publications, *Science Direct*, and the Wiley Online Library. In addition, we reviewed the reference lists from the included studies. Two of the three authors we contacted provided additional information.

Study Selection

We aimed to identify RCTs and observational studies related to any type of AED that included suicidality (defined as completed or attempted suicides) as a primary or secondary outcome. Studies that included suicidal ideation or deliberate self-harm with no intention to die or unknown intention as outcomes were only included if the authors also collected information on completed or attempted suicides, as defined by Posner et al. [13].

P.F. screened the titles and abstracts yielded by the bibliographic search, and E.B. screened the above-mentioned journals electronically to assess whether they met the eligibility criteria. We retrieved the full-text article if an abstract was selected or if there was uncertainty regarding the eligibility of a study. The inclusion criteria were RCTs or observational studies, and a population aged 18 years or older. The reference group was placebo or no treatment. We excluded case reports and studies conducted with data from spontaneous report databases.

The search on ClinicalTrials.gov was limited to the trials that used a random allocation method, had a safety-related outcome and were limited by age (≥ 18 years). We excluded ongoing trials.

Data Extraction and Quality Assessment

P.F. and E.B. extracted the data using a predetermined form. To better assess the heterogeneity between the studies, we developed a checklist specifically for this SR of adverse effects (see online supplementary material; for all online suppl. material, see www.karger.com/doi/10.1159/000356807). Any discrepancies were resolved by discussion.

Data Synthesis

Because we expected clinical (e.g. different drug exposures, different participants, different indications for use, different definitions of suicide) and methodological (inclusion of randomized and observational studies, different confounders included in the adjusted models) heterogeneity, we decided to conduct a narrative synthesis [14].

Results

We initially included 10 publications. See figure 1 for the numbers of studies that were screened, assessed for eligibility and included in the final analyses, as well as the reasons for exclusion; 1 prospective cohort study [15] had flaws in its statistical results and was therefore excluded. Since this search was conducted, a new SR [16] and a new-user design study [17] have been published and included in this SR. Ultimately, we included 11 published studies. For a description of the 11 included studies and the cohort study excluded, see table 1.

Gibbons et al. [18] conducted 2 population-based prospective cohort studies between 2000 and 2006 – 1 study involving patients with bipolar disorder reported a risk of suicide for any AED of 0.88 (95% CI 0.72–1.08), and another study [19] which included patients who had filled one prescription of gabapentin showed an effect of this AED on suicide of 0.93 (95% CI 0.76–1.14). Gabapentin on patients with bipolar disorder in this study showed a protective effect (OR 0.62, 95% CI 0.41–0.94). In both studies, the measurement of the exposure did not account for compliance, dosage and duration of treatment, and it focused on any use over a time span of 1 year. This methodology may have led to nondifferential exposure misclassification. Suicide may have been underreported, resulting in nondifferential outcome misclassification. Not all potential confounders were considered, although in the study of the bipolar patients, the authors adjusted for suicide attempts in the year before the diagnosis.

Sondergård et al. [20] found an increased risk of suicide associated with one prescription of any AED among patients with a severe bipolar disorder (OR 3.30, 95% CI 2.17–4.99); however, they did not consider previous suicide attempts or other cotreatments in the model. In an

