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Sex differences in suspected adverse drug reactions of anti-seizure medications reported in EudraVigilance

Michael Magdy Fahmy Girgis [a], Gergely Farkasinszky [b], Klára Fekete [c], István Fekete [c], Miklós Vecsernyés [a], Ildikó Bácskay [d,e], László Horváth [a,*]

[a] Department of Pharmaceutical Surveillance and Economics, Faculty of Pharmacy, University of Debrecen, Debrecen, Hungary
[b] Division of Nuclear Medicine and Translational Imaging, Department of Medical Imaging, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
[c] Department of Neurology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
[d] Healthcare Industry Institute, University of Debrecen, Debrecen, Hungary
[e] Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Debrecen, Debrecen, Hungary

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ABSTRACT

Introduction: Epilepsy is one of the most common neurological disorders and requires long-term treatment with anti-seizure medication (ASM) which may cause adverse drug reactions (ADRs). Our aims were to investigate potential sex differences in reporting suspected ADR (sADRs) of ASMs through studying their seriousness, outcomes and Sudden Unexpected Death in Epilepsy (SUDEP).

Methods: Using EudraVigilance database, reported sADRs with different ASMs over a ten year period were extracted. List of ASMs was compiled according to Anatomical Therapeutic Chemical Classification System. Reporting Odds Ratio (ROR), 95 % confidence interval (95 % CI), p-value were calculated.

Results: In general, more sADRs were reported from females (603,936, 57.46 %). Males showed positive association with the following seriousness criteria: *'life threatening'* (ROR=1.02, 95 %CI: 1.01–1.04; $p < 0.001$), *'caused/prolonged hospitalisation'* (ROR=1.06, 95 %CI: 1.05–1.07; $p < 0.001$), *'results in death'* (ROR=1.44, 95 % CI: 1.43–1.46; $p < 0.001$), and *'congenital anomaly'* (ROR=2.43, 95 %CI: 2.41–2.45; $p < 0.001$). Only with *'not recovered / not resolved'* outcome criteria showed negative association in males (ROR=0.72, 95 %CI: 0.70–0.73; $p < 0.001$), the other outcome criteria demonstrated positive association in the followings: *'fatal'* (ROR=1.43, 95 %CI: 1.41–1.45; $p < 0.001$), *'recovered / resolved'* (ROR=1.08, 95 %CI: 1.07–1.09; $p < 0.001$), *'recovered / resolved with sequelae'* (ROR=1.06, 95 %CI: 1.01–1.12; $p < 0.001$), and *'recovering / resolving'* (ROR=1.14, 95 %CI: 1.12–1.15; $p < 0.001$).

Conclusion: Differences were observed between males and females, particularly in terms of seriousness criteria, worse outcomes but prone to recover, and associations with SUDEP to the detriment of males. When choosing an ASM for a patient or especially if the patient has previously experienced an adverse drug reaction. these aspects can also be taken into account and may be important.

1. Introduction

Epilepsy requires life-long treatment and affects millions of people. It constitutes challenge for people living with epilepsy at various life stages, their relatives and epileptologists to have the best treatment considering morbidity and mortality (Beghi, 2020). Epilepsy is more prevalent in males (Beghi, 2020;Walsh et al., 2017). This can be confirmed based on differences in the prevalence of other risk factors, as well as an increasing tendency of women to conceal their health condition owing to various sociocultural and socioeconomic reasons (Stangl et al., 2019; Omer et al., 2021; Cardoso et al., 2021).

Males have a heavier burden of epilepsy (Hu et al., 2021). Sex differences can be seen in terms of epileptogenesis and type of epilepsies (Reddy et al., 2021), generalized epilepsy is common among males and focal epilepsy among females (Carlson et al., 2014). This could determine the treatment, but only valproate was significantly higher in men

* Corresponding author at: Rex Ferenc utca 1., Debrecen, Hungary H-4002.
E-mail addresses: michael.girgis@pharm.unideb.hu (M.M.F. Girgis), farkasinszky.gergely@med.unideb.hu (G. Farkasinszky), feketek@med.unideb.hu (K. Fekete), fekete@med.unideb.hu (I. Fekete), vecsernyes.miklos@pharm.unideb.hu (M. Vecsernyés), bacskay.ildiko@pharm.unideb.hu (I. Bácskay), lhorvath@med.unideb.hu (L. Horváth).

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in a Spanish observational study (Mercadé Cerdá et al., 2020).

In general, being a female has been considered a risk factor for adverse drug reactions, which can be explained by differences in pharmacokinetics and pharmacodynamics, and because females possibly take more medicines and higher doses than males. Differences in the volume distribution of drugs (Vd) due to a higher percent of body fat in females might be a possible explanation. Nevertheless, drug clearance might be compensated by lower glomerular filtration rates in females (Anderson, 2008). In an attempt to confirm the above, renal function differences were examined and lower glomerular filtration rates were found in the female than male subjects 90 ml/min per 1.73 m^2 and 98 ml/min per 1.73 m^2, respectively (Melsom et al., 2022). Regarding the role of drug metabolizing enzymes such as cytochrome P450 (CYP) and uridine diphosphate glucuronosyl transferase (UGT) the difference is important. This can lead to variation in clearance; for instance, females were found to have lower activity of CYP1A2, CYP2E1, and UGT, higher activity of CYP3A4, CYP2A6, and CYP2B6 but no differences in CPY2C9 or CYP2D6 activity. Altogether, as a result of the above, they may influence both the therapeutic effect and potential for adverse drug reaction occurrences (Anderson, 2008).

Certain physiological life phases like pregnancy, menopause and menstrual cycles occur exclusively in females. There is limited data on the possible impact exerted by the fluctuation of oestradiol levels on anti-seizure medication serum levels during the menstrual cycle (Perucca et al., 2014). For instance, one study including 37 women with epilepsy reported an increase in seizure frequency in menstrual and premenstrual phases coinciding with a significant decrease in phenytoin plasma concentrations between the 27th and 28th day of the menstrual cycle (Rościszewska et al., 1986). Pharmacokinetics of anti-seizure medications are remarkably impacted by pregnancy due to increased metabolism and renal clearance leading to decreased serum concentrations, which is most prominent with lamotrigine. Only few studies investigated the effect of hormonal changes on anti-seizure medications levels during the menopause. As an example, one study found decline in the dose/concentration ratio of lamotrigine in women aged 51–55 years (Tomson et al., 2010).

Overall, pharmacokinetic interactions with anti-seizure medications showed no sex specificity, however, medicines that are consumed exclusively by either sex may interact with anti-seizure medications. One important example is when interactions potentially occur between contraceptive steroids and anti-seizure medications. Several anti-seizure medications can increase either oestrogen or progesterone metabolism leading to a decline in the concentration of these hormones, thereby decreasing contraceptive efficacy (Perucca et al., 2014). In males taking CYP3A4 inducers such as carbamazepine and phenytoin, the serum levels of tadalafil decreased (Cialis 2013).

Focusing on the sex-related differences in anti-seizure medication prescription trends, a Swedish study found that being a woman was among the factors related to greater likelihood of obtaining treatment by a neurologist and getting more lamotrigine prescriptions than men (Mattsson et al., 2010). In a cross-sectional Colombian study, involving a huge database comprising 6.5 million people, 13,793 patients with epilepsy were detected. The majority of those patients (52.9 %) were women and polymedication was also more frequently reported in women (59.5 %) (Morales-Plaza and Machado-Alba, 2017).

The research on the potential sex differences regarding the effects of anti-seizure medications was limited, moreover, lack of significant difference was reported among the few conducted clinical trials examining this issue (Perucca et al., 2014). Abnormalities in the profiles of sex hormones were detected in females consuming enzyme inducing anti-seizure medications like carbamazepine and phenytoin, where the levels of total serum testosterone free androgen index, dehydroepiandrosterone sulphate and oestradiol were reduced, while that of the sex-hormone-binding globulin rose (Brodie et al., 2013; Verrotti et al., 2011). Similarly, enzyme inducing anti-seizure medications led to a decrease in androgen levels and changes in sexual function: for instance, impaired fertility, reduced sperm counts and abnormalities in sperm morphology were noticed (Brodie et al., 2013).

In a retrospective cohort study based on five large United States of America healthcare databases, researchers found that – compared to men – women were 27 % more likely to develop treatment resistant epilepsy during a one-year follow up, independently of age (Cepeda et al., 2022). A study based on a literature review concluded that sex differences regarding adverse drug reaction profiles could contribute to anti-seizure medication choice (Perucca et al., 2014). Valproic acid increases the risk of major malformations, reduced intellectual development, autistic disorders in the offspring, furthermore it may induce hormonal disorders, declined fertility and polycystic ovarian syndrome; accordingly it is highly recommended to avoid valproic acid in women of childbearing age (Pisani et al., 2017). Females taking anti-seizure medications are more exposed to developing skin and bone adverse drug reactions, especially those treated with enzyme-inducing anti-seizure medications. Males taking anti-seizure medications, especially vigabatrin, they are also likely to develop adverse drug reactions, e.g. vision loss and a worsened lipid profile.

The aim of this study was to provide real-life data on potential sex differences in suspected adverse drug reactions (sADRs) of anti-seizure medications through studying and investigating their seriousness, outcomes and Sudden Unexplained Death in Epilepsy (SUDEP) reported in EudraVigilance.

2. Methods

2.1. Data source

EudraVigilance system was used to mine information on sADRs based on individual case safety reports. In accordance with Regulation (EU) 2016/679, the General Data Protection Regulation (GDPR) and Regulation (EU) 2018/1725, the EU Data Protection Legislation (EU DPR) European database of suspected adverse drug reaction reports (www.adrreports.eu) was utilized as an access tool (Krzysztofek, 2017; Office LP 2019; Ruggiero et al., 2022). Line listing functionality was applied to export results of reported sADRs with different anti-seizure medications (which were considered at the level of chemical structure or active pharmaceutical ingredient) over the period from 1st January 2012 to 31st December 2021 in a tabulated format for further analyses. Line listings were extracted. They consisted of the following information reported: European Union Local Number; Worldwide Unique Case Identification; Country; EudraVigilance Gateway Receipt Date; Year; Report Type; Primary Source Qualification; Primary Source Country for Regulatory Purposes; Literature Reference; Patient Age Group; Patient Age Group (as per reporter); Patient's Sex; Parent Child Report; Suspect/interacting Drug List; Concomitant/Not Administered Drug List; Individual Case Safety Reports Form; Reaction List preferred terms (Duration - Outcome - Seriousness Criteria).