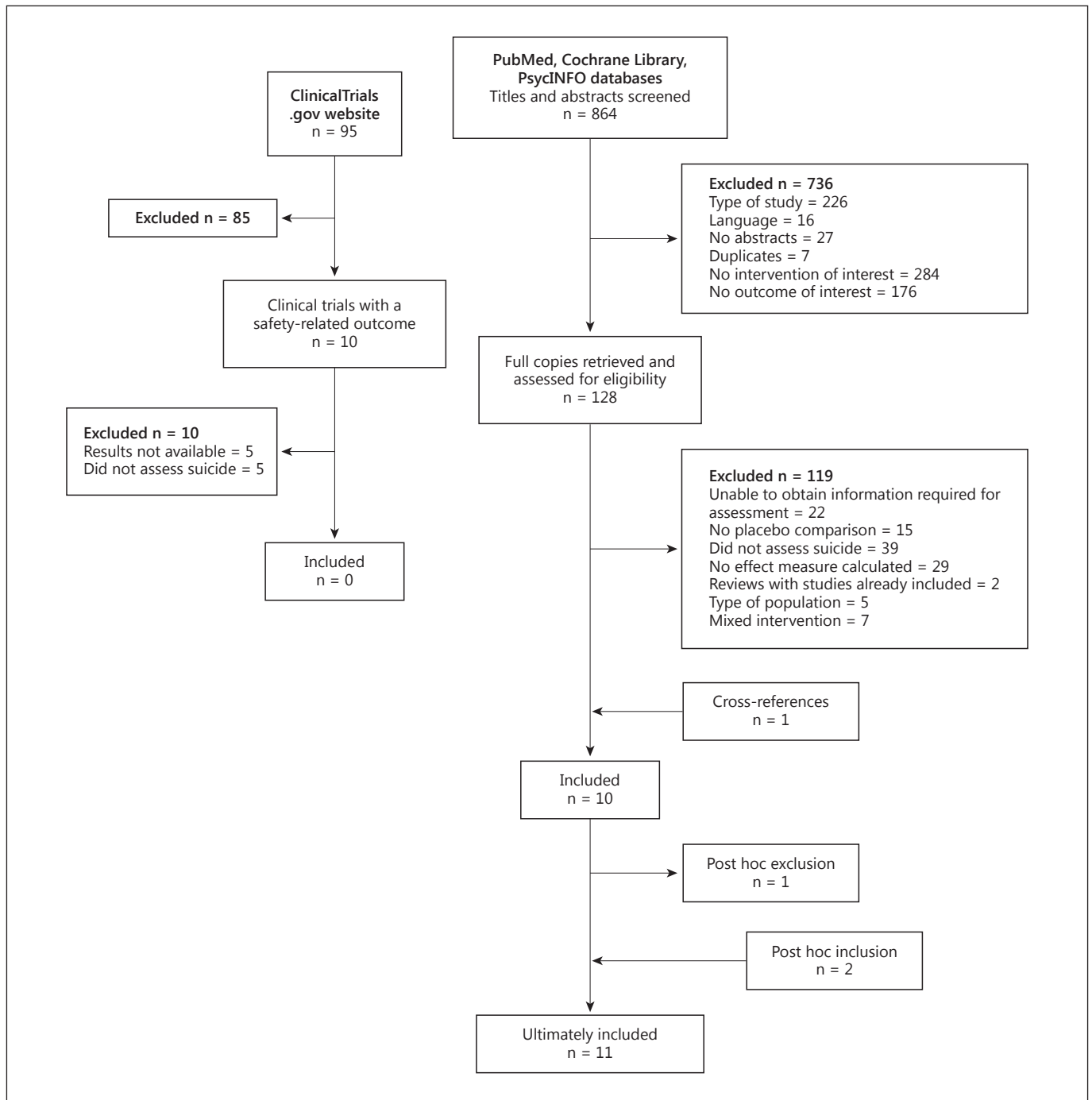


Fig. 1. Results of the search strategy.

attempt to control for confounding by indication they adjusted for readmission and the use of lithium as a marker of bipolar disorder severity. The number of prescriptions was a proxy measure for the duration of treatment. They did not consider dosage or compliance.

In the case-crossover analysis of Olesen et al. [21], the authors found a 2-fold increased risk of suicide with the use of AEDs (OR 1.84, 95% CI 1.36–2.49). There was a potential for nondifferential exposure misclassification (as an average daily dose was calculated instead of use of

Table 1. Description of the main characteristics of the 9 studies included and the cohort study excluded

Author and study design	Participants	Exposure	Outcome of interest	Factors adjusted for	Adjusted effect measure (95% CI)	Study quality (potential sources of bias)
Andrade-Machado [15], 2011 Prospective cohort study (ultimately excluded)	All patients with a first diagnosis of epilepsy at a tertiary hospital in Cuba (n = 131) Age range: 18–78 years Gender: 54.2% female Follow-up: 5 years	Monotherapy use for at least 1 week: AEDs: PHB, PHT, CBZ, VPA, LTG, TPM and PRM No time of exposure provided	Suicide risk, suicide attempts (n = 38), and depressive episodes; total events of interest = 228	Uncontrolled seizures, psychiatric comorbidity, past history of suicidal behavior or psychiatric disorders	Suicide attempts PHB: OR = 1.2 (2.2–3.4) PHT: OR = 1.2 (2.3–3.4) CBZ: OR = 3.0 (0.0–26) VPA: OR = 6.2 (1.0–7.0) LTG: OR = 6.2 (2.0–7.8) TPM: OR = 3.1 (2.0–3.9) PRM: OR = 1.4 (1.3–1.5)	Exposure misclassification: exact treatment duration unknown Differential outcome misclassification: unclear definition of a suicide attempt; ascertainment of suicidal thoughts and attempts were assessed by psychiatrists involved in the study and who were not blinded to the exposure or the hypothesis of the study Residual confounding: several scales were used to evaluate psychiatric, neurological and neuropsychological condition of each patient; no explanation on how the results of these evaluations were categorized; it seems that the variables were dichotomous Several ORs and 95% CIs seem wrongly reported (see italicized ORs)
Pugh [17], 2012 Cohort study with a new-user design	2,430,286 individuals 65 years or older receiving Veterans Health Administration care between fiscal years 2004 and 2006: (1) 90,263 exposed to AEDs; (2) 2,056,911 not exposed to AEDs; (3) 282,914 (11%) excluded because of chronic or multiple AED use or incomplete data Mean age: 74.4 years Male: 98.3% White: 65% Follow-up: 1 year after the prescription of an AED for those exposed to AEDs; 1 year after entering the cohort for those not exposed to AEDs	Individuals receiving 1 AED in the Veterans Health Administration pharmacy claims database AEDs included: PHB (n = 5,289, 5.9%), PHT (n = 4,136, 4.6%), CBZ (n = 2,976, 3.3%), VPA (n = 5,833, 6.5%), GBP (n = 68,725, 76.2%), LTG (n = 815, 0.9%), LEY (n = 636, 0.7%), OXC (n = 169, 0.19%), TGB (n = 53, 0.06%), TPM (n = 1,516, 1.7%), PGB (n = 83, 0.09%), ZNS (n = 32, 0.04%)	Suicidal ideation, suicide and self-inflicted injury defined by ICD-9-CM codes in inpatient and outpatient data files the year after meeting inclusion criteria; it included deliberate self-harm with unknown suicidal intention Suicide events: exposed to AEDs, n = 92; not exposed to AEDs, n = 240	Propensity score developed with the following covariates: psychiatric diagnoses included in administrative data identified through ICD-9-CM codes, prior prescription of an antidepressant or antipsychotic, prior psychiatric hospitalization (based on inpatient admission with ICD-9-CM codes 290–311), epilepsy, chronic pain, migraine and dementia Differences in depression and suicide-related behaviors remained between strata Healthcare facility Age, gender, race/ethnicity, married/unmarried	Any AED: HR = 3.90, (2.93–5.19) CBZ: HR = 1.19 (0.30–4.68) GBP: HR = 2.56 (1.96–4.16) LTG: HR = 36.63 (15.89–84.46) LEY: HR = 8.23 (1.41–48.11) PHB: HR = 1.65 (0.40–6.74) PHT: HR = 5.33 (1.55–18.34) TPM: HR = 6.83 (1.90–24.51) VPA: HR = 15.44 (9.44–25.44)	Residual confounding as depression and prior suicide-related behavior remained unbalanced between those exposed and unexposed to AEDs Nondifferential misclassification of exposure as treatment adherence, intensity and dosage were not considered Nondifferential misclassification of suicide as diagnostic codes were not validated Although a 'wash-out' period of 1 year, these new-users could be noncompliant prevalent users: no sensitivity analyses to assess the robustness of the model

Table 1 (continued)