2.2. Adverse drug reactions

Medical Dictionary for Regulatory Activities version 24.0 was used to determine the system organ classes of individual reported preferred terms for each sADR.

According to EudraVigilance, seriousness is classified as *'other medically important condition'*, *'caused/prolonged hospitalisation'*, *'congenital anomaly'*, *'disabling'*, *'life threatening'*, and *'results in death'*; outcome is classified as *'fatal'*, *'not recovered/not resolved'*, *'recovered/resolved'*, *'recovered/resolved with sequelae'*, and *'recovering/resolving'* (Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs): European Medicines Agency 2010). These criteria are predefined terminology with their medical meaning.

2.3. Antiseizure medications

A list of anti-seizure medications (also known as anti-epileptics or anticonvulsants) was compiled according to Anatomical Therapeutic Chemical (ATC) classification system N03A subgroups (WHOCC 2016). The chemical grouping of the ATC Classification System was employed for aggregate analysis.

The old and new types of anti-seizure medications:

a.) Old types:
Aminobutyric acid, barbexaclone, beclamide, carbamazepine, clonazepam, clorazepate potassium, ethosuximide, ethotoin, mephenytoin, mesuximide, metharbital, methylphenobarbital, paramethadione, phenacemide, pheneturide, phenobarbital, phensuximide, phenytoin, primidone, sultiame, trimethadione, valproic acid and sodium valproate.

b.) New types:
Brivaracetam, cenobamate, clobazam, eslicarbazepine, felbamate, fenfluramine, fosphenytoin, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, retigabine, rufinamide, stiripentol, tiagabine, topiramate, vigabatrin, zonisamide.

2.4. Statistical analysis

Microsoft Office Excel 2019 and SPSS for Windows 25.0 (SPSS Inc. Chicago, USA) were used to carry out data arrangement and analysis. Analysis of outcomes and seriousness in different anti-seizure medications were calculated as follows: Reporting Odds Ratio (ROR) with 95 % confidence interval (95 %CI), p-value (Bate and Evans, 2009; Rothman et al., 2004). Differences were considered significant if $p < 0.05$.

We presented this methodology in our previous publication (Girgis et al., 2024).

Volcano plot was used for visualization that is a type of scatter-plot that is used to quickly identify changes in large data sets composed of replicate. (https://huygens.science.uva.nl/VolcaNoseR/)

3. Results

3.1. Reports overview

In a total of 276,694 reports, 106,834 (38.61 %) and 148,957 (53.83 %) were on males and females, respectively, while no sex was specified in 20,903 (7.56 %) of the cases. In the exported line listings, 1051,144 separate sADRs were reported as preferred terms in the EudraVigilance database, whereas the figures in sADRs for males and females were 391,174 (37.21 %) and 603,936 (57.45 %), respectively. The relevant information applied for as many as 56,034 (5.34 %) non-specified subjects. The number of reported sADRs were 3.66/ male patients, 4.05/ female patients and 2.68/ not specified patients.

3.2. Reported preferred terms

Among the males, the ten most frequently reported preferred terms were as follows: *'seizure'* (14,602; 1.39 %), *'drug ineffective'* (9106; 0.87 %), *'somnolence'* (5117; 0.49 %), *'off label use'* (4585; 0.44 %), *'dizziness'* (4033; 0.38 %), *'drug interaction'* (4006; 0.38 %), *'rash'* (3685; 0.35 %), *'epilepsy'* (3635; 0.35 %), *'toxicity to various agents'* (3457; 0.33 %) and *'pyrexia'* (3211; 0.31 %)., However, *'seizure'* (16,168; 1.54 %), *'drug ineffective'* (13,459; 1.28 %), *'dizziness'* (8239; 0.78 %), *'somnolence'* (7534; 0.72 %), *'pain'* (6793; 0.65 %), *'off label use'* (6255; 0.60 %), *'rash'* (6078; 0.58 %), *'fatigue'* (5968; 0.57 %), *'nausea'* (5918; 0.56 %) and *'headache'* (5765; 0.55 %) were the ten most frequently reported preferred terms among the females.

3.3. Seriousness

Males had a negative association for *'other medically important condition'* and *'disabling'* (ROR=0.81, 95 %CI: 0.80–0.82; $p < 0.001$ and ROR=0.91, 95 %CI: 0.89–0.93; $p < 0.001$, respectively). Meanwhile, the rest of seriousness criteria showed a positive association with *'life threatening'* (ROR=1.02, 95 %CI: 1.01–1.04; $p < 0.001$), *'caused/prolonged hospitalisation'* (ROR=1.06, 95 %CI: 1.05–1.06; $p < 0.001$), *'results in death'* (ROR=1.44, 95 %CI: 1.43–1.46; $p < 0.001$), and *'congenital anomaly'* (ROR=2.43, 95 %CI: 2.41–2.45; $p < 0.001$).

For those treated with barbiturates, the seriousness criterion of *'congenital anomaly' 'caused/prolonged hospitalisation', 'congenital anomaly'* and *'results in death'* showed a significant positive association in males (Table S A1) and a significant negative association in females. As far as the seriousness criteria *'caused/prolonged hospitalisation'* and *'congenital anomaly'* are regarded, there was a significant positive association with methylphenobarbital in males (Table S B1).

When taking benzodiazepines, the seriousness criteria *'caused/prolonged hospitalisation'* and *'disabling'* were in a negative significant association in males compared to the positive significant association in females (Tables S A2 and A3). Taking clorazepate potassium showed a significant positive association in males regarding two seriousness criteria, i.e. *'other medically important condition'* and *'caused/prolonged hospitalisation'* and (Table S B1 and Fig. 1). As regards *'life threatening'* seriousness, males had a significant positive association with clobazam (Table S B1).

Focusing on seriousness of carboxamides, there was a significant positive association with *'caused/prolonged hospitalisation'* in males taking rufinamide compared to a significant negative association in females (Tables S B1 and 4). Only females taking rufinamide had a significant positive association with the seriousness criterion *'disabling'*.

With respect to fatty acid derivatives, males had a significant negative association with the seriousness criterion of *'caused/prolonged hospitalisation'* (Table S A2) and a significant positive association with *'congenital anomaly'* (Table S A1). As for the *'life threatening'* seriousness criterion, males had a significant negative association compared to a significant positive association observed in females (Table S A3). Only females had a significant positive association in aminobutyric acid and valproate with *'life threatening'* seriousness criterion (Table S B3).

Looking at seriousness of hydantoins, as a *'caused/prolonged hospitalisation', 'life threatening'* and *'results in death'* criteria, a significant positive association was found in males (Table S A1) in comparison to a significant negative association in females (Table S A4). Females had a significant positive association in phenytoin with *'results in death'* (Table S B4) and males had with all seriousness criteria except *'results in death'* (Table S B1). As regards the *'caused/prolonged hospitalisation'* seriousness criterion, there was a significant positive association with mephenytoin in females only.

Among other anti-epileptics, males had a significant negative association in general (Table S A2) while, in contrast, females had a significant positive association (Table S A3), *'other medically important condition'* criterion is an exemption. There was a significant positive association in fenfluramine (females only), lamotrigine (females only), retigabine (males only) and brivaracetam (males only) with *'results in death'* seriousness (Tables S B1 and 3). As regards *'caused/prolonged hospitalisation'* seriousness, there was a significant positive association with sultiame (males only), fenfluramine (females only), gabapentin (females only), retigabine (males only) and topiramate (females only). As for the *'congenital anomaly'* seriousness, males had a significant positive association with topiramate and zonisamid. There was a significant positive association in stiripentol (males only) and retigabine (females only) concerning the seriousness criterion *'disabling'*. Regarding *'life threatening'* seriousness, a significant positive association was found in fenfluramine (females only), cenobamate (males only), and perampanel (males only) (Figs. 1 and 2).

Focusing on seriousness with oxazolidines, only females had a

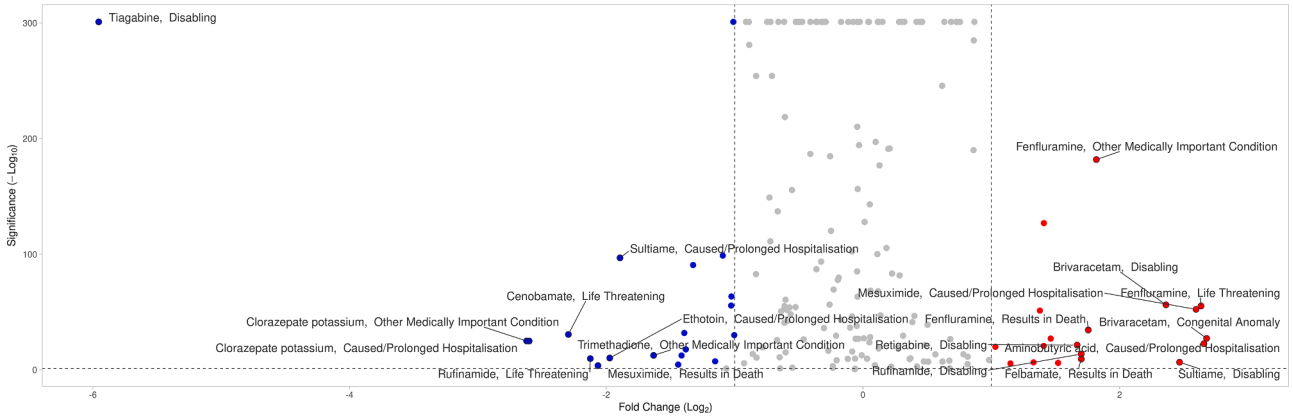

Fig. 1. Top ten positive associations of seriousness by anti-seizure medications.