Author and study design	Participants	Exposure	Outcome of interest	Factors adjusted for	Adjusted effect measure (95% CI)	Study quality (potential sources of bias)
Gibbons [19], 2010 Prospective cohort study (secondary data source: PHARMetrics database)	131,178 patients receiving at least 1 prescription of GBP who were enrolled in a health plan 1 year before and after the prescription was filled Mean age: 48.9 years Female: 63% 57,085 patients on GBP monotherapy (excluded the subjects with any CNS drugs after the index date) Approximately 70–80% of the patients had a concomitant pain disorder	GBP Exposure risk period was 360 days, regardless of the length of actual exposure and of the duration of the prescription Sensitivity analyses conducted for the length of the prescription (on a monthly basis)	Suicidality was defined as ICD-9 codes E950–959. It included deliberate self-harm with unknown suicidal intention n = 456 events before the prescription and 453 after the prescription For GBP monotherapy, n = 17 before the prescription and n = 9 after the prescription	Age, gender and other drugs (other AEDs, antidepressants, antipsychotics and lithium) Suicide attempts to the year before the start of GBP Age, gender and concomitant diagnoses	Comparison before and after starting treatment Overall effect of GBP: ERR = 0.93 (0.76–1.14) All psychiatric diagnoses: ERR = 0.73 (0.59–0.70) Bipolar disorder (2.9%): ERR = 0.62 (0.41–0.94) Major depressive disorder (19.2%): ERR = 0.65 (0.52–0.82) Epilepsy (1.1%): ERR = 0.83 (0.34–2.04) Pain disorder (82.2%): ERR = 0.99 (0.76–1.14) Schizophrenia (0.5%): ERR = 0.74 (0.41–1.35) Other psychiatric disorder (24.3%): ERR = 0.69 (0.55–0.88) GBP monotherapy: ERR = 0.53 (0.16–1.73)	Residual confounding: comorbidity is not adjusted for Misclassification of exposure: treatment adherence, intensity, or dosage not considered Confounding by indication Nondifferential outcome misclassification Conflict of interest
Gibbons [18], 2009 Prospective cohort study (secondary data source: PHARMetrics database)	47,918 patients with bipolar disorder (ICD-9 code) enrolled in the same healthcare plan at least 1 year before and after the index date (illness diagnosis): 3 groups: (1) 13,385 any AED; (2) 11,207 no medication; (3) 25,432 no AED and no lithium Characteristics of the patients were not provided 154 suicide events occurred after treatment	Any of 11 AEDs, AED only 11 AEDs: GBP, VPA, FBM, LTG, LEV, OXC, PGB, TGB, TPM, ZNS, CBZ Comparison groups: (1) no AEDs or lithium; (2) no CNS drugs	Suicidality was defined as ICD-9 codes E950–959; it included deliberate self-harm with unknown suicidal intention n = 1,226 patients with at least 1 suicide attempt	Concomitant other AEDs other than the 11 described in the study, antidepressants, antipsychotics, previous suicide attempts (in the year prior to the index diagnoses), age, gender and year of study (2000–2006)	Suicide attempts after treatment with AEDs vs. no treatment GBP: ERR = 1.16 (0.66–2.05) VPA: ERR = 0.72 (0.51–1.02) LTG: ERR = 0.85 (0.62–1.16) OXC: ERR = 0.98 (0.62–1.56) TPM: ERR = 1.87 (1.22–2.87) CBZ: ERR = 2.37 (1.21–4.67) Any AED: ERR = 0.88 (0.72–1.08) AED only: ERR = 0.19 (0.08–0.47)	Nondifferential exposure misclassification Potential selection bias: the characteristics of patients with bipolar disorder were not specified Potential nondifferential outcome misclassification as suicide may be underreported Confounding by indication Other confounders of interest not considered: comorbidity Conflict of interest
Sondergård [20], 2008 Prospective cohort study (secondary data source: Danish national registries)	5,926 patients with a diagnosis (ICD-8 or ICD-10 codes depending on the year of diagnoses) of mania, mixed episodes or bipolar disorder at discharge from psychiatric ambulatory, hospital or community centers, between 1995 and 2000; total of 18,557.2 person-years; 75.6% readmitted Age range: 18–110 years Female: 61.9% Prescription for lithium only, n = 891 Prescription for any AEDs only, n = 2,111 Prescription for lithium and AEDs, n = 2,924 No prescription purchased, n = 1,179 (19.9% of discharged patients)	Lithium and AEDs, defined by the Anatomical Therapeutic Chemical classification (N03A, mainly VPA, LTG and OXC); it excluded barbiturates and clonazepam The number of prescriptions was analyzed as a proxy for treatment duration	Suicide (ICD-10 codes); it included deliberate self-harm with unknown suicidal intention n = 51 (35 under AED treatment)	Adjusted for age, gender and readmission Corrected for additional treatment with lithium	AEDs (any N03A, mainly VPA, OXC, LTG) 1 prescription (vs. none): OR = 3.30 (2.17–4.99) ≥2 prescriptions (vs. none): OR = 0.91 (0.64–1.27)	Confounding by indication Nondifferential exposure misclassification; difficult to separate the effect of time from the effect of the drug on suicide after hospital discharge Nondifferential outcome misclassification Residual confounding

Table 1 (continued)