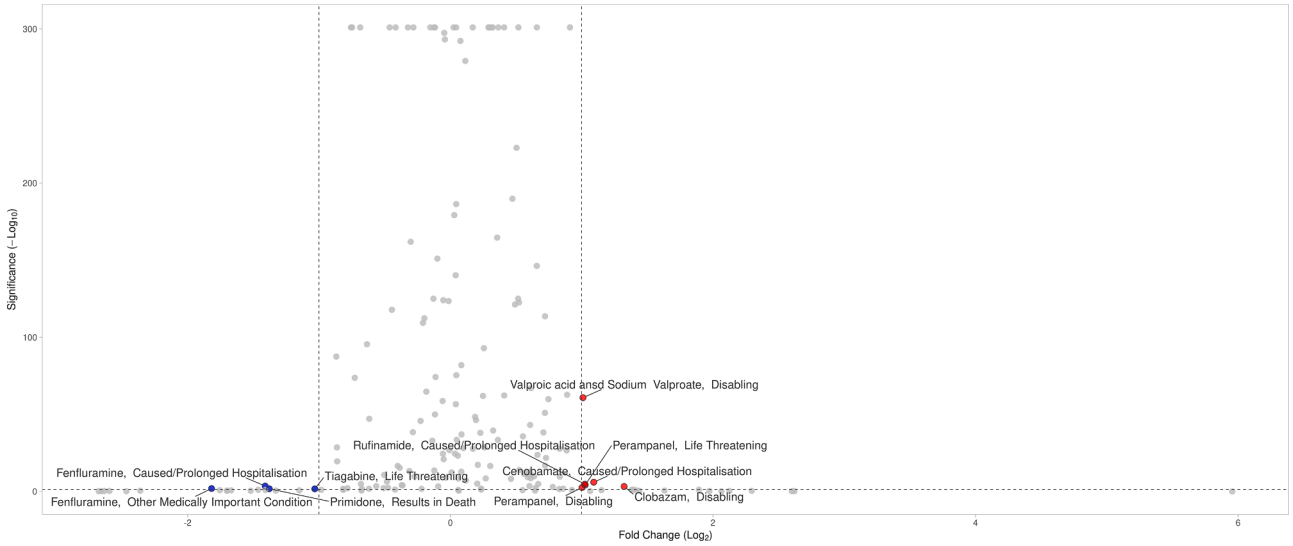

Fig. 2. Top ten negative associations of seriousness by anti-seizure medications.

significant positive association with the *'caused/prolonged hospitalisation'* seriousness criterion (Tables S A3). With respect to *'congenital anomaly'* and *'results in death'*, there was a significant positive association in males (Tables S A1). In males only, there were a significant positive association with trimethadione and ethotoin in case *'other medically important condition'* and *'caused/prolonged hospitalisation'*, respectively (Tables S B3).

In succinimides, there was a significant positive association with mesuximide in males only with *'results in death'* seriousness. Regarding *'life threatening'* seriousness, ethosuximide showed a significant positive association and mesuximide in *'other medically important condition'* and *'caused/prolonged hospitalisation'* in females only.

3.4. Outcome

A negative association in males was detected only with the outcome criteria '*not recovered / not resolved*' (ROR=0.72, 95 %CI: 0.70–0.73; $p <$ 0.001), the other outcome criteria demonstrated positive association as follows: '*fatal*' (ROR=1.43, 95 %CI: 1.41–1.45; $p < 0.001$), '*recovered / resolved*' (ROR=1.08, 95 %CI: 1.07–1.09; $p < 0.001$), '*recovered / resolved with sequelae*' (ROR=1.06, 95 %CI: 1.01–1.12; $p < 0.001$), and '*recovering / resolving*' (ROR=1.14, 95 %CI: 1.12–1.15; $p < 0.001$).

Looking at outcomes considering barbiturates, a significantly increased association were noticed with *'fatal'* and *'recovered/resolved'* in males, and *'not recovered/resolved'* in females. Only males had a significant positive association with *'fatal'* outcome if they were treated with phenobarbital (Tables S B1).

As regards benzodiazepines, a significantly positive association was found with outcomes of *'recovered/resolved with sequelae'* in females. Regarding the outcomes of *'not recovered/not resolved'* and *'fatal'*, a significant positive association was found in males compared to a significant negative association in females (Tables S A1 and A4). There was a significant positive association after giving clonazepam with outcomes *'not recovered/not resolved'* in females only compared to a significant negative association in males (Tables S B3 and B2).

With respect to carboxamides, only females exhibited a significant positive association with the outcome *'fatal'* and *'not recovered/not resolved'*, and in males *'recovered/resolved with sequelae'* (Tables S A1 and 3). Treatment with eslicarbazepine resulted in a significant positive association with the outcome *'fatal'* and *'not recovered/not resolved'* in males only (Tables S B1).

Among fatty acid derivates, *'fatal'* and *'not recovered/not resolved'* criteria showed positive associations in females, while *'recovered/resolved'*, *'recovered/resolved with sequalae'* and *'recovering/resolving'* were among the positive associations for males (Tables S A1 and 3).

As regards hydantoins, *'recovered/resolved'* outcome was described in males only, medication with ethotoin being a trigger of a significant positive association (Tables S B2). Similarly, only females had a significant positive association with mephenytoin treatment resulting in the outcome '*not recovered/not resolved*'.

Regarding other anti-epileptics, there was a significant positive association in females and a significant negative association in males when the outcome was identified as *'fatal', 'recovered/resolved'* and *'recovered/resolved with sequelae'* (Tables S A4 and A1). There was a significant positive association with cannabidiol and perampanel in males only (Tables S B1), in contrast with a significant positive associations of fenfluramine, and topiramate in females with *'fatal'* outcome (Tables S B3 and Fig. 3) but topiramate had negative association in males (Fig. 4). Giving fenfluramine and topiramate induced a significant positive association with the outcome *'not recovered/not resolved'* among the females included in the studies (Fig. 3).

With respect to oxazolidines, a significant positive association could be confirmed only in males, the outcome being *'fatal'* (Tables S A1).

As for succinimides: treatment with mesuximide turned out to be '*fatal*' only in females, confirming a significant positive association (Tables S A3).

3.5. Sudden unexplained death in epilepsy

Male patients are more likely to have SUDEP than female patients (ROR=1.68, 95 %CI: 1.47–1.88; $p < 0.001$).

A significant positive association was observed among men taking anti-seizure medications, i.e. eslicarbazepine and oxcarbazepine from the carboxamide group (Tables S B1).

Regarding fatty acid derivatives, only males taking vigabatrin had a significant positive association with SUDEP.

In the group of other anti-epileptics, males had a significant increased association with SUDEP in comparison to a significant negative association in females. Only males taking stiripentol and topiramate had a significant positive association with SUDEP (Tables S B1). Only females taking sultiame, brivaracetam and cenobamate had a significant increased association with SUDEP (Tables S B3).

No SUDEP cases were reported either among males in association with treatment using barbexaclone, cenobamate, ethosuximide, primidone, rufinamide, and sultiame, or females on stiripentol and tiagabine. In addition, SUDEP has not been reported in patients of either sex with the following anti-seizure medications: aminobutyric acid, beclamide, clorazepate potassium, ethotoin, fosphenytoin, gabapentin, mephenytoin, mesuximide, metharbital, methylphenobarbital, paramethadione, phenacemide, pheneturide, phensuximide, and trimethadione.

4. Discussion

Previously, some studies were conducted on a large population (Namazi et al., 2011; Bansal et al., 2013) or used big databases but investigated a single anti-seizure medication (Huang et al., 2024). To our knowledge, the current paper is the first comprehensive study using EudraVigilance describing sex differences in the seriousness and outcome of the treatment with anti-seizure medications.

Adverse drug reactions caused by anti-seizure medications can play a crucial role in the selection of the suitable anti-seizure medication for each patient (Devinsky et al., 2018). The anatomical and physiological differences between males and females affect the pharmacokinetic and pharmacodynamic properties of medicines including but not limited to metabolism and elimination by liver metabolism and renal function. These result in differences in adverse drug reactions, including their frequency and severity.

EudraVigilance provides a deep insight into the reported sADRs investigating sex differences. Our research covered a ten-year-period including an era when many new anti-seizure medications appeared in the market and letting sufficient time and a huge amount of data gather for reports on their adverse drug reactions. These resulted in and added evidential strength to our findings.

In our study, more than half of the reports and the number of adverse drug reactions pertained to female patients. Similarly, in another population-based study, the researchers found a slightly increased majority of females compared to our findings (Baftiu et al., 2019).

Investigating the most commonly reported preferred terms, we found certain differences regarding sex. The 'top' preferred terms such as *'pain', 'fatigue', 'nausea', and* 'headache' were most commonly associated with females but hardly affected males; while *'drug interaction', 'toxicity to various agents'* and *'pyrexia'* were closely associated with males. Some of the preferred terms such as *'seizure', 'drug ineffective'*, and *'epilepsy'* may be related to the failure of anti-seizure medication use, and were a bit higher in females (male: 2.61 % vs female: 2.81 %). It is also crucial to state that certain interactions decreased the effectiveness of an anti-seizure medication, potentially causing ineffectiveness, seizure or could lead to intoxication resulting in seizure, somnolence or dizziness. The large number of reported preferred terms may indicate that the patients were more likely to experience no seizure control rather than seizure exacerbation with an anti-seizure medication or paradoxical drug reaction (Jaramillo et al., 2022; Gesche et al., 2021).

Furthermore, the withdrawal of or non-adherence to an anti-seizure medication may cause seizure. Since anti-seizure medications act on the central nervous system, the most frequently reported preferred terms

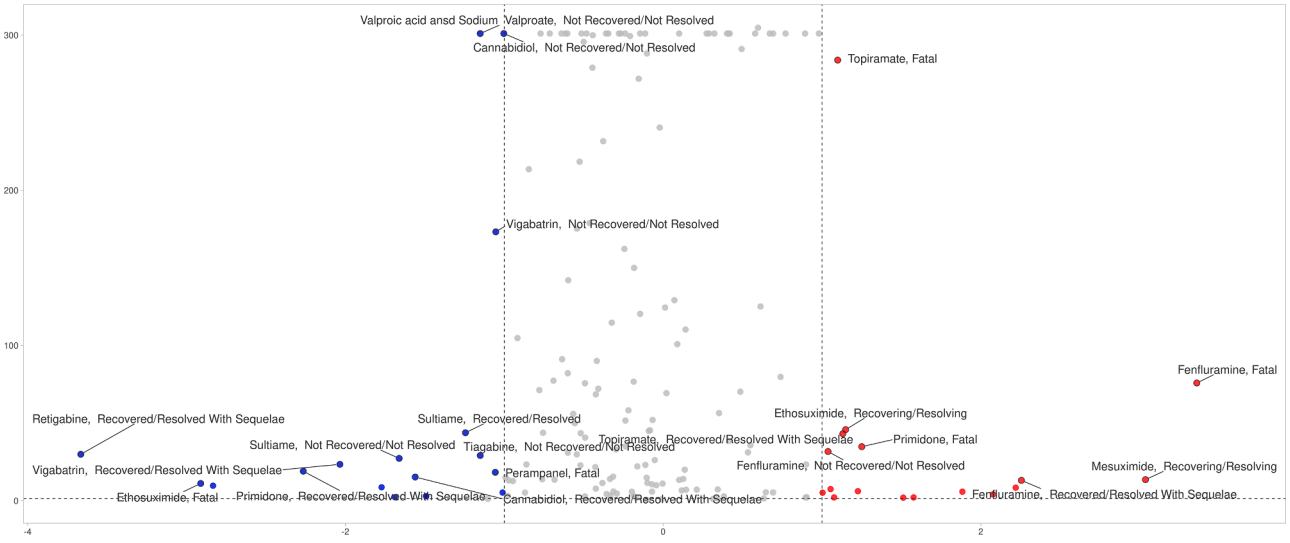

Fig. 3. Top ten positive associations of outcome criteria by anti-seizure medications.