Author and study design	Participants	Exposure	Outcome of interest	Factors adjusted for	Adjusted effect measure (95% CI)	Study quality (potential sources of bias)
Olesen [21], 2010 Case-crossover analysis (secondary data source: several Danish registries) Cohort analysis excluded as the reference group was carbamazepine	Nationwide register-based study between 1997 and 2006 Age range: ≥10 years Mean age: 54 years Male: 72.1% Only individuals with an event were included in the analysis Case period: 30 days prior to the suicide Control periods: 120–90 days, and 90–60 days prior to the suicide n = 6,780	PHB, PRM, PHT, clonazepam, CBZ, OXC, VPA, TGB, LTG, TPM, GBP, LEV, ZNS, PGB, clobazam; treatment periods were calculated for each AED (number of tablets dispensed/EDD); the EDD compared the cumulative dosage and the elapsed time between 7 prescriptions; treatment breaks (<60 days of treatment) were in-treatment periods Any use of an AED in a given period	Suicide events: ICD-10 codes X60–X84 on the National Causes of Death Register; it included deliberate self-harm with unknown suicidal intention n = 422 were on AEDs at the time of suicide n = 365 were only on AEDs at this specific time	Patients were automatically matched on: The Charlson Comorbidity Index modified for ICD-10 Psychiatric disorders and epilepsy Cotreatment (up to 1 year prior to the AED prescription): antidepressants, antipsychotics, anxiolytics Cotreatment: opioids claimed ≤180 days before the first AED prescription (the patient was categorized as using an AED for analgesia) Socioeconomic status and civil status	Overall AED: OR = 1.84 (1.36–2.49) Clonazepam: OR = 2.01 (1.25–3.25) VPA: OR = 2.08 (1.04–4.16) LTG: OR = 3.15 (1.35–7.34) PHT: OR = 1.96 (1.02–3.75) GBP: OR = 2.20 (0.83–5.83) CBZ: OR = 0.48 (0.21–1.12) OXC: OR = 0.84 (0.30–2.32) PHT: OR = 0.37 (0.03–4.44) TPM: OR = 2.72 (0.23–32.78) Clobazam: OR = 0.59 (0.05–7.43)	Non-differential exposure misclassification, as an average daily dose is used instead of prescribed daily dose Potential for reversal causation bias as during the case time period subjects may have presented symptoms that may have led to the prescription of AEDs Confounding by changes in indication or the severity of the disease
Araná [22], 2010 Community case-control study (secondary data source: THIN database)	5,130,795 participants between 1988 and 2008 Total of 31,527,585 person-years of follow-up Age: any age Female: 51.4% Cohorts (patients with a personal or family history of suicide were excluded): (1) Nonusers of AEDs: No epilepsy, depression, bipolar disorder, n = 4,514,366 Epilepsy only, n = 16,120 Depression only, n = 435,790 Bipolar disorder only, n = 3,814 Bipolar disorder and epilepsy, n = 47 (2) Users of AEDs: No epilepsy, depression, bipolar disorder, n = 77,319 Epilepsy only, n = 39,325 Depression only, n = 30,772 Bipolar disorder only, n = 1,809 Bipolar disorder and epilepsy, n = 171 Controls: risk-set control sampling; end of follow-up: the date the case (event) assigned to control occurred Control 1: random sample of 5 controls, matched on age, gender and clinical practice Control 2: matched on age, gender, clinical practice and psychiatric or neurological condition; 103 cases were not matched	CBZ, GBP, LTG, LEV, OXC, PGB, TGB, TPM, VPA and ZNS Current user: between the prescription date and 75 days after that date Previous user: after 75 days and no other AED was prescribed No users: no AED code	Suicide events (completed suicide, attempted suicide, intentional self-inflicted injuries plus suicide) n = 8,212 (464 completed suicides) Diagnostic codes (code classification system not reported) Positive predictive value of 97% for suicide-related events and 87% for completed suicides; the outcome assessor was blinded to the exposure	Age, duration of disease, previous use of AED, lithium, antipsychotic or antidepressants, history of alcohol abuse, mental disorder and chronic disease score Subgroup analysis (users vs. nonusers of AEDs): matched by diagnosis category, age, sex and clinical practice; adjustment for age, duration of disease, previous use of AEDs, lithium, antipsychotic drugs, antidepressants, presence/absence of a history of alcohol abuse or mental disorders, chronic disease score The same factors were adjusted for the individual AED effects on suicide events	Overall use of AEDs on suicide events in patients with no epilepsy, depression or bipolar disorder: OR = 2.57 (1.78, 3.71) Epilepsy: OR = 0.59 (0.35–0.98) Depression only: OR = 1.65 (1.24–2.19) Bipolar disorder only: OR = 1.13 (0.35–3.61) Epilepsy and depression: OR = 1.24 (0.56–2.72) CBZ: OR = 1.35 (1.02–1.79) GBP: OR = 0.89 (0.45–1.77) LTG: OR = 1.07 (0.58–1.98) LEV: OR = 0.70 (0.12–4.00) PGB: OR = 0.24 (0.03–2.17) TPM: OR = 0.52 (0.15–1.78) VPA: OR = 1.44 (0.99–2.08)	Confounding by indication Non-differential exposure misclassification Non-differential outcome misclassification: suicide is underreported in the THIN database

Table 1 (continued)