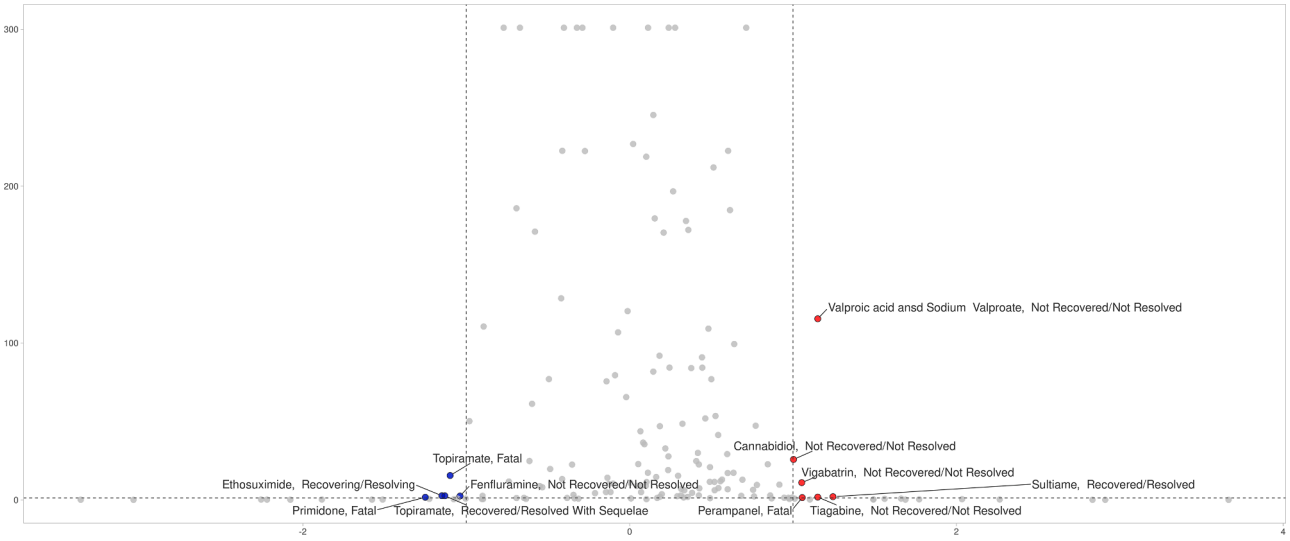

Fig. 4. Top five negative associations of outcome criteria by anti-seizure medications.

included '*somnolence*', '*dizziness*', '*fatigue*', '*nausea*', '*headache*' and '*pyrexia*' all of which were more common in females.

In the NorPD database, '*rash*' was the most frequently reported preferred term. It was followed by '*dizziness*', '*SUDEP*', '*cross-sensitivity reaction*' and '*pyrexia*' but sex differences were not in the focus of attention (Baftiu et al., 2019).

Despite males showed a greater willingness to participate in spontaneous reports in a Chinese study (Xiang et al., 2021), adverse drug reactions were more frequently reported by females (Yu et al., 2016). There may be a lot of factors that can account for the disproportionality. Despite the higher report rates among females, males were more likely to report 'serious' criteria. It is important to note that barbiturates, benzodiazepines and oxazolidines are the most commonly prescribed groups of medicines associated with the aforementioned categories. Nowadays, in most countries, these drugs are used in special cases. As far as benzodiazepines are regarded, the new generation preparations of this anti-seizure medication are used. In our previous publication we found that new anti-seizure medications had less serious adverse drug reactions (Girgis et al., 2024).

The '*congenital anomaly*' seriousness was observed mainly in male offsprings born to mothers who were taking anti-seizure medication. In line with the existing guidelines, the use of fatty acid derivatives and drugs potentially causing congenital anomalies in the offspring should be avoided by both sexes (e.g. valproate).

Examining the outcome criteria, the criterion '*fatal*' was more common in male patients when comparing the two sexes. As for the review of non-fatal criteria, the most common result was for the category '*recovered/resolved*', which means if the adverse drug reaction occurred in male patients and they survived it they would have a good chance to recover fully.

Negative associations were detected in case female patients were treated with brivaracetam, eslicarbazepine, and tiagabine, while in males responded similarly, if they got brivaracetam and cenobamate. Most of these drugs are brand-new anti-seizure medications on the market, that is perhaps why fewer reports were received. tiagabine is not commonly used, it is recommended only in special syndromes. Nevertheless, it should not be forgotten that the aforementioned drugs were developed and improved from molecules of previously used anti-seizure medications. Most of the pronounced positive associations were detected in case old type and rarely used anti-seizure medications were given to subjects of the either sex. (Some of those medicines are no longer available on the market.) However, an important unfavourable association could be detected in men in case they were treated with clonazepam, gabapentin, and vigabatrin. Vigabatrin is given in severe epilepsy syndromes. Gabapentin is a new anti-seizure medication with few adverse drug reactions and is preferably given in polyneuropathies and to older patients since interactions might pose a danger. clonazepam is in the focus of interest because it also shows a positive association with SUDEP.

Examining the criterion '*recovered/resolved*', females had higher probability to recover in case adverse drug reaction was caused by clorazepate potassium, tiagabine, mephenytoin, pheneturide, and perampanel. These anti-seizure medications are used relatively seldom.

Although the number of reported SUDEPs was low, it is noteworthy, that the reported anti-seizure medications were different among males and females. It should be noted that many of the anti-seizure medications involved in these reports were prescribed for severe epilepsy syndromes or refractory epilepsies where usually a single anti-seizure medication is not enough therefore more are prescribed. Besides this, these patients might have had severe central nervous system or other pathologies in the background, which required other non-anti-seizure medications as well. Of course, these are only assumptions but more attention should be paid to interactions in the prevention of SUDEPs.

In some instances, the low reporting rate may be related to the availability and accessibility of anti-seizure medications. The frequency of usage of both old and new anti-seizure medications varies from country to country and shows large differences (Baftiu et al., 2015).

Altogether, our study supports the literature review by Perucca et al. with real-life data based on EudraVigilance. Although, the database did not contain data on the efficacy of anti-seizure medications related to sex differences (the database was not aimed at it), nonetheless, we made an attempt to explore some sex differences in adverse drug reactions.

5. Conclusion

To our knowledge, this is the first comprehensive study using EudraVigilance describing sex differences in the seriousness and outcome of the treatment of anti-seizure medications. The analysis of EudraVigilance has shown a promising potential to mitigate adverse drug reactions at prescription by discovering the real-life adverse drug reaction profile of anti-seizure medications. Our findings revealed that females are more prone to adverse drug reactions than males in terms of anti-seizure medications. Differences were observed between males and females, particularly in terms of seriousness criteria, worse outcomes but prone to recover, and associations with SUDEP to the detriment of males. Nevertheless, fatal adverse drug reactions are more common in male patients. Although more reports were received for new anti-seizure medications, almost all seriousness criteria showed positive associations

with old anti-seizure medications in both sexes. However, we found that different anti-seizure medications are responsible for positive or negative associations of criteria depending on sexes. These aspects may also be important when physicians prescribe an anti-seizure medication for a patient or when a patient reports an adverse drug reaction. When choosing an ASM for a patient or especially if the patient has previously experienced an adverse drug reaction. these aspects can also be taken into account and may be important.

Limitation

The authors are aware that the study has several limitations. Epilepsy is not the exclusive indication for prescribing anti-seizure medications. Mandatory reporting in EudraVigilance is required only in serious cases of sADRs. Many factors, such as media coverage, public awareness, workload of healthcare professionals and others can influence reporting, which can lead to either under-reporting or over-reporting. Despite all that, the huge number of reports and studies on preferred terms, the majority of information was reported by healthcare professionals, which is also a strength of our study: in addition to the high number of reported preferred terms, it can support the evidence included in EudraVigilance (Girgis et al., 2024).

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

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CRediT authorship contribution statement

Michael Magdy Fahmy Girgis: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Gergely Farkasinszky:** Writing – review & editing, Methodology. **Klára Fekete:** Writing – review & editing, Writing – original draft, Investigation. **István Fekete:** Writing – review & editing, Validation. **Miklós Vecsernyés:** Writing – review & editing, Supervision. **Ildikó Bácskay:** Writing – review & editing, Supervision, Resources, Funding acquisition. **László Horváth:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendices

A Differences in sex associations by the chemical subgroups of anti-seizure medications

Table A1
Positive associations in males by the chemical subgroups of anti-seizure medications.

Seriousness and outcome criteria, SUDEP		*Chemical subgroup*	*ROR*	*Lower 95 %CI*	*Upper 95 %CI*	*p-value*
Seriousness	**Other Medically Important Condition**	Hydantoins	1.34	1.32	1.36	<0.001
		Other Antiepileptics	1.19	1.18	1.20	<0.001
	Caused/Prolonged Hospitalisation	Barbiturates	1.43	1.41	1.46	<0.001
		Benzodiazepines	1.24	1.23	1.26	<0.001
		Carboxamides	1.57	1.55	1.58	<0.001
		Hydantoins	1.59	1.57	1.61	<0.001
	Congenital Anomaly	Barbiturates	1.69	1.64	1.74	<0.001
		Fatty Acid derivatives	11.45	11.43	11.47	<0.001
		Oxazolidines	24.06	23.62	24.49	<0.001
	Disabling	Benzodiazepines	1.11	1.08	1.15	<0.001
		Fatty Acid derivatives	1.49	1.46	1.51	<0.001
	Life Threatening	Barbiturates	1.51	1.45	1.56	<0.001
		Benzodiazepines	1.65	1.62	1.68	<0.001
		Carboxamides	1.42	1.39	1.44	<0.001
		Hydantoins	1.55	1.51	1.59	<0.001
	Results in Death	Barbiturates	2.11	2.07	2.15	<0.001
		Benzodiazepines	1.99	1.97	2.01	<0.001
		Hydantoins	1.74	1.71	1.78	<0.001
		Oxazolidines	5.25	4.74	5.75	<0.001
Outcome	**Fatal**	Barbiturates	2.02	1.97	2.07	<0.001
		Benzodiazepines	2.28	2.25	2.30	<0.001
		Hydantoins	1.55	1.51	1.59	<0.001
		Oxazolidines	4.66	4.07	5.25	<0.001
	Not Recovered/Not Resolved	Benzodiazepines	1.23	1.21	1.25	<0.001
		Other Antiepileptics	1.50	1.49	1.52	<0.001
	Recovered/Resolved	Barbiturates	1.35	1.32	1.38	<0.001
		Carboxamides	1.57	1.56	1.58	<0.001
		Fatty Acid derivatives	1.03	1.02	1.04	<0.001
		Hydantoins	1.38	1.36	1.41	<0.001
		Succinimides	1.32	1.21	1.42	<0.001