Author and study design	Participants	Exposure	Outcome of interest	Factors adjusted for	Adjusted effect measure (95% CI)	Study quality (potential sources of bias)
Andersohn [23], 2010 Community case-control study (secondary data source: General Practice Research database)	Patients with a diagnosis of epilepsy or nonfebrile seizures registered 1 year at General Practice Research database who received at least 1 AED prescription, n = 44,300 A total of 243,095 person-years of follow-up Cases, n = 453 Controls: risk-set control sampling of 20 controls matched on age, gender and year of cohort entry, n = 8,962 Mean age: 36.0 years Female: 51.0% More cases with a history of psychiatric disorders Any prescription of an AED Index date: first occurrence of suicidality	Antiepileptics categories: (1) barbiturates (PHB, PRM, methylPHB); (2) conventional AEDs (CBZ, VPA, PHT, ESM, acetazolamide); (3) new AED with low risk of depression (OXC, LTG, GBP, PGB); (4) new AED with high risk of depression (LEV, TGB, TPM, VGB); duration of each prescription was calculated Current (14 days before index date), recent (15–183 days), past exposure (184–365 days) and nonuse (no AED prescription the year before the index date – this is the reference group)	Suicidal events (completed, attempted suicide, and self-harm without clear suicidal intention) Predefined medical codes (code classification system not reported), review of medical records and questionnaire	Type of epilepsy (undefined, generalized, partial, partial and generalized), treatment with benzodiazepines and psychiatric comorbidity before cohort entry (history of self-harm, depression treated with and without antidepressant), psychotic disorders, mania, anxiety disorder, borderline personality disorder, other personality disorders, alcohol dependence/abuse and other substances dependence)	Current use: New AED (high risk of depression): OR = 3.08 (1.22–7.77) New AED (low risk of depression): OR = 0.87 (0.47–1.59) Conventional AED: OR = 0.74 (0.53–1.03) Barbiturates: OR = 0.66 (0.25–1.73) PHB: OR = 0.66 (0.23–1.90) CBZ: OR = 0.83 (0.57–1.20) VPA: OR = 0.68 (0.56–1.01) PHT: OR = 0.67 (0.42–1.08) ESM: OR = 1.31 (0.17–10.26) LTG: OR = 0.93 (0.49–1.76) GBP: OR = 0.70 (0.18–2.75) LEV: OR = 6.42 (1.24–33.36) TPM: OR = 2.42 (0.54–10.77) VGB: OR = 2.44 (0.52–11.48) Recent use: OR = 1.18 (0.81–1.72) Past use: OR = 0.85 (0.47–1.51)	Unclear to what extent prior suicidal behavior was considered Potential underreporting of suicides; very small numbers of suicide events for individually assessed AEDs Residual confounding as the type of epilepsy was poorly ascertained Nondifferential exposure misclassification: the classification of AEDs as high and low risk of depression seems arbitrary
Fountoulakis [16], 2012 Systematic review and narrative synthesis	Search in 1 database (MEDLINE) Initial search: n=893 studies Ultimately included: n = 5 (no flow chart provided) Excluded papers which included solely patients with mood disorders or only comparisons of AEDs and lithium	CBZ, VPA, FBM, GBP, LTG, LEV, OXC, PGB, TGB, TPM, ZNS, ESM, PRM Comparator: placebo or any other AED or lithium	Any kind of suicide-related issues: not specified what the authors mean by suicidal behavior	Not applicable	Not applicable The studies included in the review of Fountoulakis et al. [16] of interest for our study (comparator placebo or no treatment) have already been retrieved with our search strategy [2, 20]	Inadequately reported search strategy; selection bias as only 1 database was used and only articles published in English were used; potential for publication bias No systematic quality assessment of the included studies although the authors point to potential sources of bias in the 5 included studies
Van Lieshout [25], 2011 Systematic review and meta-analyses of mood stabilizers as a group with RCTs of efficacy	Search in 6 databases Initial search: n = 2,355 studies Included: n = 18 studies Participants: n = 4,105 with bipolar disorder and acute major depression Quality criteria assessed by the Jadad scale (it was an inclusion criterion) Posterior quality assessment by grading recommendations assessment, development and evaluation Heterogeneity assessed by visual inspection of funnel plots and Q statistic Magnitude assessed by I ²	Lithium, VPA, CBZ, LTG, TPM, GBB, benzodiazepines, and typical antipsychotics Fixed or flexible dosages Comparison group: placebo	Suicidal behavior (all noted and reported cases of suicide attempts and completions) n = 1,916 (6 studies)	None	Mood stabilizer monotherapy CBZ, 0 events: OR = not estimable LTG 1/127 versus 2/65 events: OR = 0.26 (0.02–2.77) VPA, 0/13 vs. 0/12 events: OR = not estimable	Ascertainment bias of adverse events Conflicts of interest for the 2nd author

Table 1 (continued)

Author and study design	Participants	Exposure	Outcome of interest	Factors adjusted for	Adjusted effect measure (95% CI)	Study quality (potential sources of bias)
FDA systematic review [2], 2008	199 clinical trials: n = 27,863 AEDs n = 16,029 placebo RCTs, first period of cross-over trials with at least 30 patients Age range: ≥5 years Mean age: 45 years (AED), 43 years (placebo) Female: 56% (AED), 54% (placebo)	CBZ, VPA, FBM, GBP, LTG, LEV, OXC, PGB, TGB, TPM, ZNS	Suicide events Completed suicide: n = 4 (AED) vs. 0 (placebo) Suicide attempt: n = 30 (AED) vs. 8 (placebo) Preparatory acts toward suicide: n = 3 (AED) vs. 1 (placebo) Suicidal ideation: n = 67 (AED) vs. 38 (placebo) Only the most critical event per patient Primary endpoint: suicidal behavior and ideation (suicidal behavior as the secondary endpoint plus suicidal thought) Secondary endpoint: suicidal behavior (i.e. completed suicide or suicide attempt or preparatory acts toward suicide)	Primary analyses: several covariates were collected but we do not know which one was in the model Sensitivity analyses were conducted for zero-event trials; between trial heterogeneity of the effect measure and the duration of the treatment (post hoc) Confounders examined: person-time analyses to adjust for differences in duration of treatment and demographics	Primary endpoint: suicidal behavior or ideation Overall all AEDs: OR = 1.80 (1.24–2.66) CBZ: OR = 0.65 (0.08–4.42) VPA: OR = 0.72 (0.29–1.84) FBM: not determined GBP: OR = 1.57 (0.12–47.66) LTG: OR = 2.08 (1.3–4.40) LEV: OR = 2.75 (0.62–19.36) OXC: OR = 1.91 (0.15–56.33) PGB: OR = 1.88 (0.41–13.58) TGB infinite TPM: OR = 2.53 (1.21–5.85) ZNS: OR = 2.52 (0.26–2.66) By indication: Epilepsy: OR = 3.53 (1.28–12.10) Psychiatric disorder: OR = 1.52 (0.95–2.45) Other: OR = 1.87 (0.81–4.76) Suicidal behavior: OR = 2.92 (1.44–6.47) Suicidal ideation: OR = 1.45 (0.93–2.30)	Selection bias Ascertainment bias of adverse events Confounding by previous suicide behavior Potential for heterogeneity as in epilepsy patients AEDs were mainly used as an adjunct therapy to other AEDs; the majority of participants used AEDs for indications other than epilepsy and mental illnesses
Premkumar [26], 2006 Cochrane's systematic review with RCT on efficacy	Cochrane's Schizophrenia Group Register 5 RCTs included, of 22 studies; 3 had unclear allocation concealment procedures Participants with schizophrenia and schizoaffective disorder Follow-up: 12 weeks; 25% of the patients withdrew early from the study (unrelated to adverse effects) Total participants: n = 537 Age range: 30–40 years	LTG as adjunct (100–400 mg/day) vs. placebo adjunct	Adverse effects: suicide attempts, n = 217 (1 RCT) Suicide ideas, n = 429 (2 RCTs) No deaths identified	None	Suicide attempt: RR = 2.97 (0.12–72.18) Suicide ideation: RR = 1.05 (0.15–7.06)	Ascertainment bias of adverse effects Selection bias: 25% of patients withdrew from trials Short duration (12 weeks)

PHB = Phenobarbital; PHT = phenytoin; CBZ = carbamazepine; VPA = valproic acid; LTG = lamotrigine; TPM = topiramate; PRM = primidone; GBP = gabapentin; LEV = levetiracetam; OXC = oxcarbazepine; ZNS = zonisamide; FBM = felbamate; PGB = pregabalin; TGB = tiagabine; ESM = ethosuximide; VGB = vigabatrin; EDD = estimated daily dosage; HR = hazard ratio; ERR = event rate ratio; RR = relative risk.

prescribed daily dose) and for confounding by changes in indication or the severity of the risk of suicide over time. The authors did not state the reason for the time window they selected and failed to include sensitivity analyses for different time exposure windows. There is also a potential for reverse causation bias. The cohort analysis was not considered in this review as the reference drug was carbamazepine.

There were 2 community-based case-control studies. On the one hand, Arana et al. [22] reported an association between suicide and the use and nonuse of AEDs in 11 cohorts and concluded that the increased risk was dependent on the underlying disease. On the other hand, they also reported an increased risk of suicide in patients on AEDs without epilepsy, depression or bipolar disorder (OR 2.57, 95% CI 1.78–3.71). The authors reported that 17% of these patients had a pain-related diagnosis. In the subgroup analyses, comparing current users and nonusers of AEDs, the current use of AEDs provided a protective effect for patients with epilepsy alone (OR 0.59, 95% CI 0.35–0.98); however, patients with depression alone had an increased risk of suicide (OR 1.65, 95% CI 1.24–2.19). Conversely, in patients with bipolar disorder, the use of AEDs seemed uneventful (OR 1.13, 95% CI 0.35–3.61). Andersohn et al. [23] showed that only AEDs with high risk of depression were associated with an increased risk of suicide in epilepsy patients (OR 3.08, 95% CI 1.22–7.77). In both studies [22, 23], the results could be biased by confounding by indication. Furthermore, there was a possibility of nondifferential outcome misclassification because suicides may have been underestimated. Residual confounding from the type of epilepsy was also a possible explanation for the results in the study of Andersohn et al. [23] because the code-defined diagnoses for type of epilepsy were not validated. The small numbers of cases and controls could have also decreased the power of the study to detect an effect, particularly for individual drugs. In the study of Arana et al. [22], the authors excluded all individuals with a familial or personal history of suicide, which could have led to an overall underestimation of the risk of suicide.

Pugh et al. [17] conducted a study with in- and outpatients aged 65 years and older. Demographic, psychiatric comorbidity and chronic pain variables were used to construct a propensity score to control for confounding in the model. The authors reported a hazard ratio of 3.90 (95% CI 2.93–5.19) for any AED use. The authors did not assess the effect of prevalent users on the results. Except for levetiracetam, marketed in 2004, all the other AEDs have long been on the market. Thus, some of the patients

included may not have been naive to AEDs. The authors developed a propensity score model and gave a c-statistic value of 0.66. The c-statistic tells us how well the model with the observed covariates predicted the probability of receiving an AED. The c-statistic usually ranges between 0.5 (chance classification) and 1 (perfect classification) [24]. However, Pugh et al. [17] did not provide the distribution of the propensity scores among the AED users and nonusers, which would have been more informative of the distribution of the confounders between groups [24]. Thus, it was difficult to assess whether there was any error in their estimation. In addition, there was the potential for nondifferential misclassification of suicide.

Three SRs [2, 25, 26] included randomized trials of efficacy; suicide was collected as a potential adverse event in these trials. The FDA's meta-analysis [2] reported an increased risk of suicide for all AEDs (OR 1.80, 95% CI 1.24–2.66). Van Lieshout and MacQueen [25] and Premkumar and Pick [26] reported on the effects of lamotrigine on suicide in patients with bipolar disorder and depression (OR 0.26, 95% CI 0.02–2.77) and with schizophrenia (OR 2.97, 95% CI 0.12–72.18). The results of all these 3 SRs could have suffered from an ascertainment bias of adverse events, even though the FDA's meta-analyses used a standardized protocol to detect and assess potential suicide events [2]. In the FDA's meta-analysis, suicide was described post hoc by the sponsor of the drug. In addition, there were differences in the duration of treatment and treatment discontinuation between the placebo and treatment arms, with higher rates of discontinuation in the drug arm and a longer duration in the placebo arm.

The review by Fountoulakis et al. [16] concluded that there were not enough data to confirm the association between an increased risk of suicide and AEDs as a group. With regard to individual drugs, they concluded that lamotrigine and topiramate may increase the risk of suicide, whereas carbamazepine and valproic acid were protective. However, this review searched a single bibliographic database. It included all population subgroups except patients with mood disorders, any type of comparator except studies that only compared AEDs and lithium, and any type of suicidal behavior. The authors restricted the type of studies to those with a naturalistic design, database studies and prospective trials, without further specifications. They did not assess the quality of the included studies.