(*continued on next page*)

Table A1 (*continued*)

Seriousness and outcome criteria, SUDEP		*Chemical subgroup*	*ROR*	*Lower 95 %*CI	*Upper 95 %*CI	*p-value*
	Recovered/Resolved With Sequelae	Carboxamides	1.20	1.12	1.28	<0.001
		Fatty Acid derivatives	1.11	1.04	1.19	<0.001
		Hydantoins	1.39	1.26	1.52	<0.001
		Succinimides	2.09	1.62	2.55	<0.001
	Recovering/Resolving	Barbiturates	1.42	1.38	1.46	<0.001
		Carboxamides	1.96	1.94	1.97	<0.001
		Fatty Acid derivatives	1.14	1.12	1.15	<0.001
		Hydantoins	1.11	1.07	1.14	<0.001
		Succinimides	1.83	1.70	1.96	<0.001
Event of special interest	**Sudden unexplained death in epilepsy**	Carboxamides	2.17	1.57	2.77	<0.001
		Other Antiepileptics	1.83	1.57	2.10	<0.001

Table A2
Negative associations in males by the chemical subgroups of anti-seizure medications.

Seriousness and outcome criteria, SUDEP		*Chemical subgroup*	*ROR*	*Lower 95 %*CI	*Upper 95 %*CI	*p-value*
Seriousness	**Other Medically Important Condition**	Barbiturates	0.82	0.80	0.85	<0.001
		Carboxamides	0.85	0.84	0.86	<0.001
		Fatty Acid derivatives	0.79	0.78	0.80	<0.001
		Succinimides	0.77	0.68	0.86	<0.001
	Caused/Prolonged Hospitalisation	Fatty Acid derivatives	0.90	0.89	0.91	<0.001
		Other Antiepileptics	0.73	0.73	0.74	<0.001
		Succinimides	0.80	0.70	0.89	<0.001
	Congenital Anomaly	Benzodiazepines	0.43	0.38	0.48	<0.001
		Carboxamides	0.57	0.53	0.60	<0.001
		Hydantoins	0.46	0.39	0.53	<0.001
		Other Antiepileptics	0.17	0.15	0.20	<0.001
	Disabling	Barbiturates	0.69	0.61	0.78	<0.001
		Carboxamides	0.55	0.51	0.60	<0.001
		Other Antiepileptics	0.97	0.94	0.99	<0.001
	Life Threatening	Other Antiepileptics	0.64	0.62	0.65	<0.001
	Results in Death	Carboxamides	0.82	0.80	0.85	<0.001
		Fatty Acid derivatives	0.82	0.80	0.85	<0.001
		Other Antiepileptics	0.75	0.74	0.77	<0.001
Outcome	**Fatal**	Carboxamides	0.77	0.74	0.81	<0.001
		Fatty Acid derivatives	0.82	0.79	0.85	<0.001
		Other Antiepileptics	0.74	0.72	0.76	<0.001
	Not Recovered/Not Resolved	Barbiturates	0.55	0.50	0.60	<0.001
		Carboxamides	0.60	0.58	0.62	<0.001
		Fatty Acid derivatives	0.69	0.67	0.70	<0.001
		Hydantoins	0.65	0.61	0.68	<0.001
		Succinimides	0.85	0.70	0.99	<0.001
	Recovered/Resolved	Benzodiazepines	0.98	0.96	0.99	<0.001
		Other Antiepileptics	0.74	0.73	0.75	<0.001
	Recovered/Resolved With Sequelae	Benzodiazepines	0.78	0.66	0.89	<0.001
		Other Antiepileptics	0.86	0.81	0.92	<0.001
	Recovering/Resolving	Benzodiazepines	0.91	0.89	0.94	<0.001
		Other Antiepileptics	0.65	0.64	0.66	<0.001
Event of special interest	**Sudden unexplained death in epilepsy**	None				

Table A3
Positive associations in females by the chemical subgroups of anti-seizure medications.

Seriousness and outcome criteria, SUDEP		*ASM chemical subgroup*	*ROR*	*Lower 95 %*CI	*Upper 95 %*CI	*p-value*
Seriousness	**Other Medically Important Condition**	Barbiturates	1.21	1.19	1.24	<0.001
		Carboxamides	1.18	1.17	1.19	<0.001
		Fatty Acid derivatives	1.27	1.26	1.28	<0.001
		Succinimides	1.30	1.21	1.39	<0.001
	Caused/Prolonged Hospitalisation	Fatty Acid derivatives	1.11	1.10	1.13	<0.001
		Other Antiepileptics	1.36	1.35	1.37	<0.001
		Oxazolidines	3.52	2.89	4.16	<0.001
		Succinimides	1.26	1.16	1.36	<0.001
	Congenital Anomaly	Benzodiazepines	2.34	2.29	2.39	<0.001
		Carboxamides	1.77	1.73	1.81	<0.001
		Hydantoins	2.19	2.12	2.26	<0.001
		Other Antiepileptics	5.75	5.72	5.77	<0.001
		Succinimides	3.71	3.29	4.13	<0.001
	Disabling	Barbiturates	1.44	1.36	1.53	<0.001
		Carboxamides	1.80	1.76	1.84	<0.001

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Table A3 (*continued*)

Seriousness and outcome criteria, SUDEP		*ASM chemical subgroup*	*ROR*	*Lower 95 %*CI	*Upper 95 %*CI	*p-value*
		Hydantoins	1.06	1.00	1.11	<0.001
		Other Antiepileptics	1.04	1.01	1.06	<0.001
	Life Threatening	Other Antiepileptics	1.57	1.55	1.59	<0.001
	Results in Death	Carboxamides	1.21	1.19	1.24	<0.001
		Fatty Acid derivatives	1.21	1.19	1.24	<0.001
		Other Antiepileptics	1.32	1.31	1.34	<0.001
		Succinimides	4.41	4.03	4.80	<0.001
Outcome	**Fatal**	Carboxamides	1.30	1.26	1.33	<0.001
		Fatty Acid derivatives	1.22	1.19	1.25	<0.001
		Other Antiepileptics	1.35	1.33	1.37	<0.001
		Succinimides	4.74	4.25	5.23	<0.001
	Not Recovered/Not Resolved	Barbiturates	1.81	1.76	1.86	<0.001
		Carboxamides	1.66	1.64	1.68	<0.001
		Fatty Acid derivatives	1.46	1.44	1.48	<0.001
		Hydantoins	1.55	1.51	1.58	<0.001
		Oxazolidines	12.04	10.06	14.01	<0.001
		Succinimides	1.18	1.04	1.33	<0.001
	Recovered/Resolved	Benzodiazepines	1.02	1.00	1.04	<0.001
		Other Antiepileptics	1.35	1.34	1.36	<0.001
		Oxazolidines	20.76	18.79	22.73	<0.001
	Recovered/Resolved With Sequelae	Benzodiazepines	1.29	1.17	1.41	<0.001
		Other Antiepileptics	1.16	1.10	1.21	<0.001
	Recovering/Resolving	Benzodiazepines	1.09	1.07	1.12	<0.001
		Other Antiepileptics	1.54	1.53	1.55	<0.001
Event of special interest	**Sudden unexplained death in epilepsy**	None				

Table A4
Negative associations in females by the chemical subgroups of anti-seizure medications.

Seriousness and outcome criteria, SUDEP		*ASM chemical subgroup*	*ROR*	*Lower 95 %*CI	*Upper 95 %*CI	*p-value*
Seriousness	**Other Medically Important Condition**	Hydantoins	0.74	0.72	0.77	<0.001
		Other Antiepileptics	0.84	0.83	0.85	<0.001
	Caused/Prolonged Hospitalisation	Barbiturates	0.70	0.67	0.72	<0.001
		Benzodiazepines	0.81	0.79	0.82	<0.001
		Carboxamides	0.64	0.63	0.65	<0.001
		Hydantoins	0.63	0.61	0.65	<0.001
	Congenital Anomaly	Barbiturates	0.59	0.54	0.64	<0.001
		Fatty Acid derivatives	0.09	0.07	0.11	<0.001
	Disabling	Benzodiazepines	0.90	0.86	0.93	<0.001
		Fatty Acid derivatives	0.67	0.65	0.70	<0.001
	Life Threatening	Barbiturates	0.66	0.61	0.72	<0.001
		Benzodiazepines	0.61	0.58	0.63	<0.001
		Carboxamides	0.71	0.68	0.73	<0.001
		Hydantoins	0.64	0.60	0.68	<0.001
	Results in Death	Barbiturates	0.47	0.43	0.52	<0.001
		Benzodiazepines	0.50	0.48	0.53	<0.001
		Hydantoins	0.57	0.54	0.61	<0.001
Outcome	**Fatal**	Barbiturates	0.49	0.44	0.55	<0.001
		Benzodiazepines	0.44	0.41	0.47	<0.001
		Hydantoins	0.64	0.60	0.69	<0.001
	Not Recovered/Not Resolved	Benzodiazepines	0.82	0.80	0.83	<0.001
		Other Antiepileptics	0.66	0.65	0.68	<0.001
	Recovered/Resolved	Barbiturates	0.74	0.71	0.77	<0.001
		Carboxamides	0.64	0.62	0.65	<0.001
		Fatty Acid derivatives	0.97	0.96	0.98	<0.001
		Hydantoins	0.72	0.70	0.75	<0.001
		Succinimides	0.76	0.65	0.86	<0.001
	Recovered/Resolved With Sequelae	Carboxamides	0.83	0.75	0.92	<0.001
		Fatty Acid derivatives	0.90	0.82	0.98	<0.001
		Hydantoins	0.72	0.59	0.85	<0.001
		Succinimides	0.48	0.01	0.94	<0.001
	Recovering/Resolving	Barbiturates	0.70	0.66	0.75	<0.001
		Carboxamides	0.51	0.49	0.53	<0.001
		Fatty Acid derivatives	0.88	0.86	0.90	<0.001
		Hydantoins	0.90	0.87	0.94	<0.001
		Succinimides	0.55	0.42	0.68	<0.001
Event of special interest	**Sudden unexplained death in epilepsy**	Other Antiepileptics	0.55	0.28	0.81	<0.001

B Differences in sex associations by anti-seizure medications

Table B1
Positive associations in males by anti-seizure medications.