Concerning individual drugs, studies have shown an increased risk of suicide for patients taking phenobarbital (1 study [21]), phenytoin (1 study [17]), carbamazepine (1 study [22]), valproic acid (3 studies [17, 21, 22]), la-

Table 2. Effect measure (95% CI) by drug and by subgroup of population

	General population	Epilepsy	Mental illness	Other disorder	Study
All antiepileptic drugs	3.90 (2.93–5.19)				Pugh [17], 2012
			0.19 (0.08–0.47)		Gibbons [18], 2009
	1.84 (1.36–2.49)				Olesen [21], 2010
		Epilepsy only: 0.59 (0.35–0.98)	Depression: 1.65 (1.24–2.19)	No epilepsy, no depression, no bipolar disorder: 2.57 (1.78–3.71)	Arana [22], 2010 (by indication)
		Epilepsy and depression: 1.24 (0.56–2.72)	Bipolar disorder: 1.13 (0.35–3.61)		
		AEDs with high risk of depression: 3.08 (1.22–7.77)			Andersohn [23], 2010
	AEDs with low risk of depression: 0.87 (0.47–1.59)				
	1.80 (1.24–2.66)	3.53 (1.28–12.1)	1.51 (0.95–2.45)	1.87 (0.81–4.76)	FDA [2], 2008 (by indication)
			0.88 (0.72–1.08)		Gibbons [18], 2009
			1 prescription vs. none: 3.30 (2.17–4.99)		Sondergård [20], 2008
Phenobarbital	1.65 (0.40–6.74)				Pugh [17], 2012
	1.96 (1.02–3.75)				Olesen [21], 2010
		0.66 (0.23–1.90)			Andersohn [23], 2010
Phenytoin	5.33 (1.55–18.3)				Pugh [17], 2012
	0.37 (0.03–4.44)				Olesen [21], 2010
		0.67 (0.42–1.08)			Andersohn [23], 2010
Carbamazepine	1.19 (0.30–4.68)				Pugh [17], 2012
	0.48 (0.21–1.12)				Olesen [21], 2010
				No epilepsy, no depression, no bipolar disorder: 1.35 (1.02–1.79)	Arana [22], 2010
		0.83 (0.57–1.20)			Andersohn [23], 2010
	0.65 (0.08–4.42)			FDA [2], 2008	
Valproic acid	15.44 (9.4–25.4)				Pugh [17], 2012
			0.73 (0.51–1.02)		Gibbons [18], 2009
	2.08 (1.04–4.16)				Olesen [21], 2010
				No epilepsy, no depression, no bipolar disorder: 1.44 (0.99–2.08)	Arana [22], 2010
		0.68 (0.56–1.01)			Andersohn [23], 2010
	0.72 (0.29–1.84)			FDA [2], 2008	
Lamotrigine	36.6 (15.9–84.5)				Pugh [17], 2012
			0.85 (0.62–1.16)		Gibbons [18], 2009
	3.15 (1.35–7.34)				Olesen [21], 2010
				No epilepsy, no depression, no bipolar disorder: 1.07 (0.58–1.98)	Arana [22], 2010
		0.93 (0.49–1.76)			Andersohn [23], 2010
			0.26 (0.02–2.77)		Van Lieshout [25], 2010
	2.08 (1.30–4.40)				FDA [2], 2008
		2.97 (0.12–72.18)		Premkumar [26], 2006	
Topiramate	6.83 (1.9–24.51)				Pugh [17], 2012
			1.87 (1.22–2.87)		Gibbons [18], 2009
	2.72 (0.23–32.78)				Olesen [21], 2010
				No epilepsy, no depression, no bipolar disorder: 0.52 (0.15–1.78)	Arana [22], 2010
		2.42 (0.54–10.77)			Andersohn [23], 2010
	2.53 (1.21–5.85)			FDA [2], 2008	

Table 2 (continued)

	General population	Epilepsy	Mental illness	Other disorder	Study
Gabapentin	2.56 (1.96–4.16)				Pugh [17], 2012
	0.93 (0.76–1.14)	0.83 (0.34–2.04)	All psychiatric diagnoses: 0.73 (0.54–0.99)	Pain disorder: 0.99 (0.76–1.14)	Gibbons [18], 2010
			1.16 (0.66–2.05)		Gibbons [18], 2009
	2.20 (0.83–5.83)				Olesen [21], 2010
				No epilepsy, no depression, no bipolar disorder: 0.89 (0.45–1.77)	Arana [22], 2010
			0.70 (0.18–2.75)		Andersohn [23], 2010
	1.57 (0.12–47.66)			FDA [2], 2008	
Levetiracetam	8.23 (1.41–48.11)				Pugh [17], 2012
				No epilepsy, no depression, no bipolar disorder: 0.70 (0.12–4.0)	Arana [22], 2010
		6.42 (1.24–33.36)			Andersohn [23], 2010
	2.75 (0.62–19.36)				FDA [2], 2008
Oxcarbazepine			0.98 (0.62–4.56)		Gibbons [18], 2009
	0.84 (0.30–2.32)				Olesen [21], 2010
	1.91 (0.15–56.33)				FDA [2], 2008

motrigine (3 studies [2, 17, 21]), topiramate (3 studies [2, 17, 18]), gabapentin (1 study [17]) and levetiracetam (2 studies [17, 23]). However, a similar number of studies demonstrated a protective effect – valproic acid (1 study [23]) and gabapentin (1 study [19]) – or no effect – phenobarbital (2 studies [17, 23]), phenytoin (2 studies [21, 23]), valproic acid (3 studies [2, 18, 22]), lamotrigine (5 studies [18, 22, 23, 25, 26]), topiramate (2 studies [22, 23]), gabapentin (5 studies [2, 18, 21–23]), levetiracetam (3 studies [2, 22]) and oxcarbazepine (3 studies [2, 18, 21]) – of these AEDs on suicide.

Table 2 shows the effect measures and the corresponding 95% CIs grouped by population subgroup and/or indication for use and AEDs.