Seriousness and outcome criteria, SUDEP		*Antiseizure medication*	*ROR*	*Lower 95 %*CI	*Upper 95 %*CI	*p-value*
Seriousness	**Other Medically Important Condition**	Brivaracetam	1.19	1.12	1.27	<0.001
		Cannabidiol	1.68	1.61	1.75	<0.001
		Carbamazepine	1.24	1.22	1.26	<0.001
		Cenobamate	1.51	1.33	1.69	<0.001
		Clobazam	1.58	1.53	1.62	<0.001
		Clorazepate potassium	6.15	5.05	7.25	<0.001
		Fosphenytoin	1.58	1.47	1.70	<0.001
		Lacosamide	1.22	1.19	1.25	<0.001
		Levetiracetam	1.23	1.21	1.25	<0.001
		Methylphenobarbital	1.48	1.29	1.66	<0.001
		Perampanel	1.63	1.55	1.72	<0.001
		Phenobarbital	1.42	1.38	1.46	<0.001
		Phenytoin	1.43	1.41	1.46	<0.001
		Primidone	1.47	1.37	1.57	<0.001
		Retigabine	1.65	1.51	1.78	<0.001
		Stiripentol	1.78	1.61	1.95	<0.001
		Sultiame	1.59	1.31	1.87	<0.001
		Trimethadione	3.10	2.29	3.91	<0.001
		Valproic acid and Sodium Valproate	1.88	1.86	1.90	<0.001
		Vigabatrin	1.65	1.60	1.70	<0.001
	Caused/Prolonged Hospitalisation	Brivaracetam	1.14	1.03	1.25	<0.001
		Cannabidiol	1.65	1.57	1.72	<0.001
		Carbamazepine	1.13	1.10	1.15	<0.001
		Cenobamate	2.13	1.95	2.32	<0.001
		Clobazam	1.85	1.79	1.91	<0.001
		Clorazepate potassium	6.07	4.98	7.16	<0.001
		Ethotoin	3.93	2.78	5.07	<0.001
		Fosphenytoin	1.20	1.06	1.34	<0.001
		Lacosamide	1.25	1.21	1.29	<0.001
		Levetiracetam	1.33	1.30	1.35	<0.001
		Methylphenobarbital	1.23	1.05	1.42	<0.001
		Perampanel	1.52	1.44	1.61	<0.001
		Phenobarbital	1.39	1.34	1.43	<0.001
		Phenytoin	1.29	1.26	1.32	<0.001
		Primidone	1.66	1.54	1.77	<0.001
		Retigabine	1.56	1.36	1.75	<0.001
		Rufinamide	2.03	1.81	2.26	<0.001
		Stiripentol	1.44	1.27	1.61	<0.001
		Sultiame	3.71	3.39	4.04	<0.001
		Valproic acid and Sodium Valproate	1.58	1.56	1.60	<0.001
		Vigabatrin	1.44	1.38	1.49	<0.001
	Congenital Anomaly	Methylphenobarbital	2.71	1.46	3.97	<0.001
		Oxcarbazepine	1.38	1.14	1.62	<0.001
		Phenytoin	1.53	1.32	1.74	<0.001
		Topiramate	1.19	1.09	1.28	<0.001
		Zonisamide	2.62	2.21	3.04	<0.001
	Disabling	Carbamazepine	1.78	1.69	1.88	<0.001
		Clobazam	2.50	2.28	2.73	<0.001
		Fosphenytoin	1.90	1.13	2.67	<0.001
		Levetiracetam	1.85	1.75	1.94	<0.001
		Oxcarbazepine	1.49	1.31	1.66	<0.001
		Perampanel	2.00	1.68	2.33	<0.001
		Phenytoin	1.15	1.03	1.26	<0.001
		Stiripentol	2.22	1.44	3.00	<0.001
		Tiagabine	62.04	60.06	64.03	<0.001
		Valproic acid and Sodium Valproate	2.01	1.96	2.07	<0.001
	Life Threatening	Carbamazepine	1.41	1.35	1.46	<0.001
		Cenobamate	4.91	4.12	5.70	<0.001
		Clobazam	1.53	1.35	1.71	<0.001
		Fosphenytoin	1.51	1.30	1.71	<0.001
		Lacosamide	1.29	1.17	1.41	<0.001
		Levetiracetam	1.53	1.46	1.60	<0.001
		Perampanel	2.04	1.80	2.28	<0.001
		Phenobarbital	1.25	1.14	1.37	<0.001
		Phenytoin	1.33	1.25	1.41	<0.001
		Primidone	1.57	1.13	2.01	<0.001
		Retigabine	1.78	1.27	2.29	<0.001
		Rufinamide	4.36	3.05	5.67	<0.001
		Stiripentol	2.60	2.04	3.16	<0.001
		Valproic acid and Sodium Valproate	1.28	1.23	1.33	<0.001
	Results in Death	Brivaracetam	1.72	1.37	2.07	<0.001
		Cannabidiol	1.52	1.35	1.69	<0.001
		Eslicarbazepine	1.81	1.36	2.26	<0.001
		Gabapentin	1.05	1.01	1.10	<0.001

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Table B1 (*continued*)

Seriousness and outcome criteria, SUDEP		*Antiseizure medication*	*ROR*	*Lower 95 %CI*	*Upper 95 %CI*	*p-value*
		Mesuximide	4.18	1.99	6.38	<0.001
		Perampanel	1.52	1.16	1.88	<0.001
		Pregabalin	1.08	1.04	1.13	<0.001
		Retigabine	2.66	1.97	3.36	<0.001
		Valproic acid and Sodium Valproate	1.43	1.38	1.48	<0.001
		Vigabatrin	1.17	1.05	1.29	<0.001
Outcome	**Fatal**	Cannabidiol	1.72	1.54	1.89	<0.001
		Eslicarbazepine	1.93	1.43	2.43	<0.001
		Ethosuximide	7.52	5.43	9.62	<0.001
		Gabapentin	1.07	1.02	1.13	<0.001
		Levetiracetam	1.14	1.06	1.21	<0.001
		Perampanel	2.08	1.64	2.52	<0.001
		Phenobarbital	1.14	1.02	1.25	<0.001
		Pregabalin	1.11	1.05	1.17	<0.001
		Retigabine	2.01	1.16	2.87	<0.001
		Tiagabine	1.83	1.05	2.61	<0.001
		Valproic acid and Sodium Valproate	1.36	1.29	1.43	<0.001
	Not Recovered/Not Resolved	Barbexaclone	3.42	2.32	4.51	<0.001
		Brivaracetam	1.25	1.15	1.35	<0.001
		Cannabidiol	2.00	1.92	2.09	<0.001
		Carbamazepine	1.28	1.23	1.33	<0.001
		Cenobamate	1.48	1.31	1.65	<0.001
		Clobazam	1.80	1.69	1.90	<0.001
		Eslicarbazepine	1.41	1.27	1.55	<0.001
		Lacosamide	1.56	1.50	1.61	<0.001
		Levetiracetam	1.53	1.49	1.57	<0.001
		Oxcarbazepine	1.18	1.10	1.26	<0.001
		Perampanel	1.52	1.37	1.66	<0.001
		Phenobarbital	1.51	1.40	1.62	<0.001
		Phenytoin	1.36	1.29	1.43	<0.001
		Primidone	1.69	1.46	1.91	<0.001
		Retigabine	1.82	1.48	2.15	<0.001
		Rufinamide	1.61	1.20	2.01	<0.001
		Sultiame	3.16	2.62	3.70	<0.001
		Tiagabine	2.22	1.85	2.59	<0.001
		Valproic acid and Sodium Valproate	2.22	2.18	2.26	<0.001
		Vigabatrin	2.08	1.94	2.21	<0.001
		Zonisamide	1.33	1.19	1.46	<0.001
	Recovered/Resolved	Cannabidiol	1.30	1.23	1.37	<0.001
		Carbamazepine	1.08	1.05	1.11	<0.001
		Cenobamate	1.43	1.24	1.62	<0.001
		Clobazam	1.71	1.63	1.78	<0.001
		Ethosuximide	1.23	1.04	1.42	<0.001
		Ethotoin	7.13	4.98	9.27	<0.001
		Fosphenytoin	1.89	1.73	2.05	<0.001
		Lacosamide	1.11	1.06	1.15	<0.001
		Levetiracetam	1.21	1.18	1.24	<0.001
		Methylphenobarbital	1.52	1.27	1.76	<0.001
		Oxcarbazepine	1.20	1.15	1.25	<0.001
		Perampanel	1.44	1.36	1.52	<0.001
		Phenobarbital	1.40	1.34	1.46	<0.001
		Phenytoin	1.43	1.39	1.47	<0.001
		Primidone	1.55	1.41	1.69	<0.001
		Retigabine	1.41	1.21	1.60	<0.001
		Rufinamide	1.46	1.22	1.69	<0.001
		Stiripentol	1.47	1.29	1.65	<0.001
		Sultiame	2.37	2.05	2.68	<0.001
		Valproic acid and Sodium Valproate	1.64	1.61	1.66	<0.001
		Vigabatrin	1.46	1.36	1.55	<0.001
	Recovered/Resolved With Sequelae	Brivaracetam	2.81	1.11	4.51	<0.001
		Cannabidiol	2.95	2.26	3.64	<0.001
		Lamotrigine	1.18	1.00	1.35	<0.001
		Phenobarbital	1.70	1.28	2.11	<0.001
		Phenytoin	1.34	1.08	1.60	<0.001
		Primidone	4.81	3.81	5.81	<0.001
		Retigabine	12.69	10.62	14.76	<0.001
		Stiripentol	2.81	1.11	4.51	<0.001
		Valproic acid and Sodium Valproate	1.61	1.45	1.77	<0.001
		Vigabatrin	4.10	3.34	4.86	<0.001
	Recovering/Resolving	Cannabidiol	1.18	1.04	1.32	<0.001
		Carbamazepine	1.18	1.14	1.22	<0.001
		Clobazam	1.34	1.21	1.46	<0.001
		Clonazepam	1.16	1.10	1.21	<0.001
		Fosphenytoin	1.43	1.16	1.70	<0.001
		Lacosamide	1.11	1.02	1.19	<0.001
		Levetiracetam	1.27	1.22	1.32	<0.001

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Table B1 (*continued*)

Seriousness and outcome criteria, SUDEP		*Antiseizure medication*	*ROR*	*Lower 95 %*CI	*Upper 95 %*CI	*p-value*
		Phenobarbital	1.38	1.29	1.47	<0.001
		Phenytoin	1.41	1.34	1.48	<0.001
		Sultiame	1.99	1.52	2.46	<0.001
		Tiagabine	1.96	1.46	2.46	<0.001
		Valproic acid and Sodium Valproate	1.52	1.48	1.56	<0.001
		Vigabatrin	1.34	1.20	1.48	<0.001
		Zonisamide	1.16	1.03	1.30	<0.001
Event of special interest	**Sudden unexplained death in epilepsy**	Eslicarbazepine	4.04	2.40	5.68	<0.001
		Lacosamide	1.90	1.25	2.55	<0.001
		Oxcarbazepine	5.09	3.81	6.37	<0.001
		Pregabalin	3.47	1.68	5.26	<0.001
		Retigabine	2.93	1.32	4.53	<0.001
		Topiramate	5.30	4.23	6.37	<0.001
		Vigabatrin	2.20	1.14	3.26	<0.001
		Zonisamide	4.64	2.37	6.90	<0.001

Table B2
Negative associations in males by anti-seizure medications.