Discussion

Since the publication of the FDA alert on the risk of suicide associated with 11 AEDs, several observational studies [27, 28], as well as reviews and expert opinions [29–32], have attempted to disentangle this controversial relationship. We ultimately reviewed 11 studies that reported findings on the effects of AEDs on suicide compared to a placebo or no treatment; 3 studies [2, 17, 21] reported a 2- to 4-fold overall increased risk of suicide with AEDs as a group. For epilepsy, the FDA meta-analysis [2] showed an increased risk of suicide, whereas Ara-

na et al. [22] did not find an increased risk of suicide for patients with epilepsy, but did find an increased risk of suicide in depressive patients. However, the close relationship between epilepsy and other neurological and psychiatric disorders has determined the use of AEDs for different indications [33]. Andersohn et al. [23] showed that the risk of suicide in epilepsy patients depended on whether the AEDs had a high or low risk of depression. Concerning mental illness, Arana et al. [22] showed an increased risk of suicide among patients with depression, but not among patients with bipolar disorder. Sondergård et al. [20] showed that any AED could increase the risk of suicide in patients with bipolar disorder under specialty out- and inpatient care. Gibbons et al. [18] showed a protective effect of AEDs for the same type of patients, although this study included the outpatient healthcare sector and as it required a 1-year follow-up of patients to be included, patients who committed suicide during this time period might have been excluded. In the study of Arana et al. [22] it seemed that the effect of AEDs on bipolar patients was uneventful. For indications other than epilepsy, depression and bipolar disorder, Arana et al. [22] showed a 3-fold increased risk of suicide.

For Pugh et al. [17] and Sondergård et al. [20] the use of AEDs may be a marker of disease severity, as patients in hospital have an increased risk of suicide attempts. Moreover, in Pugh et al. [17], depression and previous suicidality were more prevalent among patients exposed

to AEDs. Confounding by indication could partly explain their results. In the study of Olesen et al. [21], during the case time period an increased risk of suicide could precede the prescription of an AED. Several studies presented in this review [18, 20, 21] did not adjust for previous suicidal behavior, which has been reported as the most significant risk factor for attempted and completed suicides [34]. Gibbons et al. [18] adjusted for suicide attempts in the year before the diagnosis of bipolar disorder. Andersohn et al. [23] reported that they adjusted for prior suicidal behavior, but the extent of the adjustment was unclear. The same issue applied in the adjustment for the type of epilepsy. Residual confounding could have masked the effect of an association in all of the observational studies we included. In the FDA's meta-analysis [2], the epilepsy patients took the AED under study as an adjuvant to other AEDs, which may indicate more severe disease. Suicide in this group of patients could be related to the 'forced normalization' phenomenon [35].

Another potential flaw in all the studies presented in this review is the nondifferential misclassification of suicide which was assumed to be a limitation in all healthcare database studies. Theoretically, nondifferential disease misclassification would bias the effect estimate towards the null, which may cause a problem for interpreting the results of studies reporting a null or very weak association between AEDs and suicide [36]. There was no description of how adverse events were collected or how causality of an adverse event to the drug was assessed in the clinical trials reviewed in the included SRs. In the FDA's meta-analysis [2], adverse events were measured retrospectively based on the patient's spontaneous reports.

The dosage of the treatment and the compliance could not be estimated in several observational studies [17, 18–23]. This fact could introduce nondifferential exposure misclassification. Andersohn et al. [23] did calculate the duration of the prescription minimizing this type of bias. The nondifferential misclassification of AEDs could bias the effect estimate towards the null. Furthermore, many studies [17–19, 21] focused on 'ever use' of an AED over a long time span, which may also have biased the effect estimate towards the null.

This review showed that the effect estimates were heterogeneous across populations or by indication. An explanation for these contradictory findings could be, for example, that the patients on AEDs represented a subgroup of patients at particularly high risk of suicide, and AEDs would serve as a marker for the severity of disease.

The main strength of this SR is that we included studies that had a placebo or nontreatment group as the reference group. The inclusion of randomized and observational studies resulted in a broad overview of the relationship between AEDs and suicide. Another strength of this study is the standardized narrative synthesis. In an attempt to assess clinical heterogeneity we grouped the study results by population subgroup or by indication. Because of the few numbers of studies we could not group by type of study. Comparing the results between studies is difficult because of the differences in the definition of the exposure or outcome as well as the confounders adjusted for in the statistical model. In addition, we developed a checklist to assess the studies we included in this SR of adverse effects. Although this checklist needs to be validated, it is a step toward assessing the quality of any type of study included in such SRs.

Even though we searched in several bibliographic databases, we did not search EMBASE, which is a complementary bibliographic database to the PubMed database. We did not attempt to search gray literature. Hence, there is potential for publication bias. Moreover, we did not identify any clinical trials, although they were in our inclusion criteria. However, we assessed the effect of AEDs on suicide using SRs that included randomized trials of AED efficacy. This problem was the result of the difficulty in searching the bibliographic databases for adverse events in RCTs on efficacy. It is unlikely that clinical trials include any terms related to assessment of adverse events in their titles, abstracts or keywords.

In an attempt to overcome some of the flaws detected in the published studies we believe that a new study should be conducted retrieving the information from a large healthcare database because suicide is a rare event. The exposure to AEDs should be as detailed as possible to account for the duration of the exposure. In addition, to avoid outcome misclassification, the study should try to link the database with a mortality register to better capture the causes of death, or search for cases in the database using free words. Alternatively, a review of a sample of medical charts to validate the diagnoses could be conducted to ensure the detection of all potential cases. Due to the close relationship between several neuropsychiatric disorders and suicide, and the perils of confounding by indication, all of the diagnostic codes for the covariates relevant to the study should also be validated. We propose a set of confounders: epilepsy (type, age at onset, mono- or polytherapy), mood disorders, schizophrenia, neuropathic pain or other indications including off-label use, antipsychotics, other central nervous system drugs, per-

sonal history of previous suicide attempts, and socioeconomic status. Age and gender should be considered potential effect modifiers. Ideally, the severity of the diseases included as confounders should be thoroughly assessed, directly or through a proxy variable such as referrals to the hospital or to specialty care. In addition, any new RCT conducted to determine the efficacy of a new AED or to determine a new AED indication should include suicidality as a specific safety-related outcome.

Conclusions

There is no clear evidence to confirm or rule out an association between the use of AEDs and suicide because of the heterogeneity at the clinical and the methodological level.

Most of the studies considered an overall effect of AEDs as a single class effect. This assumption may need to be revisited in light of the different effects of the different AEDs on mood.

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