Seriousness and outcome criteria, SUDEP		*Antiseizure medication*	*ROR*	*Lower 95 %*CI	*Upper 95 %*CI	*p-value*
Seriousness	**Other Medically Important Condition**	Clonazepam	0.92	0.90	0.94	<0.001
		Fenfluramine	0.28	0.06	0.51	0.01
		Gabapentin	0.90	0.88	0.92	<0.001
		Lamotrigine	0.82	0.80	0.84	<0.001
		Pregabalin	0.60	0.58	0.61	<0.001
		Tiagabine	0.76	0.59	0.93	<0.001
		Topiramate	0.59	0.57	0.62	<0.001
		Zonisamide	0.93	0.87	0.99	<0.001
	Caused/Prolonged Hospitalisation	Clonazepam	0.80	0.77	0.82	<0.001
		Eslicarbazepine	0.85	0.74	0.97	<0.001
		Fenfluramine	0.38	0.17	0.58	<0.001
		Gabapentin	0.92	0.90	0.95	<0.001
		Lamotrigine	0.73	0.70	0.75	<0.001
		Pregabalin	0.62	0.60	0.64	<0.001
		Topiramate	0.75	0.71	0.79	<0.001
	Congenital Anomaly	Gabapentin	0.71	0.50	0.91	<0.001
		Pregabalin	0.62	0.35	0.90	<0.001
	Disabling	Clonazepam	0.65	0.57	0.74	<0.001
		Gabapentin	0.87	0.79	0.94	0.04
		Pregabalin	0.55	0.50	0.60	<0.001
		Topiramate	0.55	0.44	0.66	<0.001
	Life Threatening	Clonazepam	0.60	0.54	0.67	<0.001
		Gabapentin	0.91	0.84	0.98	<0.001
		Lamotrigine	0.64	0.59	0.70	<0.001
		Pregabalin	0.81	0.76	0.87	<0.001
		Tiagabine	0.49	0.07	0.90	0.02
		Topiramate	0.88	0.79	0.98	<0.001
		Zonisamide	0.77	0.59	0.94	<0.001
	Results in Death	Methylphenobarbital	0.72	0.44	0.99	<0.001
		Primidone	0.38	0.07	0.70	<0.001
		Oxcarbazepine	0.82	0.70	0.94	<0.001
		Phenytoin	0.87	0.80	0.94	<0.001
		Lamotrigine	0.73	0.68	0.79	<0.001
		Topiramate	0.55	0.46	0.64	<0.001
Outcome	**Fatal**	Lamotrigine	0.66	0.59	0.73	<0.001
		Methylphenobarbital	0.54	0.19	0.88	0.003
		Oxcarbazepine	0.78	0.63	0.93	<0.001
		Primidone	0.42	0.06	0.78	0.02
		Topiramate	0.47	0.36	0.58	<0.001
	Not Recovered/Not Resolved	Clonazepam	0.75	0.71	0.79	<0.001
		Fenfluramine	0.49	0.16	0.81	0.003
		Gabapentin	0.80	0.76	0.84	<0.001
		Lamotrigine	0.83	0.78	0.87	<0.001
		Pregabalin	0.59	0.56	0.61	<0.001
		Topiramate	0.51	0.44	0.57	<0.001
	Recovered/Resolved	Clonazepam	0.93	0.90	0.97	<0.001
		Eslicarbazepine	0.65	0.54	0.77	<0.001
		Gabapentin	0.82	0.78	0.85	<0.001
		Lamotrigine	0.76	0.73	0.79	<0.001
		Pregabalin	0.63	0.60	0.65	<0.001
		Tiagabine	0.60	0.44	0.76	<0.001
		Topiramate	0.54	0.49	0.58	<0.001

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Table B2 (*continued*)

Seriousness and outcome criteria, SUDEP		*Antiseizure medication*	*ROR*	*Lower 95 %*CI	*Upper 95 %*CI	*p-value*
		Zonisamide	0.91	0.82	0.99	<0.001
	Recovered/Resolved With Sequelae	Carbamazepine	0.75	0.56	0.94	<0.001
		Gabapentin	0.69	0.46	0.92	<0.001
		Pregabalin	0.71	0.57	0.86	<0.001
		Topiramate	0.46	0.16	0.75	<0.001
	Recovering/Resolving	Eslicarbazepine	0.68	0.47	0.90	<0.001
		Ethosuximide	0.45	0.16	0.74	0.002
		Gabapentin	0.75	0.69	0.80	<0.001
		Lamotrigine	0.67	0.63	0.71	<0.001
		Pregabalin	0.62	0.58	0.66	<0.001
		Topiramate	0.71	0.64	0.78	<0.001
Event of special interest	**Sudden unexplained death in epilepsy**	None				

Table B3
Positive associations in females by anti-seizure medications.

Seriousness and outcome criteria, SUDEP		*ASM*	*ROR*	*Lower 95 %*CI	*Upper 95 %*CI	*p-value*
Seriousness	**Other Medically Important Condition**	Barbexaclone	1.72	1.29	2.15	<0.001
		Clonazepam	1.09	1.07	1.11	<0.001
		Felbamate	1.24	1.04	1.45	<0.001
		Fenfluramine	3.53	3.30	3.75	<0.001
		Gabapentin	1.11	1.09	1.13	<0.001
		Lamotrigine	1.22	1.20	1.23	<0.001
		Mesuximide	2.65	2.13	3.18	<0.001
		Pregabalin	1.68	1.67	1.69	<0.001
		Tiagabine	1.32	1.15	1.49	<0.001
		Topiramate	1.69	1.66	1.72	<0.001
		Zonisamide	1.07	1.01	1.14	<0.001
	Caused/Prolonged Hospitalisation	Aminobutyric acid	6.31	5.11	7.50	<0.001
		Clonazepam	1.25	1.23	1.28	<0.001
		Eslicarbazepine	1.17	1.06	1.28	<0.001
		Fenfluramine	2.66	2.45	2.86	<0.001
		Gabapentin	1.08	1.06	1.11	<0.001
		Lamotrigine	1.38	1.36	1.40	<0.001
		Mephenytoin	2.22	1.30	3.14	<0.001
		Mesuximide	6.04	5.31	6.78	<0.001
		Pregabalin	1.61	1.59	1.63	<0.001
		Topiramate	1.34	1.30	1.37	<0.001
	Congenital Anomaly	Brivaracetam	6.40	5.30	7.49	<0.001
		Eslicarbazepine	2.51	1.56	3.46	<0.001
		Gabapentin	1.42	1.22	1.62	<0.001
		Pregabalin	1.60	1.32	1.88	<0.001
		Vigabatrin	1.98	1.34	2.62	<0.001
	Disabling	Brivaracetam	5.14	4.54	5.74	<0.001
		Clonazepam	1.53	1.45	1.62	<0.001
		Fenfluramine	2.76	2.28	3.23	<0.001
		Gabapentin	1.16	1.08	1.23	<0.001
		Pregabalin	1.83	1.77	1.88	<0.001
		Primidone	1.76	1.28	2.25	<0.001
		Retigabine	3.18	2.56	3.80	<0.001
		Rufinamide	3.25	2.44	4.06	<0.001
		Sultiame	5.53	3.46	7.60	<0.001
		Topiramate	1.82	1.70	1.93	<0.001
	Life Threatening	Clonazepam	1.66	1.59	1.72	<0.001
		Ethosuximide	1.59	1.06	2.13	<0.001
		Fenfluramine	6.21	5.48	6.94	<0.001
		Gabapentin	1.09	1.02	1.16	<0.001
		Lamotrigine	1.55	1.50	1.61	<0.001
		Methylphenobarbital	1.48	1.11	1.85	<0.001
		Pregabalin	1.23	1.18	1.29	<0.001
		Tiagabine	2.05	1.63	2.46	<0.001
		Topiramate	1.14	1.04	1.23	<0.001
		Zonisamide	1.31	1.13	1.49	<0.001
	Results in Death	Felbamate	3.25	2.25	4.25	<0.001
		Fenfluramine	3.38	2.87	3.89	<0.001
		Lamotrigine	1.36	1.30	1.42	<0.001
		Methylphenobarbital	1.40	1.12	1.67	<0.001
		Oxcarbazepine	1.22	1.10	1.34	<0.001
		Phenytoin	1.15	1.08	1.22	<0.001
		Primidone	2.60	2.28	2.92	<0.001
		Topiramate	1.82	1.73	1.91	<0.001
		Trimethadione	2.87	1.74	4.00	<0.001

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Table B3 (*continued*)

Seriousness and outcome criteria, SUDEP		*ASM*	*ROR*	*Lower 95 %CI*	*Upper 95 %CI*	*p-value*
Outcome	**Fatal**	Felbamate	4.66	3.14	6.18	<0.001
		Fenfluramine	10.26	9.24	11.29	<0.001
		Lamotrigine	1.51	1.44	1.59	<0.001
		Methylphenobarbital	1.87	1.52	2.21	<0.001
		Oxcarbazepine	1.28	1.13	1.43	<0.001
		Primidone	2.38	2.02	2.74	<0.001
		Topiramate	2.14	2.03	2.25	<0.001
	Not Recovered/Not Resolved	Clonazepam	1.33	1.29	1.37	<0.001
		Fenfluramine	2.05	1.73	2.38	<0.001
		Gabapentin	1.25	1.21	1.29	<0.001
		Lamotrigine	1.21	1.16	1.26	<0.001
		Mephenytoin	4.22	2.14	6.30	<0.001
		Mesuximide	3.69	2.21	5.17	<0.001
		Pregabalin	1.71	1.68	1.73	<0.001
		Topiramate	1.97	1.91	2.04	<0.001
	Recovered / Resolved	Aminobutyric acid	2.01	1.14	2.87	<0.001
		Barbexaclone	2.34	1.43	3.25	<0.001
		Clonazepam	1.07	1.04	1.11	<0.001
		Eslicarbazepine	1.53	1.41	1.65	<0.001
		Gabapentin	1.22	1.19	1.26	<0.001
		Lamotrigine	1.32	1.29	1.35	<0.001
		Pregabalin	1.59	1.57	1.62	<0.001
		Tiagabine	1.67	1.51	1.83	<0.001
		Topiramate	1.86	1.81	1.90	<0.001
		Zonisamide	1.10	1.01	1.19	<0.001
	Recovered / Resolved With Sequelae	Carbamazepine	1.33	1.14	1.52	<0.001
		Fenfluramine	4.77	3.56	5.99	<0.001
		Gabapentin	1.45	1.22	1.68	<0.001
		Pregabalin	1.40	1.26	1.55	<0.001
		Topiramate	2.19	1.90	2.48	<0.001
		Zonisamide	2.08	1.36	2.80	<0.001
	Recovering / Resolving	Eslicarbazepine	1.46	1.25	1.68	<0.001
		Ethosuximide	2.22	1.93	2.51	<0.001
		Gabapentin	1.34	1.28	1.39	<0.001
		Lamotrigine	1.49	1.45	1.54	<0.001
		Mesuximide	8.20	6.16	10.25	<0.001
		Pregabalin	1.62	1.58	1.65	<0.001
		Topiramate	1.41	1.34	1.48	<0.001
Event of special interest	**Sudden unexplained death in epilepsy**	None				

Table B4
Negative associations in females by anti-seizure medications.

Seriousness and outcome criteria, SUDEP		*Antiseizure medication*	*ROR*	*Lower 95 %CI*	*Upper 95 %CI*	*p-value*
Seriousness	**Other Medically Important Condition**	Brivaracetam	0.84	0.76	0.91	<0.001
		Cannabidiol	0.60	0.53	0.66	<0.001
		Carbamazepine	0.81	0.79	0.82	<0.001
		Cenobamate	0.66	0.48	0.85	<0.001
		Clobazam	0.63	0.59	0.68	<0.001
		Fosphenytoin	0.63	0.51	0.75	<0.001
		Lacosamide	0.82	0.79	0.85	<0.001
		Levetiracetam	0.81	0.79	0.83	<0.001
		Methylphenobarbital	0.68	0.49	0.86	<0.001
		Perampanel	0.61	0.52	0.70	<0.001
		Phenobarbital	0.70	0.66	0.75	<0.001
		Phenytoin	0.70	0.67	0.72	<0.001
		Primidone	0.68	0.58	0.78	<0.001
		Retigabine	0.61	0.47	0.74	<0.001
		Stiripentol	0.56	0.39	0.73	<0.001
		Sultiame	0.63	0.35	0.91	<0.001
		Valproic acid and Sodium Valproate	0.53	0.52	0.55	<0.001
		Vigabatrin	0.61	0.56	0.66	<0.001
	Caused/Prolonged Hospitalisation	Brivaracetam	0.88	0.77	0.99	<0.001
		Cannabidiol	0.61	0.53	0.68	<0.001
		Carbamazepine	0.89	0.87	0.91	<0.001
		Cenobamate	0.47	0.28	0.65	<0.001
		Clobazam	0.54	0.48	0.60	<0.001
		Fosphenytoin	0.83	0.70	0.97	<0.001
		Lacosamide	0.80	0.76	0.84	<0.001
		Levetiracetam	0.75	0.73	0.78	<0.001
		Methylphenobarbital	0.81	0.63	0.99	<0.001
		Perampanel	0.66	0.57	0.74	<0.001

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Table B4 (*continued*)

Seriousness and outcome criteria, SUDEP		*Antiseizure medication*	*ROR*	*Lower 95 %CI*	*Upper 95 %CI*	*p-value*
		Phenobarbital	0.72	0.68	0.77	<0.001
		Phenytoin	0.78	0.75	0.81	<0.001
		Primidone	0.60	0.49	0.72	<0.001
		Retigabine	0.64	0.45	0.83	<0.001
		Rufinamide	0.49	0.27	0.71	<0.001
		Stiripentol	0.69	0.52	0.87	<0.001
		Valproic acid and Sodium Valproate	0.63	0.61	0.65	<0.001
		Vigabatrin	0.70	0.64	0.75	<0.001
	Congenital Anomaly	Oxcarbazepine	0.73	0.49	0.97	<0.001
		Phenytoin	0.65	0.44	0.87	<0.001
		Topiramate	0.84	0.75	0.93	<0.001
	Disabling	Carbamazepine	0.56	0.47	0.66	<0.001
		Clobazam	0.40	0.17	0.63	<0.001
		Levetiracetam	0.54	0.45	0.64	<0.001
		Oxcarbazepine	0.67	0.50	0.85	<0.001
		Perampanel	0.50	0.17	0.82	0.003
		Phenytoin	0.87	0.76	0.99	<0.001
		Valproic acid and Sodium Valproate	0.50	0.44	0.55	<0.001
	Life Threatening	Carbamazepine	0.71	0.66	0.77	<0.001
		Clobazam	0.65	0.47	0.83	<0.001
		Fosphenytoin	0.66	0.46	0.87	<0.001
		Lacosamide	0.78	0.66	0.90	<0.001
		Levetiracetam	0.65	0.58	0.72	<0.001
		Perampanel	0.49	0.25	0.73	<0.001
		Phenobarbital	0.80	0.69	0.91	<0.001
		Phenytoin	0.75	0.67	0.84	<0.001
		Valproic acid and Sodium Valproate	0.78	0.73	0.83	<0.001
	Results in Death	Brivaracetam	0.58	0.23	0.93	<0.001
		Cannabidiol	0.66	0.49	0.83	<0.001
		Gabapentin	0.95	0.90	0.99	<0.001
		Pregabalin	0.92	0.88	0.97	<0.001
		Valproic acid and Sodium Valproate	0.70	0.65	0.75	<0.001
		Vigabatrin	0.85	0.73	0.98	<0.001
Outcome	**Fatal**	Cannabidiol	0.58	0.41	0.76	<0.001
		Gabapentin	0.93	0.88	0.99	<0.001
		Levetiracetam	0.88	0.80	0.96	<0.001
		Perampanel	0.48	0.04	0.92	0.03
		Phenobarbital	0.88	0.77	0.99	<0.001
		Pregabalin	0.90	0.84	0.96	<0.001
		Valproic acid and Sodium Valproate	0.74	0.67	0.80	<0.001
	Not Recovered/Not Resolved	Brivaracetam	0.80	0.70	0.90	<0.001
		Cannabidiol	0.50	0.41	0.59	0.01
		Carbamazepine	0.78	0.73	0.83	<0.001
		Cenobamate	0.68	0.50	0.85	<0.001
		Clobazam	0.56	0.45	0.66	<0.001
		Eslicarbazepine	0.71	0.57	0.85	<0.001
		Lacosamide	0.64	0.59	0.70	<0.001
		Levetiracetam	0.65	0.61	0.69	<0.001
		Oxcarbazepine	0.84	0.76	0.92	<0.001
		Perampanel	0.66	0.51	0.80	<0.001
		Phenobarbital	0.66	0.55	0.77	<0.001
		Phenytoin	0.73	0.67	0.80	<0.001
		Primidone	0.59	0.37	0.82	<0.001
		Retigabine	0.55	0.21	0.89	0.001
		Tiagabine	0.45	0.08	0.82	0.02
		Valproic acid and Sodium Valproate	0.45	0.41	0.49	<0.001
		Vigabatrin	0.48	0.35	0.62	<0.001
		Zonisamide	0.75	0.62	0.89	0.01
	Recovered/Resolved	Cannabidiol	0.77	0.70	0.84	<0.001
		Carbamazepine	0.92	0.90	0.95	<0.001
		Cenobamate	0.70	0.51	0.89	<0.001
		Clobazam	0.59	0.51	0.66	<0.001
		Fosphenytoin	0.53	0.37	0.69	<0.001
		Lacosamide	0.90	0.86	0.95	<0.001
		Levetiracetam	0.82	0.79	0.86	<0.001
		Methylphenobarbital	0.66	0.42	0.90	<0.001
		Oxcarbazepine	0.83	0.78	0.88	<0.001
		Perampanel	0.69	0.61	0.78	<0.001
		Phenobarbital	0.72	0.66	0.78	<0.001
		Phenytoin	0.70	0.66	0.74	<0.001
		Primidone	0.64	0.50	0.78	<0.001
		Retigabine	0.71	0.52	0.91	<0.001
		Rufinamide	0.69	0.45	0.92	<0.001
		Stiripentol	0.68	0.50	0.86	<0.001
		Sultiame	0.42	0.11	0.74	0.009
		Valproic acid and Sodium Valproate	0.61	0.58	0.63	<0.001

(*continued on next page*)

Table B4 (*continued*)

Seriousness and outcome criteria, SUDEP		*Antiseizure medication*	*ROR*	*Lower 95 %CI*	*Upper 95 %CI*	*p-value*
		Vigabatrin	0.69	0.59	0.78	<0.001
	Recovered/Resolved With Sequelae	Valproic acid and Sodium Valproate	0.62	0.46	0.78	<0.001
	Recovering/Resolving	Cannabidiol	0.85	0.70	0.99	<0.001
		Carbamazepine	0.85	0.81	0.89	<0.001
		Clobazam	0.75	0.63	0.87	<0.001
		Clonazepam	0.87	0.81	0.92	<0.001
		Fosphenytoin	0.70	0.43	0.97	<0.001
		Lacosamide	0.90	0.82	0.99	<0.001
		Levetiracetam	0.79	0.74	0.84	<0.001
		Phenobarbital	0.73	0.64	0.81	<0.001
		Phenytoin	0.71	0.64	0.78	<0.001
		Sultiame	0.50	0.03	0.97	<0.001
		Valproic acid and Sodium Valproate	0.66	0.62	0.70	<0.001
		Vigabatrin	0.75	0.60	0.89	<0.001
		Zonisamide	0.86	0.73	0.99	<0.001
Event of special interest	**Sudden unexplained death in epilepsy**	None				

Data availability

Data will be made available on request.

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